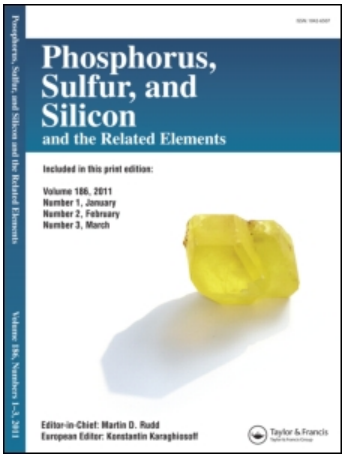

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Thio Analogues of Pyrimidine Bases: Syntheses and Spectral Study of New Potentially Biologically Active 2,4-Di-*Ortho*-(*Meta*- and *Para*-)Bromo-(Chloro and Nitro)-Benzylthio-5-Bromouracils (and 6-Methyluracils)

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THIO ANALOGUES OF PYRIMIDINE BASES: SYNTHESES AND SPECTRAL STUDY OF NEW POTENTIALLY BIOLOGICALLY ACTIVE 2,4-Di-*ORTHO*-(*META*- AND *PARA*-)BROMO- (CHLORO AND NITRO)-BENZYLTHIO-5-BROMOURACILS (AND 6-METHYLURACILS)

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Eighteen new 2,4-di-ortho- (meta- and para-) bromo-(chloro- and nitro-)benzylthio-5-bromouracils (and 6-methyluracils) have been prepared. The structures of these compounds were confirmed by spectral (IR, UV/vis, ^{1}H NMR) and elemental analyses. Estimation of pharmacotherapeutic potential has been made for synthesized compounds on the basis of prediction of activity spectra for substances (PASS).

Keywords 2,4-Dibenzylthio-5-bromo-6-methyluracils; 2,4-dibenzylthio-5-bromouracils; ^{1}H NMR; IR; PASS; structural isomers; UV/vis

INTRODUCTION

Thio derivatives of pyrimidine bases are of interest because of their biological and pharmacological activities, e.g., as minor components of t-RNA or as antithyroidal and anticancer drugs, as well as sedatives.[1–7] Various analogues of 5-bromo-*N*-benzyl substituted thiouracils constitute a novel class of central-acting agents.[8] The pyrimidine thioethers with phenylthio substituent have been reported to constitute a novel class of non-nucleoside HIV-1 reverse transcriptase inhibitors.[9]

Recently, we have reported the syntheses, physicochemical properties, and results of EI mass spectrometric study of *ortho*- (*meta*- and *para*-) substituted derivatives of 2-benzylthio-5-bromo-6-methyluracils.[10] However, to the best of our knowledge, no work has been published on the synthesis and physicochemical properties of *S*,*S*-dibenzyl substituted derivatives of 2,4-dithio-5-bromouracil and 2,4-dithio-5-bromo-6-methyluracil. On the other hand, novel pharmacological actions of these compounds have been found on the basis of the computer-aided drug discovery approach with the computer program Prediction of Activity Spectra for Substances (PASS).[11–14] It is based on a robust analysis of structure–activity relationship[12] in a heterogeneous training set currently including about

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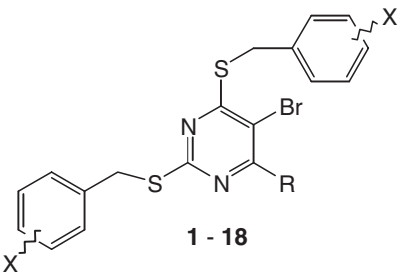


1	R = H	X = *o*-Br	**10**	R = CH_3	X = *o*-Br
2	R = H	X = *m*-Br	**11**	R = CH_3	X = *m*-Br
3	R = H	X = *p*-Br	**12**	R = CH_3	X = *p*-Br
4	R = H	X = *o*-Cl	**13**	R = CH_3	X = *o*-Cl
5	R = H	X = *m*-Cl	**14**	R = CH_3	X = *m*-Cl
6	R = H	X = *p*-Cl	**15**	R = CH_3	X = *p*-Cl
7	R = H	X = *o*-NO_2	**16**	R = CH_3	X = *o*-NO_2
8	R = H	X = *m*-NO_2	**17**	R = CH_3	X = *m*-NO_2
9	R = H	X = *p*-NO_2	**18**	R = CH_3	X = *p*-NO_2

Figure 1 Structures of substituted 2,4-dibenzylthio-5-bromouracils **1–9** and 2,4-dibenzylthio-5-bromo-6-methyluracils **10–18**.

