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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW SULPHONAMIDES OF PYRIMIDINE

Jerzy Cieplik[a], Janusz Pluta [b], Olaf Gubrynowicz[b]
a) Department of Organic Chemistry, Medical Academy, Grodzka 9, 50-137 Wrocław, Poland
b) Department of Applied Pharmacy, Medical Academy, Szewska 38, 50-137 Wrocław, Poland

Summary

The paper presents the synthesis of 5-substituted pyrimidine sulphonamides as well as the results of studies on the antibacterial and antifungal activity of obtained derivatives.

Introduction

Results of previous research on synthesis and biological properties of pyrimidine ring have demonstrated that the system is capable of extremely potent biological activity. The obtained derivatives revealed both cytostatic [1,2], immunomodulating [3,4] and first of all antibacterial [5,6,7] properties. That is why we found useful to carry out a number of syntheses aiming at obtaining 5-substituted pyrimidine sulphonamides.

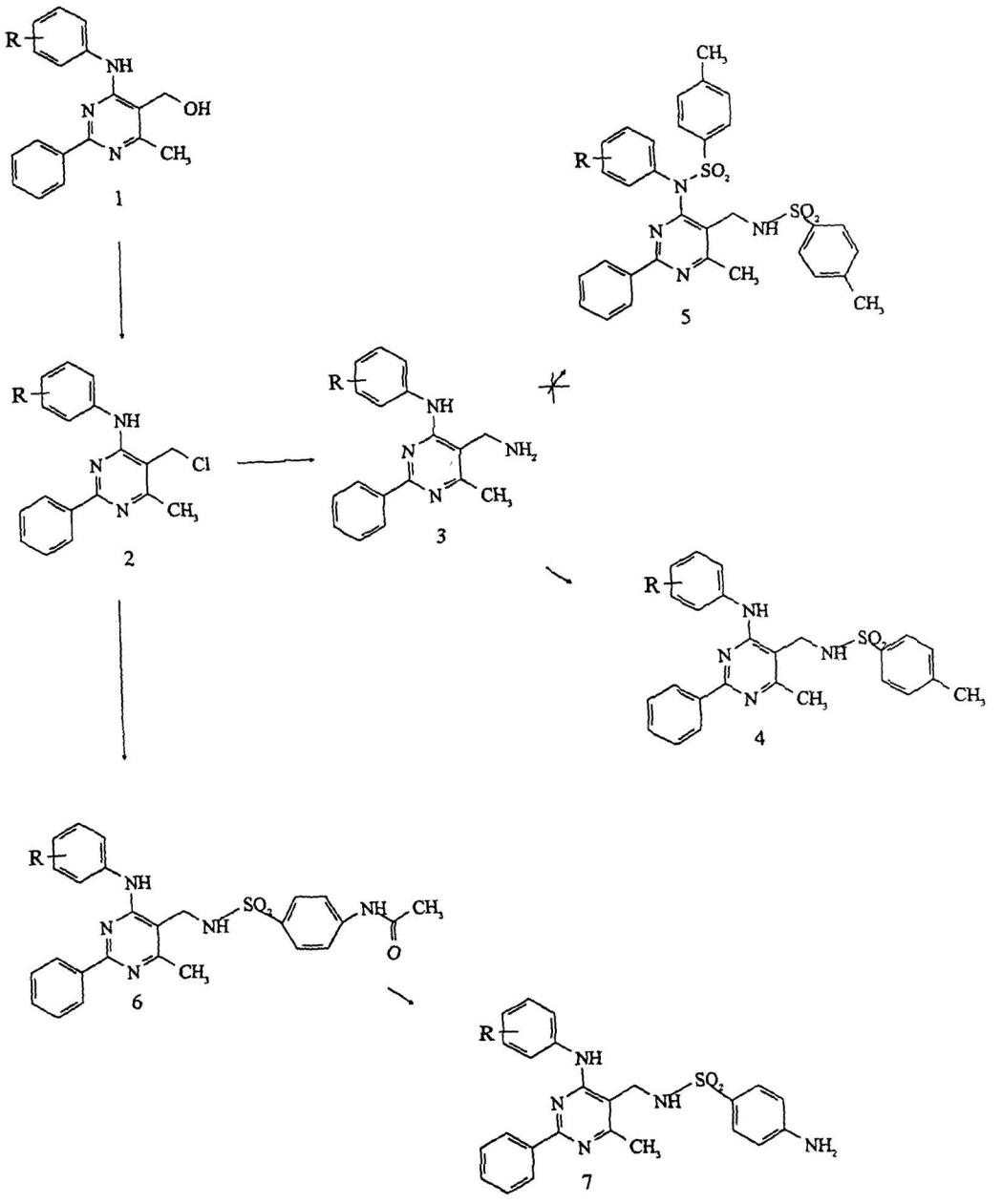
CHEMISTRY

The substrate in our studies was 4-aryl-6-methyl-2-phenyl-5-hydroxymethylpyrimidine (1), which after treatment with $SOCl_2$, was transformed into 2-aryl-6-methyl-2-phenyl-5-chloromethylpyrimidine (**2**). Next 5-substituted pyrimidine sulphonamides were obtained by means of two methods. The first one consisted in treatment of 5-chlorderivative of pyrimidine **2** with aqueous solution of ammonia gave 5-aminoderivative **3**, which was condensed with p-toluilosulphonic acid chloride giving adequate sulphonamides. The second method consisted in direct action of N-acetylsulfanilamide on 5-chloroderivative of pyrimidine **2**. Despite of several trials, we failed to obtain double sulphonamides, compound **5**. The arylaminegroup at site 4 of the pyrimidine ring does not react with sulphonic chlorides.

Physical and spectral properties of the compounds are given in Table 1.

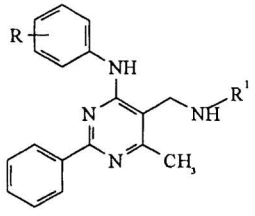
Key words Pyrimidine, sulphonamides, antibacterial activity

