

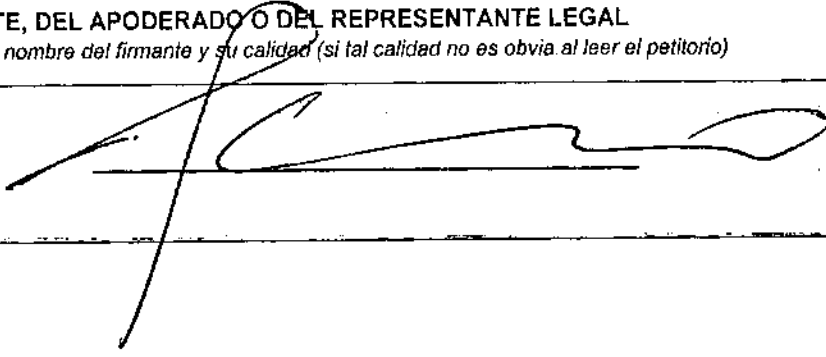


No. 14-124179- -00006-0000

Fecha: 2015-02-26 16:32:19 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII -Eve: 378 FASENACIONAL
Act. 457 PROCEDIPPH Folios: 72

DIRECCIÓN DE NUEVAS CREACIONES
Procedimiento acelerado de exámenes de patente (pph)

1	NÚMERO DE SOLICITUD ANTE LA SIC	14.124.179
2	OFICINA DE PRIMERA PRESENTACIÓN (OPP)	USPTO
3	NÚMERO(S) DE SOLICITUD O PUBLICACIÓN DE LA(S) SOLICITUD(ES) (OPP):	1.US 2013/673,610 2.US 2013/0123231
4	☐ REPRESENTANTE LEGAL ☒ APODERADO	
CORREA APELLIDOS		ALVARO NOMBRES
C.C. 79.143.366		T.P. 20.281
DIRECCIÓN	Av. 82 No. 10-62 Piso 5	No. TELÉFONO 6341500
CIUDAD	Bogotá	CORREO ELECTRÓNICO Alvaro.correa@bakermckenzie.com
PAIS	Colombia	No. RADICACIÓN O PROTOCOLO DE PODER GENERAL
5	CONDICIONES PARA ACCEDER A ESTE PROCESO:	
5.1.	DATOS DE PRIORIDAD ☒ SI ☐ NO	
(33) PAIS DE ORIGEN		CÓDIGO PAIS
1. Estados Unidos de América		US
2. Estados Unidos de América		US
3. Estados Unidos de América		US
4. Estados Unidos de América		US
		(31) NÚMERO
		61/559,023
		61/615,092
		61/651,878
		61/675,513
		(32) FECHA (AAAA/MM/DD)
		11/11/2011
		23/03/2012
		25/05/2012
		25/07/2012
5.2.	DATOS SOLICITUD INTERNACIONAL PCT ☒ SI ☐ NO	
Solicitud Internacional No. PCT/US2012/064528		Fecha 09/11/2012
Publicación Internacional No. WO2013/071169		Fecha 16/05/2013
El solicitante presenta una copia de la(s) reivindicación(es) patentable(s) u otorgable(s) de la solicitud de la Oficina de Primera Presentación que profirió el examen de patentabilidad, junto con una traducción al castellano. ☒ SI ☐ NO		
REQUISITOS PARA EL RECONOCIMIENTO DE LOS RESULTADOS DE EXÁMENES DE PATENTABILIDAD EFECTUADOS A SOLICITUDES EXTRANJERAS		
Para que la Superintendencia de Industria y Comercio pueda reconocer los resultados de exámenes de patentabilidad producidos por otras Oficinas de Propiedad Industrial se debe cumplir con las siguientes condiciones:		
(a) Al momento de solicitar el examen de patentabilidad, si el solicitante pide que se reconozcan exámenes de patentabilidad de otras oficinas extranjeras, deberá aportar junto con el pago de la tasa correspondiente, los siguientes anexos:		
(i) Copia de las resoluciones, fallos o decisiones que han sido relevantes para la determinación de la patentabilidad de la(s) solicitud(es) en la Oficina que haya proferido el examen de patentabilidad que contienen reivindicaciones patentables u otorgables que son la base de la petición, y si es del caso, su traducción al castellano. ☒ SI ☐ NO		
(ii) Copia de todas las reivindicaciones determinadas como patentables u otorgables en la Oficina que profirió el examen de patentabilidad y, si es del caso, su traducción al castellano. ☒ SI ☐ NO		
(iii) Copia de los antecedentes, información o documentos citados por el examinador de la Oficina de Primera Presentación del examen de patentabilidad, en las resoluciones, fallos o decisiones correspondientes, incluyendo la literatura no patente. Los documentos de patente deberán presentarse siempre y cuando no estén disponibles para la Superintendencia de Industria y Comercio mediante el simple acceso a bases de datos gratuitas. ☒ SI ☐ NO		
(iv) Una tabla de correspondencias de las reivindicaciones que han sido determinadas como patentables u otorgables en la solicitud de la Oficina que haya proferido el examen de patentabilidad.		

7	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL <i>Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)</i>
	

6	TABLA DE CORRESPONDENCIA DE REIVINDICACIONES		
	Reivindicaciones en la solicitud en Colombia	Reivindicaciones otorgables en la solicitud internacional US 8,969,557	Explicación sobre la suficiente correspondencia ó Comentarios que explican la correspondencia
	REIVINDICACIÓN 7) Un compuesto de formula II II o una o una sal farmacéuticamente aceptable del mismo, en donde: R ¹ es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R) ₂ , - N(R)C(O)R, - C(O)N(R) ₂ , -N(R)C(O)N(R) ₂ , -N(R)C(O)OR, -OC(O)N(R) ₂ , -N(R)SO ₂ R, -SO ₂ N(R) ₂ , -	1) Un compuesto de formula II II o una o una sal farmacéuticamente aceptable del mismo, en donde: R ¹ es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R) ₂ , - N(R)C(O)R, - C(O)N(R) ₂ , -N(R)C(O)N(R) ₂ , -N(R)C(O)OR, -OC(O)N(R) ₂ , -N(R)SO ₂ R, -SO ₂ N(R) ₂ , -	 <

C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; R² es Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; R³ es hidrógeno, halógeno, -CN, -OR, -	C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; R² es Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; R³ es hidrógeno, halógeno, -CN, -OR, -	
--	--	--

SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, - N(R)C(O)N(R)₂, - N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, - SO₂N(R)₂, -C(O)R, -C(O)OR, - OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; R⁴ es un anillo fenilo o naftilo opcionalmente sustituido; cada uno de R⁵ y R^{5'} es independientemente -R, -OR, -SR, - N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, - N(R)C(O)N(R)₂, -N(R)C(O)OR, - OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, - C(O)R, -C(O)OR, -OC(O)R, -S(O)R o - SO₂R; o R⁵ y R^{5'} se toman juntos para	SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, - N(R)C(O)N(R)₂, - N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, - SO₂N(R)₂, -C(O)R, -C(O)OR, - OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; R⁴ es un anillo fenilo o naftilo opcionalmente sustituido; cada uno de R⁵ y R^{5'} es independientemente -R, -OR, -SR, - N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, - N(R)C(O)N(R)₂, -N(R)C(O)OR, - OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, - C(O)R, -C(O)OR, -OC(O)R, -S(O)R o - SO₂R; o R⁵ y R^{5'} se toman juntos para	.
--	--	----------

6
formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo; y

Cada uno de R^7 y $R^{7'}$ es independientemente hidrógeno, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^7 y $R^{7'}$ se toman juntos para formar un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, o un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre y cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un

formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo; y

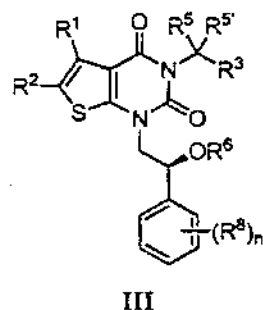
Cada uno de R^7 y $R^{7'}$ es independientemente hidrógeno, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^7 y $R^{7'}$ se toman juntos para formar un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, o un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre y cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un

grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan	grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan	
--	--	--

independientemente de nitrógeno, oxígeno o azufre.	independientemente de nitrógeno, oxígeno o azufre.	
REIVINDICACION 7 El compuesto de conformidad con la reivindicación 1, en donde R ¹ es metilo o trifluorometilo o una sal farmacéuticamente aceptable del mismo.	2)El compuesto de conformidad con la reivindicación 1, en donde R ¹ es metilo o trifluorometilo o una sal farmacéuticamente aceptable del mismo.	La reivindicación 2 aceptada en la patente estadounidense es una limitación de la reivindicación 7 colombiana cuando se menciona: <i>R1 es ... un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno,</i>
REIVINDICACION 4 El compuesto de conformidad con la reivindicación 2, en donde R ² es oxazolilo, o una sal farmacéuticamente aceptable del mismo.	3)El compuesto de conformidad con la reivindicación 2, en donde R ² es oxazolilo, o una sal farmacéuticamente aceptable del mismo.	La reivindicación 4 de la solicitud colombiana establece que R ² es oxazolilo.
REIVINDICACION 6 El compuesto de acuerdo con la reivindicación 2, en donde R ³ es tetrazolilo, -C(O)OR, -C(O)N(R) ₂ , u - OR, o una sal farmacéuticamente aceptable del mismo.	4. El compuesto de acuerdo con la reivindicación 2, en donde R ³ es tetrazolilo, -C(O)OR, -C(O)N(R) ₂ , u - OR, o una sal farmacéuticamente aceptable del mismo.	La reivindicación 6 de la solicitud colombiana establece que R ³ es tetrazolilo, -C(O)OR, -C(O)N(R) ₂ , u - OR.

REIVINDICACION 8

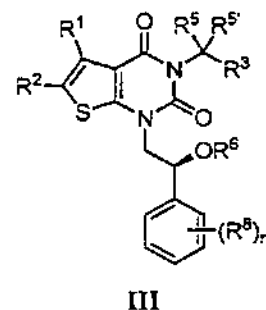
Un compuesto de formula III:



o una sal farmacéuticamente aceptable del mismo, en donde

R¹ es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -

5. Un compuesto de formula III:



o una sal farmacéuticamente aceptable del mismo, en donde

R¹ es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -

La reivindicación 8 de la solicitud colombiana se relaciona con el compuesto de formula III

N(R)C(O)R, - C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; R² es Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5	N(R)C(O)R, - C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; R² es Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5	
---	---	--

heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -

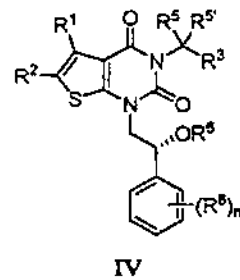
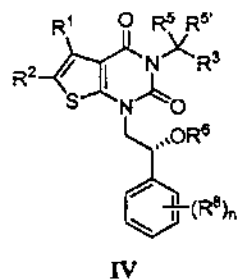
heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -

C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; o R⁵ y R^{5'} se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo; R⁶ es -R, -C(O)N(R)₂ o -C(O)R; cada R⁸ se selecciona independientemente de halógeno, -R, -OR, -SR, -N(R)₂ o deuterio; y cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2	C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; o R⁵ y R^{5'} se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo; R⁶ es -R, -C(O)N(R)₂ o -C(O)R; cada R⁸ se selecciona independientemente de halógeno, -R, -OR, -SR, -N(R)₂ o deuterio; y cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de	
--	---	--

heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.	4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.	
REIVINDICACION 9 Un compuesto de formula IV:	6. Un compuesto de formula IV:	La reivindicación 9 de la solicitud colombiana se relaciona con el compuesto de formula IV



o una sal farmacéuticamente aceptable del mismo, en donde

R¹ es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂RN(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R;

R² es Hy, donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente

o una sal farmacéuticamente aceptable del mismo, en donde

R¹ es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂RN(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R;

R² es Hy, donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente

insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se

insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R³ es hidrógeno, halógeno, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se

selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, - $N(R)_2$, - $N(R)C(O)R$, - $C(O)N(R)_2$, - $N(R)C(O)N(R)_2$, - $N(R)C(O)OR$, - $OC(O)N(R)_2$, - $N(R)SO_2R$, - $SO_2N(R)_2$, - $C(O)R$, - $C(O)OR$, - $OC(O)R$, - $S(O)R$ o - SO_2R ; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R^6 es -R, - $C(O)N(R)_2$ o - $C(O)R$;

cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, - $N(R)_2$ o deuterio; cada R es independientemente hidrógeno, o un grupo opcionalmente

selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, - $N(R)_2$, - $N(R)C(O)R$, - $C(O)N(R)_2$, - $N(R)C(O)N(R)_2$, - $N(R)C(O)OR$, - $OC(O)N(R)_2$, - $N(R)SO_2R$, - $SO_2N(R)_2$, - $C(O)R$, - $C(O)OR$, - $OC(O)R$, - $S(O)R$ o - SO_2R ; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R^6 es -R, - $C(O)N(R)_2$ o - $C(O)R$;

cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, - $N(R)_2$ o deuterio; cada R es independientemente hidrógeno, o un grupo opcionalmente

sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan	sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan	
--	--	--

independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.	independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.	
REIVINDICACION 10 Una composición que comprende un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un portador, adyuvante o vehículo farmacéuticamente aceptable.	7. Una composición que comprende un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un portador, adyuvante o vehículo farmacéuticamente aceptable.	La reivindicación 10 de la solicitud colombiana menciona una composición que comprende el compuesto de la reivindicación 1
REIVINDICACION 7 El compuesto de la reivindicación 1 donde R^5 y $R^{5'}$ son cada uno metilo, o una sal farmacéuticamente aceptable del mismo.	8. El compuesto de la reivindicación 1 donde R^5 y $R^{5'}$ son cada uno metilo, o una sal farmacéuticamente aceptable del mismo.	La reivindicación 8 aceptada en la patente estadounidense es una limitación de la reivindicación 7 colombiana cuando se menciona: cada uno de R^5 y $R^{5'}$ es independientemente -R, ...cada R es un grupo alifático de 1 a 6 átomos de carbono

REIVINDICACION 6 El compuesto de la reivindicación 1 en donde R^3 es $-C(O)OR$ o $-C(O)N(R)_2$, o una sal farmacéuticamente aceptable del mismo.	9. El compuesto de la reivindicación 1 en donde R^3 es $-C(O)OR$ o $-C(O)N(R)_2$, o una sal farmacéuticamente aceptable del mismo.	La reivindicación 6 de la solicitud colombiana define el grupo R^3
REIVINDICACION 6 El compuesto de la reivindicación 9 en donde R^3 es $-C(O)OH$, o una sal farmacéuticamente aceptable del mismo.	10. El compuesto de la reivindicación 9 en donde R^3 es $-C(O)OH$, o una sal farmacéuticamente aceptable del mismo.	La reivindicación 6 de la solicitud colombiana define el grupo R^3



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

24280 7590 09/30/2014
CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER

WEST, THEODORE R

ART UNIT

PAPER NUMBER

1628

DATE MAILED: 09/30/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13673,610	11/09/2012	Geraldine C. Harriman	2009184-0023	1149

TITLE OF INVENTION: ACC INHIBITORS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	12/30/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or **Fax** (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

24280 7590 09/30/2014
CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

Note: A certificate of mailing can only be used for domestic mailings of the fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/673,610	11/09/2012	Geraldine C. Harriman	2009184-0023	1149

TITLE OF INVENTION: ACC INHIBITORS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	12/30/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEST, THEODORE R	1628	514-278000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (for Change of Correspondence Address form PTO/SI/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SI/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. _____
2. _____
3. _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.14. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE (CITY AND STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SI/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____
Typed or printed name _____ Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/673,610	11/09/2012	Geraldine C. Harriman	2009184-0023	1149

24280 7590 09/30/2014
CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER

WEST, THEODORE R

ART UNIT PAPER NUMBER

1628

DATE MAILED: 09/30/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

24

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/673,610	HARRIMAN ET AL.	
	Examiner	Art Unit	
	Theodore R. West	1628	

All participants (applicant, applicant's representative, PTO personnel):

(1) Theodore R. West. (3) _____

(2) Thomas H. McLean. (4) _____

Date of Interview: 19 September 2014.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 24 and 25.

Identification of prior art discussed: None.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The examiner called applicant's representative to inform him that claims 24-25 lack antecedent basis (specifically, the "L1" group). It was therefore agreed that these two claims would be cancelled as set forth in the attached examiner's amendment and thereby place the application in condition for allowance.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Theodore R. West/ Examiner, Art Unit 1628	
---	--

13

Notice of Allowability	Application No. 13/673,610	Applicant(s) HARRIMAN ET AL.	
	Examiner Theodore R. West	Art Unit 1628	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 9/18/2014.
☐ A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 3,4,6-10 and 21-23. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:
a) ☐ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)	5. ☒ Examiner's Amendment/Comment
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____	6. ☐ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	7. ☐ Other _____
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date <u>mailed herewith</u> .	

/Theodore R. West/ Examiner, Art Unit 1628	
---	--

96

Application/Control Number: 13/673,610
Art Unit: 1628

Page 2

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Thomas H. McLean on September 19, 2014.

The application has been amended as follows: **Claims 24-25 have been cancelled.**

Correspondence Information

Any inquiry concerning this communication from the examiner should be directed to Theodore R. West whose telephone number is 571-270-5993. The examiner can normally be reached on Monday to Friday, 8:30 am to 5:00 pm (Eastern Time). The examiner generally welcomes interviews, which preferably should be scheduled in the early afternoon of a Tuesday, Wednesday, or Thursday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen, can be reached at 571-272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of this application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Application/Control Number: 13/673,610

Page 3

Art Unit: 1628

Status information for unpublished applications is only available through Private PAIR.

Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 or 571-272-1000.

/Theodore R. West/
Examiner, Art Unit 1628

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/673,610	HARRIMAN ET AL.	
	Examiner	Art Unit	
	Theodore R. West	1628	

All participants (applicant, applicant's representative, PTO personnel):

(1) Theodore R. West. (3) _____

(2) Thomas H. McLean. (4) _____

Date of Interview: 19 September 2014.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☒ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 24 and 25.

Identification of prior art discussed: None.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The examiner called applicant's representative to inform him that claims 24-25 lack antecedent basis (specifically, the "L1" group). It was therefore agreed that these two claims would be cancelled as set forth in the attached examiner's amendment and thereby place the application in condition for allowance.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Theodore R. West/ Examiner, Art Unit 1628	
---	--

29

Notice of References Cited	Application/Control No. 13/673,610	Applicant(s)/Patent Under Reexamination HARRIMAN ET AL.	
	Examiner Theodore R. West	Art Unit 1628	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	"Thieno[2,3-d]pyrimidine-3-acetic acids. A new class of nonpeptide endothelin receptor antagonists" by Cho et al., Chem. Pharm. Bull. 46, 1724-37 (1998).
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Aviso de Aceptación	Solicitud No. 13/673.610	Solicitante HARRIMAN ET AL	
	Examinador Theodore R. West	Unidad técnica 1628	AIA (Primer inventor en presentar) Estado No

- La FECHA DE ENVÍO de esta comunicación aparece sobre la hoja de cubierta con la dirección correspondiente-

Todas las reivindicaciones son aceptables. EL TRÁMITE SOBRE LOS MERITOS (O RESTOS) SE CIERRA en esta solicitud. Si no se ha incluido aquí (o previamente enviado), un Aviso de Aceptación (PTOL-85) u otra comunicación apropiada será enviada pronto. ESTE AVISO DE ACEPTACIÓN NO ES UN OTORGAMIENTO DE DERECHOS DE PATENTE. Esta solicitud está sujeta a ser retirada de emisión de oficio o por solicitud del solicitante. Ver 37 CFR 1.313 y MPEP 1308.

1. ☒ Esta comunicación se debe responder hasta 9/18/2014.

☐ Una declaración/affidavit según 37 CFR 1.130(b) se presentó el _____.

2. ☐ El solicitante hizo una elección en respuesta a un requerimiento de restricción establecido durante la entrevista el _____; el requerimiento de restricción y la elección han sido incorporados en este oficio.

3. ☒ Las reivindicaciones aceptadas son 3, 4, 6-10 y 21-23. Como resultado de las reivindicaciones aceptadas, usted es elegible para beneficiarse del programa Autopista de trámite de Patentes en una Oficina de propiedad intelectual participante para la solicitud correspondiente. Para mayor información, por favor consulte http://www.uspto.gov/init_events/pph/index.jsp o envíe una consulta a PPHfeedback@uspto.gov.

4. ☐ Se reconoce una reclamación de prioridad extranjera bajo 35 U.S.C. § 119(a)-(d) o (f).
Copias certificadas:
a) ☐ Todas b) ☐ Algunas *c) ☐ ninguna entre:

1. ☐ Copias certificadas de los documentos de prioridad han sido recibidas.

2. ☐ Se han recibido las copias certificadas de los documentos de prioridad en la Solicitud No.

3. ☐ Se han recibido las copias certificadas de los documentos de prioridad en esta solicitud de fase nacional desde la Oficina Internacional (Regla PCT 17.2(a)).

*No se recibieron las copias certificadas: _____.

