CONDENSED THIENOPYRIMIDINES 3.[1] SYNTHESIS OF ANGULAR ANNELATED OXAZOLO[2,3-b]THIENOPYRIMIDIN-5-ONE DERIVATIVES

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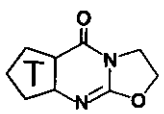
Abstract——Angular annelated tricyclic oxazolothienopyrimidine derivatives, 1,2-dihydro-5H-oxazolo[2,3-b]thieno[3,2-d]-, [3,4-d]-, and [2,3-d]pyrimidin-5-one (2), were prepared and evaluated for gastric antisecretory activity in pylorus-ligated rats.

The linear annelated oxazolo[3,2-a]thienopyrimidin-5-one derivatives (1) were recently prepared and it was found that 1 exhibited a potent gastric antisecretory activity in the pylorus-ligated rats without producing significant side-effects.[1b] In this paper, we report the synthesis of the angular annelated oxazolo[2,3-b]thienopyrimidin-5-one derivatives (2a-g), which are compounds having novel heterocyclic ring systems and positional isomers of linear annelated compounds (1).



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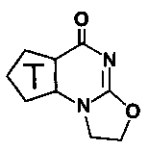
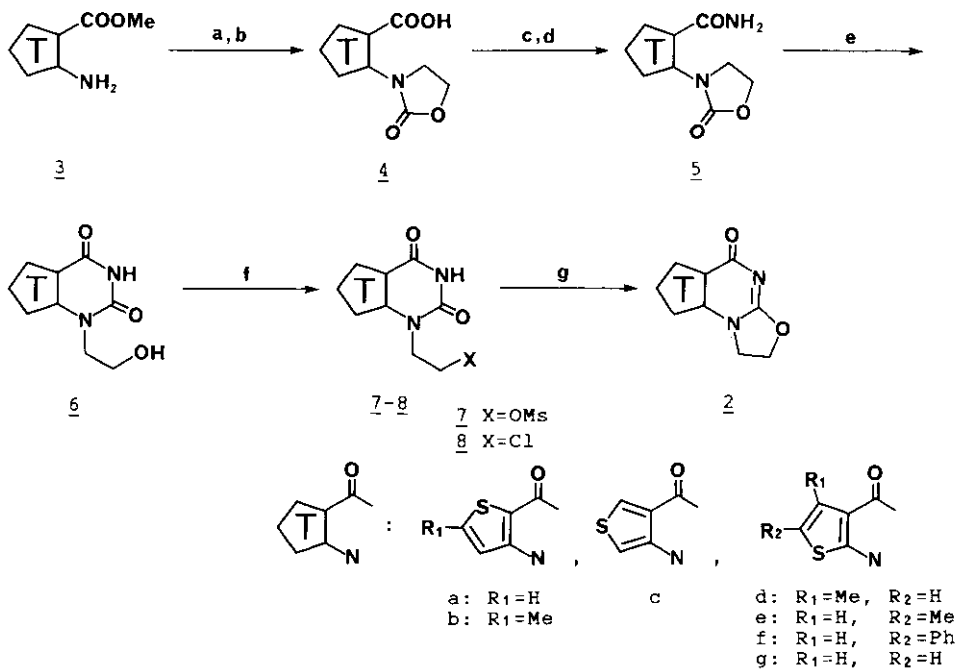


2

: Thiophene Ring

The oxazolo[2,3-b]thienopyrimidine derivatives (2) were synthesized from amino-thiophenecarboxylates (3) as follows. Direct 2-hydroxyethylation of amino moiety on 3 with ethylene oxide or ethylene chlorohydrine gave a mixture and only a trace of the pure product was isolated. A practical method for the preparation of 2-anilinoethanols was reported by Adams et al.[2] The synthesis of 3-(2-hydroxy-ethyl)thienopyrimidine derivatives (6a-e) was performed by the Adams' method. Heating of 3a-c with 2-chloroethyl chloroformate in toluene gave 2-chloroethyl



a. $ClCOOCH_2CH_2Cl$, b. KOH, c. ClCOOEt, d. NH_3, e. KOH,
f. MsCl (or $SOCl_2$), g. DBU