sixty thousand biologically active compounds from different chemical series, with about 4500 types of biological activity. Since only the structural formula of a chemical compound is necessary to obtain a PASS prediction, this approach can be used at the earliest stage of investigation. There are many examples of successful use of PASS approach leading to finding new pharmacological agents.[15–18]

The analysis of PASS prediction results of 2,4-dibenzylthio-5-bromouracils and 2,4-di-benzylthio-5-bromo-6-methyluracils have prompted us to synthesize a series of new 2,4-di-*ortho*- (*meta*- and *para*-) bromo-(chloro- and nitro-)benzylthio-5-bromouracils **1–9** and 2,4-di-*ortho*- (*meta*- and *para*-) bromo-(chloro- and nitro-)benzylthio-5-bromo-6-methyluracils **10–18** (Figure 1).

This article deals with the synthesis and physicochemical properties of **1–18**. Additionally the analysis of biological activity spectra prediction for **1–18** made in this publication is a good example of *in silico* study of chemical compounds.

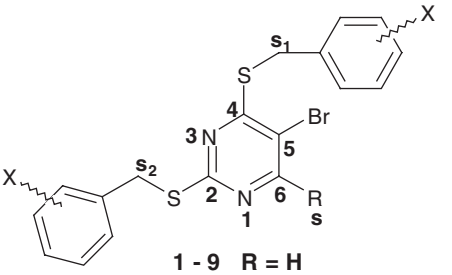
RESULTS AND DISCUSSION

A series of 18 new 2,4-di-*ortho*- (*meta*- and *para*-) bromo-(chloro- and nitro-) benzylthio-substituted 5-bromouracils **1–9** and 5-bromo-6-methyluracils **10–18** were synthesized by direct bromination of the appropriate 2,4-dibenzylthiouracils and 2,4-dibenzylthio-6-methyluracils with bromine in tetrachloromethane at room temperature. The treatment of these *ortho*- (*meta*- and *para*-) bromo-(chloro- and nitro-) substituted derivatives of 2,4- dibenzylthiouracils and 2,4-dibenzylthio-6-methyluracils with the excess of bromine in tetrachloromethane followed by short time boiling of the crude product in ethanol solution led to 2,4-dibenzylthio-5-bromouracils **1–9** and 2,4-dibenzylthio-5-bromo-6-methyluracils **10–18**. The C5 bromine containing compounds **1–18** were confirmed by examination of their UV/vis, IR (Table I) and ^{1}H NMR (Table II) spectra as well as elemental analyses (Table III).

Table I IR and UV/vis spectral data of compounds **1–18**

	IR (cm^{-1})			UV/Vis	
Compound	ν S−CH_2	ν C_5=C_6	ν C_5-Br	λ_{max} (nm)	logε
1	2445	1559	585	228.4	4.10
				254.6	4.29
				302.4	3.83
2	2507	1561	580	226.0	3.96
				255.0	4.10
				302.4	3.67
3	2435	1557	550	230.4	4.10
				255.0	4.17
				302.4	3.64
4	2471	1559	581	225.6	3.91
				252.0	4.18
				302.0	3.75
5	2449	1562	582	225.0	3.90
				254.0	4.12
				302.0	3.64
6	2458	1560	599	227.2	3.85
				255.4	3.92
				299.8	3.40
7	2854	1562	663	225.0	3.71
				254.0	3.99
				303.0	3.54
8	2858	1562	664	225.0	3.84
				253.0	4.17
				300.0	3.73
9	2854	1561	664	226.0	3.78
				258.0	4.18
				300.0	3.63
10	2473	1558	582	225.6	3.82
				255.2	4.00
				300.8	3.49
11	2470	1558	580	225.2	3.82
				254.6	3.89
				297.0	3.49
12	2466	1556	590	230.6	4.10
				254.0	4.16
				295.6	3.70
13	2466	1553	586	224.2	3.82
				255.0	4.06
				298.6	3.55
14	2460	1555	585	224.2	3.90
				254.0	4.10
				297.2	3.65
15	2462	1559	580	227.8	4.12
				254.8	4.21
				298.0	3.74
16	2482	1556	565	225.0	3.57
				255.0	3.87
				303.0	3.39
17	2485	1559	567	226.0	3.59
				257.0	3.90
				304.0	3.40
18	2483	1560	679	224.5	3.68
				258.5	3.95
				303.5	3.61

Table II ^{1}H NMR shifts of **1–18** (ppm)