(*) Herrn Prof. Fleischhacker zum 65. Geburtstag gewidmet



Scheme 1

Physical and spectral of the compounds are given in Table 1.



Comp	R	R^1	Formula (M.W.)	M.P. (^{0}C)	Yield (%)	ANALYSIS calc. found C	H	N
3a	H	H	$C_{18}H_{18}N_4$ (290)	117-119	92.3	74.48 74.56	6.20 6.36	19.31 19.52
3b	4-Cl	H	$C_{18}H_{17}N_4Cl$ (324)	148-150	88.2	66.66 66.50	5.24 4.95	17.28 16.96
3c	4-OC_2H_5	H	$C_{20}H_{22}N_4O$ (334)	109-111	85.3	71.85 71.55	6.58 6.50	16.76 17.03
3d	4-OH	H	$C_{18}H_{18}N_4O$ (306)	110-112	82.2	70.58 70.62	5.88 5.90	18.30 18.26
3e	4-CH_3	H	$C_{19}H_{20}N_4$ (304)	120-122	79.2	75.00 75.22	6.57 6.66	18.42 18.56
4a	H	-SO_2-C_6H_4 -4-CH_3	$C_{25}H_{24}N_4O_2S$ (444)	164-166	64.5	67.58 67.40	5.40 5.65	12.61 12.33
4b	4-Cl	-SO_2-C_6H_4 -4-CH_3	$C_{25}H_{23}N_4O_2SCl$ (478)	138-140	63.5	62.76 62.54	4.81 5.12	11.47 11.62
4c	4-OC_2H_5	-SO_2-C_6H_4 -4-CH_3	$C_{27}H_{28}N_4O_3S$ (488)	213-215	61.1	66.39 66.20	5.73 5.54	11.47 11.62
6a	H	-SO_2-C_6H_4-NH-CO-CH_3	$C_{26}H_{25}N_5O_3S$ (487)	158-161	76.3	64.04 64.12	5.13 4.95	14.37 14.26
6b	4-Cl	-SO_2-C_6H_4-NH-CO-CH_3	$C_{26}H_{25}N_5O_3S$ (521)	123-125	72.2	59.88 60.11	4.60 4.55	13.43 13.20
6c	4-OC_2H_5	-SO_2-C_6H_4-NH-CO-CH_3	$C_{28}H_{29}N_5O_4S$ (531)	189-191	68.7	63.27 63.35	5.46 5.52	13.18 13.24
6d	4-OH	-SO_2-C_6H_4-NH-CO-CH_3	$C_{26}H_{25}N_5O_4S$ (503)	160-162	75.2	62.02 62.25	4.97 4.85	13.91 13.82
6e	4-CH_3	-SO_2-C_6H_4-NH-CO-CH_3	$C_{27}H_{27}N_5O_3S$ (501)	150-152	72.4	64.67 64.73	5.38 5.42	13.97 13.99
7a	H	-SO_2-C_6H_4-NH_2	$C_{24}H_{23}N_5O_2S$ (445)	110-112	84.4	69.73 70.12	5.56 5.63	16.94 17.25
7b	4-Cl	-SO_2-C_6H_4-NH_2	$C_{24}H_{22}N_5O_2SCl$ (479)	174-176	81.7	60.12 60.23	4.59 4.70	14.61 14.72
7c	4-OC_2H_5	-SO_2-C_6H_4-NH_2	$C_{26}H_{27}N_5O_3S$ (489)	178-180	77.2	63.80 63.55	5.52 5.45	14.31 14.48
7d	4-OH	-SO_2-C_6H_4-NH_2	$C_{24}H_{23}N_5O_3S$ (461)	160-162	75.3	62.47 62.55	4.98 5.12	15.18 15.20
7e	4-CH_3	-SO_2-C_6H_4-NH_2	$C_{25}H_{25}N_5O_2S$ (459)	125-127	72.2	65.35 65.40	5.44 5.25	15.25 15.33