El solicitante tiene TRES MESES DESDE LA "FECHA DE ENVÍO" de esta comunicación para presentar una respuesta que cumpla con los requerimientos anotados adelante. La falla en cumplir a tiempo resultará en el ABANDONO de esta solicitud.
ESTE PERIODO DE TRES MESES NO ES PRORROGABLE.

5. ☐ DIBUJOS CORREGIDOS (como "hojas de remplazo") deben ser presentados.
☐ Incluyendo los cambios requeridos por las correcciones/Comentarios del Examinador adjuntos o en la Acción Oficial del documento No./fecha de envío _____.

La señal de identificación tal como el número de solicitud (ver 37 CFR 1.84(c)) debe estar escrita en el dibujo al frente (no en el respaldo) de cada hoja. La(s) hoja(s) de remplazo debe(n) estar marcada(s) como tal en el encabezamiento de acuerdo con la norma 37 CFR 1.121(d).

6. ☐ debe presentarse DEPÓSITO DE y/o INFORMACIÓN acerca del depósito de MATERIAL BIOLÓGICO. Nótese el comentario adjunto del Examinador respecto del REQUERIMIENTO DE DEPÓSITO DE MATERIAL BIOLÓGICO.

Anexo(s)

1. ☒ Aviso de las Referencias Citadas (PTO-892)
2. ☐ Declaraciones de información de divulgación (PTO/SB/08)
3. ☐ Comentario del Examinador respecto del Requisito de Depósito de Material Biológico
4. ☒ Resumen de la entrevista (PTO-413).
Documento No/ Fecha de envío enviado aquí.
5. ☒ Corrección/Comentario del Examinador
6. ☐ Declaración del Examinador de las Razones para la Aceptación
7. ☐ Otros _____.

/Theodore R. West/
Examinador, Unidad Técnica 1628

Número de Solicitud/Control: 13/673.610

Página 2

Unidad Técnica: 1628

CORRECCIÓN DEL EXAMINADOR

Una corrección del Examinador aparece enseguida para el registro. Si los cambios o adiciones son inaceptables para el Solicitante, se puede presentar una modificación de acuerdo con la 37 CFR 1.312. Para asegurar la consideración de tal modificación, DEBE presentarse no más tarde que el pago de la tasa de emisión.

La autorización para esta corrección del Examinador fue dada en una entrevista telefónica con Thomas H. McLean el 19 de septiembre de 2014.

La solicitud fue modificada como sigue: **Las reivindicaciones 24-25 fueron eliminadas.**

Información de Correspondencia

Cualquier inquietud relacionada con esta comunicación del Examinador debe ser dirigida a Theodore R. West cuyo número de teléfono es 571-270-5993. El Examinador puede normalmente encontrarse de lunes a viernes, entre 8:30 am a 5:00 pm (Hora Este). El examinador en general prefiere las entrevistas, que hayan sido programadas temprano en la tarde de un Martes, Miércoles o Jueves. Si los intentos de encontrar al examinador por teléfono son infructuosos, el supervisor del examinador, Winston Shen, puede ser localizado al 571-272-3157. El número de fax de la organización en donde esta solicitud o proceso fue asignado es 571-273-8300.

La información con respecto al estado de esta solicitud puede ser obtenida en el Sistema de Recuperación de Información de Solicitudes de Patente (PAIR). La información del estado de solicitudes publicadas puede obtenerse de un PAIR Privado o un PAIR Público.

Número de Solicitud/Control: 13/673.610

Página 3

Unidad Técnica: 1628

La información de solicitudes no publicadas solo está disponible por la PAIR Privada. Si tiene preguntas sobre el acceso al sistema PAIR privado, por favor póngase en contacto con el Centro de Negocios Electrónicos (EBC) al teléfono 866-217-9197. Si usted desea ayuda de un Representante De Servicio al Cliente de la USPTO o acceso al sistema automatizado de información, llame al 800-786-9199 o al 571-272-1000.

/Theodore R. West/

Examinador, Unidad Técnica 1628

Resumen de la entrevista iniciada por el Examinador	Solicitud No. 13/673.610	Solicitante HARRIMAN ET AL	
	Examinador Theodore R. West	Unidad técnica 1628	AIA (Primer inventor en presentar) Estado No

Todos los participantes (solicitante, representante del solicitante, personal de la PTO):
 (1) Theodore R. West. (3) _____
 (2) Thomas H. McLean. (4) _____

Fecha de la entrevista: 19 de septiembre de 2014.

Tipo: ☒ Telefónica ☐ Videoconferencia
☐ Personal [Copia dada al: ☐ solicitante ☐ Representante del Solicitante]

Prueba mostrada o demostración conducida: ☐ Si ☐ No.

En caso positivo, de una breve descripción: _____.

Asuntos Discutidos ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☒ Otros
 (Para cada una de las cajas marcadas, describa por favor abajo el asunto y descripción detallada de la discusión)

Reivindicaciones discutidas: 24 y 25

Identificación del arte previo discutido: Ninguno

Sustancia de la entrevista
 (Para cada asunto discutido, suministre una descripción detallada e indique si se llegó a un acuerdo. Algunos tópicos pueden incluir: identificación o clarificación de una referencia o una porción de esta, interpretación de la reivindicación, modificaciones propuestas, argumentos de cualesquier referencias aplicadas, etc...)

El examinador llamó al representante del solicitante para informarle que las reivindicaciones 24-25 carecen de base de antecedentes (específicamente, el grupo "L1"). Se acordó por lo tanto que estas dos reivindicaciones deberían ser eliminadas como se estableció en las modificaciones del examinador y por lo cual la solicitud queda en condición de aceptación.

Instrucciones de registro para el solicitante: no es necesario que el solicitante suministre un registro separado de la sustancia de la entrevista.

Instrucciones de registro para el examinador: Los examinadores deben resumir la sustancia de cualquier entrevista registrada. Un registro completo y apropiado de la sustancia de una entrevista debe incluir los elementos listados en la MPEP 713.04 para un completo y apropiado registro incluyendo la identificación de la idea clave general de cada argumento o asunto discutido, una indicación general de cualesquier otras materias pertinentes discutidas respecto de la patentabilidad y los resultados generales o conclusión de la entrevista, incluir una indicación en cuanto a si se llegó o no a un acuerdo sobre los asuntos surgidos.

☐ Anexo(s)

BB

/Theodore R. West/ Examinador, Unidad Técnica 1628	
---	--

Resumen de la entrevista

Doc. No. 20140919

ab

US 8,969,557 B2 -- ALLOWED CLAIMS

1. (Canceled).

2. (Canceled).

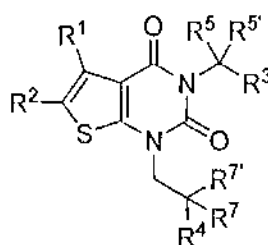
3. (Allowed) The compound according to claim 7, wherein R^1 is methyl or trifluoromethyl, or a pharmaceutically acceptable salt thereof.

4. (Allowed) The compound according to claim 3, wherein R^2 is oxazolyl, or a pharmaceutically acceptable salt thereof.

5. (Canceled)

6. (Allowed). The compound according to claim 3, wherein R^3 is tetrazolyl, $-C(O)OR$, $-C(O)N(R)_2$, or $-OR$, or a pharmaceutically acceptable salt thereof.

7. (Allowed) A compound of formula II:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, $-OR$, $-SR$, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, or $-SO_2R$;

R^2 is Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10

membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

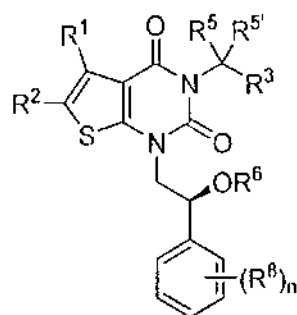
R^4 is an optionally substituted phenyl or naphthyl ring;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO₂R; or R^5 and $R^{5'}$ are taken together to form a cyclopropyl, cyclobutyl, or oxetanyl group;

each of R^7 and $R^{7'}$ is independently hydrogen, -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO₂R; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

8. (Allowed) A compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO₂R;

R^2 is Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO₂R; or R^5 and $R^{5'}$ are taken together to form a cyclopropyl, cyclobutyl, or oxetanyl group;

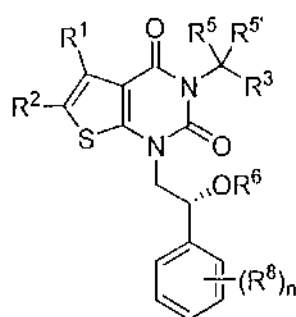
R^6 is -R, -C(O)N(R)₂, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, -N(R)₂ or deuterium;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated

or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and
n is 0-5.

9. (Allowed) A compound of formula IV:



IV

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO₂R;

R^2 is Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO₂R; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

R^6 is -R, -C(O)N(R)₂, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, -N(R)₂ or deuterium;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

n is 0-5.

10. **(Allowed)** A composition comprising a compound according to claim 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

11-20. **(Canceled)**.

21. **(Allowed)** The compound of claim 7 wherein R^5 and $R^{5'}$ are each methyl, or a pharmaceutically acceptable salt thereof.

22. **(Allowed)** The compound of claim 7 wherein R^3 is -C(O)OR or -C(O)NR₂, or a pharmaceutically acceptable salt thereof.

23. **(Allowed)** The compound of claim 22 wherein R^3 is -C(O)OH, or a pharmaceutically acceptable salt thereof.

41

24. (Canceled)

25. (Canceled)

11

REIVINDICACIONES ACEPTADAS US 8,969,557

1. (Cancelada)

2. (Cancelada)

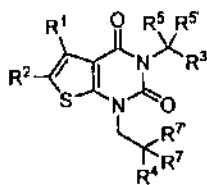
3. (Aceptada) El compuesto de conformidad con la reivindicación 7, en donde R^1 es metilo o trifluorometilo o una sal farmacéuticamente aceptable del mismo.

4. El compuesto de conformidad con la reivindicación 3, en donde R^2 es oxazolilo, o una sal farmacéuticamente aceptable del mismo.

5. (Cancelada)

6. (Aceptada) El compuesto de acuerdo con la reivindicación 3, en donde R^3 es tetrazolilo, $-C(O)OR$, $-C(O)N(R)_2$, u $-OR$, o una sal farmacéuticamente aceptable del mismo.

7. (Aceptada) Un compuesto de formula II



o una o una sal farmacéuticamente aceptable del mismo, en donde:
 R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R;

R^2 es Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan

independientemente de nitrógeno, oxígeno o azufre;

R^4 es un anillo fenilo o naftilo opcionalmente sustituido;

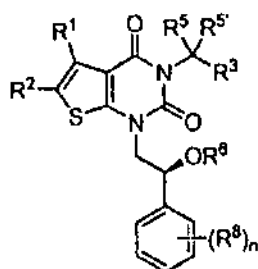
cada uno de R^5 y $R^{5'}$ es independientemente $-R$, $-OR$, $-SR$, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo; y

Cada uno de R^7 y $R^{7'}$ es independientemente hidrógeno, $-R$, $-OR$, $-SR$, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^7 y $R^{7'}$ se toman juntos para formar un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, o un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre y

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de

AG

8. (Aceptada) Un compuesto de formula III:



III

o una sal farmacéuticamente aceptable del mismo, en donde

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R;

R^2 es H_y , en donde H_y se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se

seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

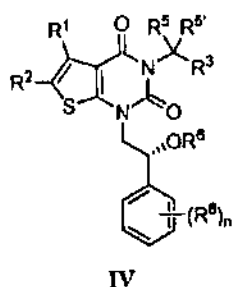
R^6 es -R, -C(O)N(R)₂ o -C(O)R;

cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, -N(R)₂ o deuterio; y

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o

parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.

9. ((**Aceptada**) Un compuesto de formula IV:



o una sal farmacéuticamente aceptable del mismo, en donde R¹ es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂RN(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -

A

S(O)R o -SO₂R;

R² es Hy, donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R³ es hidrógeno, halógeno, -CN, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R⁵ y R^{5'} es independientemente -R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; o R⁵ y R^{5'} se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R⁶ es -R, -C(O)N(R)₂ o -C(O)R;

cada R⁸ se selecciona independientemente de halógeno, -R, -OR, -SR, -N(R)₂ o deuterio;

49

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.

10. **(Aceptada)** Una composición que comprende un compuesto de conformidad con la reivindicación 7, o una sal farmacéuticamente aceptable del mismo, y un portador, adyuvante o vehículo farmacéuticamente aceptable.

11-20. **(Cancelada)**.

21. **(Aceptada)** El compuesto de la reivindicación 7 donde R^5 y $R^{5'}$ son cada uno metilo, o una sal farmacéuticamente aceptable del mismo.

22. **(Aceptada)** El compuesto de la reivindicación 7 en donde R^3 es $-C(O)OR$ o $-C(O)N(R)_2$, o una sal farmacéuticamente aceptable del mismo.

23. **(Aceptada)** El compuesto de la reivindicación 22 en donde R^3 es $-C(O)OH$, o una sal farmacéuticamente aceptable del mismo.

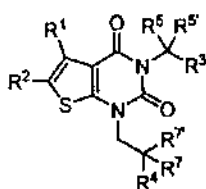
24. **(Cancelada)**.

25. **(Cancelada)**.

REIVINDICACIONES ACEPTADAS RENUMERADAS Y ORGANIZADAS DE

US 8,969,557

1) Un compuesto de formula II



II

o una o una sal farmacéuticamente aceptable del mismo, en donde:
 R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R;

R^2 es Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan

52

independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, -
N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -
N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -
OC(O)R, -S(O)R, -SO₂R, -B(OH)₂ o un anillo opcionalmente
sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6
miembros que tiene 1 a 4 heteroátomos que se seleccionan
independientemente de nitrógeno, oxígeno o azufre;

R^4 es un anillo fenilo o naftilo opcionalmente
sustituido;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR,
-N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -
OC(O)N(R)₂, -N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R
o -SO₂R; o R^5 y $R^{5'}$ se toman juntos para formar un grupo
ciclopropilenilo, ciclobutilenilo u oxetanilo; y

Cada uno de R^7 y $R^{7'}$ es independientemente hidrógeno, -
R, -OR, -SR, -N(R)₂, -N(R)C(O)R, -
C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -
SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R; o R^7 y $R^{7'}$ se
toman juntos para formar un anillo carbocíclico monocíclico
saturado o parcialmente insaturado de 3 a 8 miembros, o un anillo
heterocíclico monocíclico saturado o parcialmente insaturado de 4
a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan
independientemente de nitrógeno, oxígeno o azufre y

83

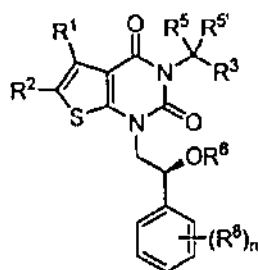
cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

2. El compuesto de conformidad con la reivindicación 1, en donde R^1 es metilo o trifluorometilo o una sal farmacéuticamente aceptable del mismo.

3. El compuesto de conformidad con la reivindicación 2, en donde R^2 es oxazolilo, o una sal farmacéuticamente aceptable del mismo.

4. El compuesto de acuerdo con la reivindicación 2, en donde R^3 es tetrazolilo, $-C(O)OR$, $-C(O)N(R)_2$, u $-OR$, o una sal farmacéuticamente aceptable del mismo.

5. Un compuesto de formula III:



III

o una sal farmacéuticamente aceptable del mismo, en donde

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -

OR, -SR, -N(R)₂, -N(R)C(O)R, -

C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -

N(R)SO₂R, -SO₂N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R;

R^2 es H_y , en donde H_y se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático

bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{SO}_2\text{R}$, $\text{SO}_2\text{N}(\text{R})_2$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{S}(\text{O})\text{R}$, $-\text{SO}_2\text{R}$, $-\text{B}(\text{OH})_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente $-\text{R}$, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{SO}_2\text{R}$, $-\text{SO}_2\text{N}(\text{R})_2$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{S}(\text{O})\text{R}$ o $-\text{SO}_2\text{R}$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

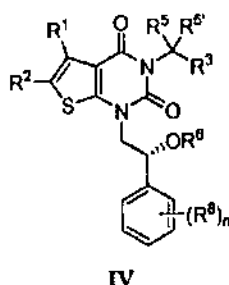
R^6 es $-\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$ o $-\text{C}(\text{O})\text{R}$;

cada R^8 se selecciona independientemente de halógeno, $-\text{R}$, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$ o deuterio; y

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan

independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.

6. Un compuesto de formula **IV**:



o una sal farmacéuticamente aceptable del mismo, en donde R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, -N(R)₂, -N(R)C(O)R, -C(O)N(R)₂, -N(R)C(O)N(R)₂, -N(R)C(O)OR, -OC(O)N(R)₂, -N(R)SO₂R, -SO₂RN(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o -SO₂R;

R^2 es Hy, donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan

53

independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente $-R$, $-OR$, $-SR$, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R^6 es $-R$, $-C(O)N(R)_2$ o $-C(O)R$;

cada R^8 se selecciona independientemente de halógeno, $-R$, $-OR$, $-SR$, $-N(R)_2$ o deuterio;

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo

carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y n es 0 a 5.

7. Una composición que comprende un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un portador, adyuvante o vehículo farmacéuticamente aceptable.

8. El compuesto de la reivindicación 1 donde R^5 y $R^{5'}$ son cada uno metilo, o una sal farmacéuticamente aceptable del mismo.

9. El compuesto de la reivindicación 1 en donde R^3 es $-C(O)OR$ o $-C(O)N(R)_2$, o una sal farmacéuticamente aceptable del mismo.

10. El compuesto de la reivindicación 9 en donde R^3 es $-C(O)OH$, o una sal farmacéuticamente aceptable del mismo.

Thieno[2,3-*d*]pyrimidine-3-acetic Acids A New Class of Nonpeptide Endothelin Receptor Antagonists

Nobuo CHO,*^{a,c} Yoshi NARA,^a Mioko HARADA,^a Tsukasa SUGO,^a Yasushi MASUDA,^a Akemi ABE,^b Keiji KUSUMOTO,^b Yasuaki ITOH,^a Tetsuya OUTAKI,^a Toshifumi WATANABE,^b and Shuichi FURUYA^a

Discovery Research Division, Takeda Chemical Industries, Ltd.,^a Wadai 10, Tsukuba-shi, Ibaraki 300-4293, Japan and Pharmaceutical Research Division, Takeda Chemical Industries, Ltd.,^b 17-85, Jusohommachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan. Received July 13, 1998; accepted July 31, 1998

On the basis of structural information for the cyclic hexapeptide endothelin (ET) receptor antagonist, TAK-044, a series of thieno[2,3-*d*]pyrimidine-2,4-dione derivatives bearing a carboxyl group and aromatic rings that were important for receptor binding were designed, synthesized, and evaluated for ET receptor binding affinities and inhibitory activities against ET-induced vasoconstriction.

Optimization of each substituent in the thieno[2,3-*d*]pyrimidine ring led to the discovery of a novel and potent nonpeptide ET receptor antagonist, 6-(4-methoxymethoxyphenyl)-5-methylsulfonylaminoethyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetic acid (32g), which binded to human ET_A and ET_B receptor subtypes with affinities (IC₅₀) of 7.6 and 180 nM, respectively.

Compound 32g effectively antagonized ET-induced vasoconstriction and the inhibitory effect mediated by the ET_B receptor was more potent than that of bosentan, while the inhibitory effect mediated by the ET_A receptor was slightly less potent than that of bosentan.

Key words: thieno[2,3-*d*]pyrimidine-3-acetic acid; endothelin receptor antagonist; endothelin receptor binding affinity; ET-induced vasoconstriction; bosentan

The discovery of endothelin-1 (ET-1), an extremely potent and long-acting vasoconstrictor peptide comprised of 21 amino acid residues, led to considerable pathophysiologic interest.¹⁾ ET-1 is one member of a family of isopeptides, including ET-2 and ET-3,²⁾ that are structurally and functionally related to the cardiotoxic sarafotoxins.³⁾ In addition, further studies have revealed the existence of two receptor subtypes designated ET_A and ET_B,⁴⁾ which are both G protein-coupled receptors (GPCR). The ET_A receptor binds ET-1 and ET-2 with greater affinity than ET-3, and mediates vasoconstriction^{5,6)} and smooth muscle proliferation.⁷⁾ In contrast, the ET_B receptor does not discriminate between ET-1, ET-2, and ET-3, and mediates both vasoconstriction⁸⁾ and vasodilation.⁹⁾

Due to their peculiar pharmacological effects, ETs are thought to play a major role in chronic diseases such as myocardial infarction, heart failure, renal failure, pulmonary hypertension, and subarachnoid hemorrhage.¹⁰⁾ Therefore, blockade of the ET receptors might be therapeutically effective in the treatment of the above conditions.