1 - 9 R = H

10 - 18 R = CH_3

Comp.	S-CH_2 s_1	S-CH_2 s_2	C_6-H/C_6-CH_3 s	 m
1	4.64	4.69	8.39	7.29–7.70
2	4.49	4.53	8.38	7.20–7.52
3	4.46	4.50	8.40	7.42–7.50
4	4.64	4.66	8.39	7.30–7.72
5	4.52	4.60	8.37	7.30–7.53
6	4.51	4.54	8.34	7.42–7.49
7	4.68	4.81	8.32	7.55–8.00
8	4.63	4.65	8.29	7.60–8.73
9	4.62	4.68	8.38	7.80–8.20
10	4.59	4.61	2.40	7.25–7.50
11	4.53	4.58	2.51	7.20–7.50
12	4.50	4.56	2.50	7.40–7.50
13	4.69	4.72	2.52	7.25–7.69
14	4.54	4.56	2.51	7.18–7.58
15	4.52	4.54	2.50	7.34–7.45
16	4.62	4.67	2.51	7.58–8.10
17	4.50	4.52	2.50	7.63–8.39
18	4.47	4.49	2.52	7.80–8.20

Spectra determined in dimethyl-d_6 sulfoxide at 25°C, and shifts are reported in ppm (δ) downfield from tetramethylsilane.

The ^{1}H NMR spectra of these compounds show the lack of the characteristic resonances of the protons situated at C5 of the pyrimidine rings when referred to the ^{1}H NMR spectra of the substrates, that is the appropriate 2,4-dibenzylthiouracils and 2,4-dibenzylthio-6-methyluracils. The ^{1}H NMR data of **1–18** are given in Table II. Assignments of the ^{1}H NMR resonances of these compounds were deduced on the basis of the signal multiplicities and by the concerted application of two-dimensional NMR technique ^{1}H,^{1}H-COSY. The ^{1}H NMR spectra of **1–9** reveal singlets of S—CH_2 at 4.46–4.68 ppm and 4.50–4.81 ppm, respectively. The singlets of C6—H of **1–9** are situated at 8.29–8.40 ppm. The signals of protons of *ortho*- (*meta*- and *para*-) substituted benzyl groups of **1–9** are seen in the range 7.20–8.73 (Table II).

The ^{1}H NMR spectra of **10–18** reveal singlets of S—CH_2 at 4.47–4.69 ppm and 4.49–4.72 ppm, respectively. The singlets of C6—CH_3 of **10–18** are situated at 2.40–2.52 ppm. The signals of protons of *ortho*- (*meta*- and *para*-) substituted benzyl groups of **10–18** are seen in the range 7.18–8.39 ppm (Table II).

Table III Physical and analytical data of compounds **1–18**

Compound	Formula MW	Mp (°C)	Yield (%)	R_f TLC*	Analysis (calc./found.%) C	H	N
1	$C_{18}H_{13}N_2S_2Br_3$	167–170	30	0.91	38.53	2.33	4.99
	561.16				38.30	2.30	4.92
2	$C_{18}H_{13}N_2S_2Br_3$	157–159	35	0.90	38.53	2.33	4.99
	561.16				38.42	2.42	4.90
3	$C_{18}H_{13}N_2S_2Br_3$	178–180	47	0.87	38.53	2.33	4.99
	561.16				38.60	2.20	4.80
4	$C_{18}H_{13}N_2S_2Cl_2Br$	127–129	54	0.86	45.78	2.77	5.93
	472.26				45.60	2.58	5.90
5	$C_{18}H_{13}N_2S_2Cl_2Br$	119–130	65	0.90	45.78	2.77	5.93
	472.26				45.82	2.72	5.80
6	$C_{18}H_{13}N_2S_2Cl_2Br$	159–160	45	0.92	45.78	2.77	5.93
	472.26				45.70	2.60	5.78
7	$C_{18}H_{13}N_4O_4S_2Br$	168–170	70	0.88	43.82	2.66	11.36
	493.36				43.80	2.60	11.20
8	$C_{18}H_{13}N_4O_4S_2Br$	208–210	69	0.90	43.82	2.66	11.36
	493.36				42.72	2.40	11.18
9	$C_{18}H_{13}N_4O_4S_2Br$	128–130	16	0.85	43.82	2.66	11.36
	493.36				43.60	2.50	11.25
10	$C_{19}H_{15}N_2S_2Br_3$	164–166	72	0.93	39.68	2.63	4.87
	575.19				39.60	2.58	4.80
11	$C_{19}H_{15}N_2S_2Br_3$	168–170	62	0.94	39.68	2.63	4.87
	575.19				39.72	2.40	4.78
12	$C_{19}H_{15}N_2S_2Br_3$	145–147	48	0.92	39.68	2.63	4.87
	575.19				39.58	2.65	4.60
13	$C_{19}H_{15}N_2S_2Cl_2Br$	173–176	50	0.89	46.93	3.11	5.76
	486.28				46.45	3.00	5.70
14	$C_{19}H_{15}N_2S_2Cl_2Br$	105–107	65	0.94	46.93	3.11	5.76
	486.28				47.20	2.98	5.55
15	$C_{19}H_{15}N_2S_2Cl_2Br$	117–120	89	0.92	46.93	3.11	5.76
	486.28				47.10	3.10	5.78
16	$C_{19}H_{15}N_4O_4S_2Br$	198–200	68	0.90	44.98	2.98	11.04
	507.39				44.80	3.00	11.00
17	$C_{19}H_{15}N_4O_4S_2Br$	188–191	69	0.90	44.98	2.98	11.04
	507.39				44.96	2.98	10.98
18	$C_{19}H_{15}N_4O_4S_2Br$	200–201	56	0.92	44.98	2.98	11.04
	507.39				44.87	2.90	10.90