Table 1

The obtained chemical compounds were examined from the point of view of their microbiological activity, which was assessed on selected bacterial strains.

Assessment of the activity of ivestigated substances was carried out according to FP V [8]. Absolute activity was determined by defining lowest concentration able to inhibit the growth of bacterial stain (MIC) in fluid medium and wxpressed in micrograms (μg) of investigated substanced per 1 ml. Relative activity was determined MIC value of the investigated substance by MIC value of a pattern (Urenil, Erytromycin).

Antibacterial potential was determined by means of cylinder-plate method assuming the average from 9 trials (3 weighed samples by 3 measurements).

The obtained results are presented in Table 2, 3.

Table 2: Antibacterial activity (MIC, μg/ml)

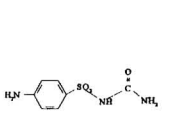
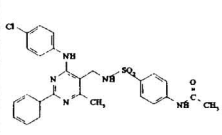
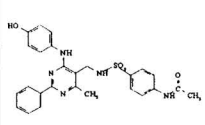
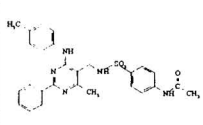
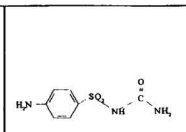
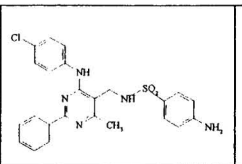
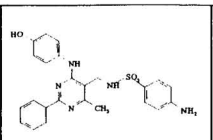
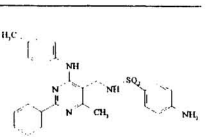
				
	Urenil	**6b**	**6d**	**6e**
	MIC μg/ml	MIC μg/ml	MIC μg/ml	MIC μg/ml
	500 100 25 12 6 3	500 100 25 12 6 3	500 100 25 12 6 3	500 100 25 12 6 3
Escherichia coli	202 125 117 108 101 90	236 108 93 92 91 90	234 120 102 94 92 90	238 125 111 94 92 90
Enterobacter fecalis	181 117 105 99 90 90	188 140 131 108 94 90	133 123 111 106 94 90	148 118 93 92 90 90
Staphylococ--cus aureus	190 124 108 97 94 90	126 102 94 94 90 90	129 96 92 90 90 90	105 98 96 92 90 90
Pseudomonas aeruginosa	206 112 103 98 90 90	250 109 94 92 90 90	212 136 98 95 90 90	220 110 98 96 90 90
Bacillus subtilis	234 176 120 104 98 90	142 120 107 98 96 90	191 137 104 98 96 90	148 106 94 92 90 90
Serratia marcesceus	211 120 110 96 92 90	167 120 105 98 90 90	181 109 98 96 90 90	164 106 98 96 90 90
Proteus vulgaris	186 118 104 96 90 90	158 108 98 90 90 90	183 114 95 92 90 90	157 99 96 92 90 90
Staphylococcus epidermidis	151 115 100 94 90 90	174 112 95 92 90 90	98 96 94 90 90 90	134 96 94 92 90 90
Klebsiella pneumoniae	164 110 105 98 90 90	254 157 102 94 90 90	260 194 109 97 90 90	256 224 113 100 90 90
Candida albicans	180 114 101 90 90 90	238 140 110 100 95 90	259 137 104 100 90 90	250 148 128 110 102 90