A large number of peptide ET receptor antagonists, represented by FR-139317¹¹⁾ and BQ-123,¹²⁾ have been reported. Moreover, nonpeptide ET receptor antagonists have been reported during the course of our work described in this paper. These include Ro 46-2005,¹³⁾ Ro 47-0203 (1, bosentan),¹⁴⁾ BMS 182874,¹⁵⁾ SB 209670,¹⁶⁾ A-127722,¹⁷⁾ L-749329,¹⁸⁾ and PD 156707.¹⁹⁾

In our search for a novel nonpeptide ET antagonist, we first focused on the rigidity of the cyclic hexapeptide ET antagonist TAK-044 (2),²⁰⁾ which results from the presence of β -turn and γ -turn structures. Introduction of crucial functional moieties for ET receptor binding, i.e. a carboxyl group and aromatic rings,²¹⁾ onto a bicyclic heterocycle 'scaffold' which mimics the fixed main chain of TAK-044, provides nonpeptide ET receptor ligands. Using the same strategy, we

have also discovered a novel, potent, and orally active nonpeptide LIR1 receptor antagonist.²²⁾ In addition, several heterocyclic compounds bearing important functional groups for receptor binding have been described in the literature as synthetic nonpeptide antagonists of GPCRs, such as angiotensin II,²³⁾ cholecystokinin,²⁴⁾ substance P,²⁵⁾ and vasopressin.²⁶⁾

The thieno[2,3-*d*]pyrimidine-2,4-dione nucleus, bearing a phenyl ring attached to the thiophene ring was selected as a bicyclic heterocycle scaffold. Among the early compounds synthesized based on this structure, the thieno[2,3-*d*]pyrimidine-3-acetic acid derivative (7d), bearing a *p*-methoxyphenyl group at the 6-position, was found to be a lead compound possessing micromolar binding affinities for cloned human ET receptors (Fig. 1).

In this paper, we describe our synthetic studies starting from the lead compound (7d) which culminated in the discovery of a new class of potent nonpeptide ET antagonists, represented by, 6-(4-methoxymethoxyphenyl)-5-methylsulfonylaminoethyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetic acid (32g), 5-ethylsulfonylaminoethyl-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetic acid (32h), and 6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-2,4-dioxo-5-propylsulfonylaminoethyl-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetic acid (32i).

Chemistry The thieno[2,3-*d*]pyrimidine-3-acetic acids bearing various alkyl and aralkyl groups at the 1-position (7a-m) were generally synthesized by the route shown in Chart 1. The 2-aminothiophene derivatives 4a-c were prepared from the corresponding phenylacetone 3a-c using the previously reported procedure.²⁷⁾ In addition, compound 4d was obtained from 4c by catalytic hydrogenation over 10% palladium-charcoal. Compounds 4a, 4b, and 4d were con-

* To whom correspondence should be addressed.

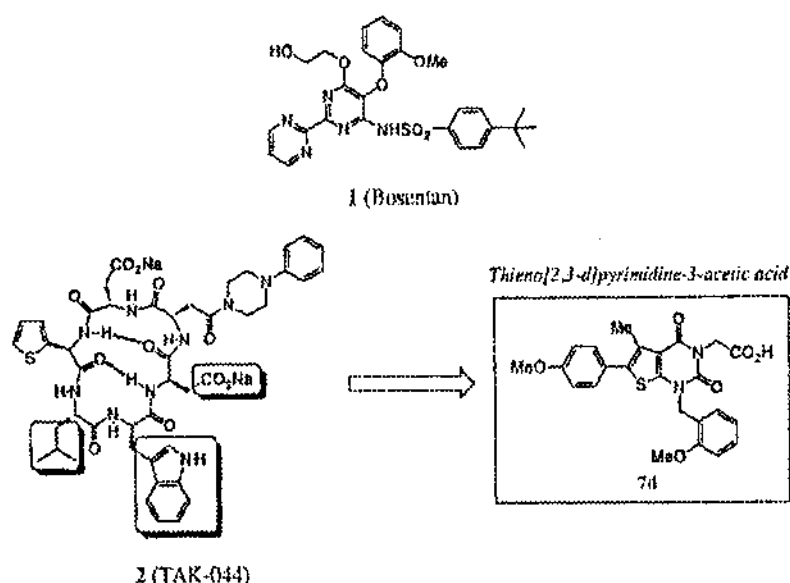


Fig. 1

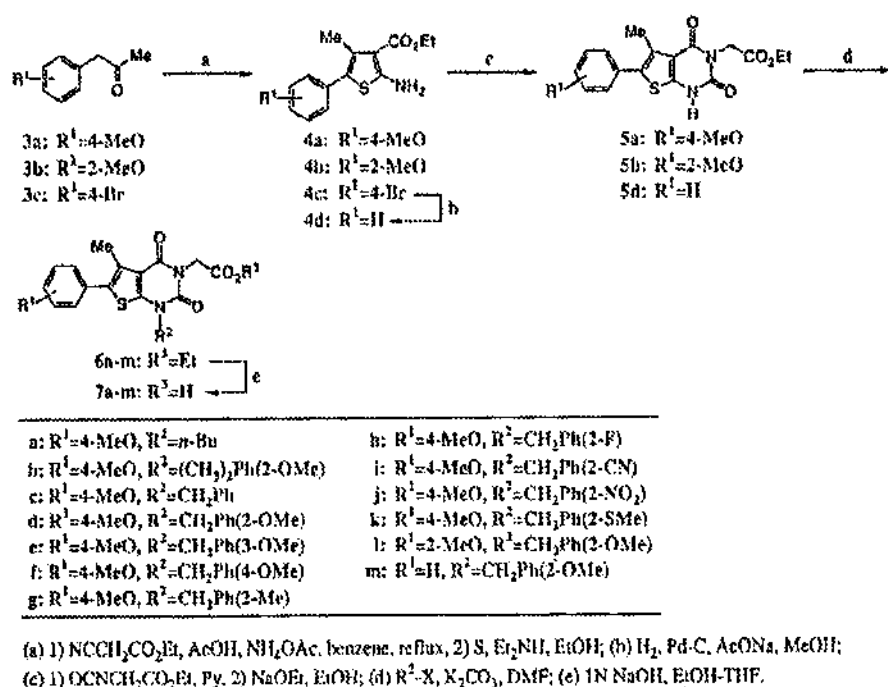


Chart 1

verted to the thieno[2,3-d]pyrimidine-2,4-dione derivatives 5a, 5b, and 5d by reaction with ethyl isocyanatoacetate, followed by cyclization with sodium ethoxide. After alkylation of 5a, 5b, and 5d at the 1-position in the presence of potassium carbonate, saponification of the ethyl ester group produced the carboxylic acids 7a---m. The nitro compound 6j was reduced with iron powder-acetic acid, formylated with acetic formic anhydride,²⁸⁾ and then reacted with borane-methyl sulfide complex²⁹⁾ to afford 8, which was hydrolyzed to yield the methylamino derivative 9. Oxidation of the methylthio group of 6k with *m*-chloroperbenzoic acid (1 or 2 equivalents) and subsequent alkaline hydrolysis furnished 11a, b (Chart 2).

Using the general procedure shown in Chart 1, it would be

cumbersome to synthesize the substituted phenyl derivatives at the 6-position starting from the corresponding phenylacetones. Thus, a Suzuki aryl-coupling reaction³⁰⁾ with an arylboronic acid and a palladium catalyst was examined as an alternative method. The key intermediates 14a, b were prepared by reaction of 13 with 1 eq of *N*-bromosuccinimide (NBS) and subsequent alkylation. Compound 13 was readily obtained from the 2-aminothiophene 12. The 6-bromo derivatives 14a, b reacted with arylboronic acids in the presence of tetrakis(triphenylphosphine)palladium (0) and 2 M aqueous sodium carbonate to produce 15a, b, which were converted to the carboxylic acids 16a, b by alkaline hydrolysis (Chart 3). The arylboronic acids were prepared from the corresponding bromobenzene derivatives by treatment with *n*-

butyllithium, followed by reaction with triisopropyl borate and subsequent acidic hydrolysis.³¹⁾

The synthesis of *para*-substituted phenyl derivatives at the

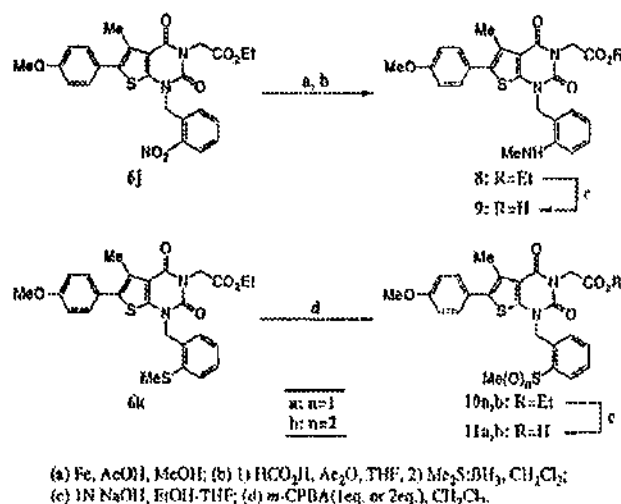


Chart 2

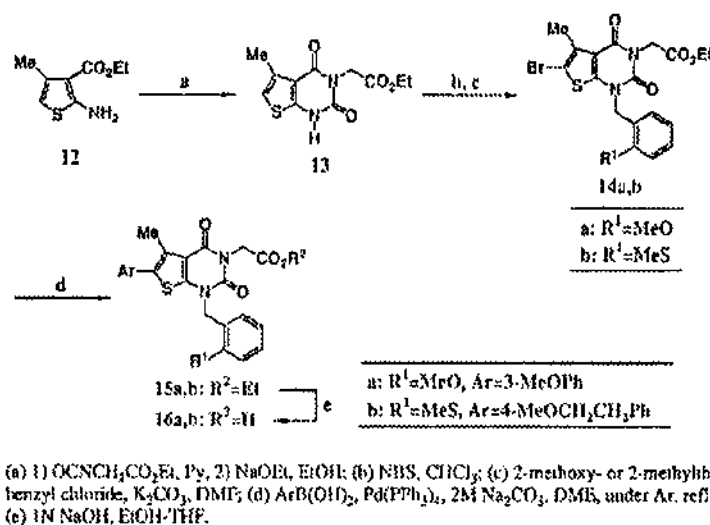


Chart 3

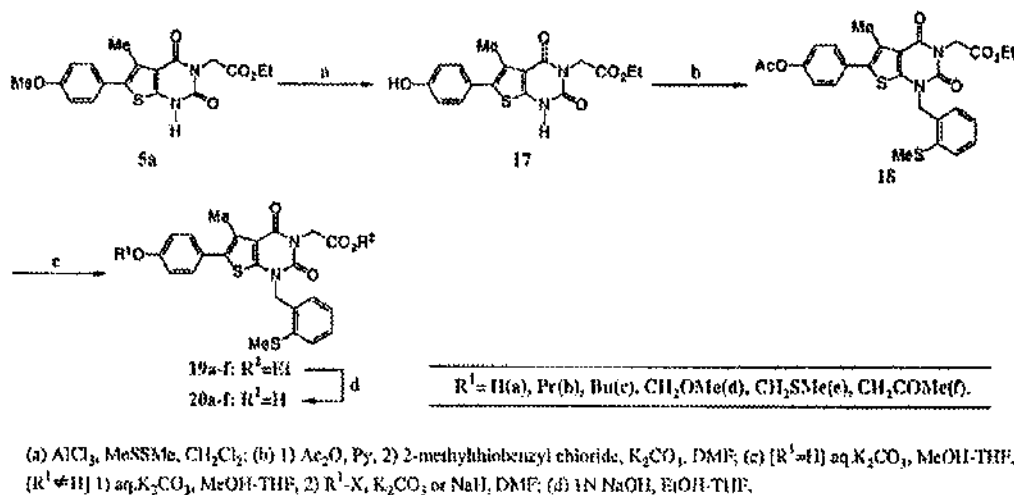


Chart 4

6-position was achieved by the procedures shown in Charts 4 and 5. After demethylation of 5a with aluminum chloride, acetylation of 17 and subsequent benzylation yielded 18. Compound 18 was then treated with aqueous potassium carbonate, followed by alkylation to afford 19a—f (Chart 4). Compound 22 was obtained by the Friedel-Crafts acylation of 5d, followed by benzylation. In addition, nitration of 5d with sodium nitrate and concentrated sulfuric acid produced 24, which was converted to the amide 26 by benzylation, reduction, and subsequent acylation (Chart 5). Saponification of these esters 19a—f, 22, 25, and 26 furnished the corresponding carboxylic acids 20a—f, 23, 27, and 28.

Chart 6 shows the route used for the preparation of 5-acyl- and 5-sulfonylaminomethyl derivatives. After bromination of 19d with NBS in the presence of 2,2'-azobis(isobutyronitrile), the aminomethyl derivative 29 was obtained by reaction with potassium phthalimide and subsequent hydrazinolysis (Gabriel synthesis). Compound 29 was reacted with acid chlorides, sulfonyl chlorides, and isocyanate to give 30a—j. Compound 33 was prepared from 30g by reaction with iodomethane in the presence of sodium hydride. The esters 29, 30a—j, and 33 were converted to the carboxylic acids 31,

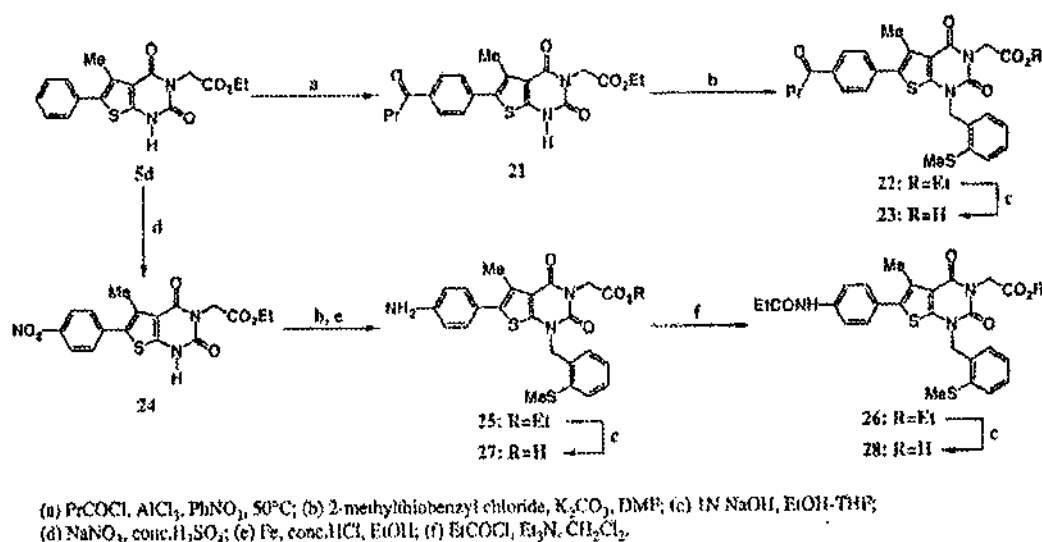


Chart 5

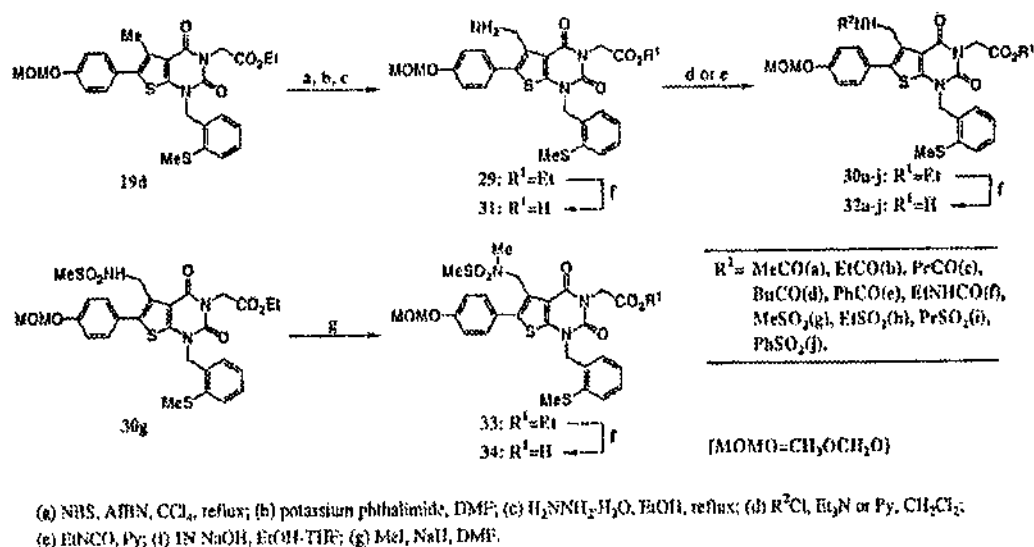


Chart 6

32a—j, and 34 by alkaline hydrolysis.

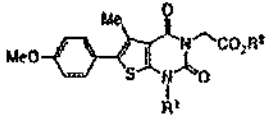
Biology All the compounds prepared were evaluated for inhibition of [^{125}I]ET-1 binding to cloned human ET_A and ET_B receptors. The *in vitro* antagonistic activities of compounds exhibiting high ET receptor binding affinities were examined for the ability to inhibit the constriction of ring preparations of porcine coronary artery induced by ET-1 at 3 nM and that of vein preparations induced by sarafotoxin S6c, an ET_B selective agonist, at 1 nM .

Results and Discussion

First, the ethyl ester (6d) was prepared in order to confirm the role of the carboxylic function in the initial lead 7d as the recognition site to interact with ET receptors. Subsequently, we then carried out modification of the substituent at the 1-position of 7d (7a—k, 9, 11a, b). The results are summarized in Table 1. Ester (6d) had insignificant binding to both ET_A and ET_B receptors at the concentration examined, whereas the corresponding acid (7d) exhibited significant binding affinities with IC_{50} values of $1.9\text{ }\mu\text{M}$ for the ET_A re-

ceptor and $12\text{ }\mu\text{M}$ for the ET_B receptor. These results demonstrate that the carboxylic acid moiety at the 3-position was important for ET receptor binding. With respect to the substituents at the 1-position, butyl (7a) and *o*-methoxyphenethyl (7b) derivatives were less potent than the *o*-methoxybenzyl derivative (7d). Therefore, substituted benzyl derivatives were next examined. Deletion of the *o*-methoxy moiety on the phenyl ring of 7d (7c) caused *ca.* 5-fold decrease in the affinities for both ET_A and ET_B receptors. Transposition of the methoxy group of 7d into the *meta* position (7e) maintained comparable affinities to 7d, but transposition to the *para* position (7f) decreased binding affinities. In the series of *ortho*-substituted benzyl derivatives, electron-donating substituents tended to improve binding affinities. Methyl (7g) and methylamino (9) derivatives were almost equipotent to 7d. Moreover, the methylthio derivative (7k) had 3-fold higher affinity compared with 7d. On the other hand, bulky and electron-withdrawing substituents, such as methylsulfinyl (11a) and methylsulfonyl (11b) derivatives, reduced affinities.

Table 1. SAR of Thieno[2,3-d]pyrimidine-3-acetic Acids at the 1- and 3-Positions



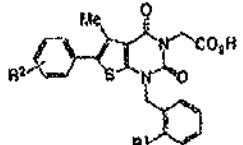
Compd.	R ¹	R ²	IC ₅₀ (μM) ^{a)}	
			ET _A (S19)	ET _B (S19)
7a	Bu	H	160	230
7b		H	31	76
7c	H	H	11	40
7d	2-OMe	H	1.9	12
6d	2-OMe	Et	>20	>20
7e	3-OMe	H	5.1	16
7f	4-OMe	H	110	120
7g	2-Me	H	1.8	14
7h	2-F	H	5.1	20
7i	2-CN	H	13	63
7j	2-NO ₂	H	18	67
9	2-NHMe	H	1.2	6
7k	2-SMe	H	0.71	6.8
11a	2-SOMe	H	170	440
11b	2-SOMe	H	100	190

a) All data are expressed as means of three or more determinations.

Table 2 shows the effects of substituents on the phenyl group at the 6-position on receptor affinities. In the series of 1-position *o*-methoxybenzyl derivatives, 6-(*p*-methoxyphenyl) derivative (7d) was the most potent compound, in comparison with 6-phenyl (7m), 6-(*o*-methoxyphenyl) (7i), and 6-(*m*-methoxyphenyl) (16a) derivatives. This result led us to examine 6-(*p*-substituted)phenyl derivatives. In the series of 1-position *o*-methylthiobenzyl derivatives, introduction of a *p*-alkoxy group into the 6-phenyl ring enhanced binding affinities. The affinities increased in the order of hydroxy (20a) < methoxy (7k) < butoxy (20c) < propoxy (20b). Replacement of the 2-methylene moiety in the 4-propoxy group of 20b with an oxygen (20d, IC₅₀ values of 0.085 μM for the ET_A receptor and 0.92 μM for the ET_B receptor) or a sulfur atom (20e, IC₅₀ values of 0.066 μM for the ET_A and 0.66 μM for the ET_B) markedly enhanced binding affinities. However, replacement of the phenolic oxygen of 20d with methylene (16b), or the methoxyl oxygen of 20d with a carbonyl moiety (20f) resulted in loss of this effect. Moreover, ketone (23) and amide (28) were 10- and 480-fold less potent than 20b in the affinity for the ET_A receptor, respectively. These results revealed that both the phenolic oxygen and the other oxygen or sulfur atom of 20d and 20e were important for high binding affinities, presumably due to the hydrogen bond accepting characteristic of the methoxymethoxy and methylthiomethoxy groups. In addition, the *p*-methoxymethoxy and *p*-methylthiomethoxy groups on the 6-phenyl ring were stable and no degradation of 20d and 20e was observed in this binding experiment [Tris-HCl, pH=7.2] (data not shown).