Chart 1

carbamate derivatives, which were hydrolyzed and cyclized with ethanolic potassium hydroxide (KOH) to afford the thiophenecarboxylic acid derivatives (4a-c). However, in the cases of 3d-f, 2-(2-hydroxyethylamino)thiophene-3-carboxylate derivatives (9d-f, for example, Chart 2) were obtained as the major products together with 4d-f, and no desired product (4g) was formed owing to the lability of 3g under these conditions. The amides 5a-e were prepared from 4a-e by the

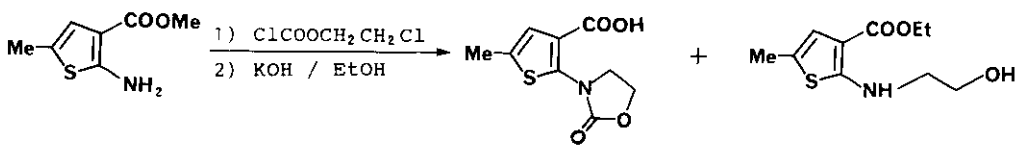
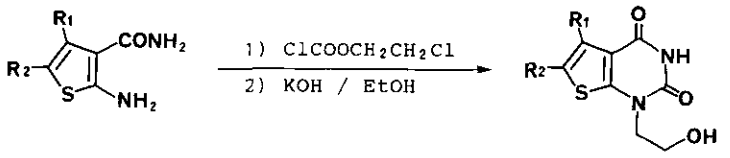


Chart 2

formation of mixed anhydride with ethyl chloroformate followed by the treatment with ammonia. Heating of 5a-e with ethanolic KOH afforded the desired 1-(2-hydroxyethyl)thienopyrimidine derivatives (6a-e) in quantitative yields.

It is noteworthy that the reaction of 2-aminothiophene-3-carboxamides (10d-g)[3]

with 2-chloroethyl chloroformate followed by the treatment with ethanolic KOH gave 1-(2-hydroxyethyl)thieno[2,3-d]pyrimidin-2,4(1H,3H)-dione derivatives (6d-g) in good yields (Chart 3). The chlorination of 6a-c,e,f with thionyl chloride ($SOCl_2$)



10d-g 6d-g

Chart 3

afforded the corresponding 1-(2-chloroethyl)thienopyrimidine derivatives (8a-c,e,f) in satisfactory yields, whereas, in the cases of 6d,g, the resinous products were formed. Therefore, these results led us to use mesyl substituent (Ms) as a leaving group instead of chloro substituent. Thus, the angular annelated tricyclic products (2a-g) were produced successfully by the conversion of 6a-g into mesylates (7a-g) followed by cyclization with 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU).

The tricyclic compounds (2a-c,e,f) were also prepared from 8a-c,e,f by the treatment with DBU.

These angular annelated tricyclic compounds, 1,2-dihydro-5H-oxazolo[2,3-b]thieno-pyrimidin-5-one derivatives, have new heterocyclic ring systems (Table 7).

Gastric antisecretory activity was determined in pylorus-ligated rats. Most of these derivatives had moderate activities. Among them, 2a showed a good result (80% inhibition, 50mg/kg, i. d.).

Further investigation on the pharmacological effects of these derivatives is in progress.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (ir) were measured on a JASCO A-102 spectrophotometer. Nuclear magnetic resonance spectra (nmr) were recorded with a Varian T-60A (60MHz) or EM-390 (90MHz) spectrometer and the chemical shifts are expressed in ppm from tetramethylsilane as an internal standard. Mass spectra (ms) were obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer. Merck silica gel (Kieselgel 60 Art. 7734) was employed for column chromatography.

3-(2-Oxo-3-oxazolidinyl)thiophene-2-carboxylic Acid (4a) (General Procedure)

A solution of methyl 3-aminothiophene-2-carboxylate (3a) (10.0 g, 63.6 mmol) and

2-chloroethyl chloroformate (11.8 g, 82.7 mmol) in toluene (70 ml) was refluxed for 1 h and then the solvent was evaporated in vacuo. After addition of water to the residue, the crude 2-chloroethylcarbamate derivative was collected by filtration and washed with water. The crystal was dissolved in ethanolic KOH [prepared from KOH (12.5 g, 189 mmol) and EtOH (250 ml)] and the whole was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in water and washed with CH_2Cl_2. The aqueous layer was acidified with 10% HCl, the precipitated powder was collected, washed with water, and recrystallized from MeOH-AcOEt to give 4a (7.8 g, 57%) as colorless needles. Ms (m/z): 213 (M^+). Other data are listed in Tables 1 - 6.