Table3: Antibacterial activity (MIC, μg/ml)

				
	Urenil	**7b**	**7d**	**7e**
	MIC μg/ml	MIC μg/ml	MIC μg/ml	MIC μg/ml
	500 100 25 12 6 3	500 100 25 12 6 3	500 100 25 12 6 3	500 100 25 12 6 3
Escherichia coli	202 125 117 108 101 90	223 111 97 92 90 90	245 127 106 95 90 90	232 104 96 90 90 90
Enterobacter fecalis	181 117 105 99 90 90	160 122 116 111 92 90	164 128 105 90 90 90	178 102 96 90 90 90
Staphylococcus aureus	190 124 108 97 94 90	150 101 94 90 90 90	130 94 90 90 90 90	90 90 90 90 90 90
Pseudomonas aeruginosa	206 112 103 98 90 90	244 106 96 93 90 90	256 123 104 92 90 90	194 102 90 90 90 90
Bacillus subtilis	234 176 120 104 98 90	120 108 90 90 90 90	172 116 90 90 90 90	289 187 140 124 118 90
Serratia marcesceus	211 120 110 96 92 90	175 90 90 90 90 90	185 103 90 90 90 90	153 90 90 90 90 90
Proteus vulgaris	186 118 104 96 90 90	167 95 90 90 90 90	164 101 90 90 90 90	156 90 90 90 90 90
Staphylococcus epidermidis	151 115 100 94 90 90	90 90 90 90 90 90	155 106 90 90 90 90	127 90 90 90 90 90
Klebsiella pneumoniae	164 110 105 98 90 90	256 166 105 101 90 90	232 179 100 94 90 90	259 107 90 90 90 90
Candida albicans	180 114 101 90 90 90	227 186 133 122 104 90	259 137 104 100 90 90	250 148 128 110 102 90

RESULTS AND DISCUSSION

Seven newly obtained pyrimidine derivatives were studied microbiologically on 10 bacterial strains: *Escherichia coli, Enterococcus faecalis, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Serratia marcesceus, Proteus vulgaris, Staphylococcus epidermidis, Klebsiella pneomoniae,*

*Candida albicans.*In comparison with the pattern (sulphonamide used in medicine – *Urenil*), the obtained compounds have revealed interesting antibacterial as well as antifungal activity. Compounds **6b**, **6d**, **6e** have revealed satisfactory antibacterial properties, however their activity increased significantly when the amine group in phenyl ring of sulphonamide group was deblocked from acetyl radical (compounds **7b**, **7d**, **7e).** The activity decreased significantly if alkyl radical was used to replace the amino group in phenyl ring of sulphonamide group as in compound **4**. Phenylamine substituent at site 4 of the pyrimidine ring also plays an important role. Substitution of p-chloroaniline, p-aminophenol or p-toluidine at carbon 4 of the pyrimidine ring increases significantly the antibacterial activity. The above mentioned derivatives reveal extremely potent properties of inhibiting the growth of Gram (+) *Enterobacter faecalis,* Gram (-) *Pseudomonas aeruginosa,* Gram (-) *Klebsiella pneumoniae.*

It should be stressed that above-mentioned sulphoderivatives 7 also reveal antifungal properties, inhibiting strongly the growth of *Candida albicans*, what holds promise in further research.

Expeimental

Melting points were determined in Kőfler apparatus.

