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SUPERINDUSTRIA Y CIENCIA
Radicación : 00079628 00000003 Folios 2
Fecha (AMD) 2002-11-20 16 36 20
Tramite 002 PATENTES D 1 REGISTRO/ 536 PETICION
Dependencia: 2028 DIVISION DE NUEVAS CREACIONES

AS 04 339

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E S D

REF Expediente No 00 039 628 solicitud de Patente a nombre de
MONSANTO COMPANY

RAMIRO CASTRO DUQUE, vecino de Bogotá, portador de la tarjeta profesional No 1003 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad MONSANTO COMPANY, según lo acredita el documento de poder protocolizado en la Secretaría General bajo el No 300, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No 02-71,440 por valor de \$318 000

Señor Superintendente,


RAMIRO CASTRO DUQUE
C C No 170 322 de Bogotá
Código 340
T P No 1003 del C S J
Cra 7 No 16-56 Piso 9

Noviembre 19, 2002
CPB/hr

Industria y Comercio
SUPERINTENDENCIA

Radicación: 80039628 80040003 Folios 2
Fecha (AND): 2002-11-20 16:36:28
Trámite: 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT 800176089-2

RECIBO OFICIAL DE CAJA 02 - 71,440
FECHA OCTUBRE 24 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PAGO	Vr PAGO
BRIBARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	5165316	23/10/2002	8,834,000 00

***** CONCEPTO *****

CANT	DETALLE	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000 00
		TOTAL	\$ 318,000 00

SON TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

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593
591

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D C .

Doctor
RAMIRO CASTRO DUQUE
(Apoderado)

ASUNTO

Radicación 00039628
Trámite 002
Evento 001
Actuación 430
Oficio
Folios 048

06543

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica

Documentos estudiados

Los textos estudiados fueron la descripción (Folios 6 a 357) y las reivindicaciones 1 a 49 (Folios 495 a 587)

La presente solicitud no reivindica prioridad

Objeto de invención

La presente solicitud se titula "Anillo policíclico y pirazinonas de heteroarilo sustituidos útiles para la inhibición selectiva de la cascada de coagulación"

El objeto de la presente solicitud se refiere a compuestos, composiciones y métodos para la prevención y el tratamiento de estados trombóticos, tales como la enfermedad cerebrovascular y de arteria coronaria. La solicitud se relaciona particularmente con los compuestos de anillo policíclico y la pirazinona de heteroarilo que inhiben las proteasas de serina de la cascada de coagulación.

Según la descripción, la sangre debe permanecer fluida dentro de los sistemas vasculares y al mismo tiempo poder someterse rápidamente a hemostasis, interrupción de pérdida de sangre de un vaso lesionado. La hemostasis o coagulación comienza cuando las plaquetas se adhieren primero a las macromoléculas en las regiones subendoteliales de los vasos lesionados y/o dañados. Esas plaquetas se agrupan para formar el tapón hemostático primario y estimular la activación local de los factores de coagulación del plasma, produciendo a la generación de un coágulo de fibrina que refuerza las plaquetas agrupadas.

Los factores de coagulación incluyen los factores II, V, VII, VIII, IX, X, XI y XII, que reciben el nombre de zimógenos de proteasa. Estos factores de coagulación o zimógenos de proteasa se activan mediante proteasas de serina que llevan a la coagulación en una "cascada de coagulación" o reacción en cadena. La coagulación ocurre de dos formas a través de dos caminos diferentes. Un camino intrínseco o de

contacto conduce del XII a XIII a XIa a IXa y a la conversión de X a Xa. Xa con el factor Va convierte la protrombina (II) a trombina (IIa) conduciendo a la conversión de fibrinógeno a fibrina. La polimerización de la fibrina lleva a la formación de un coágulo de fibrina. Se inicia un camino extrínseco mediante la conversión del factor de coagulación VII a VIIa por Xa. La presencia del Factor Tisular y VIIa acelera la formación de Xa en presencia de ión de calcio y fosfolípidos. La formación de Xa lleva a la formación de trombina, fibrina y a un coágulo de fibrina. La presencia de uno o más de estos muy diferentes factores de coagulación y dos caminos definidos de coagulación podrían hacer posible el control efectivo, selectivo y una mejor comprensión de las partes del proceso de coagulación.

De acuerdo con la presente solicitud la prevención o tratamiento de coágulos en un vaso sanguíneo puede ser terapéuticamente útil inhibiendo la formación de agrupaciones de plaquetas sanguíneas, inhibiendo la formación de fibrina, de trombos, de émbolos y para el tratamiento o prevención de angina inestable, angina refractaria, infarto al miocardio, ataques isquémicos, ataque embólico, etc. Se han presentado varios informes de compuestos no peptídicos y peptídicos que actúan como inhibidores de un factor coagulante presente en el proceso de coagulación de la cascada de coagulación.