Formation of Ethyl 2-(2-Hydroxyethylamino)-5-methylthiophene-3-carboxylate (9e) on the Synthesis of 4e

A solution of methyl 2-amino-5-methylthiophene-3-carboxylate (3e) (3.00 g, 17.5 mmol) and 2-chloroethyl chloroformate (3.01 g, 21.1 mmol) in toluene (20 ml) was refluxed for 1 h and then the solvent was evaporated to dryness. After addition of water to the residue, the crude 2-chloroethylcarbamate derivative was collected by filtration and washed with water. The crystal was dissolved in ethanolic KOH [prepared from KOH (2.54 g, 38.5 mmol) and EtOH (60 ml)] and then the whole was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in water and extracted with AcOEt. A residue obtained from the extracts was chromatographed on silica gel and eluted with CH_2Cl_2-MeOH (97:3) to give 9e (2.67 g, 66%) as an oil. The aqueous layer was acidified with 10% HCl and the precipitated powder was collected. The crude product was recrystallized from MeOH-AcOEt to afford 4e (565 mg, 14%) as colorless prisms. 9e: Anal. Calcd for $C_{10}H_{15}NO_3S \cdot 1/10H_2O$: C,51.97; H,6.63; N,6.06; S,13.87. Found: C,51.83; H,6.66; N,6.17; S,14.17. Ir($CHCl_3$): 1675cm^{-1}. Nmr($CDCl_3$) δ : 1.30(3H,t,J=7.2Hz), 2.27 (3H,d,J=1.5Hz), 3.23-3.49(2H,m), 3.73-3.95(2H,m), 4.22(2H,q,J=7.2Hz), 6.67 (1H,d, J=1.5Hz), 2.55-2.90 and 7.23-7.73(each 1H,br). Ms (m/z): 229(M^+).

3-(2-Oxo-3-oxazolidinyl)thiophene-2-carboxamide (5a) (General Procedure)

To an ice-cooled solution of 4a (4.59 g, 21.5 mmol) and Et_3N (2.61 g, 25.8 mmol) in CH_2Cl_2 (130 ml) was added dropwise ethyl chloroformate (2.57 g, 23.7 mmol) and the whole was stirred for 30 min. Anhydrous ammonia was bubbled into the reaction mixture for 1 h under ice cooling and then the whole was stirred at room temperature for 2 h. After filtration, the filtrate was washed with water, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization from MeOH gave 5a (3.23 g, 71%) as colorless needles. Ms (m/z): 212 (M^+). Other data are listed in Tables 1 - 6.

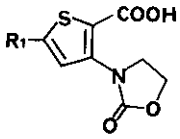
1-(2-Hydroxyethyl)thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione (6a) (General Procedure)

A solution of 5a (3.50 g, 16.5 mmol) and ethanolic KOH [prepared from KOH (2.18 g, 33.0 mmol) and EtOH (60 ml)] was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved in water and washed with AcOEt. The aqueous layer was acidified with 10% HCl, the precipitate was collected by filtration, washed with water, and recrystallized from DMF to give 6a (3.15 g, 90%) as colorless needles. Ms (m/z): 212 (M^+). Other data are listed in Tables 1 - 6.