The structure-activity relationship (SAR) of the sub-

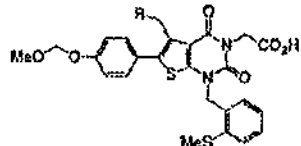
Table 2. SAR of Thieno[2,3-d]pyrimidine-3-acetic Acids at the 1- and 6-Positions



Compd.	R ¹	R ²	IC ₅₀ (μM) ^{a)}	
			ET _A (S19)	ET _B (S19)
7m	MeO	H	12	39
7d	MeO	4-OMe	1.9	12
16a	MeO	3-OMe	130	94
7l	MeO	2-OMe	90	130
7k	MeS	4-OMe	0.71	6.8
20a	MeS	4-OH	1.6	11
20b	MeS	4-OPr	0.25	2.6
20c	MeS	4-OBu	0.49	4.5
20d	MeS	4-OCH ₂ OMe	0.085	0.92
20e	MeS	4-OCH ₂ SMe	0.066	0.66
20f	MeS	4-OCH ₂ COMe	0.4	7.1
23	MeS	4-COPr	2.4	13
16b	MeS	4-CH ₂ CH ₂ OMe	1.9	11
27	MeS	4-NH ₂	4.0	12
28	MeS	4-NHCOEt	120	77

a) All data are expressed as means of three or more determinations.

Table 3. SAR of Thieno[2,3-d]pyrimidine-3-acetic Acids at the 5-Position



Compd.	R	IC ₅₀ (μM) ^{a)}	
		ET _A (S19)	ET _B (S19)
20d	H	0.085	0.92
31	NH ₂	0.62	3.8
32a	NHCOMe	0.018	0.57
32b	NHCOEt	0.047	1.0
32c	NHCOPr	0.036	0.7
32d	NHCOBu	0.18	1.6
32e	NHCOPh	1.5	0.54
32f	NHCONHEt	0.069	2.0
32g	NHSO ₂ Me	0.0076	0.10
32h	NHSO ₂ Et	0.0061	0.054
32i	NHSO ₂ Pr	0.022	0.047
32j	NHSO ₂ Ph	2.1	3.7
34	N(Me)SO ₂ Me	0.42	0.13

a) All data are expressed as means of three or more determinations.

stituents at the 5-position was investigated, whereby the *p*-methoxymethoxyphenyl moiety was used as the substituent at the 6-position, which exhibited apparent *in vitro* antagonistic activities as discussed later (Table 3). Although introduction of an amino moiety to the 5-methyl group of 20d (31) attenuated binding affinities, acylation of the amino-methyl group of 31 (32a–e) tended to enhance activities. Introduction of a larger acyl group, as in the case of 32d and 32e, tended to decrease activities. In addition, the ethylureido derivative (32f) was 2-fold less potent than the butyrylamino

Table 4. *In Vitro* Antagonistic Activities and Binding Affinities of Thieno[2,3-*d*]pyrimidine-3-acetic Acids for the ET Receptor Subtypes

Compd.	Relaxation (%)								Binding affinity	
	Artery (ET-1 3 nM) ^{a)}				Vein (S6c 1 nM) ^{b)}				IC ₅₀ (nM) ^{c)}	
	0.01	0.1	1	10	0.01	0.1	1	10	ET _A	ET _B
TAK-044	67	87			54	98			0.82	118
Bosentan		0	62	93		28	48	88	7	240
20d			3 ^{e)}	49 ^{e)}			58 ^{e)}	99 ^{e)}	85	920
20e				0 ^{e)}			66 ^{e)}		66	660
32g			36 ^{e)}			66 ^{e)}	100 ^{e)}		7.6	100
32h			33 ^{e)}			53 ^{e)}	98 ^{e)}		6.1	54
32i			0 ^{e)}			66 ^{e)}	99 ^{e)}		22	47

All data are expressed as means of three or more determinations. ^{a)} Percentage values in relaxation of isolated porcine coronary artery constricted by ET-1 at 3 nM. ^{b)} Percentage values in relaxation of isolated porcine coronary vein constricted by sarafotoxin S6c at 1 nM. ^{c)} Concentrations of the compound used in these experiments. ^{d)} IC₅₀ values of [¹²⁵I]ET-1 binding to the cloned human ET_A and ET_B receptors (S19). ^{e)} These data were obtained using the corresponding potassium salts of the test compounds.

derivative (32c). In the case of sulfonamide derivatives, a tendency similar to the results described for the acylamino derivatives was observed. Small alkyl sulfonamides (32g–i) were more potent than 20d, whereas the phenylsulfonlamino derivative (32j) was less potent than 20d. Furthermore, *N*-methylation of the methylsulfonlamino moiety (34) decreased affinity for the ET_A receptor compared with 32g. The methylsulfonlamino (32g, IC₅₀ values of 0.0076 μ M for the ET_A and 0.10 μ M for the ET_B) and the ethylsulfonlamino (32h, IC₅₀ values of 0.0061 μ M for the ET_A and 0.054 μ M for the ET_B) derivatives had the optimum ET receptor binding affinities in this series. The propylsulfonlamino derivative (32i) had the most potent activity for the ET_B receptor (IC₅₀ value of 0.047 μ M) in this assay.

Next, the *in vitro* antagonistic activities of the compounds (20d, e, 32g, h, i) were examined. As already mentioned, the ET_B receptor mediates both vasoconstriction and vasodilation. Taking into account the relationship between ETs and chronic diseases, the inhibitory effects of these compounds on vasoconstriction mediated by ET_A and ET_B receptors were evaluated. Artery constriction is predominantly mediated by the ET_A receptor, and vein constriction is mediated predominantly by the ET_B receptor.⁵¹ Inhibition of constriction of ring preparations of porcine coronary artery induced by ET-1 and that of vein preparations induced by sarafotoxin S6c was investigated.

Table 4 shows the *in vitro* antagonistic activities and binding affinities of TAK-044, bosentan, and thieno[2,3-*d*]pyrimidine-3-acetic acids (20d, e, 32g, h, i). Bosentan, 20d, 32g, and 32h at 1 μ M caused 62, 3, 36, and 33% relaxation of pre-constricted artery, respectively. Moreover, bosentan, 20d, 20e, 32g, 32h, and 32i at 1 μ M caused 48, 58, 66, 100, 98, and 99% relaxation of pre-constricted vein, respectively. Inhibition of the effects mediated by the ET_B receptor by compounds 32g, 32h, and 32i was more potent than with bosentan, whereas for the effects mediated by the ET_A receptor, 32g and 32h were slightly less potent than bosentan. With compounds 20d, 20e, 32g, 32h, and 32i, the order of the potencies of relaxation of the artery and vein almost corresponded to those of the binding affinities for the cloned ET_A and ET_B receptor subtypes, respectively. The ability of all compounds to relax vein was more potent than the ability to relax artery. On the other hand, the affinities of all com-

pounds for the ET_A receptor are higher than those for the ET_B receptor.

These results suggest that compounds 32g, 32h, and 32i are selective ET_B antagonists in the functional assay, but non-selective ET antagonists in the receptor binding assay. Recently, intensive studies have suggested that there are pharmacologically discernible ET_B receptor subtypes and/or major species differences.^{6,32} The cloned human ET_B receptor was used for the binding assay, but a ring preparation of porcine coronary vein was used for the functional assay. This might explain the difference between binding affinity and antagonistic activity for the ET_B receptor, but the details remain unclear.

In summary, we selected a thieno[2,3-*d*]pyrimidine-2,4-dione nucleus bearing a phenyl ring as a scaffold, and introduced a carboxyl group and aromatic rings, which were important for receptor binding, to this bicyclic heterocycle. SAR studies of the lead compound (7d) led to the discovery of novel and potent nonpeptide ET antagonists, 32g, 32h, and 32i. These compounds represent a new class of nonpeptide ET antagonists possessing potent ET_B antagonistic activities.

Experimental

Chemistry All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The proton nuclear magnetic resonance (¹H-NMR) spectra were recorded on either a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sext=sextet, m=multiplet, dd=doublets of doublet, brs=broad singlet. The infrared (IR) spectra were recorded on a JACSIO FT/IR-7000 spectrometer. FAB mass spectra were recorded on a JEOL JMS-4HX100. Elemental analyses were within $\pm 0.3\%$ of theoretical values and were determined in Takeda Research Analytical Laboratories, Osaka. Flash chromatography was performed with Merck silica gel 60 (Art. 9385, 230–400 mesh). The yields were not optimized.

Ethyl 2-Amino-5-(4-methoxyphenyl)-4-methylthiophene-3-carboxylate (4a) A mixture of 4-methoxyphenylacetone 3a (16.5 g, 0.10 mol), ethyl cyanoacetate (12.2 g, 0.10 mol), ammonium acetate (1.55 g, 20 mmol), acetic acid (4.6 ml, 80 mmol), and benzene (20 ml) was refluxed for 24 h while water was azeotropically removed using Dean-Stark apparatus. After removal of the solvent *in vacuo*, the residue was diluted with CH₂Cl₂ and washed with aqueous NaHCO₃ and brine. The organic layer was dried (MgSO₄) and concentrated *in vacuo* to give a dark brown oil, which was dissolved in EtOH (30 ml). To the solution were added sulfur powder (3.21 g, 0.10 mol) and diethylamine (10.4 ml, 0.10 mol). The reaction mixture was

Table 5. Physicochemical Data of Ethyl 2,4-Dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetates

Compd.	Yield (%)	mp (°C) Recryst. solvent ^a	Formula	Analysis (%)			¹ H-NMR (in CDCl ₃) δ
				Calcd (Found)			
				C	H	N	
6a	81	134.5—136 EA-H	C ₂₂ H ₂₀ N ₂ O ₅ S	61.38 (61.36)	6.09 (6.24)	6.51 (6.36)	0.98 (3H, t, <i>J</i> = 7.6 Hz), 1.30 (3H, t, <i>J</i> = 7.1 Hz), 1.43 (2H, sext, <i>J</i> = 7.6 Hz), 1.80 (2H, quint, <i>J</i> = 7.6 Hz), 2.50 (3H, s), 3.86 (3H, s), 3.96 (2H, t, <i>J</i> = 7.6 Hz), 4.24 (2H, q, <i>J</i> = 7.1 Hz), 4.78 (2H, s), 6.97 (2H, d, <i>J</i> = 8.8 Hz), 7.36 (2H, d, <i>J</i> = 8.8 Hz)
6b	81	113—115 EA-H	C ₂₂ H ₂₀ N ₂ O ₅ S	63.76 (63.72)	5.55 (5.40)	5.51 (5.31)	1.31 (3H, t, <i>J</i> = 7.2 Hz), 2.48 (3H, s), 3.11 (2H, t, <i>J</i> = 7.1 Hz), 3.85 (3H, s), 3.86 (3H, s), 4.14 (2H, t, <i>J</i> = 7.7 Hz), 4.25 (2H, q, <i>J</i> = 7.2 Hz), 4.79 (2H, s), 6.82—7.33 (8H, m)
6c	81	126—128 EA-H	C ₂₅ H ₂₄ N ₂ O ₅ S	64.64 (64.65)	5.21 (5.44)	6.03 (5.77)	1.31 (3H, t, <i>J</i> = 7.2 Hz), 2.48 (3H, s), 3.84 (3H, s), 4.26 (2H, q, <i>J</i> = 7.2 Hz), 4.83 (2H, s), 5.19 (2H, s), 6.94 (2H, d, <i>J</i> = 8.8 Hz), 7.30—7.38 (7H, m)
6d	78	141—142 EE-H	C ₂₅ H ₂₆ N ₂ O ₅ S	63.14 (63.01)	5.30 (5.48)	5.66 (5.48)	1.30 (3H, t, <i>J</i> = 7.2 Hz), 2.49 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 4.25 (2H, q, <i>J</i> = 7.2 Hz), 4.83 (2H, s), 5.24 (2H, s), 6.86—6.96 (4H, m), 7.09—7.14 (4H, m), 7.22—7.31 (3H, m)
6e	91	144—145 EA-EE	C ₂₅ H ₂₆ N ₂ O ₅ S	63.14 (62.93)	5.30 (5.38)	5.66 (5.59)	1.30 (3H, t, <i>J</i> = 7.1 Hz), 2.48 (3H, s), 3.79 (3H, s), 3.84 (3H, s), 4.25 (2H, q, <i>J</i> = 7.1 Hz), 4.83 (2H, s), 5.16 (2H, s), 6.80—6.97 (5H, m), 7.22—7.32 (3H, m)
6f	87	167—168 EA-EE	C ₂₅ H ₂₆ N ₂ O ₅ S	63.14 (62.88)	5.30 (5.28)	5.66 (5.40)	1.30 (3H, t, <i>J</i> = 7.1 Hz), 2.47 (3H, s), 3.78 (3H, s), 3.84 (3H, s), 4.25 (2H, q, <i>J</i> = 7.1 Hz), 4.82 (2H, s), 5.12 (2H, s), 6.86 (2H, d, <i>J</i> = 8.8 Hz), 6.94 (2H, d, <i>J</i> = 8.8 Hz), 7.29 (2H, d, <i>J</i> = 8.8 Hz), 7.35 (2H, d, <i>J</i> = 8.8 Hz)
6g	78	127—128.5 EA-H	C ₂₆ H ₂₄ N ₂ O ₅ S	65.25 (65.21)	5.48 (5.27)	5.85 (5.66)	1.31 (3H, t, <i>J</i> = 7.2 Hz), 2.40 (3H, s), 2.50 (3H, s), 3.83 (3H, s), 4.25 (2H, q, <i>J</i> = 7.2 Hz), 4.85 (2H, s), 5.22 (2H, s), 6.90—7.29 (8H, m)
6h	77	125—127 EA-H	C ₂₅ H ₂₆ N ₂ O ₅ S	62.23 (62.42)	4.80 (4.89)	5.81 (5.93)	1.31 (3H, t, <i>J</i> = 7.2 Hz), 2.49 (3H, s), 3.84 (3H, s), 4.26 (2H, q, <i>J</i> = 7.2 Hz), 4.84 (2H, s), 5.28 (2H, s), 6.93 (2H, d, <i>J</i> = 8.9 Hz), 7.05—7.15 (2H, m), 7.25—7.31 (4H, m)
6i	80	176—177 EA-H	C ₂₅ H ₂₆ N ₂ O ₅ S	63.79 (63.84)	4.74 (4.84)	5.58 (5.41)	1.32 (3H, t, <i>J</i> = 7.2 Hz), 2.50 (3H, s), 3.84 (3H, s), 4.26 (2H, q, <i>J</i> = 7.2 Hz), 4.85 (2H, s), 5.46 (2H, s), 6.93 (2H, d, <i>J</i> = 9.0 Hz), 7.28 (2H, d, <i>J</i> = 9.0 Hz), 7.30—7.74 (4H, m)
6j	62	154—156 EA-H	C ₂₅ H ₂₆ N ₂ O ₅ S	58.93 (58.78)	4.55 (4.46)	8.25 (8.26)	1.31 (3H, t, <i>J</i> = 7.2 Hz), 2.53 (3H, s), 3.83 (3H, s), 4.25 (2H, q, <i>J</i> = 7.2 Hz), 4.83 (2H, s), 5.65 (2H, s), 6.92 (2H, d, <i>J</i> = 8.8 Hz), 7.27 (2H, d, <i>J</i> = 8.8 Hz), 7.22—8.21 (4H, m)
6k	88	144—145 E	C ₂₆ H ₂₈ N ₂ O ₅ S ₂	61.16 (60.98)	5.13 (5.34)	5.49 (5.34)	1.30 (3H, t, <i>J</i> = 7.1 Hz), 2.53 (3H, s), 3.87 (3H, s), 4.25 (2H, q, <i>J</i> = 7.1 Hz), 4.83 (2H, s), 5.25 (2H, s), 6.87—6.94 (2H, m), 7.10—7.15 (1H, m), 7.23—7.44 (6H, m)
6l	90	147—148 EA	C ₂₈ H ₂₆ N ₂ O ₅ S · 0.1H ₂ O	62.91 (62.73)	5.32 (5.29)	5.64 (5.48)	1.30 (3H, t, <i>J</i> = 7.1 Hz), 2.36 (3H, s), 3.80 (3H, s), 3.86 (3H, s), 4.25 (2H, q, <i>J</i> = 7.1 Hz), 4.83 (2H, s), 5.24 (2H, s), 6.86—7.02 (4H, m), 7.12—7.39 (4H, m)
6m	89	151—152 EA	C ₂₅ H ₂₆ N ₂ O ₅ S	64.64 (64.72)	5.21 (5.21)	6.03 (6.23)	1.30 (3H, t, <i>J</i> = 7.1 Hz), 2.53 (3H, s), 3.87 (3H, s), 4.25 (2H, q, <i>J</i> = 7.1 Hz), 4.83 (2H, s), 5.25 (2H, s), 6.87—6.94 (2H, m), 7.10—7.15 (1H, m), 7.23—7.44 (6H, m)
22	91	124—125 EA-EE	C ₂₈ H ₂₆ N ₂ O ₅ S ₂ · 0.3EtOAc	62.85 (62.56)	5.65 (5.46)	4.85 (4.54)	1.01 (3H, t, <i>J</i> = 7.3 Hz), 1.31 (3H, t, <i>J</i> = 7.1 Hz), 1.78 (2H, q, <i>J</i> = 7.3 Hz), 2.54 (3H, s), 2.58 (3H, s), 2.94 (2H, t, <i>J</i> = 7.3 Hz), 4.26 (2H, q, <i>J</i> = 7.1 Hz), 4.80 (2H, s), 5.36 (2H, s), 7.01—7.36 (4H, m), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.98 (2H, d, <i>J</i> = 8.4 Hz)

a) Recrystallization solvent: EA=ethyl acetate, EE=ethyl ether, E=ethanol, H=hexane.

stirred at 60 °C for 2 h. After evaporation of the solvent *in vacuo*, the residue was diluted with water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo* and the residue purified by flash column chromatography (CH₂Cl₂). The resulting oily product was crystallized from ether-hexane to give 4a (11.5 g, 40%) as pale yellow plates, mp 79—80 °C. ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J* = 7.1 Hz), 2.28 (3H, s), 3.83 (3H, s), 4.31 (2H, q, *J* = 7.1 Hz), 6.05 (2H, br s), 6.91 (2H, d, *J* = 8.8 Hz), 7.27 (2H, d, *J* = 8.8 Hz). IR (KBr): 3426, 3328, 1651, 1586, 1550, 1505, 1485 cm⁻¹. FAB-MS *m/z*: 291 (M⁺). Anal. Calcd for C₁₇H₁₅N₂O₅S: C, 61.83; H, 5.88; N, 4.81; S, 11.01. Found: C, 61.81; H, 5.75; N, 4.74; S, 10.82.

Compounds 4b and 4c were prepared from 3b and 3c by a similar procedure to that used for the preparation of 4a, in 12 and 47% yields, respectively. 4b: mp 70—71 °C (from ether-hexane). ¹H-NMR (CDCl₃) δ: 1.36 (3H, t, *J* = 7.1 Hz), 2.16 (3H, s), 3.82 (3H, s), 4.30 (2H, q, *J* = 7.1 Hz), 6.05 (2H, br s), 6.93—7.01 (2H, m), 7.22—7.36 (2H, m). Anal. Calcd for C₁₇H₁₅N₂O₅S: C, 61.83; H, 5.88; N, 4.81; S, 11.01. Found: C, 61.97; H, 5.88; N, 4.83; S, 11.06. 4c: mp 105—106 °C (from ether-hexane). ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J* = 7.1 Hz), 2.30 (3H, s), 4.32 (2H, q, *J* = 7.1 Hz), 6.12 (2H, s), 7.21 (2H, d, *J* = 8.4 Hz), 7.49 (2H, d, *J* = 8.4 Hz). FAB-MS *m/z*: 339 (M⁺, ³Br), 341 (M⁺, ¹Br). Anal. Calcd for C₁₇H₁₅BrN₂O₅S: C, 49.42;

H, 4.15; N, 4.12; S, 9.42. Found: C, 49.43; H, 4.06; N, 4.13; S, 9.46.