Según la descripción, la solicitud WO 98/42342 describe que alquilo, cicloalquilo y trifluorometilo sustituidos adicionales en derivados de pirazinonas reportan haber inhibido la trombina humana. La solicitud WO 99/59591 describe que pirazinonas de 1-((N-daminopindil sustituto y N-fenil sustituto)amidocarbonilmetileno) reportan haber inhibido trombina. La solicitud WO 99/64446 describe que pirazinonas de 1-((N-amidinoaminoxialquileno y N-amidinohidrazinoalquileno)amidocarbonilmetileno) reportan haber inhibido proteasas de senna del tipo tripsina y trombina.

Lo que se reivindica como novedoso es lo siguiente:

Un compuesto derivado de anillo policíclico y pirazinonas de heteroanillo sustituidos de fórmula I (ver folio 495)

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/495

Claridad de la solicitud

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción."

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

De acuerdo con lo anterior, las reivindicaciones no son concisas y están abarcando un sinnúmero de compuestos por lo que no se puede apreciar con claridad el alcance de la invención.

Excepciones de Patentabilidad

El artículo 20 de la Decisión 486 se establece "No serán patentables a) las invenciones cuya explotación comercial en el territorio del País Miembro respectivo deba impedirse necesariamente para proteger el orden público o la moral. A estos efectos la explotación comercial de una invención no se considerará contraria al orden público o a la moral solo debido a la existencia de una disposición legal."

o administrativa que prohíba o que regule dicha explotación b) las invenciones cuya explotación comercial en el País Miembro respectivo deba impedirse necesariamente para proteger la salud o la vida de las personas o de los animales o para preservar los vegetales o el medio ambiente A estos efectos la explotación comercial de una invención no se considerará contraria a la salud o la vida de las personas de los animales o para la preservación de los vegetales o del medio ambiente sólo por razón de existir una disposición legal o administrativa que prohíba o que regule dicha explotación, c) las plantas, los animales y los procedimientos esencialmente biológicos para la producción de plantas o animales que no sean procedimientos no biológicos o microbiológicos, d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales "

De acuerdo con lo anterior, la(s) reivindicación(es) 40 a 49 (Folios 585 a 587), que se refieren a un metodo para inhibir las condiciones trombóticas en la sangre, no es (son) patentable(s)

Determinación del estado de la técnica

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de Patente o en su caso de la prioridad reconocida

Sólo para el efecto de la determinación de la novedad también se considerará dentro del estado de la técnica el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40"

Considerando que la fecha de presentación de la solicitud de patente es 29-05-2000, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma

Se encontró como antenoridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica pnoridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud

Nº	Documento	Título	Fecha de Publicación
1	WO 99/59591	Pyrazinone thrombin inhibitors	25 de noviembre de 1999
2	US 5866573	Pyrazinone thrombin inhibitors	2 de febrero de 1999
3	WO 99/64446	Pyrazinone protease inhibitors	16 de diciembre de 1999
4	WO 99/11267	Pyrazinone thrombin inhibitors	11 de marzo de 1999
5	US 5792779	Pyndinone thrombin inhibitors	11 de agosto de 1998
6	WO 97/30708	Pyndinone thrombin inhibitors	28 de agosto de 1997

Nº	Documento	Título	Fecha de Publicación
7	WO 97/01338	Pyridinone-thrombin inhibitors	16 de enero de 1997
8	WO 98/42342	Thrombin inhibitors	1 de octubre de 1998
9	WO 97/01338	Pyridinone-thrombin inhibitors	16 de enero de 1997

Evaluación de los requisitos de Patentabilidad

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece "Los Países Miembros otorgarán Patentes para las invenciones sean de producto o de procedimiento en todos los campos de la tecnología siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio

Evaluación de Novedad

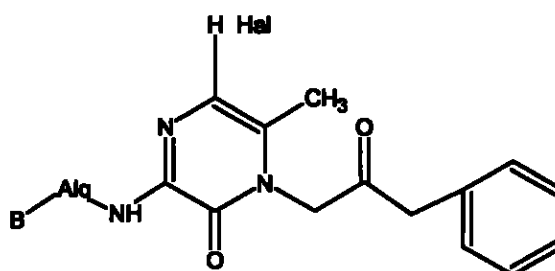
El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Una invención se considerará nueva cuando no esté comprendida en el estado de la técnica" "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida"

Sólo para el efecto de la determinación de la novedad también se considerará dentro del estado de la técnica el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40"

Esta se evaluó por comparación entre lo solicitado y los documentos encontrados en el estado de la técnica y que se relacionan con el objeto reivindicado y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que