^{1}H NMR spectra were recorded on BS-487-C, 80 MHz Tesla spectrometer. Infrared (IR) spectra were recorded in nujol with a Specord spectrophotometer at Analytical Laboratory of Medical Academy in Wrocław. Elemental analyses indicated by the symbols were within +/- 0.4% of the theoretical values.

6-Methyl-2-phenyl-4-phenylamine-5-aminomethylpyrimidine (3a)

4 g (12.9 mmol) of 6-methyl-2-phenyl-4-phenylamine-5-chloromethyl-pyrimidine (2a) were added to 30 ml of 25% aqueous solution of ammonia. The mixture was heated under reflux condenser and stirred intensively throughout the process. After 5 h the postreaction mixture was diluted with 100 ml of water and three times extracted with chloroform. The chloroform extracts were combined, dried over $MgSO_4$ and after filtration vacuum condensed. Obtained oily product was crystallised from acetone – chloroform 1:1 mixture, giving 3.46 g (92.3%) of cream-white crystals with m.p. 117-119^0 C.

Spectra data of **3a** IR [ν ,cm^{-1}]: 2924 (NH), 1442 (NH), 1378 (NH_2).

^{1}H NMR [δ, ppm, $CDCl_3$]: 2.45 (s, 3H;CH_3), 4.30 (t, 2H; CH_2), 5.12 (s,1H; NH) 6.80-8.45 (m, 10H aromatic), 9.58 (s, 1H; ArNH).

Spectral data of **3b:** IR [ν, cm^{-1},]: 2924 (NH), 1554 (NH), 1490 (NH_2).

^{1}H NMR [δ, ppm, $CDCl_3$]: 2.50 (s, 3H; CH_3), 4.35 (t, 2H; CH_2), 5.26 (t, 2H; NH_2), 6.70-8.55 (m, 9H aromatic), 9.12 (s, 1H;ArNH).

Spectral data of **3c:** IR [ν, cm^{-1}]: 2930 (NH), 1455 (NH), 1395 (NH_2).

^{1}H NMR [δ, ppm, $CDCl_3$]: 1.25 (t, 3H; CH_3), 2.60 (s, 3H; CH_3), 3.70 (q,2H; CH_2), 4.40 (t, 2H; CH_2), 4.70 (s,1H; ArNH), 5.30 (t, 2H; NH_2), 7.20-850 (m, 9H; aromatic), 9.20 (s, 1H; ArNH).

Spectral data of **3d:** IR [ν, cm^{-1}]: 2930 (NH), 1550 (NH),1495 (NH_2).

^{1}H NMR [δ, ppm, $CDCl_3$]: 2.55 (s, 3H; CH_3), 4.30 (t, 2H; CH_2), 5.30 (t, 2H; NH_2), 5.58 (s,1H; Ar-OH), 6.74-8.55 (m, 9H aromatic), 9.15 (s,1H; ArNH).

Spectral data of **3e:** IR [ν, cm^{-1}]: 2940 (NH), 1560 (NH), 1498 (NH_2).
^1H NMR [δ, ppm, $CDCl_3$]: 2.00 (s, 3H; Ar-CH_3) 2.55 (s, 3H; CH_3), 4.30 (t, 2H; CH_2), 5.30 (t, 2H; NH_2), 5.58 (s, 1H; Ar-OH), 6.74-8.55 (m, 9H aromatic),
9.15 (s, 1H; ArNH).

6-Methyl-4-(phenylamine)-2-phenyl-5-(4'-methylphenyl)sulphonamidomethyl-pyrimidine (4b)

4 g (13.7 mmol) of 6-methyl-4-phenylamine-2-phenyl-5-aminmethylpyrimidine (3a) were diluted in 50 ml of benzene and 2.5 g of p-toluensulphonic chloride were added gradually. The mixture was heated under reflux condenser for 8 h. Next the postreaction mixture was cooled and poured to 100 ml of water. The solution was three times extracted with 50 ml of chloroform. The chloroform extracts were combined and dried over $MgSO_4$, and next after filtration vacuum condensed . Oily residue was purified on chromatographic column filled with silica gel 60 (35-70 mesh ASTM), using the mixture of chloroform-acetone 3:1. 3.9 g (64.5%) of sulphonamide **4a** with m.p. of 164-166^{0}C were obtained.