*Solvent: $CHCl_3$-CH_3OH, 5:1.

The IR spectra of **1–9** show absorption bands of medium intensities in the region of 590–664 cm^{-1} assigned to $\nu_{C\text{-}Br}$ vibrations (Table I). The absorption bands of $\nu_{C\text{-}Br}$ vibrations of **10–18** are seen in IR spectra of **10–18** in the region 565–679 cm^{-1} (Table I). The UV/vis spectra of **1–9** show λ_{max} in the range 225–303 nm (Table I) and bathochromic shifts as well as increase in absorption in comparison with the corresponding UV/vis data of *ortho*- (*meta*- and *para*-) substituted 2,4-dibenzyl thiouracils.[19] Similarly the UV/vis spectra of **10–18** show λ_{max} in the range 224.2–303.5 nm (Table I) and bathochromic shifts as well as increase in absorption in comparison with the corresponding UV/vis data of *ortho*- (*meta*- and *para*-) substituted 2,4-dibenzylthio-6-methyluracils.[19]

In the present article, the biological activity spectra were predicted for all 18 synthesized compounds (**1–18**) using PASS.[11–14, 20] We have also selected the types of activities that were predicted for a particular compound with the highest probability (focal activities). They are presented in Table IV. According to these data, the most frequently predicted types of biological activities are mucomembraneous protector, prolylaminopeptidase inhibitor, cyclooxygenase-1 inhibitor, and antiseborrheic. It ought to be pointed out that in the series of the derivatives of 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthio-6-methyluracils **10–18**, such activities as interferon agonist, Factor VIIa inhibitor, and glutamate receptor antagonist have also been predicted.