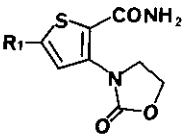
1-(2-Hydroxyethyl)thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione (6g) (General Procedure for 6d-f)

A solution of 2-aminothiophene-3-carboxamide[3] (10g) (3.00 g, 21.1 mmol) and 2-chloroethyl chloroformate (3.02 g, 21.1 mmol) in toluene (35 ml) was refluxed for 1 h and then the solvent was evaporated in vacuo. After addition of water to the

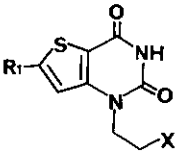
Table 1. Intermediates (4a,b, 5a,b, 6a,b, 7a,b, and 8a,b) for 1,2-Dihydro-5H-oxazolo[2,3-b]thieno[3,2-d]pyrimidin-5-ones (2a,b)



4a-b



5a-b



6a-b X=OH
7a-b X=OMs
8a-b X=Cl

Compd. No.	R_1	Yield (%)	mp(℃)	Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
4a	H	57	185-188 (decomp)	MeOH-AcOEt	$C_8H_7NO_4S$	45.07 (44.90)	3.31 (3.22)		6.57 (6.68)	15.04 (15.09)
4b	Me	55	166-169 (decomp)	MeOH	$C_9H_9NO_4S$	47.57 (47.74)	3.99 (3.98)		6.16 (6.28)	14.11 (14.08)
5a	H	71	145-147	MeOH	$C_8H_8N_2O_3S$	45.28 (45.37)	3.80 (3.96)		13.20 (13.25)	15.11 (14.98)
5b	Me	77	195-197	MeOH	$C_9H_{10}N_2O_3S$	47.78 (47.74)	4.46 (4.45)		12.38 (12.30)	14.17 (14.29)
6a	H	90	259-262	DMF	$C_8H_8N_2O_3S$	45.28 (45.19)	3.80 (3.82)		13.20 (13.17)	15.11 (14.87)
6b	Me	97	>300	DMF	$C_9H_{10}N_2O_2S$	47.78 (47.82)	4.46 (4.45)		12.38 (12.30)	14.17 (14.00)
7a	H	84	169-171 (decomp)	DMF-MeOH	$C_9H_{10}N_2O_5S_2$	37.23 (37.22)	3.47 (3.60)		9.65 (9.50)	22.09 (22.07)
7b	Me	75	178-179 (decomp)	DMF	$C_{10}H_{12}N_2O_5S_2$	39.47 (39.25)	3.97 (3.92)		9.20 (9.23)	21.07 (21.33)
8a	H	82	241-244	DMF-MeOH	$C_8H_7N_2O_2ClS$	41.66 (41.77)	3.06 (3.25)	15.37 (15.12)	12.14 (12.41)	13.90 (13.65)
8b	Me	82	239-241	DMF-MeOH	$C_9H_9N_2O_2ClS$	44.18 (44.00)	3.71 (3.79)	14.49 (14.49)	11.45 (11.39)	13.10 (13.05)

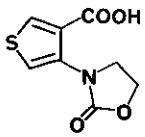
Table 2. Spectral Data for 4a,b, 5a,b, 6a,b, 7a,b, and 8a,b

Compd. No.	Ir (KBr) ν (cm^{-1})	Nmr (DMSO-d_6) δ (ppm), J (Hz)
4a	1710, 1680	3.91-4.08 (2H,m), 4.37-4.53 (2H,m), 7.27 and 7.86 (each 1H,d,J=5,4)
4b	1720(sh), 1710	2.47 (3H,s), 3.89-4.07 (2H,m), 4.35-4.54 (2H,m), 7.03 (1H,s)
5a	1755, 1660	3.81-4.17 (2H,m), 4.30-4.65 (2H,m), 7.22 and 7.70 (each 1H,d,J=5.2), 7.31-7.60 (2H,br)
5b	1759, 1656	2.43 (3H,s), 3.86-4.02 (2H,m), 4.35-4.51 (2H,m), 6.96 (1H,s), 7.17-7.65 (2H,br)
6a	1680	3.54-3.82 (2H,m), 4.05 (2H,t,J=5.4), 4.85 (1H,t,J=5.7), 7.33 and 8.11 (each 1H,d,J=5.7), 11.30-11.43 (1H,br)
6b	1677	2.53 (3H,s), 3.49-3.78 (2H,m), 3.99 (2H,t,J=5.7), 4.82 (1H,t,J=5.9), 7.11 (1H,s), 11.28-11.58 (1H,br)
7a	1683, 1668(sh)	3.12 (3H,s), 4.21-4.58 (4H,m), 7.36 and 8.16 (each 1H,d, J=5.4), 11.50-11.77 (1H,br)
7b	1693, 1689	2.55 (3H,s), 3.13 (3H,s), 4.15-4.55 (4H,m), 7.13 (1H,s), 11.42-11.59 (1H,br)
8a	1690, 1660	3.88 (2H,t,J=6.2), 4.34 (2H,t,J=6.2), 7.43 and 8.16 (each 1H,d,J=5.7), 11.47-11.85 (1H,br)
8b	1687	2.55 (3H,s), 3.87 (2H,t,J=6.3), 4.29 (2H,t,J=6.3), 7.20 (1H,s), 11.32-11.70 (1H,br)