Spectra data of **4a** IR [ν, cm^{-1}]: 2040 (NH), 1450 (NH), 1308 (SO_2).
^1H NMR [δ, ppm, $CDCl_3$]: 2.55 (s.3H; CH_3), 3.45 (s. 3H; CH_3), 6.25 (1H; NH), 7.25-8.60 (14H; aromatic).

Spectral data of **4b:** IR [ν, cm^{-1}]: 2940 (NH), 1560 (NH), 1498 (NH_2).
^1H NMR [δ, ppm, $CDCl_3$]: 2.50 (s, 3H; CH_3), 3.40 (s, 3H; CH_3), 4.40 (d, 2H; CH_2), 4.75 (s, 1H; ArNH), 6.25 (t, 1H; NH).

Spectral data of **4c:** IR [ν, cm^{-1}]: 2950 (NH), 1415 (NH), 1312 (SO_2).
^1H NMR [δ, ppm, $CDCl_3$]: 1.70 (t, 3H; CH_3), 2.45 (s, 3H; CH_3), 3.30 (s, 3H; CH_3), 3.80 (q, 2H; CH_2), 4.35(d, 2H; CH_2), 4.70(s, 1H; ArNH), 6.20(t, 1H; NH), 7.30-8.60(m, 13H; aromatic)

6-Methyl-2-phenyl-4-phenylamine-5-(4'-N-acetylaminphenyl)-sulphonamido-methylpyrimidine (6a)

4 g (12.9 mmol) of 6-methyl-2-phenyl-6-phenylamin-5-chloromethylpyrimidine (2) were diluted in 50 ml of chloroform and 3 g of N-acetylsulphanilic acid amide were added. The mixture was heated for 12 h under reflux condenser and stirred vigorously. Next, the mixture was cooled and 100 ml of water was added. The mixture was extracted three times with 50 ml of chloroform. The chloroform extracts were combined, dried over $MgSO_4$ and after filtration vacuum condensed. Oily residue was purified chromatographically with silica gel 60 (35-70 mesh ASTM) using chloroform-aceton 3:1 mixture, giving 4.8 g (76.3%) of precipitate with m.p. 158-161^{0}C.

Spectra data of IR [ν, cm^{-1}]: 2836 (NH), 1556 (NH), 1496 (SO_2).
^1H NMR [δ, ppm, $CDCl_3$]: 1.30 (s, 1H; AcNH), 2.55 (s, 3H; CH_3), 3.50 (s, 3H; CH_3), 4.75 (d, 2H; CH_2), 4.80 (s, 1H; ArNH), 5.20 (t, 1H; NH), 7.35-8.55 (m, 14H;aromatic).

Spectral data of **6b:** IR [ν, cm^{-1}]: 2940 (NH), 1560 (NH), 1498 (NH_2).
^1H NMR [δ, ppm, $CDCl_3$]: 1.25(s, 1H; AcNH), 2.50 (s, 3H; CH_3), 3.45 (s, 3H; CH_3), 4.70 (d, 2H; CH_2), 4.75 (s, 1H; ArNH), 5.20 (d, 1H; NH), 7.30-8.50 (m, 13H; aromatic).

Spectral data of **6c:** IR [ν, cm^{-1}]: 2940 (NH), 1560 (NH), 1498 (NH_2).

^{1}H NMR [δ, ppm, $CDCl_3$]: 1.20 (s, 1H; AcNH), 1.30 (t, 3H; CH_3), 2.20 (s, 3H; CH_3), 2.35 (s, 3H; CH_3), 3.40 (q, 2H; CH_2), 3.60 (t, 1H; NH), 3.85 (d, 2H; CH_2), 4.70 (s, 1H; ArNH).