Ethyl 2-Amino-4-methyl-5-phenylthiophene-3-carboxylate (4d) A mixture of 4e (10 g, 29.4 mmol) and sodium acetate (4.90 g, 59.7 mmol) in MeOH (300 ml) was hydrogenated over 10% palladium-charcoal (containing 50% H₂O, 1.0 g) with vigorous stirring at room temperature for 5 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was diluted with water and extracted with CHCl₃. The extract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo* to give the product (7.40 g, 96%) as a pale yellow oil. Crystallization from ether-hexane afforded colorless needles, mp 64—65 °C (lit.²⁷ mp 95 °C). ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J* = 7.1 Hz), 2.33 (3H, s), 4.32 (2H, q, *J* = 7.1 Hz), 6.09 (2H, br), 7.24—7.42 (5H, m). IR (KBr): 3388, 3278, 1665, 1584, 1549, 1481 cm⁻¹. Anal. Calcd for C₁₇H₁₅N₂O₅S: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.51; H, 5.77; N, 5.29.

Ethyl 6-(4-Methoxyphenyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (5a) A mixture of 4a (5.0 g, 17.2 mmol) and ethyl isocyanatoacetate (2.9 ml, 25.8 mmol) in pyridine (20 ml) was stirred at 45 °C for 3 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in absolute EtOH (30 ml). To this solution was added ethanolic sodium ethoxide (prepared from sodium (0.79 g, 34.3 mmol) and absolute EtOH (30 ml)). After being stirred at room temperature for 1.5 h, the mixture

Table 6. Physicochemical Data of 2,4-Dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetic Acids

Compd.	Yield (%)	mp (°C) Recryst. solvent ^a	Formula	Analysis (%)			¹ H-NMR δ
				C	H	N	
7a	96	195—197 E	C ₂₀ H ₂₂ N ₂ O ₄ S	59.69 (59.57)	5.51 5.38	6.96 6.80	0.94 (3H, t, <i>J</i> = 7.2 Hz), 1.37 (2H, sext, <i>J</i> = 7.2 Hz), 1.68 (2H, quint, <i>J</i> = 7.2 Hz), 2.44 (3H, s), 3.83 (3H, s), 3.95 (2H, t, <i>J</i> = 7.2 Hz), 4.58 (2H, s), 7.07 (2H, d, <i>J</i> = 8.8 Hz), 7.43 (2H, d, <i>J</i> = 8.8 Hz) ^b
7b	82	201.5—203 E	C ₂₃ H ₂₄ N ₂ O ₄ S	62.49 (62.38)	5.03 5.07	5.83 5.71	2.46 (3H, s), 3.09 (2H, t, <i>J</i> = 7.1 Hz), 3.82 (3H, s), 3.84 (3H, s), 4.13 (2H, t, <i>J</i> = 7.1 Hz), 4.83 (2H, s), 6.79—7.31 (8H, m) ^c
7c	78	194 E	C ₂₃ H ₂₆ N ₂ O ₄ S	63.29 (63.06)	4.62 4.57	6.42 6.51	2.49 (3H, s), 3.85 (3H, s), 4.91 (2H, s), 5.20 (2H, s), 6.94 (2H, d, <i>J</i> = 9.0 Hz), 7.31—7.38 (7H, m) ^c
7d	93	216—218 EE-H	C ₂₃ H ₂₇ N ₂ O ₄ S	61.79 (61.60)	4.75 4.87	6.00 6.16	2.41 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 4.61 (2H, s), 5.14 (2H, s), 6.85—6.92 (1H, m), 6.98—7.07 (4H, m), 7.25—7.36 (3H, m) ^c
7e	54	181—182 EA-EE	C ₂₃ H ₂₇ N ₂ O ₄ S ·0.5H ₂ O	60.62 (60.76)	4.88 4.74	5.89 5.87	2.40 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 4.63 (2H, s), 5.17 (2H, s), 6.85—6.92 (3H, m), 7.02 (2H, d, <i>J</i> = 8.8 Hz), 7.23—7.36 (3H, m) ^b
7f	81	193—195 E	C ₂₄ H ₂₇ N ₂ O ₄ S ·0.1H ₂ O	61.55 (61.26)	4.78 4.83	5.98 5.90	2.40 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 4.62 (2H, s), 5.12 (2H, s), 6.91 (2H, d, <i>J</i> = 8.8 Hz), 7.03 (2H, d, <i>J</i> = 8.8 Hz), 7.30 (2H, d, <i>J</i> = 6.3 Hz), 7.35 (2H, d, <i>J</i> = 6.3 Hz) ^b
7g	87	239—240 E	C ₂₄ H ₂₈ N ₂ O ₄ S	63.99 (63.92)	4.92 4.97	6.22 6.29	2.38 (3H, s), 2.48 (3H, s), 3.82 (3H, s), 4.91 (2H, s), 5.21 (2H, s), 6.85—7.27 (8H, m) ^c
7h	59	196—197 E	C ₂₃ H ₂₆ FN ₂ O ₄ S	60.78 (60.73)	4.21 4.24	6.16 6.06	2.49 (3H, s), 3.84 (3H, s), 4.91 (2H, s), 5.20 (2H, s), 6.94 (2H, d, <i>J</i> = 8.8 Hz), 7.05—7.31 (6H, m) ^c
7i	71	260—262 E	C ₂₃ H ₂₆ N ₂ O ₄ S ·0.1H ₂ O	62.22 (61.92)	4.17 4.23	9.07 8.90	2.42 (3H, s), 3.79 (3H, s), 4.61 (2H, s), 5.39 (2H, s), 7.00—7.93 (8H, m) ^b
7j	58	190—191 E	C ₂₃ H ₂₆ N ₂ O ₄ S	57.38 (57.10)	3.98 3.78	8.73 8.91	2.45 (3H, s), 3.78 (3H, s), 4.61 (2H, s), 5.56 (2H, s), 7.00 (2H, d, <i>J</i> = 8.8 Hz), 7.34 (2H, d, <i>J</i> = 8.8 Hz), 7.26—8.23 (4H, m) ^b
7k	87	185—189 EA-H	C ₂₃ H ₂₆ N ₂ O ₄ S ₂ ·0.1EtOAc	58.93 (58.62)	5.29 5.36	4.90 4.63	2.50 (3H, s), 2.53 (3H, s), 3.83 (3H, s), 4.92 (2H, s), 5.35 (2H, m), 6.89—7.32 (9H, m) ^c
7l	67	216—217.5 EE-H	C ₂₃ H ₂₆ N ₂ O ₄ S ·0.1H ₂ O	61.55 (61.39)	4.78 4.79	5.98 6.00	2.24 (3H, s), 3.75 (3H, s), 3.84 (3H, s), 4.62 (2H, s), 5.13 (2H, s), 6.85—7.13 (3H, m), 7.22—7.45 (3H, m) ^b
7m	79	252—255 EA	C ₂₃ H ₂₆ N ₂ O ₄ S ·0.1H ₂ O	63.03 (62.80)	4.65 4.71	6.39 6.32	2.46 (3H, s), 3.85 (3H, s), 4.62 (2H, s), 5.16 (2H, s), 6.85—6.92 (1H, m), 7.02—7.07 (2H, m), 7.25—7.51 (6H, m) ^b
9	100	204—206 EA-H	C ₂₃ H ₂₇ N ₂ O ₄ S	61.92 (61.66)	4.98 5.02	9.03 8.82	2.45 (3H, s), 2.78 (3H, s), 3.81 (3H, s), 4.65 (2H, s), 5.07 (2H, s), 5.40 (3H, s), 6.53—6.65 (2H, m), 6.82 (1H, d, <i>J</i> = 7.2 Hz), 7.03 (2H, d, <i>J</i> = 8.4 Hz), 7.17 (1H, t, <i>J</i> = 7.2 Hz), 7.35 (2H, d, <i>J</i> = 8.4 Hz) ^b
11a	67	223—224 E	C ₂₃ H ₂₇ N ₂ O ₄ S ₂	57.82 (57.67)	4.45 4.59	5.62 5.59	2.45 (3H, s), 2.83 (3H, s), 3.81 (3H, s), 4.65 (2H, s), 5.24, 5.49 (each 1H, ABq, <i>J</i> = 16.7 Hz), 7.05 (2H, d, <i>J</i> = 8.8 Hz), 7.27 (1H, d, <i>J</i> = 7.6 Hz), 7.36 (2H, d, <i>J</i> = 8.8 Hz), 7.54 (1H, t, <i>J</i> = 7.6 Hz), 7.64 (1H, t, <i>J</i> = 7.6 Hz), 7.97 (1H, d, <i>J</i> = 7.6 Hz) ^b
11b	96	142—145 EA-H	C ₂₃ H ₂₆ N ₂ O ₄ S ₂ ·0.5EtOAc	55.90 (55.73)	4.69 4.75	5.01 5.06	2.47 (3H, s), 3.43 (3H, s), 3.80 (3H, s), 4.65 (2H, s), 5.67 (2H, s), 7.63 (2H, d, <i>J</i> = 8.8 Hz), 7.26 (1H, d, <i>J</i> = 8.8 Hz), 7.36 (2H, d, <i>J</i> = 8.8 Hz), 7.61—7.73 (2H, m), 8.65 (1H, d, <i>J</i> = 8.8 Hz) ^b
16a	84	221—222 EA-EE	C ₂₃ H ₂₆ N ₂ O ₄ S ·0.1H ₂ O	61.55 (61.35)	4.78 4.94	5.98 5.77	2.46 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 4.62 (2H, s), 5.15 (2H, s), 6.86—6.97 (4H, m), 7.02—7.06 (2H, m), 7.27—7.39 (2H, m) ^b
16b	73	186—187 E	C ₂₆ H ₂₈ N ₂ O ₄ S ₂ ·0.5H ₂ O	60.10 (60.10)	5.24 5.12	5.39 5.41	2.47 (3H, s), 2.57 (3H, s), 2.84 (2H, t, <i>J</i> = 6.7 Hz), 3.25 (3H, s), 3.56 (2H, t, <i>J</i> = 6.7 Hz), 4.65 (2H, s), 5.21 (2H, s), 6.97—7.42 (8H, m) ^c
20a	72	244—246 EA-H	C ₂₃ H ₂₆ N ₂ O ₄ S ₂	56.78 (56.71)	4.56 4.29	5.76 5.55	2.43 (3H, s), 2.57 (3H, s), 4.65 (2H, s), 5.21 (2H, s), 6.84 (2H, d, <i>J</i> = 8.8 Hz), 6.99 (1H, d, <i>J</i> = 7.9 Hz), 7.12—7.45 (5H, m), 9.76 (1H, s) ^b
20b	78	185—188 E	C ₂₆ H ₂₆ N ₂ O ₄ S ₂ ·0.5H ₂ O	60.10 (60.34)	5.24 5.05	5.39 5.40	0.99 (3H, t, <i>J</i> = 7.3 Hz), 1.74 (2H, sext, <i>J</i> = 7.3 Hz), 2.44 (3H, s), 2.57 (3H, s), 3.96 (2H, d, <i>J</i> = 7.3 Hz), 4.64 (2H, s), 5.21 (2H, s), 6.97—7.44 (8H, m) ^c
20c	72	178—180 E	C ₂₇ H ₂₈ N ₂ O ₄ S ₂	61.81 (61.83)	5.38 5.46	5.34 5.22	0.98 (3H, t, <i>J</i> = 7.3 Hz), 1.49 (2H, sext, <i>J</i> = 7.3 Hz), 1.78 (2H, quint, <i>J</i> = 7.3 Hz), 2.50 (3H, s), 2.53 (3H, s), 3.98 (2H, t, <i>J</i> = 7.3 Hz), 4.92 (2H, s), 5.34 (2H, s), 6.88—7.32 (8H, m) ^c
20d	79	142—144 EA-EE-H	C ₂₆ H ₂₈ N ₂ O ₄ S ₂ ·0.5H ₂ O	57.57 (57.84)	4.83 4.69	5.37 5.36	2.43 (3H, s), 2.55 (3H, s), 3.38 (3H, s), 4.63 (2H, s), 5.19 (2H, s), 5.21 (2H, s), 6.96—7.17 (4H, m), 7.28—7.42 (4H, m) ^b
20e	79	152—154 EA-EE-H	C ₂₆ H ₂₈ N ₂ O ₄ S ₂	56.80 (56.52)	4.58 4.62	5.30 5.29	2.18 (3H, s), 2.43 (3H, s), 2.55 (3H, s), 4.63 (2H, s), 5.20 (2H, s), 5.30 (2H, s), 6.96—7.18 (4H, m), 7.29—7.42 (4H, m) ^b
20f	78	285—290(d) E	C ₂₆ H ₂₈ N ₂ O ₄ S ₂ ·0.5CH ₂ Cl ₂	56.12 (55.85)	4.44 4.51	4.93 4.70	2.17 (3H, s), 2.44 (3H, s), 2.57 (3H, s), 4.32 (2H, s), 4.87 (2H, s), 5.17 (2H, s), 6.95—7.37 (8H, m) ^b
23	50	197—199 E	C ₂₃ H ₂₆ N ₂ O ₄ S	61.84 (61.64)	5.04 5.09	5.34 5.32	0.94 (3H, t, <i>J</i> = 7.2 Hz), 1.66 (2H, q, <i>J</i> = 7.2 Hz), 2.55 (3H, s), 2.58 (3H, s), 3.02 (2H, t, <i>J</i> = 7.2 Hz), 4.66 (2H, s), 5.24 (2H, s), 7.02 (1H, d, <i>J</i> = 7.7 Hz), 7.16 (1H, t, <i>J</i> = 7.7 Hz), 7.32—7.45 (2H, m), 7.58 (2H, d, <i>J</i> = 8.2 Hz), 8.03 (2H, d, <i>J</i> = 8.2 Hz) ^b
27	70	>300 E	C ₂₃ H ₂₆ N ₂ O ₄ S ₂ ·2.8HCl	48.49 (48.32)	4.21 4.22	7.37 7.11	2.41 (3H, s), 2.56 (3H, s), 4.40 (2H, s), 5.16 (2H, s), 5.38 (2H, br s), 6.60 (2H, d, <i>J</i> = 8.6 Hz), 6.95—7.45 (6H, m) ^b
28	73	274—275 E	C ₂₆ H ₂₈ N ₂ O ₄ S ₂ ·0.5H ₂ O	58.63 (58.71)	4.92 4.90	7.89 7.79	1.05 (3H, t, <i>J</i> = 7.5 Hz), 2.34 (2H, q, <i>J</i> = 7.5 Hz), 2.46 (3H, s), 2.57 (3H, s), 4.65 (2H, s), 5.20 (2H, s), 6.98 (1H, d, <i>J</i> = 7.6 Hz), 7.15 (1H, t, <i>J</i> = 7.6 Hz), 7.31—7.43 (4H, m), 7.68 (2H, d, <i>J</i> = 8.6 Hz), 10.02 (1H, s) ^b

Table 6. (continued)

Compd.	Yield (%)	mp (°C) Recryst. solvent ^a	Formula	Analysis (%)			¹ H-NMR δ
				Calcd (Found)			
				C	H	N	
31	100	>300 EA	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·1.6H ₂ O	53.96 (53.76)	5.11 5.00	7.44 7.34	2.54 (3H, s), 3.36 (3H, s), 3.88 (2H, s), 4.45 (2H, s), 5.21 (2H, s), 5.22 (2H, s), 6.99—7.15 (4H, m), 7.29—7.40 (4H, m) ^b
32a	58	205—212 EA-H	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·1.8H ₂ O	53.86 (53.92)	5.12 4.90	6.98 6.71	1.78 (3H, s), 2.55 (3H, s), 3.37 (3H, s), 4.36 (2H, s), 4.37—4.40 (4H, m), 5.19 (2H, s), 5.22 (2H, s), 7.00—7.16 (4H, m), 7.34—7.41 (4H, m), 7.86—7.87 (1H, m) ^b
32b	62	170—175 M-EE	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·0.8H ₂ O	56.23 (56.20)	5.16 5.27	7.03 7.21	1.13 (3H, t, <i>J</i> =7.5 Hz), 2.21 (2H, q, <i>J</i> =7.5 Hz), 2.53 (3H, s), 3.47 (3H, s), 4.52 (2H, d, <i>J</i> =6.6 Hz), 4.94 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 7.02—7.34 (6H, m), 7.50 (2H, d, <i>J</i> =8.8 Hz) ^a
32c	69	170—172 M	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·0.5H ₂ O	57.41 (57.26)	5.32 5.43	6.93 6.75	0.92 (3H, t, <i>J</i> =7.4 Hz), 1.57—1.78 (2H, m), 2.13—2.17 (2H, m), 2.53 (3H, s), 3.47 (3H, s), 4.52 (2H, d, <i>J</i> =6.6 Hz), 4.95 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 7.01—7.35 (6H, m), 7.50 (2H, d, <i>J</i> =8.5 Hz) ^a
32d	96	177—179 M	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·H ₂ O	57.22 (57.26)	5.60 5.35	6.67 6.86	0.89 (3H, t, <i>J</i> =7.3 Hz), 1.26—1.38 (2H, m), 1.54—1.64 (2H, m), 2.17 (2H, t, <i>J</i> =7.7 Hz), 2.53 (3H, s), 3.47 (3H, s), 4.52 (2H, d, <i>J</i> =6.4 Hz), 4.95 (2H, s), 5.18 (2H, s), 5.36 (2H, s), 7.02—7.34 (6H, m), 7.50 (2H, d, <i>J</i> =8.5 Hz) ^a
32e	46	215—218 EA-H	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·2.5H ₂ O	56.79 (56.51)	5.06 4.79	6.21 6.25	2.54 (3H, s), 3.35 (3H, s), 4.37 (2H, s), 4.66 (2H, s), 5.19 (4H, s), 7.03—7.11 (4H, m), 7.28—7.50 (7H, m), 7.71 (2H, d, <i>J</i> =8.5 Hz), 8.56 (1H, t, <i>J</i> =6.6 Hz) ^b
32f	84	202—204 M	C ₂₃ H ₂₃ N ₃ O ₅ S ₂	56.17 (55.97)	5.05 5.27	9.36 9.38	1.05 (3H, t, <i>J</i> =7.2 Hz), 2.52 (2H, s), 3.07 (2H, q, <i>J</i> =7.2 Hz), 3.47 (3H, s), 4.45 (2H, s), 4.88 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 7.02—7.34 (6H, m), 7.48 (2H, d, <i>J</i> =8.6 Hz) ^a
32g	71	204—206 EA-EE	C ₂₃ H ₂₃ N ₃ O ₅ S ₂	51.56 (51.76)	4.49 4.69	6.94 6.88	2.55 (3H, s), 2.89 (3H, s), 3.38 (3H, s), 4.30 (2H, d, <i>J</i> =5.4 Hz), 4.67 (2H, s), 5.23 (4H, s), 6.93 (1H, t, <i>J</i> =5.4 Hz), 6.98—7.00 (1H, m), 7.09—7.17 (3H, m), 7.31—7.43 (4H, m) ^b
32h	80	125—128 EA-H	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·H ₂ O	50.85 (51.15)	4.90 4.78	6.59 6.54	1.33 (3H, t, <i>J</i> =7.4 Hz), 2.53 (3H, s), 2.96 (2H, q, <i>J</i> =7.4 Hz), 3.48 (3H, s), 4.35 (2H, d, <i>J</i> =6.6 Hz), 4.92 (2H, s), 5.19 (2H, s), 5.36 (2H, s), 6.05 (1H, t, <i>J</i> =6.6 Hz), 7.01—7.37 (8H, m) ^a
32i	93	123—124 EA-H	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·0.5H ₂ O	52.32 (52.21)	5.02 4.87	6.54 6.51	0.98 (3H, t, <i>J</i> =7.2 Hz), 1.77—1.78 (2H, m), 2.86—2.92 (2H, m), 2.53 (3H, s), 3.48 (3H, s), 4.35 (2H, d, <i>J</i> =6.8 Hz), 4.92 (2H, s), 5.19 (2H, s), 5.36 (2H, s), 6.04—6.05 (1H, m), 7.00—7.18 (5H, m), 7.32—7.37 (3H, m) ^a
32j	52	128—129 IPE	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·0.5H ₂ O	55.02 (54.85)	4.47 4.44	6.21 6.31	2.34 (3H, s), 3.40 (3H, s), 4.19 (2H, d, <i>J</i> =5.4 Hz), 4.52 (2H, s), 5.13 (2H, s), 5.24 (2H, s), 6.87—7.55 (15H, m) ^a
34	93	200—204 EA-EE	C ₂₃ H ₂₃ N ₃ O ₅ S ₂ ·2.5H ₂ O	48.78 (48.60)	5.16 4.95	6.32 6.27	2.54 (3H, s), 2.55 (3H, s), 2.84 (3H, s), 3.38 (3H, s), 4.39 (2H, s), 4.56 (2H, s), 5.21 (4H, s), 7.03—7.15 (4H, m), 7.28—7.44 (4H, m) ^b

a) Recrystallization solvent: EA=ethyl acetate, EE=ethyl ether, E=ethanol, H=hexane, IPE=isopropyl ether, M=methanol. b) in DMSO-*d*₆. c) in CDCl₃.

was acidified with 2N HCl (20 ml, 40 mmol) and concentrated *in vacuo* (removal of EtOH). The precipitate was collected by filtration, dried, and recrystallized from EtOH to give 5a (0.18 g, 96%) as colorless needles, mp 164—165°C. ¹H-NMR (CDCl₃) δ : 1.30 (3H, t, *J*=7.2 Hz), 2.45 (3H, s), 3.85 (3H, s), 4.26 (2H, q, *J*=7.2 Hz), 4.78 (2H, s), 6.95 (2H, d, *J*=8.8 Hz), 7.31 (2H, d, *J*=8.8 Hz), 10.58 (1H, s). IR (KBr): 2914, 1742, 1713, 1655, 1605, 1568, 1528, 1499, 1450 cm⁻¹. Anal. Calcd for C₁₃H₁₃N₃O₅S: C, 57.74; H, 4.85; N, 7.48. Found: C, 57.78; H, 5.03; N, 7.45.

