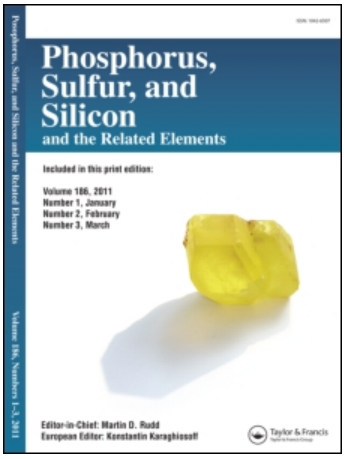

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Thio Analogs of Pyrimidine Bases: Synthesis And Spectroscopic Study of New Potentially Biologically Active Disulfides of *N,O*-(*N,N*- or *O,O*-)-Di- and *N,N,O*-Tri-(*o*-, *m*-, and *p*-)bromobenzyl-2-thiouracils

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THIO ANALOGS OF PYRIMIDINE BASES: SYNTHESIS AND SPECTROSCOPIC STUDY OF NEW POTENTIALLY BIOLOGICALLY ACTIVE DISULFIDES OF *N,O*-(*N,N*- OR *O,O*-)-DI- AND *N,N,O*-TRI-(*o*-, *m*-, AND *p*-)BROMOBENZYL-2-THIOURACILS

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Nine new disulfides of N,O-(N,N- or O,O-)-di- and N,N,O-tri-(o-, m- and p-)bromobenzyl-2-thiouracils have been prepared. The structures of these compounds were confirmed by spectroscopic (FT-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 FT-IR; ^{1}H NMR; *o*-(*m*- and *p*-)bromobenzyl bromides; Prediction of Activity Spectra for Substances (PASS); structural isomers; 2-thiouracils (2-TU); UV-Vis

INTRODUCTION

The variety of organosulfur compounds that contain disulfide bonds have been reported to be effective in cardiovascular diseases, because of their hypocholesterolemic, hypolipidemic, antihypertensive, antidiabetic, antithrombotic, and antihyperhomocysteinemia effects, and to possess many others biological activities including antimicriolisial, antioxidant, anticancerogenic, antimutagenic, antiasthmatic, immunomodulatory, and prebiotic activities.[1–6]

Recently, we have reported the syntheses, physicochemical properties, and results of a spectroscopic (FT-IR, UV/Vis, ^{1}H NMR) study of 2,4-di-*o*-(*m*- and *p*-)bromo-(chloro- and nitro-)benzylthio-5-bromouracils (and 6-methyluracils).[7] However, to the best of our knowledge, no work has been published on the synthesis and physicochemical properties of disulfides derivatives of *N*,*O*-(*N*,*N*- or *O*,*O*-)-di- and *N*,*N*,*O*-tri-(*o*-, *m*-, and *p*-)bromobenzyl-2-thiouracils. The novel pharmacological actions of these compounds have been found on the basis of a computer-aided drug discovery approach with the compounds program Prediction of Activity Spectra for Substances (PASS).[8–12] It is based on a robust analysis of structure–activity relationships in a heterogeneous training set currently including about 60,000 biologically active compounds from different chemical series with about 4500 types of biological activity. Since only the structural formula of the chemical compound is necessary to obtain a PASS prediction, this approach can be used at the earliest