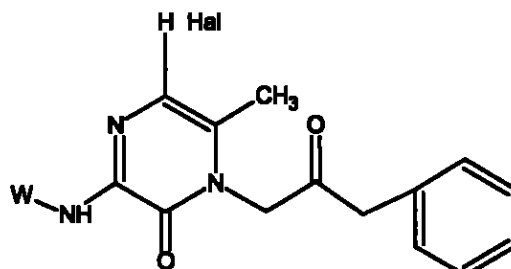
La Solicitud de Patente Colombiana No 00039628 menciona compuestos derivados de anillo policíclicos y pirazinonas de heteroanillo sustituidos de fórmula



B puede ser fenilo, o heterociclo cuyos heteroátomos pueden ser N, O, S

Alq es alquilo
Hal es halógeno

El documento **WO 99/59591** (folios 599 a 605) menciona compuestos derivados de pirazinona que son inhibidores de trombina, de fórmula I



W es fenilo-alquilo
Hal es halógeno

Como se observa, el objeto de esta solicitud puede ser idéntico a lo comprendido en el estado de la técnica, con lo cual se considera que podría no cumplir con el requisito de Novedad

Evaluación de Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención tiene nivel inventivo si para una persona del oficio normalmente versada en la materia técnica correspondiente esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina

Los documentos WO 99/59591 (folios 599 a 605), US 5866573 (folios 606 a 609), WO 99/64446 (folios 610 a 614), WO 99/11267 (folios 615 a 621), US 5792779 (folios 622 a 624), WO 97/30708 (folios 625 a 629), WO 97/01338 (folios 630 a 633), WO 98/42342 (folios 634 a 636) y WO 97/01338 (folios 637 a 640) mencionan compuestos inhibidores de trombina que guardan relación estructural con los compuestos de la presente solicitud, es decir, tienen diferencias mínimas en alguno de los sustituyentes pero no se afecta la actividad farmacológica de los mismos, la actividad sigue siendo la misma (inhibidores de trombina)

La respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de las anterioridades en mención

Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica

Evaluación de la Aplicación Industrial

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria entendiéndose por industria la referida a cualquier actividad productiva incluidos los servicios"

El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 99/59591	1 a 39	Novedad y Nivel Inventivo
2	US 5866573	1 a 39	Nivel Inventivo
3	WO 99/64446	1 a 39	Nivel Inventivo
4	WO 99/11267	1 a 39	Nivel Inventivo
5	US 5792779	1 a 39	Nivel Inventivo
6	WO 97/30708	1 a 39	Nivel Inventivo
7	WO 97/01338	1 a 39	Nivel Inventivo
8	WO 98/42342	1 a 39	Nivel Inventivo
9	WO 97/01338	1 a 39	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

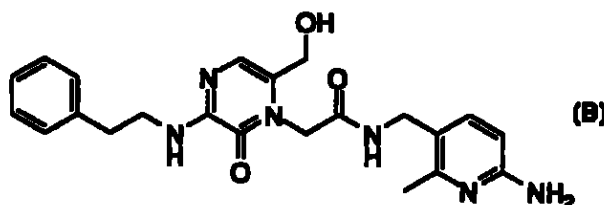
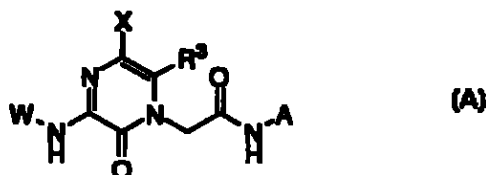
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 10 4 AGO 2005

CONCEPTO TÉCNICO N° 1104	EXAMINADOR TÉCNICO Código N° 202005	EXAMINADOR JURÍDICO Código N°
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(51) International Patent Classification ⁶ A61K 31/535	A1	(11) International Publication Number WO 99/59591 (43) International Publication Date: 25 November 1999 (25.11.99)
(21) International Application Number PCT/US99/10730 (22) International Filing Date 14 May 1999 (14.05.99) (30) Priority Data 60/085 980 19 May 1998 (19.05.98) US 9813580.9 24 June 1998 (24.06.98) GB (71) Applicant (for all designated States except US): MERCK & CO INC [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US) (72) Inventors; and (75) Inventors/Applicants (for US only): SANDERSON Philip E. [GB/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US) STANTON Matthew, G [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US) BALANI Suresh K. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US) (74) Common Representative MERCK & CO INC., 126 East Lincoln Avenue, Rahway NJ 07065 (US).	(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG) Published With international search report	

(54) Title **PYRAZINONE THROMBIN INHIBITORS**

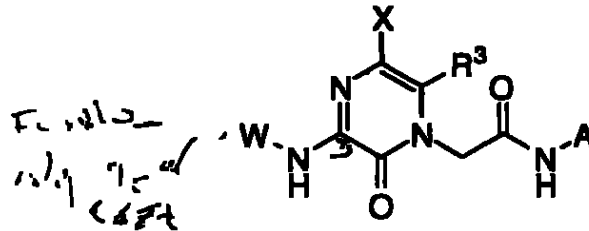
(57) Abstract

Compounds of the invention are useful in inhibiting thrombin and associated thrombotic occlusions having structure (A), wherein (B)