Compounds 5b, d, and 13 were prepared by a similar procedure to that used for the preparation of 5a, in 81, 86, and 88% yields, respectively. 5b: mp 83—84°C (from ether-hexane). ¹H-NMR (CDCl₃) δ : 1.29 (3H, t, *J*=7.1 Hz), 2.35 (3H, s), 3.83 (3H, s), 4.24 (2H, q, *J*=7.1 Hz), 4.77 (2H, s), 6.96—7.05 (2H, m), 7.25—7.43 (2H, m), 10.47 (1H, s). Anal. Calcd for C₁₃H₁₃N₃O₅S·0.1H₂O: C, 57.47; H, 4.88; N, 7.45. Found: C, 57.43; H, 4.90; N, 7.33. 5d: mp 119—120°C (from EtOH). ¹H-NMR (CDCl₃) δ : 1.30 (3H, t, *J*=7.1 Hz), 2.49 (3H, s), 4.26 (2H, q, *J*=7.1 Hz), 4.79 (2H, s), 7.35—7.47 (5H, m), 10.58 (1H, br s). Anal. Calcd for C₁₇H₁₅N₃O₅S·0.1H₂O: C, 58.91; H, 4.94; N, 7.90. Found: C, 58.98; H, 4.72; N, 8.09. 13: mp 229—230°C (from EtOH). ¹H-NMR (CDCl₃) δ : 1.21 (3H, t, *J*=7.1 Hz), 2.35 (3H, s), 4.14 (2H, q, *J*=7.1 Hz), 4.57 (2H, s), 6.74 (1H, s), 12.35 (1H, br s). Anal. Calcd for C₁₁H₁₃N₃O₅S·0.5H₂O: C, 47.65; H, 4.73; N, 10.10. Found: C, 47.90; H, 4.43; N, 10.07.

Ethyl 1-(2-Methoxybenzyl)-6-(4-methoxyphenyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (6d). A mixture of 5a (0.60 g, 1.60 mmol), 2-methoxybenzyl chloride (0.51 g, 3.26 mmol), and K₂CO₃ powder (0.45 g, 3.26 mmol) in *N,N*-dimethylformamide (DMF, 7 ml) was stirred at room temperature for 15 h. After evaporation of the solvent *in vacuo*, the residue was diluted with water and extracted with EtOAc. The ex-

tract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo* and the residue purified by flash column chromatography (EtOAc-hexane, 1:4 then 3:7). The resulting crystalline product was recrystallized from ether-hexane to give 6d (0.57 g, 72%) as colorless crystals, mp 141—142°C. ¹H-NMR (CDCl₃) δ : 1.30 (3H, t, *J*=7.2 Hz), 2.49 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 4.25 (2H, q, *J*=7.2 Hz), 4.83 (2H, s), 5.24 (2H, s), 6.86—6.96 (4H, m), 7.09—7.14 (1H, m), 7.22—7.31 (3H, m), 1R (KBr): 2982, 1756, 1710, 1665, 1607, 1562, 1535, 1477 cm⁻¹. Anal. Calcd for C₂₃H₂₃N₃O₅S: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.01; H, 5.48; N, 5.48.

Compounds 6a—c, 6e—m, and 22 were prepared by a similar procedure to that used for the preparation of 6d and their physicochemical data are listed in Table 5.

1-(2-Methoxybenzyl)-6-(4-methoxyphenyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetic Acid (7d). To a solution of 6d (0.35 g, 0.71 mmol) in MeOH (4 ml) and tetrahydrofuran (THF, 8 ml) was added 1N NaOH (3.6 ml, 3.6 mmol). After being stirred at room temperature for 1.5 h, the mixture was acidified with 1N HCl (4 ml, 4 mmol) and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was crystallized from ether-hexane to give 7d (0.31 g, 93%) as colorless crystals, mp 216—218°C. ¹H-NMR (DMSO-*d*₆) δ : 2.41 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 4.61 (2H, s), 5.14 (2H, s), 6.85—6.92 (1H, m), 6.98—7.07 (4H, m), 7.25—7.36 (3H, m). IR (KBr): 2966, 1731, 1702, 1659, 1607, 1562, 1535, 1479 cm⁻¹. Anal. Calcd for C₂₃H₂₃N₃O₅S: C, 61.79; H, 4.73; N, 6.00. Found: C, 61.60; H, 4.87; N, 6.16.

Compounds 7a—c, 7e—m, 9, 11a, b, 16a, b, 20a—f, 23, 27, 28, 31, 32a—j, and 34 were prepared by a similar procedure to that used for the

Table 7. Physicochemical Data of Ethyl 5-Substitutedmethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetates

Compd.	Yield (%)	mp (°C) Recryst. solvent ^a	Formula	Analysis (%)			¹ H-NMR (in CDCl ₃) δ
				Calcd (Found)			
				C	H	N	
30a	87	175–177 EA–H	C ₂₃ H ₁₁ N ₃ O ₅ S ₂	58.28 (57.99)	5.23 5.28	7.03 6.93	1.32 (3H, t, J=7.2 Hz), 1.96 (3H, s), 2.53 (3H, s), 3.47 (3H, s), 4.28 (2H, q, J=7.2 Hz), 4.51 (2H, d, J=6.6 Hz), 4.88 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 5.75 (3H, m), 7.02–7.34 (6H, m), 7.49 (2H, d, J=8.7 Hz), 1.13 (3H, t, J=7.5 Hz), 1.32 (3H, t, J=7.1 Hz), 2.20 (2H, q, J=7.5 Hz), 2.53 (3H, s), 3.47 (3H, s), 4.27 (2H, q, J=7.1 Hz), 4.52 (2H, d, J=6.6 Hz), 4.87 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 7.02–7.15 (4H, m), 7.26–7.34 (2H, m), 7.51 (2H, d, J=8.8 Hz)
30b	85	168–169 EA–H	C ₂₃ H ₁₁ N ₃ O ₅ S ₂ ·0.3H ₂ O	58.39 (58.38)	5.49 5.55	6.81 6.92	0.92 (3H, t, J=7.3 Hz), 1.32 (3H, t, J=7.2 Hz), 1.70–1.71 (1H, m), 2.15 (2H, t, J=7.3 Hz), 2.53 (3H, s), 3.47 (3H, s), 4.27 (2H, q, J=7.3 Hz), 4.52 (2H, d, J=6.6 Hz), 4.88 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 7.01–7.35 (6H, m), 7.50 (2H, d, J=8.5 Hz)
30c	83	159–162 EA–H	C ₂₃ H ₁₁ N ₃ O ₅ S ₂ ·0.5H ₂ O	58.66 (58.74)	5.72 5.54	6.62 6.55	0.90 (3H, t, J=7.3 Hz), 1.26–1.38 (5H, m), 1.52–1.62 (2H, m), 2.17 (2H, t, J=7.1 Hz), 2.52 (2H, s), 3.47 (3H, s), 4.27 (2H, q, J=7.3 Hz), 4.52 (2H, d, J=6.6 Hz), 4.86 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 7.02–7.35 (6H, m), 7.50 (2H, d, J=8.6 Hz)
30d	96	163–165 EA–H	C ₂₃ H ₁₁ N ₃ O ₅ S ₂	60.07 (59.87)	5.83 5.82	6.57 6.69	0.90 (3H, t, J=7.3 Hz), 1.26–1.38 (5H, m), 1.52–1.62 (2H, m), 2.17 (2H, t, J=7.1 Hz), 2.52 (2H, s), 3.47 (3H, s), 4.27 (2H, q, J=7.3 Hz), 4.52 (2H, d, J=6.6 Hz), 4.86 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 7.02–7.35 (6H, m), 7.50 (2H, d, J=8.6 Hz)
30e	90	Amorphous	C ₂₃ H ₁₁ N ₃ O ₅ S ₂ ·0.2H ₂ O	61.56 (61.52)	5.08 4.97	6.33 6.37	1.31 (3H, t, J=7.2 Hz), 2.53 (3H, s), 3.48 (3H, s), 4.28 (2H, q, J=7.2 Hz), 4.73 (2H, d, J=6.6 Hz), 4.91 (2H, s), 5.20 (2H, s), 5.36 (2H, s), 7.01–7.14 (4H, m), 7.31–7.48 (5H, m), 7.58 (2H, d, J=8.5 Hz), 7.79 (2H, d, J=7.1 Hz), 8.28 (1H, t, J=6.6 Hz)
30g	100	115–118 EA–H	C ₂₈ H ₁₁ N ₃ O ₅ S ₂ ·0.1C ₆ H ₁₄	53.48 (53.66)	5.08 5.20	6.54 6.37	1.31 (3H, t, J=7.1 Hz), 2.53 (3H, s), 2.87 (3H, s), 3.48 (3H, s), 4.27 (2H, q, J=7.1 Hz), 4.37 (2H, d, J=6.8 Hz), 4.85 (2H, s), 5.19 (2H, s), 5.36 (2H, s), 6.07 (1H, t, J=6.8 Hz), 7.01–7.18 (4H, m), 7.27–7.36 (4H, m), 1.30–1.35 (6H, m), 2.53 (3H, s), 2.95 (2H, q, J=7.4 Hz), 3.48 (3H, s), 4.27 (2H, q, J=7.2 Hz), 4.35 (2H, d, J=6.6 Hz), 4.85 (2H, s), 5.19 (2H, s), 5.36 (2H, s), 6.07 (1H, t, J=6.6 Hz), 7.01–7.08 (4H, m), 7.29–7.37 (4H, m)
30h	86	153–155 EA–H	C ₂₉ H ₁₃ N ₃ O ₅ S ₂	53.77 (53.58)	5.13 5.22	6.49 6.24	0.98 (3H, t, J=7.2 Hz), 1.32 (3H, t, J=7.2 Hz), 1.77–1.78 (2H, m), 2.53 (3H, s), 2.88–2.89 (2H, m), 3.48 (3H, s), 4.27 (2H, q, J=7.2 Hz), 4.35 (2H, d, J=6.9 Hz), 4.85 (2H, s), 5.19 (2H, s), 5.36 (2H, s), 6.06 (1H, t, J=6.9 Hz), 7.01–7.37 (8H, m)
30i	85	122–123 EA–H	C ₂₈ H ₁₃ N ₃ O ₅ S ₂	54.45 (54.19)	5.33 5.31	6.35 6.18	1.34 (3H, t, J=7.2 Hz), 2.52 (3H, s), 3.50 (3H, s), 4.26–4.33 (4H, m), 4.82 (2H, s), 5.21 (2H, s), 5.26 (2H, s), 6.63 (1H, t, J=6.8 Hz), 6.97 (1H, d, J=7.2 Hz), 7.08 (2H, d, J=9.0 Hz), 7.14–7.30 (1H, m), 7.28–7.60 (7H, m), 7.66 (2H, d, J=7.8 Hz)
30j	83	Amorphous					

a) Recrystallization solvent: EA=ethyl acetate, H=hexane.

preparation of 7d and their physicochemical data are listed in Table 6.

Ethyl 6-(4-Methoxyphenyl)-5-methyl-1-(2-methylaminoethyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (8) A mixture of 6j (0.60 g, 1.2 mmol) and iron powder (0.36 g, 6.1 mmol) in acetic acid (25 ml) was stirred at 80 °C for 2 h. After cooling, the mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The residue was diluted with saturated NaHCO₃ and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄), concentrated *in vacuo*, and the residue purified by flash column chromatography (EtOAc–hexane, 3 : 7 then 4 : 6). The resulting crystalline product was recrystallized from EtOAc–hexane to afford the 2-aminobenzyl derivative (0.445 g, 80%) as a colorless crystalline powder, mp 138–140 °C. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, J=7.1 Hz), 2.47 (3H, s), 3.85 (3H, s), 4.25 (2H, q, J=7.1 Hz), 4.47 (2H, br s), 4.82 (2H, s), 5.16 (2H, s), 6.63–6.73 (2H, m), 6.96 (2H, d, J=8.8 Hz), 7.13 (1H, t, J=7.4 Hz), 7.28–7.36 (3H, m). IR (KBr): 1754, 1705, 1636, 1562, 1528, 1502 cm⁻¹. FAB-MS *m/z*: 480 (MH⁺).

To a solution of the 2-aminobenzyl derivative (0.30 g, 0.62 mmol) in THF (5 ml) was added acetic formic anhydride [prepared from acetic anhydride (1 ml, 10.6 mmol) and formic acid (0.5 ml, 13.3 mmol) according to the reported procedure²⁹] at –20 °C. The mixture was stirred at the same temperature for 30 min. The mixture was then concentrated *in vacuo* to give a white powder which was dissolved in THF (5 ml). To the solution was added dropwise borane–methyl sulfide complex (0.25 ml, 2.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min, and then gently refluxed for 2 h. After cooling, MeOH (1 ml) was added at 0 °C and the mixture was stirred at room temperature for 1 h. The mixture was then treated with ethanolic HCl to attain pH 2, and the resulting mixture was gently refluxed for 0.5 h. After addition of MeOH (20 ml), the mixture was concentrated *in vacuo*. The residue was diluted with saturated NaHCO₃ and ex-

tracted with EtOAc. The extract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo* and the residue purified by flash column chromatography (EtOAc–hexane, 1 : 4) to afford 8 (0.16 g, 52%) as a white solid. Recrystallization from EtOAc–hexane gave colorless crystals, mp 188–189 °C. ¹H-NMR (CDCl₃) δ: 1.32 (3H, t, J=7.2 Hz), 2.46 (3H, s), 2.82 (3H, s), 3.85 (3H, s), 4.26 (2H, q, J=7.2 Hz), 4.83 (2H, s), 5.15 (2H, s), 6.59–6.69 (2H, m), 6.95 (2H, d, J=8.8 Hz), 7.21–7.36 (4H, m). IR (KBr): 3396, 1742, 1696, 1647, 1607, 1570, 1535 cm⁻¹. FAB-MS *m/z*: 494 (MH⁺). *Anal.* Calcd for C₂₆H₁₉N₃O₅S: C, 63.27; H, 5.51; N, 8.51. Found: C, 63.20; H, 5.69; N, 8.63.

Ethyl 6-(4-Methoxyphenyl)-5-methyl-1-(2-methylsulfinylethyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (10a) To an ice-cooled solution of 6k (0.35 g, 0.69 mmol) in CH₂Cl₂ (10 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (50% purity, 0.26 g, 0.75 mmol) in CH₂Cl₂ (10 ml). After 30 min at 0 °C, the mixture was diluted with saturated NaHCO₃ and extracted with CH₂Cl₂. The extract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo* and the residue purified by flash column chromatography (CH₂Cl₂–MeOH, 20 : 1 then 10 : 1) to give 10a (0.26 g, 72%) as a pale yellow amorphous powder, mp 90–95 °C. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, J=7.1 Hz), 2.50 (3H, s), 2.83 (3H, s), 3.83 (3H, s), 4.25 (2H, q, J=7.1 Hz), 4.82 (2H, s), 5.19, 5.49 (each 1H, ABq, J=16.5 Hz), 6.93 (2H, d, J=8.8 Hz), 7.23–7.28 (3H, m), 7.47 (1H, t, J=8.8 Hz), 7.57 (1H, t, J=8.8 Hz), 8.05 (1H, d, J=8.8 Hz). IR (KBr): 1748, 1709, 1665, 1609, 1564, 1535, 1477 cm⁻¹. *Anal.* Calcd for C₂₈H₂₁N₃O₅S₂·0.2H₂O: C, 58.89; H, 5.01; N, 5.28. Found: C, 58.89; H, 5.04; N, 5.22.

Compound 10b was prepared in 67% yield from 6k by essentially the same procedure (using 2 eq of *m*-chloroperbenzoic acid) described for the preparation of 10a, as pale yellow crystals (from EtOAc–hexane), mp 141–

141°C. ¹H-NMR (CDCl₃) δ: 1.28 (3H, t, J=7.1 Hz), 2.53 (3H, s), 3.26 (3H, s), 3.84 (3H, s), 4.23 (2H, q, J=7.1 Hz), 4.79 (2H, s), 5.64 (2H, s), 6.94 (2H, d, J=8.9 Hz), 7.22–7.32 (3H, m), 7.48–7.64 (2H, m), 8.11 (1H, d, J=7.6 Hz). IR (KBr): 1742, 1705, 1661, 1533, 1477, 1377 cm⁻¹. Anal. Calcd for C₂₃H₂₂N₂O₅S₂: C, 57.55; H, 4.83; N, 5.16. Found: C, 57.64; H, 4.69; N, 5.16.

Ethyl 6-Bromo-1-(2-methoxybenzyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (14a) A mixture of 13 (0.27 g, 1.01 mmol) and NBS (0.20 g, 1.11 mmol) in CHCl₃ (30 ml) was heated under reflux for 2.5 h. After cooling, the mixture was diluted with water and extracted with CHCl₃. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane, 3:7 then 4:6) to give the 6-bromo derivative (0.31 g, 90%) as pale yellow solid. Recrystallization from EtOAc-hexane afforded colorless fine needles, mp 192–193°C. ¹H-NMR (CDCl₃) δ: 1.33 (3H, t, J=7.1 Hz), 2.39 (3H, s), 4.28 (2H, q, J=7.1 Hz), 4.75 (2H, s), 10.41 (1H, brs). FAB-MS *m/z*: 347 (MH⁺, ¹⁰⁰Br), 349 (MH⁺, ⁸¹Br).

To a mixture of the 6-bromo derivative (0.30 g, 0.86 mmol), K₂CO₃ powder (0.18 g, 1.30 mmol), and KI powder (72 mg, 0.43 mmol) in DMF (7 ml) was added a solution of 2-methoxybenzyl chloride (0.16 g, 1.02 mmol) in DMF (3 ml). After being stirred at room temperature for 16 h, the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane, 1:4) to give 14a (0.38 g, 94%) as a white solid. Recrystallization from EtOAc-ether-hexane afforded colorless crystals, mp 124–126°C. ¹H-NMR (CDCl₃) δ: 1.29 (3H, t, J=7.2 Hz), 2.43 (3H, s), 3.85 (3H, s), 4.24 (2H, q, J=7.2 Hz), 4.80 (2H, s), 5.17 (2H, s), 6.89–6.94 (2H, m), 7.10–7.13 (1H, m), 7.26–7.32 (1H, m). IR (KBr): 3422, 2972, 1748, 1707, 1669, 1560, 1501, 1475 cm⁻¹. Anal. Calcd for C₂₃H₂₀BrN₂O₅S₂·0.1C₁₀H₈: C, 49.46; H, 4.32; N, 5.89. Found: C, 49.39; H, 4.09; N, 6.09.

Compound 14b was prepared in 68% yield from 13 by the same procedure described for the preparation of 14a as colorless crystals (from EtOAc-hexane), mp 150–151°C. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, J=7.1 Hz), 2.44 (3H, s), 2.55 (3H, s), 4.24 (2H, q, J=7.1 Hz), 4.82 (2H, s), 5.29 (2H, s), 6.97–7.34 (4H, m). IR (KBr): 1746, 1707, 1669, 1475 cm⁻¹. Anal. Calcd for C₂₃H₂₀N₂O₅S₂: C, 47.21; H, 3.96; N, 5.80; S, 13.27. Found: C, 47.39; H, 3.99; N, 5.80; S, 13.25.

Ethyl 1-(2-Methoxybenzyl)-6-(3-methoxyphenyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (15a) To a mixture of 14a (0.26 g, 0.56 mmol), 3-methoxyphenylboronic acid (0.12 g, 0.68 mmol), and 2M Na₂CO₃ (1.40 ml, 2.80 mmol) in 1,2-dimethoxyethane (10 ml) was added tetrakis(triphenylphosphine)palladium (0) (65 mg, 0.056 mmol) under an argon atmosphere. The mixture was heated under reflux with vigorous stirring under an argon atmosphere for 5 h. After cooling, the reaction mixture was diluted with EtOAc and filtered through Celite. The filtrate was diluted with water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane, 1:4) to give 15a (0.22 g, 80%) as a pale yellow amorphous solid. Crystallization from EtOAc-ether-hexane afforded colorless crystals, mp 140–141°C. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, J=7.1 Hz), 2.54 (3H, s), 3.82 (3H, s), 3.87 (3H, s), 4.25 (2H, q, J=7.1 Hz), 4.83 (2H, s), 5.25 (2H, s), 6.86–6.96 (5H, m), 7.10–7.14 (1H, m), 7.24–7.33 (2H, m). IR (KBr): 3438, 2976, 1748, 1709, 1661, 1593, 1562, 1531, 1495, 1473 cm⁻¹. Anal. Calcd for C₂₈H₂₆N₂O₈S₂: C, 63.14; H, 5.30; N, 5.66; S, 6.48. Found: C, 63.17; H, 5.35; N, 5.60; S, 6.58.