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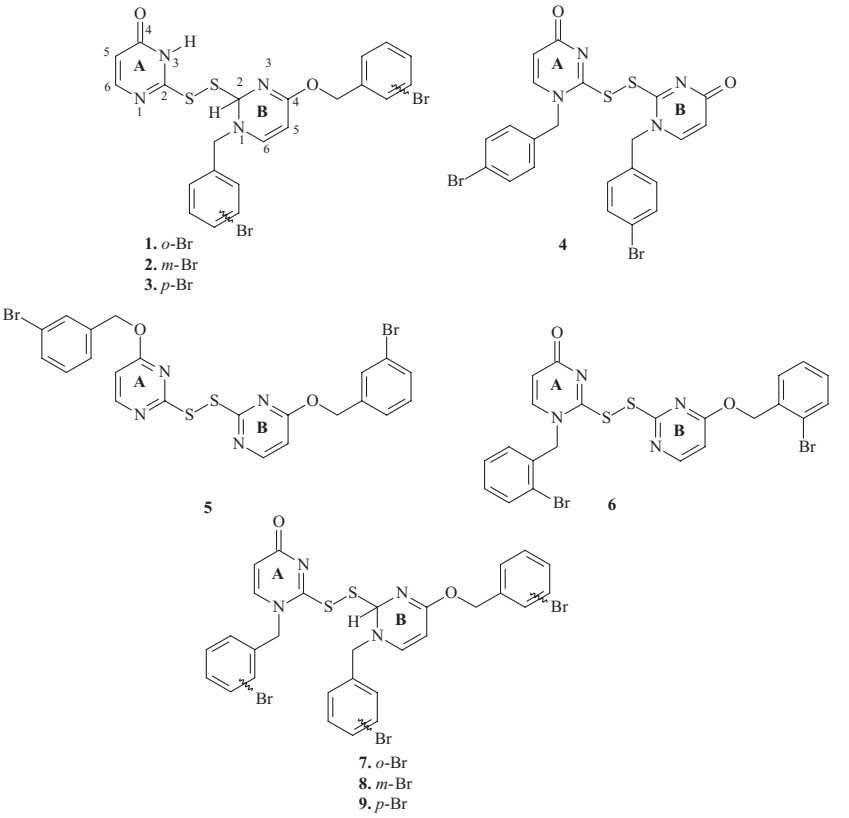

Figure 1 Structures and numbers of atoms of disulfides of *N*,*O*-(*N*,*N*- or *O*,*O*-)-di- (**1–6**) and *N*,*N*,*O*-tri-(*o*-, *m*-, and *p*-)bromobenzyl-2-thiouracils (**7–9**).

stage of investigation. There are many examples of successful uses of the PASS approach that have led to new pharmacological agents.

The analysis of PASS prediction results of *bis*[uracils] disulfide and *bis*[6-methyluracil] disulfide have prompted us to synthesize a series of new disulfide derivatives of $N_{1(B),}O_{(B)}$-di-*o*-(*m*- and *p*-)bromobenzyl-2-thiouracils (**1–3**), $N_{1(A)},N_{1(B)}$-di-*p*-bromobenzyl-2-thiouracil (**4**), $O_{(A)},O_{(B)}$-di-*m*-bromobenzyl-2-thiouracil (**5**), and $N_{1(A)},O_{(B)}$-di-*o*-bromobenzyl-2-thiouracil (**6**), as well as new disulfides derivatives of $N_{1(A)},N_{1(B)},O_{(B)}$-tri-*o*-(*m*- and *p*-) bromobenzyl-2-thiouracils (**7–9**) (Figure 1).

This article deals with the synthesis and physicochemical properties of **1–9**. Additionally the analyses of biological activity spectra prediction for **1–9** made in this article are good examples of *in silico* studies of chemical compounds.

RESULTS AND DISCUSSION

A series of new disulfides of $N_{1(B),}O_{(B)}$-di-*o*-(*m*- and *p*-)bromobenzyl-2-thiouracils (**1–3**), $N_{1(A)},N_{1(B)}$-di-*p*-bromobenzyl-2-thiouracil (**4**), $O_{(A)},O_{(B)}$-di-*m*-bromobenzyl-2-thiouracil (**5**), $N_{1(A)},O_{(B)}$-di-*o*-bromobenzyl-2-thiouracil (**6**), and $N_{1(A)},N_{1(B)},O_{(B)}$-tri-*o*-(*m*-

and *p*-)bromo- benzyl-2-thiouracils (**7–9**) (Figure 1) were made by oxidation and subsequent benzylation of 2-thiouracil. Treatment of 2-thiouracil with *o*-(*m*- and *p*-)bromobenzyl bromides and K_2CO_3 in boiling DMF gave **1–9**.