Table IV P_A values for predicted biological activities of compounds **1–18**

Comp	Focal predicted activity ($P_a > 0.7$)
1	Mucomembraneous protector (0.912), prolyl aminopeptidase inhibitor (0.864), cyclooxygenase-1 inhibitor (0.752)
2	Prolyl aminopeptidase inhibitor (0.936), mucomembraneous protector (0.903), antiseborrheic (0.808), cyclooxygenase-1 inhibitor (0.764), ferredoxin hydrogenase inhibitor (0.719), carnitinamidase inhibitor (0.717)
3	Prolyl aminopeptidase inhibitor (0.941), mucomembraneous protector (0.915), antiseborrheic (0.821), cyclooxygenase-1 inhibitor (0.786), carnitinamidase inhibitor (0.740), ferredoxin hydrogenase inhibitor (0.728)
4	Mucomembraneous protector (0.879), cyclooxygenase-1 inhibitor (0.717)
5	Mucomembraneous protector (0.877), prolyl aminopeptidase inhibitor (0.867), antiseborrheic (0.860), cyclooxygenase-1 inhibitor (0.784)
6	Mucomembraneous protector (0.892), prolyl aminopeptidase inhibitor (0.874), antiseborrheic (0.860), cyclooxygenase-1 inhibitor (0.784)
7	Mucomembraneous protector (0.889), Factor VIIa inhibitor (0.825), glutamate receptor antagonist (0.817)
8	Glutamate receptor antagonist (0.908), kainate receptor antagonist (0.840), Factor VIIa inhibitor (0.773)
9	Factor VIIa inhibitor (0.832), prolyl aminopeptidase inhibitor (0.845), antiseborrheic (0.763), glutamate receptor antagonist (0.759), mucomembraneous protector (0.743)
10	Prolyl aminopeptidase inhibitor (0.949), arrhythmogenic (0.876), arylacetonitrilase inhibitor (0.859), mucomembraneous protector (0.850), ferredoxin hydrogenase inhibitor (0.829)
11	Prolyl aminopeptidase inhibitor (0.950), mucomembraneous protector (0.896), interferon agonist (0.825), antiseborrheic (0.819), cyclooxygenase-1 inhibitor (0.708)
12	Prolyl aminopeptidase inhibitor (0.950), mucombraneous protector (0.896), interferon agonist (0.825), cyclooxygenase-1 inhibitor (0.708)
13	Mucomembraneous protector (0.871), interferon agonist (0.814), prolyl aminopeptidase inhibitor (0.838), antiseborrheic (0.750)
14	Prolyl aminopeptidase inhibitor (0.910), mucomembraneous protector (0.868), antiseborrheic (0.857), interferon agonist (0.806), cyclooxygenase-1 inhibitor (0.713)
15	Prolyl aminopeptidase inhibitor (0.915), mucomembraneous protector (0.884), antiseborrheic (0.865), interferon agonist (0.826), cyclooxygenase-1 inhibitor (0.734)
16	Mucomembraneous protector (0.885), glutamate receptor antagonist (0.826), Factor VIIa inhibitor (0.823), prolyl aminopeptidase inhibitor (0.793), anticonvulsant (0.723)
17	Prolyl aminopeptidase inhibitor (0.887), Factor VIIa inhibitor (0.822), antiseborrheic (0.768), mucomembraneous protector (0.747), glutamate receptor antagonist (0.742)
18	Prolyl aminopeptidase inhibitor (0.892), Factor VIIa inhibitor (0.830), antiseborrheic (0.780), glutamate receptor antagonist (0.771), mucomembraneous protector (0.729), interferon agonist (0.705)

CONCLUSIONS

The reactions of 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthiouracils and 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthio-6-methyluracils with an excess of bromine in tetrachloromethane at room temperature lead to 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthio-5-bromouracils **1–9** and 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthio-5-bromo-6-methyluracils **10–18**.

The results obtained by PASS method identification of the prospective pharmacological properties of **1–18** exhibit the possibility of finding new pharmacological agents from this class of compounds.

EXPERIMENTAL

The purity of all described compounds was checked by melting points, TLC, and elemental analyses. Melting points (uncorrected) were determined on a Boetius microscope hot stage. R_f values refer to silica gel F_{254} TLC plates (Merck) developed with $CHCl_3$—CH_3OH 5:1 and observed under UV light ($\lambda = 254$ and 366 nm). UV/vis spectra were recorded with a Specord UV/vis spectrophotometer in dioxane. IR spectra were recorded with a FT-IR Bruker IFS-113 spectrophotometer in KBr pellets. The ^1H NMR spectra were determined with Varian Gemini 300 (300 MHz) spectrometer in CD_3OD solution at a concentration between 0.25 and 0.40 M in the 5 mm sample tubes at ambient temperature. Chemical shifts are given in δ scale (ppm). Elemental analyses were performed with a Vector Euro EA 3000 analyser.

2,4-Di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthiouracils and 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthio-6-methyluracils have been obtained according to the literature.[19]

The Synthesis of 2,4-Di-*ortho*- (*meta*- and *para*-) Bromo- (chloro- and nitro-) benzylthio-5-bromouracils 1–9 and 6-Methyluracils 10–18

A solution of bromine (1 mmol) in tetrachloromethane (20 mL) was added dropwise over 30 min at room temperature to a stirred suspension of the appropriate 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthiouracil (0.5 mmol) or 2,4-di-*ortho*- (*meta*- and *para*-) bromo- (chloro- and nitro-) benzylthio-6-methyluracil (0.5 mmol) in tetrachloromethane (30 mL). The reaction mixture was next stirred at room temperature for 2 h. The obtained crude product was filtered off, washed with tetrachloromethane (5 mL), and dried. The resulting powder was boiled in ethanol (10 mL) under reflux condenser for 5 min. Upon cooling, a solid crystallized from this solution. It was filtered off, washed with cold ethanol (10 mL), and dried. Compounds **1–18** were shown to be analytically pure without any further purification (Table III).

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