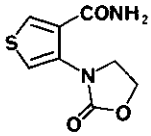
residue, the precipitate was filtered and washed with water. The crystalline product was dissolved in ethanolic KOH [prepared from KOH (2.78 g, 42.3 mmol) and EtOH (45 ml)] and the whole was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in water, and washed with AcOEt. The aqueous layer was acidified with 10% HCl, the precipitate was collected, washed with water, and recrystallized from MeOH-AcOEt to afford 6g (0.38 g, 8%) as colorless needles. Ms (m/z): 212 (M^+). Other data are listed in Tables 5 - 6.

2-(1,2,3,4-Tetrahydro-2,4-dioxothieno[3,2-d]pyrimidin-1-yl)ethyl methanesulfonate (7a) (General Procedure)

Table 3. Intermediates (4c, 5c, 6c, 7c, and 8c) for 1,2-Dihydro-5H-oxazolo[2,3-b]thieno[3,4-d]pyrimidin-5-ones (2c)



4c



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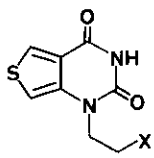


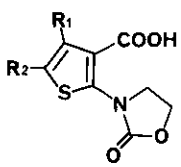
6c X=OH
7c X=OMs
8c X=Cl

Compd. No.	Yield (%)	mp(℃)	Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
4c	42	213-216 (decomp)	MeOH-AcOEt	$C_8H_7NO_4S$	45.07	3.31		6.57	15.04
					(44.98	3.25		6.53	15.13)
5c	59	162-165	MeOH	$C_8H_8N_2O_3S$	45.28	3.80		13.20	15.11
					(45.36	3.74		13.23	15.07)
6c	87	227-231	DMF	$C_8H_8N_2O_3S$	45.28	3.80		13.20	15.11
					(45.07	3.88		12.99	15.02)
7c	75	158-159 (decomp)	DMF-MeOH	$C_9H_{10}N_2O_5S_2$	37.23	3.47		9.65	22.09
					(37.18	3.52		9.70	22.41)
8c	63	186-190 (decomp)	DMF-MeOH	$C_8H_7N_2O_2ClS$	41.66	3.06	15.37	12.14	13.90
					(41.50	2.94	15.53	12.20	13.77)

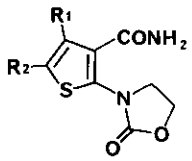
Table 4. Spectral Data for 4c, 5c, 6c, 7c, and 8c

Compd. No.	Ir (KBr) ν (cm^{-1})	Nmr (DMSO-d_6) δ (ppm), J (Hz)
4c	1677, 1648	3.80-3.96 (2H,m), 4.35-4.51 (2H,m), 7.64 and 8.29 (each 1H,d,J=3.6), 11.92-13.67 (1H,br)
5c	1720, 1675	3.82-3.99 (2H,m), 4.33-4.47 (2H,m), 7.57 and 8.05 (each 1H,d,J=3.6), 6.89-7.92 (2H,br)
6c	1694, 1677(sh)	3.53-3.81 (2H,m), 3.96 (2H,t,J=6.2), 4.78 (1H,t,J=4.1), 7.17 and 8.42 (each 1H,d,J=3.0), 11.01-11.37 (1H,br)
7c	1701, 1690	3.13 (3H,s), 4.13-4.60 (4H,m), 7.25 and 8.13 (each 1H,d,J=3.3), 11.20-11.47 (1H,br)
8c	1697, 1640(sh)	3.87 (2H,t,J=6.5), 4.25 (2H,t,J=6.5), 7.31 and 8.47 (each 1H,d,J=3.0), 11.12-11.52 (1H,br)