The reaction of 2-thiouracil with two-fold molar excess of *o*-(*m*- and *p*-)bromobenzyl bromide in boiling DMF in the presence of 1.50 equivalent of K_2CO_3 lead to **1** and **6**, **2** and **5**, and **3** and **4**, respectively. The preparation of **1–6** was probably promoted by prior conversions of 2-thiouracil into their respective disulfides with a bromide oxidizing agent. It is well known in the literature that such oxidative S—S coupling occurs in the presence of halogens.[13] The oxidation of thiols to disulfides by means of bromine/aqueous potassium hydrogen carbonate in two-phase system has also been described.[14,15] The competition in the further reaction with benzylic cation is between N_1- and *O*-. The reactions of benzylations are largely governed by the same nature of the benzylation agents, i.e., soft electrophiles (in some respect soft acids) *o*- (*m*- and *p*-)bromobenzyl bromides. The differences in the reactivity of these bromobenzyl bromides gave $N_{1(B)}$, $O_{(B)}$ (or $N_{1(A)}$, $O_{(A)}$) together with $N_{1(A)}$, $N_{1(B)}$ ($O_{(A)}$, $O_{(B)}$ or $N_{1(B)}$, $O_{(A)}$) benzyl disubstitution of the uracil ring. The pairs of isomers **1** and **6** (**2** and **5** or **3** and **4**) were obtained by these dibenzylations.

The reactions of 2-thiouracil with threefold molar excess of *o*-(*m*- and *p*-)bromobenzyl bromide in boiling DMF in the presence of 1.50 equivalent of K_2CO_3 led to disulfides of $N_{1(A)}$,$N_{1(B)}$,$O_{(B)}$-tri-*o*-(*m*- and *p*-)bromobenzyl-2-thiouracils (**7–9**).

The structures of disulfides **1–9** were confirmed by examination of their UV/Vis, FT-IR, and ^{1}H NMR spectra (Table I), as well as elemental analyses (Table II).

The ^{1}H NMR data of **1–9** are given in Table I. Assignments of the ^{1}H NMR resonances of these compounds were deduced on the basis of their signal multiplicities and by the corrected application of two-dimensional NMR technique ^{1}H-^{1}H COSY. The ^{1}H NMR spectra of **1–3** and **6** reveal singlets of 2H of N-CH_2 at 5.46 ppm, as well as a singlet of 2H of O—CH_2 at 4.48 ppm. The ^{1}H NMR spectrum of **4** reveals a singlet of 4H of N—CH_2 at 5.39 ppm, and the ^{1}H NMR spectrum of **5** reveals a singlet of O—CH_2 at 4.39 ppm.

In the ^{1}H NMR spectra of **7–9** singlets of 2H of N—CH_2 (in the ring A) are situated at 4.91, 5.21, and 5.17 ppm, respectively, and singlets of 2H of N—CH_2 (in the ring B) at 5.41, 5.42, and 5.40 ppm, respectively. The ^{1}H NMR spectra of **7–9** reveal singlets of 2H of O—CH_2 (in the ring B) at 4.48, 4.45, and 4.42, respectively. Singlets of C_2—H of ring B in the ^{1}H NMR spectra of **1–3** and **7–9** are seen at the range 2.50–2.52 ppm (Table I).

The FT-IR spectra of **1–4** and **6–9** show ν C_4=O absorption bands in the region 1671–1716 cm^{-1} (Table I). The absorption bands of ν N—CH_2 vibrations of **1–4** and **6–9** are seen in IR spectra in the region 2780–2929 cm^{-1}. The absorption bands of ν O—CH_2 vibration of **1–3** and **5–9** are seen in the IR spectra in the region 1250–1277 cm^{-1}. The UV/Vis spectra of **1–6** show λ_{max} in the range 282–296 nm. The UV/Vis spectra of **7–9** show λ_{max} in the range 271 and 295–297 nm, respectively (Table I).

In this article, the biological activity spectra were predicted for all nine synthesized compounds (**1–9**) with PASS. We have also selected the types of activity that were predicted for a potential compound with the highest probability (focal activities). They are presented in Table III. According to these data, the most frequently predicted types of biological activity are prolylaminopeptidase inhibitor, aryloalkylacylamidase inhibitor, mannotetraose-2-alpha-*N*-acetylglucosaminyltransferase inhibitor, and *N*-acetyllactosamine synthase inhibitor. In ought to be pointed out that in the series of disulfides with *o*-bromobenzyl substituent (**1**, **6**, **7**), such activities as antiviral (poxvirus) and interleukin antagonist have been predicted.