Compound 15b was prepared in 54% yield from 14b by the same procedure described for the preparation of 15a as a colorless crystalline powder (from EtOAc-hexane), mp 126–128°C. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, J=7.2 Hz), 2.51 (3H, s), 2.54 (3H, s), 2.89 (2H, t, J=6.9 Hz), 3.35 (3H, s), 3.61 (2H, t, J=6.9 Hz), 4.26 (2H, q, J=7.2 Hz), 4.86 (2H, s), 5.34 (2H, s), 7.05–7.40 (8H, m). IR (KBr): 1754, 1709, 1663, 1477 cm⁻¹. Anal. Calcd for C₂₈H₂₆N₂O₈S₂: C, 62.43; H, 5.61; N, 5.20. Found: C, 62.32; H, 5.39; N, 5.09.

Ethyl 6-(4-Hydroxyphenyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (17) To an ice-cooled mixture of anhydrous aluminum chloride (2.90 g, 21.7 mmol) and dimethyl disulfide (2.45 ml, 27.2 mmol) in CH₂Cl₂ (60 ml) was added dropwise a solution of 5a (2.0 g, 5.34 mmol) in CH₂Cl₂ (40 ml) under a nitrogen atmosphere during 30 min. After stirring at room temperature for 20 h, the mixture was poured into ice-water and the resulting suspension was concentrated *in vacuo*. The concen-

trate was diluted with water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo*, and the residue was purified by flash column chromatography (EtOAc-hexane, 4:6 then 1:1) to give 17 (1.64 g, 85%) as a white solid, mp 240–242°C. ¹H-NMR (DMSO-d₆) δ: 1.22 (3H, t, J=7.1 Hz), 2.37 (3H, s), 4.15 (2H, q, J=7.1 Hz), 4.59 (2H, s), 6.85 (2H, d, J=8.6 Hz), 7.26 (2H, d, J=8.6 Hz), 9.73 (1H, s), 12.39 (1H, s). IR (KBr): 3356, 2992, 1720, 1690, 1607, 1611, 1593, 1568, 1537, 1502 cm⁻¹. Anal. Calcd for C₁₇H₁₆N₂O₅S₂·0.1H₂O: C, 56.38; H, 4.51; N, 7.73. Found: C, 56.28; H, 4.48; N, 7.64.

Ethyl 6-(4-Acetoxyphenyl)-5-methyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (18) To a solution of 17 (16.0 g, 16.6 mmol) in pyridine (100 ml) was added acetic anhydride (32 ml, 0.330 mol). After stirring at room temperature for 3 h, the mixture was concentrated *in vacuo*. The residue was diluted with aqueous HCl and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo* to give a pale orange syrup, which was dissolved in DMF (60 ml). To this solution were added K₂CO₃ powder (4.60 g, 33.3 mmol) and a solution of 2-methylthiobenzyl chloride (5.80 g, 33.6 mmol) in DMF (20 ml), and the reaction mixture stirred at room temperature for 13 h. The mixture was concentrated *in vacuo* and the residue was diluted with water. The resulting mixture was extracted with EtOAc and the extract washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane, 1:3 then 3:7) to give 18 (6.02 g, 67%) as an orange amorphous solid. ¹H-NMR (CDCl₃) δ: 1.31 (3H, t, J=7.2 Hz), 2.31 (3H, s), 2.52 (3H, s), 2.53 (3H, s), 4.26 (2H, q, J=7.2 Hz), 4.85 (2H, s), 5.34 (2H, s), 7.01–7.18 (4H, m), 7.23–7.38 (4H, m). IR (KBr): 2982, 1765, 1752, 1707, 1665, 1564, 1533, 1475 cm⁻¹.

Ethyl 6-(4-Hydroxyphenyl)-5-methyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (19a) To a solution of 18 (6.0 g, 11.1 mmol) in MeOH (150 ml) and THF (200 ml) was added a solution of K₂CO₃ (3.10 g, 22.4 mmol) in H₂O (70 ml). After stirring at room temperature for 40 min, the mixture was acidified with 1N HCl (50 ml) at 0°C and concentrated *in vacuo*. The concentrate was diluted with water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was crystallized from EtOAc-isopropyl ether to give 19a (4.33 g, 78%) as colorless crystals, mp 177–178°C. ¹H-NMR (CDCl₃) δ: 1.32 (3H, t, J=7.2 Hz), 2.45 (3H, s), 2.52 (3H, s), 4.28 (2H, q, J=7.2 Hz), 4.87 (2H, s), 5.28 (2H, s), 5.75 (1H, s), 6.78 (2H, d, J=8.6 Hz), 6.97–7.14 (4H, m), 7.21–7.34 (2H, m). IR (KBr): 3346, 2978, 1752, 1700, 1651, 1613, 1591, 1564, 1535, 1481 cm⁻¹. Anal. Calcd for C₂₃H₂₀N₂O₅S₂·0.1H₂O: C, 60.25; H, 4.89; N, 5.62; S, 12.87. Found: C, 60.09; H, 4.66; N, 5.57; S, 12.97.

Ethyl 6-(4-Methoxymethylphenyl)-5-methyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (19d) To an ice-cooled solution of 19a (0.50 g, 1.01 mmol) in DMF (4 ml) was added sodium hydride (60% in oil, 43 mg, 1.08 mmol) under a nitrogen atmosphere. After stirring at 0°C for 30 min, chloromethyl methyl ether (0.15 ml, 1.97 mmol) was added to the mixture. The mixture was then stirred at room temperature for 3 h and concentrated *in vacuo*. The residue was diluted with aqueous ammonium chloride and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄), evaporated *in vacuo*, and the residue purified by flash column chromatography (EtOAc-hexane, 1:3) to give 19d (0.46 g, 85%) as a white amorphous solid. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, J=7.1 Hz), 2.50 (3H, s), 2.53 (3H, s), 3.48 (3H, s), 4.25 (2H, q, J=7.1 Hz), 4.85 (2H, s), 5.19 (2H, s), 5.34 (2H, s), 7.01–7.18 (4H, m), 7.22–7.35 (4H, m). IR (KBr): 2964, 1750, 1711, 1665, 1564, 1533, 1477 cm⁻¹.

Compounds 19b, c, e, f were prepared from 19a by a similar procedure to that used for the preparation of 19d, in 84, 85, 77, and 48% yields, respectively. 19b: mp 122–123°C (from EtOAc-hexane). ¹H-NMR (CDCl₃) δ: 1.04 (3H, t, J=7.3 Hz), 1.31 (3H, t, J=7.1 Hz), 1.82 (2H, sext, J=7.3 Hz), 2.50 (3H, s), 2.53 (3H, s), 3.93 (2H, t, J=6.5 Hz), 4.26 (2H, q, J=7.1 Hz), 4.85 (2H, s), 5.34 (2H, s), 6.88–7.32 (8H, m). Anal. Calcd for C₂₈H₂₆N₂O₈S₂: C, 62.43; H, 5.61; N, 5.20. Found: C, 62.24; H, 5.68; N, 5.06. 19c: mp 85–88°C (from EtOAc-hexane). ¹H-NMR (CDCl₃) δ: 0.98 (3H, t, J=7.7 Hz), 1.31 (3H, t, J=7.1 Hz), 1.49 (2H, sext, J=7.7 Hz), 1.78 (1H, quin, J=7.7 Hz), 2.50 (3H, s), 2.53 (3H, s), 3.97 (2H, t, J=7.7 Hz), 4.25 (2H, q, J=7.1 Hz), 4.85 (2H, s), 5.34 (2H, s), 6.90 (2H, d, J=8.8 Hz), 7.00–7.37 (6H, m). Anal. Calcd for C₂₈H₂₆N₂O₈S₂: C, 63.02; H, 5.84; N, 5.07. Found: C, 63.17; H, 5.94; N, 4.98. 19e: mp 110–111°C (from EtOAc-ether-hexane). ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, J=7.1 Hz), 2.26 (3H, s), 2.50 (3H, s), 2.53 (3H, s), 4.25 (2H, q, J=7.1 Hz), 4.85 (2H, s), 5.16 (2H, s), 5.34 (2H, s), 6.94–7.18 (4H, m), 7.23–7.36 (4H, m). Anal. Calcd for C₂₈H₂₆N₂O₈S₂: C, 58.25; H, 5.07; N, 5.03; S, 17.28. Found: C, 58.20; H,

5.22; N, 4.95; S, 17.07. IR: mp 127–128°C (from EtOAc-hexane). ¹H-NMR (CDCl₃) δ: 1.31 (3H, t, *J* = 7.1 Hz), 2.29 (3H, s), 2.50 (3H, s), 2.53 (3H, s), 4.25 (2H, q, *J* = 7.1 Hz), 4.56 (2H, s), 4.85 (2H, s), 5.33 (2H, s), 6.87–7.32 (8H, m). Anal. Calcd for C₂₀H₁₆N₂O₄S₂: C, 60.85; H, 5.11; N, 5.07. Found: C, 60.69; H, 5.05; N, 4.80.

Ethyl 6-(4-Butyrylphenyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (21) To an ice-cooled mixture of 5d (0.39 g, 1.10 mmol) in nitrobenzene (10 ml) were added successively aluminum chloride (0.63 g, 4.75 mmol) and butyryl chloride (0.21 ml, 2.20 mmol). The reaction mixture was then stirred at 50°C for 6 h. The mixture was poured into ice-water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane, 3:1) to give 21 (0.05 g, 14%) as a pale yellow amorphous solid. ¹H-NMR (CDCl₃) δ: 1.03 (3H, t, *J* = 7.2 Hz), 1.32 (3H, t, *J* = 7.2 Hz), 1.77 (2H, sext, *J* = 7.2 Hz), 2.54 (3H, s), 2.98 (2H, t, *J* = 7.2 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 4.78 (2H, s), 7.51 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J* = 8.4 Hz), 10.20 (1H, s). FAB-MS *m/z*: 445 (MH⁺).

Ethyl 5-Methyl-6-(4-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (24) To an ice-cooled solution of 5d (2.20 g, 6.39 mmol) in concentrated sulfuric acid (12 ml) was added dropwise a solution of sodium nitrate (0.55 g, 6.47 mmol) in concentrated sulfuric acid (15 ml) over 10 min. The mixture was stirred at 0°C for 1 h and then poured into ice-water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane-CH₂Cl₂, 1:2:2) to give 24 (1.30 g, 52%) as a yellow solid. Recrystallization from EtOAc-hexane afforded yellow crystals, mp 277–280°C. ¹H-NMR (CDCl₃) δ: 1.33 (3H, t, *J* = 7.2 Hz), 2.56 (3H, s), 4.28 (2H, q, *J* = 7.2 Hz), 4.79 (2H, s), 7.57 (2H, d, *J* = 8.8 Hz), 8.30 (2H, d, *J* = 7.2 Hz), 10.66 (1H, brs). IR (KBr): 1748, 1663, 1522, 1460, 1348 cm⁻¹. Anal. Calcd for C₁₇H₁₃N₃O₈·0.4H₂O: C, 51.48; H, 4.01; N, 10.59. Found: C, 51.64; H, 3.79; N, 10.61.

Ethyl 6-(4-Aminophenyl)-5-methyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (25) A mixture of 24 (3.30 g, 8.47 mmol), 2-methylthiobenzyl chloride (1.76 g, 10.2 mmol), K₂CO₃ powder (1.76 g, 12.7 mmol), and KI powder (0.28 g, 1.69 mmol) in DMF (100 ml) was stirred at room temperature for 48 h. The mixture was concentrated *in vacuo*, and the residue was diluted with water and extracted with EtOAc. The extract was washed with brine and dried (Na₂SO₄). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (CH₂Cl₂) to afford the 2-methylthiobenzyl derivative (2.80 g, 60%) as a yellow amorphous solid. ¹H-NMR (CDCl₃) δ: 1.32 (3H, t, *J* = 7.2 Hz), 2.54 (3H, s), 2.60 (3H, s), 4.26 (2H, q, *J* = 7.2 Hz), 4.85 (2H, s), 5.36 (2H, s), 7.01–7.36 (4H, m), 7.51 (2H, d, *J* = 8.9 Hz), 8.25 (2H, d, *J* = 8.9 Hz).

A mixture of the 2-methylthiobenzyl derivative (3.0 g, 5.71 mmol), concentrated hydrochloric acid (2.0 ml), and iron powder (1.2 g, 20.4 mmol) in EtOH (40 ml) was heated under reflux with vigorous stirring for 30 min. After cooling, the mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was diluted with saturated NaHCO₃ and extracted with EtOAc. The extract was washed with brine and dried (Na₂SO₄). The solution was concentrated *in vacuo*, and the residue was recrystallized from EtOAc-isopropyl ether to give 25 (2.08 g, 74%) as colorless prisms, mp 172–173°C. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, *J* = 7.1 Hz), 2.49 (3H, s), 2.53 (3H, s), 3.78 (2H, brs), 4.25 (2H, q, *J* = 7.1 Hz), 4.84 (2H, s), 5.32 (2H, s), 6.67 (2H, d, *J* = 8.5 Hz), 7.03–7.32 (6H, m). IR (KBr): 3372, 1752, 1702, 1657, 1609, 1537, 1479 cm⁻¹. Anal. Calcd for C₂₃H₁₉N₃O₄S₂: C, 60.59; H, 5.08; N, 8.48. Found: C, 60.56; H, 4.93; N, 8.49.

Ethyl 5-Methyl-1-(2-methylthiobenzyl)-2,4-dioxo-6-(4-propionylaminophenyl)-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (26) To a solution of 25 (0.30 g, 0.61 mmol) in CH₂Cl₂ (30 ml) were added triethylamine (0.10 ml, 0.73 mmol) and propionyl chloride (0.11 ml, 1.22 mmol). After stirring at room temperature for 1.5 h, the mixture was diluted with aqueous ammonium chloride and extracted with CH₂Cl₂. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane-CH₂Cl₂, 5:5:1). The crude product was crystallized from EtOAc-hexane to give 26 (0.25 g, 74%) as colorless crystals, mp 218–219°C. ¹H-NMR (CDCl₃) δ: 1.22–1.34 (6H, m), 2.41 (2H, q, *J* = 7.5 Hz), 2.51 (3H, s), 2.53 (3H, s), 4.26 (2H, q, *J* = 7.1 Hz), 4.85 (2H, s), 5.32 (2H, s), 7.00–7.56 (9H, m). IR (KBr): 1707, 1661, 1537, 1479 cm⁻¹. Anal. Calcd for C₂₈H₂₉N₃O₄S₂: C, 60.96; H, 5.30; N, 7.62. Found: C, 60.82; H, 5.08; N,

7.78.

Ethyl 5-Aminomethyl-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (29) To a solution of 19d (6.10 g, 11.30 mmol) in CCl₄ (200 ml) were added NBS (2.11 g, 11.85 mmol) and 2,2'-azobis(isobutyronitrile) (0.19 g, 1.13 mmol) and the reaction mixture heated under reflux for 2 h. After cooling, insoluble material was removed by filtration and the filtrate diluted with water and extracted with CHCl₃. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane, 1:3 then 3:7). The crude product was crystallized from EtOAc-ether-hexane to afford the 5-bromomethyl derivative (5.73 g, 82%) as a white crystalline powder, mp 108–110°C. ¹H-NMR (CDCl₃) δ: 1.31 (3H, t, *J* = 7.1 Hz), 2.53 (3H, s), 3.49 (3H, s), 4.26 (2H, q, *J* = 7.1 Hz), 4.79 (2H, s), 4.88 (2H, s), 5.20 (2H, s), 5.35 (2H, s), 7.04–7.19 (4H, m), 7.24–7.35 (2H, m), 7.45 (2H, d, *J* = 9.0 Hz).

A mixture of the 5-bromomethyl derivative (1.26 g, 2.03 mmol) and phthalic anhydride (0.44 g, 2.13 mmol) in DMF (30 ml) was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo*, and the residue was diluted with water and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-hexane, 3:7 then 1:1). Crystallization from EtOAc-ether gave the 5-phthalimidomethyl derivative (1.05 g, 75%) as white crystals, mp 160–182°C. ¹H-NMR (CDCl₃) δ: 1.28 (3H, t, *J* = 7.1 Hz), 2.49 (3H, s), 3.37 (3H, s), 4.22 (2H, q, *J* = 7.1 Hz), 4.81 (2H, s), 4.91 (2H, s), 5.22 (2H, s), 5.31 (2H, s), 6.70 (2H, d, *J* = 8.8 Hz), 7.04–7.32 (4H, m), 7.57–7.66 (4H, m).

To a mixture of the 5-phthalimidomethyl derivative (0.95 g, 1.38 mmol) in EtOH (50 ml) was added hydrazine monohydrate (0.34 ml, 6.92 mmol) and the reaction mixture stirred at 80°C for 16 h. After cooling, the mixture was concentrated *in vacuo* and the residue was diluted with saturated NaHCO₃. The resulting mixture was then extracted with CH₂Cl₂. The extract was washed with brine and dried (MgSO₄). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (CHCl₃-MeOH, 20:1) to give 29 (0.64 g, 84%) as a white solid. Recrystallization from EtOAc-hexane afforded a white crystalline powder, mp 114–116°C. ¹H-NMR (CDCl₃) δ: 1.31 (3H, t, *J* = 7.1 Hz), 2.53 (3H, s), 3.48 (3H, s), 3.92 (2H, s), 4.26 (2H, q, *J* = 7.1 Hz), 4.86 (2H, s), 5.19 (2H, s), 5.35 (2H, s), 7.01–7.35 (8H, m). IR (KBr): 1705, 1671, 1584, 1531 cm⁻¹. Anal. Calcd for C₂₆H₂₆N₃O₄S₂: C, 58.36; H, 5.26; N, 7.56. Found: C, 58.22; H, 5.34; N, 7.54.

Ethyl 5-(3-Ethylureidomethyl)-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (30f) A mixture of 29 (0.30 g, 0.54 mmol) and ethyl isocyanate (45 μl, 0.57 mmol) in pyridine (5 ml) was stirred at room temperature for 2 h. After evaporation of the solvent *in vacuo*, the residue was diluted with aqueous ammonium chloride and extracted with CH₂Cl₂. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was recrystallized from EtOAc-hexane to give 30f (0.33 g, 98%) as a colorless crystalline powder, mp 207–208°C. ¹H-NMR (CDCl₃) δ: 1.08 (3H, t, *J* = 7.1 Hz), 1.32 (3H, t, *J* = 7.1 Hz), 2.52 (3H, s), 3.11–3.20 (2H, m), 3.47 (3H, s), 4.16 (1H, t, *J* = 5.8 Hz), 4.26 (2H, q, *J* = 7.1 Hz), 4.46 (2H, m), 4.86 (2H, s), 5.18 (2H, s), 5.35 (2H, s), 6.07 (1H, t, *J* = 6.8 Hz), 7.01–7.34 (6H, m), 7.51 (2H, d, *J* = 8.6 Hz). IR (KBr): 1756, 1711, 1665, 1630, 1562, 1535 cm⁻¹. Anal. Calcd for C₃₂H₃₁N₃O₄S₂: C, 57.49; H, 5.47; N, 8.94. Found: C, 57.24; H, 5.63; N, 8.99.

Ethyl 6-(4-Methoxymethoxyphenyl)-5-methylsulfonylaminoethyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (30g) To an ice-cooled solution of 29 (0.80 g, 1.44 mmol) in CH₂Cl₂ (20 ml) was added triethylamine (0.22 ml, 1.58 mmol) and methanesulfonyl chloride (0.12 ml, 1.55 mmol). After stirring at 0°C for 30 min, the mixture was diluted with brine and extracted with CH₂Cl₂. The extract was washed with brine and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (EtOAc-CH₂Cl₂-MeOH, 5:1:0 then 10:2:1) to give 30g (0.91 g, 100%) as a white solid. Recrystallization from EtOAc-hexane afforded white crystals, mp 115–118°C. ¹H-NMR (CDCl₃) δ: 1.33 (3H, t, *J* = 7.1 Hz), 2.53 (3H, s), 2.87 (3H, s), 3.48 (3H, s), 4.27 (2H, q, *J* = 7.1 Hz), 4.37 (2H, d, *J* = 6.8 Hz), 4.85 (2H, s), 5.19 (2H, s), 5.36 (2H, s), 6.07 (1H, t, *J* = 6.8 Hz), 7.01–7.18 (4H, m), 7.27–7.36 (4H, m). IR (KBr): 3274, 2960, 1744, 1709, 1657, 1607, 1557, 1533, 1485 cm⁻¹. Anal. Calcd for C₃₄H₃₁N₃O₄S₃·0.1C₄H₉: C, 53.48; H, 5.08; N, 6.54; S, 14.97. Found: C, 53.66; H, 5.20; N, 6.37; S, 15.09.

Compounds 30a–e, h–j were prepared by a similar procedure to that

used for the preparation of 30g and their physicochemical data are listed in Table 7.