Spectral data of **6d:** IR [ν, cm^{-1}]: 2840 (NH), 1560 (NH), 1490 (SO_2).
^{1}H NMR [δ, ppm. $CDCl_3$]: 1.40(s, 1H; AcNH), 2.60 (s, 3H; CH_3), 3.55 (s, 3H; CH_3), 4.85 (d, 2H; CH_2), 4.80 (s, 1H; ArNH), 5.20 (t, 1H; NH), 5.50 (s, 1H; Ar-OH), 7.35-8.55 (m, 14H; aromatic)

Spectral data of **6e:** IR [ν, cm^{-1}]: 2850 (NH), 1550 (NH), 1495 (SO_2).
^{1}H NMR [δ, ppm, $CDCl_3$]: 1.40(s, 1H; AcNH), 2.20 (s, 3H; Ar-CH_3), 2.60 (s, 3H;CH_3), 3.55 (s, 3H; CH_3), 4.75 (d, 2H; CH_2), 4.70 (s, 1H; ArNH), 5.30 (t, 1H; NH), 5.50 (s, 1H; Ar-OH), 7.35-8.55 (m, 14H; aromatic).

6-Methyl-2-phenyl-4-phenylamine-5(4'-aminphenyl)-sulphonamidomethyl-pyrimidine (7a)

4 g (8.2 mmol) of 6-methyl-2-phenyl-4-phenylamine-5-(4'-acetylphenyl)-sulphonamidomethyl-pyrimidine (6a) were diluted in 50 ml of alcoholic solution of HCl. The mixture was heated under reflux condenser for 1h. Next the solution was cooled, 100 ml of water were added and three times extracted with 50 ml of chloroform. The chloroform extracts were combined, dried over $MgSO_4$ and after filtration vacuum condensed. Oily residue was purified on chloroform-acetone 3:1 column, giving crystals with m.p. 110-112^{0}C.

Spectra data of IR [ν, cm^{-1},nujol]: 2836 (NH), 1562 (NH_2), 1492 (NH), 1406 (SO_2).
^{1}H NMR [80-MHz, δ, ppm, $CDCl_3$]: 1.25 (s. 2H; NH_2), 2.45 (s. 3H; CH_3), 3.25 (t.1H; NH), 4.50 (d. 2H; CH_2), 4.75 (s.1H; ArNH), 7.40-8.50 (m. 14H; aromatic).

Spectral data of **7b:** IR [ν, cm^{-1}]: 2885 (NH), 16775 (NH_2), 1455 (NH), 1410 (SO_2).
^{1}H NMR [δ, ppm, $CDCl_3$]: 1.30 (s, 2H; NH_2), 2.50 (s, 3H; CH_3), 3.30 (t, 1H; NH), 4.45 (d, 2H; CH_2), 4.70 (s, 1H; NH), 7.40-8.50 (m, 13 H; aromatic).

Spectral data of **7c:** IR [ν, cm^{-1}]: 2850 (NH), 1660 (NH_2), 1460 (NH), 1407 (SO_2).
^{1}H NMR [δ, ppm, $CDCl_3$]: 1.20 (s, 2H; NH_2), 1.35 (t, 3H; CH_3), 2.45(s, 3H; CH_3), 3.20 (q, 2H; CH_2, 3.50 (t, 1H; NH), 3.75 (d, 2H; CH_2), 3.80 (s,1H; ArNH), 7.45-8.55 (m, 13H; aromatic)

Spectral data of **7d:** IR [ν, cm^{-1}]: 2895 (NH), 1670 (NH_2), 1445 (NH), 1415 (SO_2).
^{1}H NMR [δ, ppm, $CDCl_3$]: 1.30 (s, 2H; NH_2), 2.50 (s, 3H; CH_3), 3.25 (t, 1H; NH), 4.40 (d, 2H; CH_2), 4.70 (s, 1H; NH), 5.50 (s, 1H; Ar-OH), 7.40-8.50 (m, 13H; aromatic).

Spectral data of **7e:** IR [ν, cm^{-1}]: 2875 (NH), 1660 (NH_2), 1455 (NH), 1425 (SO_2).
^{1}H NMR [δ, ppm, $CDCl_3$]: 1.40(s, 2H; NH_2), 2.20 (s, 3H; Ar-CH_3), 2.60 (s, 3H-CH_3), 3.35 (t, 1H; NH), 4.40 (d, 2H; CH_2), 4.70 (s, 1H; NH), 5.50 (s, 1H; Ar-OH), 7.40-8.50 (m, 13H; aromatic).

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