Table I FT-IR, UV-Vis, and ^{1}H NMR data of compounds **1–9**

						^{1}H NMR (DMSO$_{d6}$) ppm		
				FT-IR cm^{-1} (KBr)		C_5-H(*d*)A C_5-H(*d*)B	N_1CH_2(*s*)A N_1CH_2(*s*)B	
Compo	UV/Vis (CH_3OH) λ_{max} nm (log ε)			$\nu C_4{=}O$ $\nu C_5{=}C_6$	$\nu N{-}CH_2$ $\nu O{-}CH_2$	C_6-H(*d*)A C_6-H(*d*)B	O-CH_2(*s*) C_2-H(*s*)B	phenyl(*m*)
1	240.0	292.0		1698	2864	6.14 J = 7 Hz	5.46 (2H)	7.13–7.59
	(4.42)	(4.13)		1540	1275	6.77 *J* = 7 Hz	—	
						7.94 *J* = 7 Hz	4.48 (2H)	
						8.43 *J* = 7 Hz	2.52 (1H)	
2	240.0	292.0		1714	2846	6.14 *J* = 7 Hz	5.41 (2H)	7.25–7.80
	(4.49)	(4.23)		1494	1250	6.77 *J* = 7 Hz	—	
						7.94 *J* = 7 Hz	4.45 (2H)	
						8.43 *J* = 7 Hz	2.51 (1H)	
3	239.0	292.0		1684	2857	6.14 *J* = 7 Hz	5.39 (2H)	7.21–7.90
	(4.49)	(4.17)		1539	1276	6.76 J = 7 Hz	—	
						7.94 J = 7 Hz	4.37 (2H)	
						8.38 J = 7 Hz	2.52 (1H)	
4	228.0	272.0		1719	2929	6.09 *J* = 7 Hz	5.39 (4H)	7.21–7.69
	(4.49)	(4.41)		1492	—	6.09 *J* = 7 Hz	—	
						7.93 *J* = 7 Hz	—	
						7.93 *J* = 7 Hz	—	
5	223.0	287.5		—	—	7.27 *J* = 7 Hz	—	7.20–7.70
	(4.46)	(4.19)		1592	1270	7.27 *J* = 7 Hz	—	
						7.49 *J* = 7 Hz	4.39 (4H)	
						7.49 *J* = 7 Hz	—	
6	225.0	290.0		1671	2820	6.10 *J* = 7 Hz	5.40 (2H)	7.18–7.67
	(4.47)	(4.27)		1497	1260	7.27 *J* = 7 Hz	—	
						7.86 *J* = 7 Hz	4.48 (2H)	
						7.49 *J* = 7 Hz	—	
7	239.5	271.5	295.0	1673	2823	6.15 *J* = 7 Hz	4.91 (2H)	7.13–7.59
	(4.16)	(4.34)	(4.33)	1594	1270	7.25 *J* = 7 Hz	5.21 (2H)	
						7.93 *J* = 7 Hz	4.48 (2H)	
						8.42 *J* = 7 Hz	2.51 (1H)	
8	239.0	271.5	296.5	1713	2780	6.32 *J* = 7 Hz	5.21 (2H)	7.18–7.67
	(4.08)	(4.25)	(4.18)	1569	1277	7.16 *J* = 7 Hz	5.42 (2H)	
						7.93 *J* = 7 Hz	4.45 (2H)	
						8.40 *J* = 7 Hz	2.50 (1H)	
9	240.5	271.0	297.5	1716	2781	6.22 *J* = 7 Hz	5.17 (2H)	7.21–7.61
	(4.35)	(4.28)	(4.23)	1542	1230	7.17 *J* = 7 Hz	5.40 (2H)	
						7.93 *J* = 7 Hz	4.42 (2H)	
						8.13 *J* = 7 Hz	2.50 (1H)	