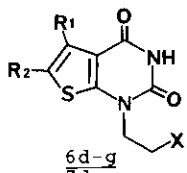
Table 5. Intermediates (4d-f, 5d,e, 6d-g, 7d-g, and 8e,f) for 1,2-Dihydro-5H-oxazolo[2,3-b]thieno[2,3-d]pyrimidin-5-ones (2d-g)



4d-f



5d,e



6d-g
7d-g
8e,f

Compd. No.	R_1	R_2	Yield (%)	mp(℃)	Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
4d	Me	H	9	153-156 (decomp)	MeOH -AcOEt	$C_9H_9NO_4S$	47.57	3.99		6.16	14.11
							(47.50	3.73		6.26	13.92)
4e	H	Me	14	170-173 (decomp)	MeOH -AcOEt	$C_9H_9NO_4S$	47.57	3.99		6.16	14.11
							(47.42	4.00		6.16	14.14)
4f	H	Ph	6	187-190 (decomp)	MeOH -AcOEt	$C_{14}H_{11}NO_4S$	58.12	3.83		4.84	11.08
							(57.92	3.87		4.93	11.33)
5d	Me	H	36	155-157	MeOH -AcOEt	$C_9H_{10}N_2O_3S$	47.78	4.46		12.38	14.17
							(47.93	4.37		12.36	14.00)
5e	H	Me	50	134-136	MeOH -AcOEt	$C_9H_{10}N_2O_3S$	47.78	4.46		12.38	14.17
							(47.77	4.38		12.38	14.21)
6d	Me	H	54 [a] (49) [b]	228-230	DMF	$C_9H_{10}N_2O_3S$	47.78	4.46		12.38	14.17
							(47.53	4.48		12.12	14.08)
6e	H	Me	70 [a] (73) [b]	257-259 (decomp)	DMF	$C_9H_{10}N_2O_3S$	47.78	4.46		12.38	14.17
							(47.75	4.44		12.40	14.09)
6f	H	Ph	54 [a]	234-237 (decomp)	DMF	$C_{14}H_{12}N_2O_3S$	58.32	4.20		9.72	11.12
							(58.15	4.11		9.75	11.31)
6g	H	H	8 [a]	206-210 (decomp)	MeOH -AcOEt	$C_8H_8N_2O_3S$	45.28	3.80		13.20	15.11
							(45.30	3.75		12.97	14.84)

Table 5. (*continued*)

Compd. No.	R_1	R_2	Yield (%)	mp(℃)	Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
7d	Me	H	82	173-175 (decomp)	DMF-MeOH	$C_{10}H_{12}N_2O_5S_2$	39.47 (39.46	3.97 3.99		9.20 9.28	21.07 20.86)
7e	H	Me	82	190-191 (decomp)	DMF-MeOH	$C_{10}H_{12}N_2O_5S_2$	39.47 (39.52	3.97 3.72		9.20 9.33	21.07 20.89)
7f	H	Ph	48	173-176 (decomp)	DMF-MeOH	$C_{15}H_{14}N_2O_5S_2 \cdot 1/10DMF$	49.17 (49.15	3.96 3.68		7.87 7.92	17.16 16.87)
7g	H	H	44	175-178 (decomp)	DMF-MeOH	$C_9H_{10}N_2O_5S_2 \cdot 3/10DMF$	38.08 (37.93	3.91 3.68		10.31 10.01	20.54 20.70)
8e	H	Me	82	259-261 (decomp)	DMF	$C_9H_9N_2O_2ClS$	44.18 (44.18	3.71 3.92	14.49 14.30	11.45 11.60	13.10 13.08)
8f	H	Ph	63	251-252 (decomp)	DMF-MeOH	$C_{14}H_{11}N_2O_2ClS$	54.81 (54.84	3.61 3.51	11.56 11.24	9.13 9.42	10.45 10.27)

a) Yield from 10. b) Yield obtained from 5 is shown in parentheses.