Ethyl 6-(4-Methoxymethoxyphenyl)-5-(N-methyl-N-methylsulfonylaminomethyl)-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrotetrahydro-2,3-dipyrroline-3-acetate (33) To an ice-cooled solution of 30g (0.23 g, 0.36 mmol) in DMF (4 ml) was added sodium hydride (60% in oil, 15 mg, 0.38 mmol) under a nitrogen atmosphere. After stirring at 0°C for 30 min, iodomethane (0.12 ml, 1.93 mmol) was added dropwise to the mixture, which was then stirred at 0°C for 30 min and at room temperature for 2 h. After evaporation of the solvent *in vacuo*, the residue was diluted with aqueous ammonium chloride and extracted with EtOAc. The extract was washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo*, and the residue purified by flash column chromatography (EtOAc-hexane, 4:6 then 9:1) to give 33 (0.21 g, 89%) as a white amorphous powder. ¹H-NMR (CDCl₃) δ: 1.31 (3H, t, *J* = 7.2 Hz), 2.54 (3H, s), 2.66 (3H, s), 2.87 (3H, s), 3.47 (3H, s), 4.25 (2H, q, *J* = 7.2 Hz), 4.65 (2H, s), 4.85 (2H, s), 5.19 (2H, s), 5.37 (2H, s), 7.03–7.08 (3H, m), 7.13–7.18 (1H, m), 7.29–7.40 (1H, m). IR (KBr): 2930, 1750, 1711, 1663, 1607, 1562, 1535, 1472 cm⁻¹. FAB-MS *m/z*: 648 (MH⁺).

Potassium Salt of 6-(4-Methoxymethoxyphenyl)-5-methylsulfonylaminomethyl-1-(2-methylthiobenzyl)-2,4-dioxo-1,2,3,4-tetrahydrotetrahydro-2,3-dipyrroline-3-acetic Acid (32g) To a solution of 32g (0.13 g, 0.215 mmol) in EtOH (7 ml)-THF (3 ml) was added a solution of K₂CO₃ (21.5 mg, 0.215 mmol) in H₂O (1.5 ml) at 70°C. After stirring at 70°C for 2 min, the mixture was stirred at room temperature for 15 min. After evaporation of the solvent *in vacuo*, the residue was recrystallized from EtOAc-ether to afford the potassium salt of 32g (0.123 g, 89%) as a white powder, mp 245–247°C. ¹H-NMR (DMSO-*d*₆) δ: 2.55 (3H, s), 2.58 (3H, s), 3.38 (3H, s), 4.22 (2H, s), 4.29 (2H, q, *J* = 4.6 Hz), 5.19 (2H, s), 5.23 (2H, s), 6.92 (1H, br s), 7.01–7.15 (4H, m), 7.29–7.42 (4H, m). IR (KBr): 3500, 3256, 2932, 1698, 1659, 1599, 1531, 1479 cm⁻¹. FAB-MS *m/z*: 644 (MH⁺). Anal. Calcd for C₂₈H₃₀KN₂O₈S₃·0.5H₂O: C, 47.84; H, 4.17; N, 6.44. Found: C, 47.86; H, 4.30; N, 6.53.

Potassium salts of 20d, 20e, 32h, and 32i were prepared by a similar procedure to that used for the preparation of the potassium salt of 32g, in 86, 91, 78, and 98% yields, respectively.

Potassium Salt of 20d mp 192–198°C (from EtOAc-EtOH). ¹H-NMR (DMSO-*d*₆) δ: 2.43 (3H, s), 2.55 (3H, s), 3.37 (3H, s), 4.17 (2H, s), 5.14 (2H, s), 5.21 (2H, s), 6.99–7.15 (4H, m), 7.26–7.40 (4H, m). Anal. Calcd for C₂₈H₃₀KN₂O₈S₃·0.5H₂O: C, 53.65; H, 4.32; N, 5.01. Found: C, 53.39; H, 4.18; N, 4.80.

Potassium Salt of 20e mp 149–155°C (from EtOAc-EtOH). ¹H-NMR (DMSO-*d*₆) δ: 2.17 (3H, s), 2.43 (3H, s), 2.55 (3H, s), 4.17 (2H, s), 5.14 (2H, s), 5.29 (2H, s), 6.99–7.15 (4H, m), 7.26–7.40 (4H, m). Anal. Calcd for C₂₈H₃₀KN₂O₈S₃·0.4C₂H₆O·1.6H₂O: C, 50.47; H, 4.69; N, 4.56. Found: C, 50.22; H, 4.93; N, 4.86.

Potassium Salt of 32h mp 155–160°C (from EtOAc-EtOH-ether). ¹H-NMR (DMSO-*d*₆) δ: 1.16 (3H, t, *J* = 7.2 Hz), 2.55 (3H, s), 2.98 (2H, q, *J* = 7.2 Hz), 3.38 (3H, s), 4.20–4.28 (4H, m), 5.19–5.23 (4H, m), 6.87–7.42 (9H, m). Anal. Calcd for C₂₈H₃₀KN₂O₈S₃·0.5H₂O: C, 48.63; H, 4.38; N, 6.30. Found: C, 48.84; H, 4.66; N, 6.37.

Potassium Salt of 32i mp 148–153°C (from EtOAc-EtOH-ether). ¹H-NMR (DMSO-*d*₆) δ: 0.91 (3H, t, *J* = 7.3 Hz), 1.59 (2H, sext, *J* = 7.3 Hz), 2.55 (3H, s), 2.92 (2H, t, *J* = 7.3 Hz), 3.38 (3H, s), 4.24–4.29 (4H, m), 5.19 (2H, s), 5.23 (2H, s), 6.85–7.15 (5H, m), 7.29–7.42 (4H, m). Anal. Calcd for C₂₈H₃₀KN₂O₈S₃·0.5H₂O: C, 49.39; H, 4.59; N, 6.17. Found: C, 49.33; H, 4.84; N, 6.28.

Expression of Human ET_A and ET_B Receptors in Sf9 Cells Human ET_A cDNA³⁴ and ET_B cDNA³⁵ were cloned from human placenta mRNA using reverse transcription and polymerase chain reaction methods. Human ET_A and ET_B cDNAs were subcloned individually into a transfer vector, pBlueBacIII (Invitrogen). The transfer vectors harboring ET_A and ET_B cDNA were co-transfected into Sf9 cells separately with AcMNPV genomic DNA to generate the recombinant baculoviruses. Human ET_A and ET_B receptors were expressed in Sf9 cells infected by the recombinant baculovirus as described previously.³⁷ Sf9 cell membranes were prepared according to the protocol previously reported.³⁸

Inhibitory Effect on the Specific Binding of [¹²⁵I] ET-1 to the Cloned Human ET_A and ET_B Receptors The receptor binding experiments were performed as described previously.³⁷ Briefly, Sf9 cell membranes (1.4 μg protein/ml for the ET_A receptor and 0.7 μg protein/ml for the ET_B receptor) suspended in binding assay buffer (20 mM Tris, 2 mM EGTA, 5 mM magnesium acetate, 0.1% bovine serum albumin, 0.5 mM phenylmethylsulfonyl fluoride, 20 μg/ml leupeptin, 4 μg/ml E-64, 1 μg/ml pepstatin A, and 0.03%

sodium azide, pH 7.2) were incubated with 100 pM [¹²⁵I]ET-1 (Amersham) and various concentrations of a test compound at 25°C for 1 h. The mixture was diluted with chilled assay buffer supplemented with 0.05% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS) and filtered through a glassfiber filter GF/F (Whatman). Radioactivity on the filter was counted in a γ-counter to determine bound [¹²⁵I]ET-1. The concentration of a test compound inducing 50% inhibition of the specific binding (IC₅₀ value) was derived by fitting the data into a pseudo Hill equation:

$$\log[\%SPB/(100 - \%SPB)] = n[\log C - \log(IC_{50})]$$

where %SPB is specific binding as a percentage of maximum specific binding, *n* is a pseudo Hill constant, and *C* is the concentration of a test compound.

Inhibitory Effect on Constriction of Ring Preparations of Porcine Coronary Artery Induced by ET-1 and of Vein Preparations Induced by Sarafotoxin S6c The vasoconstriction assay was performed according to a procedure analogous to that described previously.³⁹ Ring preparations of porcine coronary artery or vein (3 mm diameter) were placed in an organ bath filled with Krebs solution gassed with 95% O₂–5% CO₂ at 37°C and allowed to stand for 1.5 h at a resting load of 2 g tension for arteries or 0.5 g tension for veins. The preparations were constricted with 60 mM KCl for 10 min and then washed and allowed to stand for 1 h at the resting load. After pre-treatment of test compounds at various concentrations or vehicle (0.1% dimethyl sulfoxide (DMSO)) for 30 min, artery preparations constricted with ET-1 at 1 nM and vein preparations constricted with sarafotoxin S6c at 1 nM were used to determine the inhibitory effects of test compounds.

Acknowledgement We wish to thank Dr. T. Naka, Dr. H. Sugihara, and Mr. T. Yasuna for helpful advice and discussions. We also express our thanks to Dr. Y. Fujisawa for cloning of human ET_A and ET_B cDNA and Mr. K. Mitsu for supporting the synthetic studies.

References

- 1) Yanagisawa M., Kurihara H., Kimura S., Tamohe Y., Kobayashi M., Mitsui Y., Yazaki Y., Goto K., Masaki T., *Nature* (London), 332, 411–415 (1988).
- 2) a) Itoh Y., Yanagisawa M., Ohkubo S., Kimura C., Kosaka T., Inoue A., Ishida N., Mitsui Y., Onda H., Fujino M., Masaki T., *FEBS Lett.*, 231, 440–444 (1988); b) Inoue A., Yanagisawa M., Kimura S., Kasuya Y., Miyachi T., Goto K., Masaki T., *Proc. Natl. Acad. Sci. U.S.A.*, 86, 2863–2867 (1989); c) Onda H., Ohkubo S., Ogi K., Kosaka T., Kimura C., Matsumoto H., Suzuki N., Fujino M., *FEBS Lett.*, 261, 327–330 (1990); d) Ohkubo S., Ogi K., Hosoya M., Matsumoto H., Suzuki N., Kimura C., Onda H., Fujino M., *FEBS Lett.*, 274, 135–140 (1990).
- 3) a) Kling Y., Ambar I., Sokolovsky M., Kochva E., Wollberg Z., Gilula A., *Science*, 242, 268–270 (1988); b) Lee C. Y., Chippinelli V. A., *Nature* (London), 335, 303 (1988); c) Takasaki C., Yanagisawa M., Kimura S., Goto K., Masaki T., *ibid.*, 335, 303 (1988).
- 4) a) Arai H., Hori S., Aramori I., Ohkubo H., Nakanishi S., *Nature* (London), 348, 730–732 (1990); b) Sakurai T., Yanagisawa M., Takuwa Y., Miyazaki H., Kimura S., Goto K., Masaki T., *Nature* (London), 348, 732–735 (1990).
- 5) Panek R. L., Major T. C., Hingorani G. P., Doherty A. M., Taylor D. G., Rapundalo S. T., *Biochem. Biophys. Res. Commun.*, 183, 566–571 (1992).
- 6) Warner T. D., Allcock G. H., Corder R., Vane J. R., *Br. J. Pharmacol.*, 110, 777–782 (1993).
- 7) Ohlstein E. H., Arleth A., Bryan H., Elliott J. D., Sung C. P., *Eur. J. Pharmacol.*, 225, 347–350 (1992).
- 8) a) Moreland S., McMullen D. M., Delaney C. L., Lee V. G., Hunt J. T., *Biochem. Biophys. Res. Commun.*, 184, 100–106 (1992); b) Hay D. W. P., Luttmann M. A., Hubbard W. C., Underhill B. J., *Br. J. Pharmacol.*, 110, 1175–1183 (1993); c) Pollock D. M., Ogenorth T. J., *Am. J. Physiol.*, 264, R222–R226 (1993); d) Moreland S., McMullen D., Abboa-Offei B., Seymour A., *Br. J. Pharmacol.*, 112, 704–708 (1994); e) Seo B., Oemar B. S., Siebenmann R., von Segesser L., Lüscher T. F., *Circulation*, 89, 1203–1208 (1994).
- 9) a) De Nucci G., Thomas R., D'Orleans-Juste P., Antunes E., Walder C., Warner T. D., Vane J. R., *Proc. Natl. Acad. Sci. U.S.A.*, 85, 9797–9800 (1988); b) Warner T. D., Mitchell J. A., De Nucci G., Vane J. R., *J. Cardiovasc. Pharmacol.*, 13 (suppl. 5), S85–S88 (1989).
- 10) a) Doherty A. M., *J. Med. Chem.*, 35, 1493–1508 (1992); b) Miller R. C., Pelton J. T., Huggins J. P., *Trends Pharmacol. Sci.*, 14, 54–60

- (1993).
- 11) Aramori I., Nirei H., Shoubo M., Sogabe K., Nakamura K., Koju H., Natsu Y., Ono T., Nakanishi S., *Mol. Pharmacol.*, **43**, 127-131 (1993).
 - 12) a) Ihara M., Noguchi K., Sacki T., Fukuroda T., Tsuchida S., Kimura S., Fukami T., Ishikawa K., Nishikibe M., Yano M., *Life Sci.*, **50**, 247-255 (1992); b) Ishikawa K., Fukami T., Nagase T., Fujita K., Hayama T., Niyama K., Mase T., Ihara M., Yano M., *J. Med. Chem.*, **35**, 2139-2142 (1992).
 - 13) Clozel M., Breu V., Burri K., Cassal J.-M., Fischli W., Gray G. A., Hirli G., Löffler B.-M., Müller M., Neidhart W., Ramuz H., *Nature (London)*, **363**, 759-761 (1993).
 - 14) Roux S. P., Clozel M., Sprecher U., Gray G., Clozel J. P., *Circulation*, **88**, 1-170 (1993).
 - 15) a) Stein P. D., Hunt J. T., Floyd D. M., Moreland S., Dickinson R. E. J., Mitchell C., Liu E. C.-K., Webb M. L., Murgesan N., Dickey J., McMullen D., Zhang R., Lee V. G., Serafino R., Defaney C., Schaeffer T. R., Kozlowski M., *J. Med. Chem.*, **37**, 329-331 (1994); b) Stein P. D., Floyd D. M., Bisaha S., Dickey J., Girotra R. N., Gougoutas J. Z., Kozlowski M., Lee V. G., Liu E. C.-K., Malley M. E., McMullen D., Mitchell C., Moreland S., Murgesan N., Serafino R., Webb M. L., Zhang R., Hunt J. T., *J. Med. Chem.*, **38**, 1344-1354 (1995).
 - 16) a) Elliott J. D., Lago M. A., Cousins R. D., Gao A., Leber J. D., Edhard K. F., Nambi P., Elshourbagy N. A., Kumar C., Lee J. A., Bean J. W., Deffrosse C. W., Eggleston D. S., Brooks D. P., Feuerstein G., Ruffolo, Jr. R. R., Weinstein J., Gleason J. G., Peishoff C. E., Ohlstein E. H., *J. Med. Chem.*, **37**, 1553-1557 (1994); b) Ohlstein E. H., Nambi P., Douglas S. A., Edwards R. M., Gellai M., Lago A., Leber J. D., Cousins R. D., Gao A., Frazee J. S., Peishoff C. E., Bean J. W., Eggleston D. S., Elshourbagy N. A., Kumar C., Lee J. A., Yue T.-L., Loudon C., Brooks D. P., Weinstein J., Feuerstein G., Poste G., Ruffolo, Jr. R. R., Gleason J. G., Elliott J. D., *Proc. Natl. Acad. Sci. U.S.A.*, **91**, 5852-5856 (1994).
 - 17) Winn M., von Geldern T. W., Oppenorth T. J., Jue H.-S., Tasker A. S., Boyd S. A., Kester J. A., Mantei R. A., Bal R., Sorensen B. K., Wu-Wong J. R., Chiu W. J., Dixon D. H., Nicosad E. L., Hernandez L., Marsh K. C., *J. Med. Chem.*, **39**, 1039-1048 (1996).
 - 18) Walsh T. P., Fitch K. J., Chakravarty P. K., Williams D. L., Murphy K. A., Nolan N. A., O'Brien J. A., Lis E. V., Pettibone D. J., Kivlighn S. D., Gabel R. A., Zingaro G. J., Krause S. M., Siegl P. K. S., Cline-Schmidt B. V., Grodzice W. J., Abstracts of Papers, American Chemical Society National Meeting, Washington, D.C., August, 1994, MEDI 145.
 - 19) Doherty A. M., Pau W. C., Edmunds J. J., Berryman K. A., Reisdorph B. R., Plummer M. S., Shahripour A., Lee C., Cheng X.-M., Walker D. M., Halzen S. J., Keiser, J. A., Flynn M. A., Welch K. M., Hallak H., Taylor D. G., Reynolds E. E., *J. Med. Chem.*, **38**, 1259-1263 (1995).
 - 20) Kikuchi T., Ohtaki T., Kawata A., Imada T., Asami T., Masuda Y., Sugo T., Kasamoto K., Kubo K., Watanabe T., Wakimasa M., Fujino M., *Biochem. Biophys. Res. Commun.*, **200**, 1708-1712 (1994).
 - 21) a) Nakajima K., Kubo S., Kumagaye S., Nishio H., Tsunemi M., Inui T., Kuroda H., Chino N., Watanabe T. X., Kimura T., Sakakibara S., *Biochem. Biophys. Res. Commun.*, **163**, 424-429 (1989); b) Hunt J. T., Lee V. G., Stein P. D., Hedberg A., Liu E. C.-K., McMullen D., Moreland S., *Bioorg. Med. Chem. Lett.*, **1**, 33-36 (1991).
 - 22) Furuya S., Cho N., Imada T., Inaeda T., Hayase Y., Sasaki S., Harada M., Matsumoto H., Suzuki N., Okubo S., Ogi K., Onda H., Fujino M., Abstracts of Papers, 17th Symposium on Medicinal Chemistry/6th Annual Meeting of Division of Medicinal Chemistry/1997 Second Conference on Drug Discovery (The Pharmaceutical Society of Japan), Tsukuba, November, 1997, 2-P-34.
 - 23) Duncia J. V., Carini D. J., Chiu A. T., Johnson A. L., Price W. A., Wong P. C., Wexler R. R., Timmermans P. B. M. W. M., *Med. Res. Rev.*, **12**, 149-191 (1992).
 - 24) Freidinger R. M., *Med. Res. Rev.*, **9**, 271-290 (1989).
 - 25) Snider R. M., Constantine J. W., Lowe III J. A., Longo K. P., Lebel W. S., Woody H. A., Drozda S. E., Desai M. C., Vinick F. J., Spencer R. W., Hess H.-J., *Science*, **251**, 435-437 (1991).
 - 26) Yamamura Y., Ogawa H., Chihara T., Rondo K., Onogawa T., Nakamura S., Mori T., Tomimaga M., Yabuuchi Y., *Science*, **252**, 572-574 (1991).
 - 27) Gewald K., Schinke E., Büttcher H., *Chem. Ber.*, **99**, 94-100 (1966).
 - 28) Huffman C. W., *J. Org. Chem.*, **23**, 727-729 (1958).
 - 29) Krishnamurthy S., *Tetrahedron Lett.*, **23**, 3315-3318 (1982).
 - 30) Miyaura N., Yanagi T., Suzuki A., *Synth. Commun.*, **11**, 513-519 (1981).
 - 31) Thompson W. J., Gaudino J., *J. Org. Chem.*, **49**, 5237-5243 (1984).
 - 32) a) Sudjarwo S. A., Hori M., Takai M., Urade Y., Okada T., Karaki H., *Life Sci.*, **53**, 431-437 (1993); b) Warner T. D., Allcock G. H., Mickleley E. J., Corder R., Vane J. R., *J. Cardiovasc. Pharmacol.*, **22** (Suppl. 8), S117-S120 (1993); c) Reynolds E. E., Huang O., Flynn M. A., Welch K. M., Cody W. L., Steinbaugh B., He J. X., Chung F. Z., Doherty A. M., *Biochem. Biophys. Res. Commun.*, **209**, 506-512 (1995).
 - 33) Hosoda K., Nakao K., Arai H., Suga S., Ogawa Y., Mukoyama M., Shirakami G., Saito Y., Nakanishi S., Imura H., *FEBS Lett.*, **287**, 23-26 (1991).
 - 34) Ogawa Y., Nakao K., Arai H., Nakagawa O., Hosoda K., Suga S., Nakanishi S., Imura H., *Biochem. Biophys. Res. Commun.*, **178**, 248-255 (1991).
 - 35) Luckow V. A., Summers M. D., *BioTechnology*, **6**, 47-55 (1988).
 - 36) Masuda Y., Sugo T., Kikuchi Y., Kawata A., Satoh M., Fujisawa Y., Itoh Y., Wakimasa M., Ohtaki T., *J. Pharmacol. Exp. Ther.*, **279**, 675-685 (1996).
 - 37) Kikuchi T., Kubo K., Ohtaki T., Suzuki N., Asami T., Shimamoto N., Wakimasa M., Fujino M., *J. Med. Chem.*, **36**, 4087-4093 (1993).