EXPERIMENTAL

The purity of all described compounds was checked by melting points, TLC, and elemental analyses. Melting points (uncorrected) were determined on a Bőetius microscope hot stage. Rf values refer to silica gel F_{254} TLC plates (Merck) developed with $CHCl_3$:CH_3OH (40:1) (**1–6**) and $CHCl_3$:CH_3OH (10:1) (**7–9**; Table II). UV/Vis spectra were recorded with a Specord UV/Vis Spectrophotometer in $CHCl_3$. IR spectra were recorded with a FT-IR Bruker IFS-113 Spectrophotometer in KBr pellets. The ^{1}H NMR spectra were determined with Varian Gemini 300 (300 MHz) spectrometer in $CDCl_3$ solution at a concentration

Table II Physical and analytical data of compounds **1–6** and **7–9**

Compound	Formula MW	Yield (%)	Mp (°C)	Rf TLC	Analysis					
					Calculated			Found		
					C	H	N	C	H	N
1	$C_{22}H_{18}N_4S_2O_2Br_2$ 594.34	56	150–151	0.47*	44.44	3.03	9.42	44.15	3.00	9.40
2	$C_{22}H_{18}N_4S_2O_2Br_2$ 594.34	53	140–141	0.46*	44.44	3.03	9.42	44.27	3.06	9.53
3	$C_{22}H_{18}N_4S_2O_2Br_2$ 594.34	58	162–163	0.45*	44.44	3.03	9.42	44.28	3.21	9.20
4	$C_{22}H_{16}N_4S_2O_2Br_2$ 592.32	20	201–203	0.51*	44.59	2.70	9.45	44.62	2.80	9.60
5	$C_{22}H_{16}N_4S_2O_2Br_2$ 592.32	18	140–141	0.52*	44.59	2.70	9.45	44.70	2.58	9.65
6	$C_{22}H_{16}N_4S_2O_2Br_2$ 592.32	19	180–181	0.50*	44.59	2.70	9.45	44.80	2.48	9.62
7	$C_{29}H_{24}N_4S_2O_2Br_3$ 763.36	23	170–173	0.63**	45.66	2.88	7.34	45.40	2.98	7.46
8	$C_{29}H_{24}N_4S_2O_2Br_3$ 763.36	28	150–153	0.83**	45.66	2.88	7.34	45.32	2.80	7.50
9	$C_{29}H_{24}N_4S_2O_2Br_3$ 763.36	36	140–143	0.93**	45.66	2.88	7.34	45.50	3.02	7.64

*$CHCl_3$:CH_3OH (40:1).
**$CHCl_3$:CH_3OH (10:1).

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 analyzer.

The Synthesis of Disulfides 1–9

To a solution of 2-thiouracil (0.5 g, 3.90 mmol) in DMF (25 mL), K_2CO_3 (0.6 g, 6 mmol) was added. The reaction mixture was heated to reflux for 20 min until the K_2CO_3 was completely dissolved. To this mixture, 1.95 g (7.8 mmol) **1–6** or 3 g (12 mmol) **7–9** of *o*-(*m*- or *p*-)bromobenzyl bromide was added, respectively. After 3 h of boiling, the solvent was filtered and acidified with dil. HCl (HCl:H_2O, 1:1). Then the precipitated solid was collected by filtration and dissolved in 10 mL of DMF, and was applied on a silica gel column (15 g of silica gel 60-Merck; the parameters of column: length 27 cm, Φ 1.8 cm). The column was eluted successively with the following mixtures of solvents: CH_2Cl_2 (100 mL), CH_2Cl_2:CH_3OH (90:1; 100 mL), CH_2Cl_2:CH_3OH (80:1; 100 mL), CH_2Cl_2:CH_3OH (70:1; 100 mL), CH_2Cl_2:CH_3OH (60:1; 100 mL), CH_2Cl_2:CH_3OH (50:1; 100 mL). The fractions of 100 mL were collected, respectively. On the basis of analytical TLC, fractions of derived product were obtained (fraction 5: compound **1**; fraction 6: compound **2**; fraction 7: compound **3**; fraction 8: compounds **6** and **7**; fraction 9: compounds **5** and **8**; fraction 10: compounds **4** and **9**). They were dried on a rotary evaporator. Compounds **1–9** were shown to be analytically pure without need for any further purification (Tables I and II).