Table 6. Spectral Data for 4d-f, 5d,e, 6d-g, 7d-g, and 8e,f

Compd. No.	Ir (KBr) ν (cm^{-1})	Nmr (DMSO-d_6) δ (ppm), J (Hz)
4d	1724, 1679	2.28 (3H,d,J=1.5), 3.85-4.03 (2H,m), 4.37-4.55 (2H,m), 7.10 (1H,d,J=1.5), 11.10-12.77 (1H,br)
4e	1725, 1694	2.39 (3H,d,J=1.5), 3.86-4.07 (2H,m), 4.34-4.56 (2H,m), 7.01 (1H,d,J=1.5)
4f	1721, 1690	3.97-4.15 (2H,m), 4.44-4.60 (2H,m), 7.38-7.80 (6H,m)
5d	1750(sh), 1733 1661	2.18 (3H,d,J=1.8), 3.95-4.13 (2H,m), 4.38-4.56 (2H,m), 6.95 (1H,d,J=1.8), 7.27-7.87 (2H,br)
5e	1748, 1669	2.38 (3H,d,J=1.2), 3.87-4.02 (2H,m), 4.33-4.50 (2H,m), 7.00 (1H,d,J=1.2), 7.10-7.87 (2H,br)
6d	1708(sh), 1680	2.35 (3H,d,J=1.5), 3.53-4.05 (4H,m), 4.96 (1H,br t,J=5.9) 6.77 (1H,d,J=1.5), 11.16-11.48 (1H,br)
6e	1693, 1683	2.40 (3H,d,J=1.2), 3.52-3.98 (4H,m), 4.97 (1H,br t,J=5.4), 6.90 (1H,d,J=1.2), 11.18-11.48 (1H,br)
6f	1694	3.62-4.10 (4H,m), 5.04 (1H,br t,J=5.7), 7.31-7.81 (6H,m), 11.47-11.66 (1H,br)
6g	1702, 1666 1644	3.57-4.04 (4H,m), 7.23 (2H,s), 4.77-5.23 and 11.33-11.59 (each 1H,br)
7d	1708, 1698(sh) 1677	2.36 (3H,d,J=1.8), 3.15 (3H,s), 4.16 (2H,br t,J=5.1), 4.52 (2H,br t,J=5.1), 6.82 (1H,d,J=1.8), 11.31-11.55 (1H, br)
7e	1698, 1675	2.41 (3H,d,J=1.2), 3.15 (3H,s), 4.05-4.62 (4H,m), 6.93 (1H,d,J=1.2), 11.33-11.60 (1H,br)
7f	1701	3.16 (3H,s), 4.23 (2H,br t,J=5.1), 4.57 (2H,br t,J=5.1), 7.31-7.81 (6H,m), 11.48-11.74 (1H,br)
7g	1690	3.16 (3H,s), 4.10-4.63 (4H,m), 7.26 (2H,s), 11.47-11.77 (1H,br)
8e	1687	2.43 (3H,d,J=1.5), 3.85-4.29 (4H,m), 6.95 (1H,d,J=1.5), 11.38-11.63 (1H,br)
8f	1696, 1677(sh) 1669	3.87-4.42 (4H,m), 7.30-7.81 (6H,m), 11.50-11.82 (1H,br)

To an ice-cooled mixture of 6a (1.82 g, 8.58 mmol) in pyridine (15 ml) was added dropwise methanesulfonyl chloride (0.86 ml, 11.1 mmol) with stirring and then the whole was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water, the precipitate was collected, and washed with water and acetone. Recrystallization from DMF-MeOH gave 7a (2.08 g, 84%) as colorless needles. Ms (m/z): 290 (M^+). Other data are listed in Tables 1 - 6.

1-(2-Chloroethyl)thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione (8a) (General Procedure)

To a mixture of 6a (1.50 g, 7.07 mmol) and pyridine (1.68 g, 21.2 mmol) in $CHCl_3$ (30 ml) was added dropwise $SOCl_2$ (3.1 ml, 43.0 mmol) , and the whole was refluxed for 1 h. After cooling, the precipitate was collected by filtration and washed with $CHCl_3$. Recrystallization from DMF-MeOH afforded 8a (1.34 g, 82%) as colorless needles. Ms (m/z): 230(M^+). Other data are listed in Tables 1 - 6.