Table III Predicted activity (PA) values for predicted biological activity of compounds **1–9**

Compound	Focal predicted activity (PA > 0.5)
1	2,6-Dihydroxypyridine-3-monooxygenase inhibitor (0.843)
	Antiviral (Poxvirus) (0.642)
	Prolyl aminopeptidase inhibitor (0.677)
	Interleukin antagonist (0.565)
	N-Acetyllactosamine synthase inhibitor (0.564)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.572)
	Aryloalkyl acylamidase inhibitor (0.546)
2	2,6-Dihydroxypyridine-3-monooxygenase inhibitor (0.836)
	Prolyl aminopeptidase inhibitor (0.785)
	N-Acetyllactosamine synthase inhibitor (0.589)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.555)
	Aryloalkyl acylamidase inhibitor (0.526)
3	2,6-Dihydroxypyridine-3-monooxygenase inhibitor (0.841)
	Prolyl aminopeptidase inhibitor (0.792)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.587)
	N-Acetyllactosamine synthase inhibitor (0.579)
	Aryloalkyl acylamidase inhibitor (0.533)
4	Prolyl aminopeptidase inhibitor (0.918)
	N-Acetyllactosamine synthase inhibitor (0.644)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.641)
	Arylalkyl acylamidase inhibitor (0.763)
	Thiopurine *S*-methyltrnsferase inhibitor (0.640)
	Uric acid excretion stimulant (0.599)
	Dopamine beta hydroxylse inhibitor (0.561)
	Camphor 1,2-monooxgenase inhibitor (0.598)
	Leucolysin inhibitor (0.607)
	(−)-(*4S*)-Limonene synthase inhibitor (0.635)
	CDK2/cydin A inhibitor (0.525)
	Antihypoxic (0.570)
	N-Carbamoyl-L-aminoacid hydrolase inhibitor (0.545)
	1-Alkyl-2-acetylglycerophosphocholine esterase inhibitor (0.526)
	Opine dehydrogenase inhibitor (0.575)
5	Prolyl aminopeptidase inhibitor (0.891)
	Arylalkyl acylamidase inhibitor (0.667)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.697)
	Antineoplastic (0.617)
	N-Acetyllactosamine synthase inhibitor (0.603)
	1-Alkyl-2-acetylglycerophosphocholine esterase inhibitor (0.516)
	N-Carbamoyl-L-aminoacid hydrolase inhibitor (0.515)
	Antineoplastic (colorectal cancer) (0.508)
6	Prolyl aminopeptidase inhibitor (0.764)
	Antiviral (Poxvirus) (0.634)
	Arylalkyl acylamidase inhibitor (0.653)
	Thiopurine *S*-methyltrnsferase inhibitor (0.544)
	Interleukin antagonist (0.540)
	N-Acetyllactosamine synthase inhibitor (0.575)
	Dopamine beta hydroxylse inhibitor (0.501)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.562)
7	2,6-Dihydroxypyridine-3-monooxygenase inhibitor (0.879)
	Antiviral (Poxvirus) (0.847)
	Prolyl aminopeptidase inhibitor (0.730)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.660)
	Interleukin antagonist (0.599)

(Continued on next page)

Table III Predicted activity (PA) values for predicted biological activity of compounds **1–9** *(Continued)*

Compound	Focal predicted activity (PA > 0.5)
	N-Acetyllactosamine synthase inhibitor (0.619)
	Nicotinate glucosyltransferase inhibitor (0.531)
	Antiviral (Herpes) (0.512)
	Arylalkyl acylamidase inhibitor (0.587)
8	Prolyl aminopeptidase inhibitor (0.848)
	Thiopurine *S*-methyltrnsferase inhibitor (0.549)
	N-Acetyllactosamine synthase inhibitor (0.575)
	Arylalkyl acylamidase inhibitor (0.583)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.562)
9	Prolyl aminopeptidase inhibitor (0.854)
	Thiopurine *S*-methyltrnsferase inhibitor (0.551)
	N-Acetyllactosamine synthase inhibitor (0.594)
	Arylalkyl acylamidase inhibitor (0.592)
	Mannotetraose 2-aplha-*N*-acetylglucosaminyltransferase inhibitor (0.594)

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