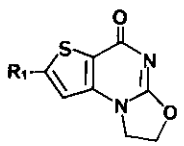
1,2-Dihydro-5H-oxazolo[2,3-b]thieno[3,2-d]pyrimidin-5-one (2a) (General Procedure)

Method A-----To a suspension of 7a (186 mg, 0.64 mmol) in EtOH (5 ml) was added DBU (99 mg, 0.65 mmol) and the whole was stirred at room temperature for 2 h.

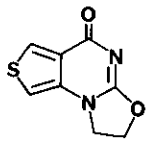
Removal of the solvent in vacuo gave an oily residue, which was chromatographed on silica gel and eluted with MeOH-CH_2Cl_2 (1:19). Recrystallization from DMF afforded 2a (98 mg, 78%) as colorless needles. Ms (m/z): 194(M^+). Other data are listed in Tables 7 and 8.

Method B-----To a suspension of 8a (262 mg, 1.14 mmol) in EtOH (10 ml) was added DBU (170 mg, 1.12 mmol) and the whole was refluxed for 15 min. Concentration of the solvent in vacuo gave an oily residue, which was chromatographed on silica gel and eluted with MeOH-CH_2Cl_2 (1:19) to afford 2a (177 mg, 79%).

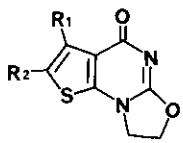
Table 7. 1,2-Dihydro-5H-oxazolo[2,3-b]thienopyrimidin-5-one Derivatives (2a-g)



2a-b



2c



2d-g

Compd. No.	R_1	R_2	Yield (%)	mp(℃)	Recryst. solvent	Formula	Analysis(%) Calcd (Found) C	H	N	S
2a	H		78(79)[a]	>300	DMF	$C_8H_6N_2O_2S$	49.48 (49.68	3.11 2.99	14.42 14.58	16.51 16.67)
2b	Me		76(87)[a]	>300	MeOH	$C_9H_8N_2O_2S$	51.91 (51.71	3.87 3.76	13.45 13.49	15.40 15.47)
2c			76(57)[a]	>300	DMF-MeOH	$C_8H_6N_2O_2S$	49.48 (49.36	3.11 3.06	14.42 14.47	16.51 16.77)
2d	Me	H	87	286-290 (decomp)	MeOH	$C_9H_8N_2O_2S$	51.91 (51.67	3.87 3.74	13.45 13.57	15.40 15.70)
2e	H	Me	60(53)[a]	>300	MeOH	$C_9H_8N_2O_2S$	51.91 (51.79	3.87 3.69	13.45 13.54	15.40 15.14)
2f	H	Ph	67(35)[a]	255-260 (decomp)	MeOH	$C_{14}H_{10}N_2O_2S \cdot 1/3H_2O$	60.86 (60.67	3.89 3.97	10.14 10.10	11.60 11.69)
2g	H	H	71	>300	DMF	$C_8H_6N_2O_2S$	49.48 (49.33	3.11 3.06	14.42 14.38	16.51 16.29)

a) Yield obtained from 8 is shown in parentheses.

Table 8. Spectral Data for 2a-g

Compd. No.	Ir (KBr) ν (cm^{-1})	Nmr (DMSO-d_6) δ (ppm), J (Hz)
2a	1653, 1607	4.30-4.60 (2H,m), 4.68-5.00 (2H,m), 7.33 and 8.03 (each 1H,d,J=5.7)
2b	1643, 1604	2.57 (3H,s), 4.25-4.48 (2H,m), 4.65-4.93 (2H,m), 7.07 (1H,s)
2c	1582	4.16-4.41 (2H,m), 4.64-4.92 (2H,m), 7.35 and 8.32 (each 1H,d,J=3.0)
2d	1593	2.20 (3H,d,J=1.8), 4.18-4.46 (2H,m), 4.55-4.92 (2H,m), 6.89 (1H,d,J=1.8)
2e	1641	2.48 (3H,s), 4.24-4.52 (2H,m), 4.72-5.00 (2H,m), 7.02 (1H,s)
2f	1600	4.27-4.55 (2H,m), 4.69-4.97 (2H,m), 7.32-7.83 (6H,m)
2g	1783, 1680 1643	4.25-4.50 (2H,m), 4.74-4.92 (2H,m), 9.31 (2H,s)

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