600
59B

WHAT IS CLAIMED IS

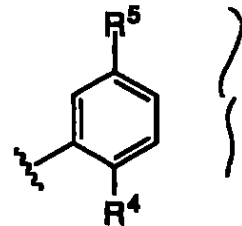
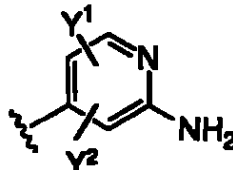
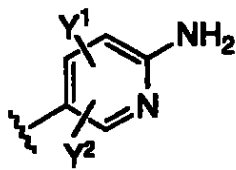
1 A compound having the formula



5

or a pharmaceutically acceptable salt thereof, wherein

A is chosen from one of the following radicals



10 wherein Y^1 and Y^2 are independently
 hydrogen,
 C1-4 alkyl,
 C1-4 alkoxy,
 C3-7 cycloalkyl,
 15 halogen, or
 trifluoromethyl,

 R^4 is

a) hydrogen,
 b) C1-4 alkyl,
 20 c) C1-4 alkoxy,
 d) halogen,
 e) $-\text{OCH}_2\text{CF}_3$,
 f) $-\text{OCH}_2\text{CN}$,
 g) $-\text{COOH}$,
 25 h) $-\text{OH}$,
 i) $-\text{COOR}^6$, where R^6 is C1-4alkyl,

601
JPP

- j) $-\text{CONR}^7\text{R}^8$, where R^7 and R^8 are independently hydrogen or C_{1-4} alkyl,
- k) $-(\text{CH}_2)_{1-4}\text{OH}$,
- l) $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$,
- 5 m) $-\text{CH}_2\text{NHC}(\text{O})\text{CF}_3$,
- n) $-\text{CH}_2\text{NHSO}_2\text{CH}_3$,
- o) $-\text{SO}_2\text{NH}_2$,
- p) $-(\text{CH}_2)_{1-4}\text{SO}_2\text{NR}^7\text{R}^8$,
- q) $-(\text{CH}_2)_{1-4}\text{SO}_2\text{R}^6$,
- 10 r) a 5- to 7- membered mono- or a 9- to 10-membered bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to four heteroatoms selected from the group consisting of N, O and S,
- s) $-\text{ZCH}_2\text{CO}_2\text{H}$,
- 15 t) $-\text{ZCH}_2\text{CO}_2\text{CH}_3$,
- u) $-\text{ZCH}_2\text{R}^{14}$,
- v) $-\text{ZCH}_2\text{CO}_2(\text{CH}_2)_{1-3}\text{CH}_3$,
- w) $-\text{Z}(\text{CHR}^9)_{1-3}\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$,
- wherein
- 20 R^9 is H or C_{1-4} alkyl,
- R^{10} and R^{11} are independently
- i) hydrogen,
- ii) C_{3-7} cycloalkyl,
- iii) aryl,
- 25 iv) heteroaryl,
- v) heterocycloalkyl,
- vi) $-(\text{CH}_2)_{1-2}\text{NCH}_2\text{CH}_3$,
- vii) C_{1-4} alkyl unsubstituted or substituted with one or more of
- 30 hydroxy,
- COOH ,
- amino,
- aryl,
- heteroaryl, or

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heterocycloalkyl, or
R¹⁰ and R¹¹ are joined to form a four to seven
membered cycloalkyl ring unsubstituted or
substituted with hydroxy, amino or aryl,

5

wherein Z is O, S or CH₂,

R⁵ is

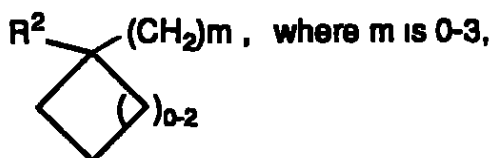
hydrogen,
10 halogen,
C1-4 alkyl,
C1-4 alkoxy,
CF₃,
CN, or
15 CO₂NH₂, and

W is

hydrogen,
20 R¹,
R¹OCO,
R¹CO,
R¹(CH₂)_nNHCO, or
(R¹)₂CH(CH₂)_nNHCO,
25 wherein n is 0-4,

R¹ is

a) R²,
b) R²(CH₂)_mC(R¹²)₂, where m is 0-3, and each R¹² can be the
30 same or different,
c) (R²)(OR²)CH(CH₂)_p, where p is 1-4,
d)

603
601

- 5 e) $R^2C(R^{12})_2(CH_2)_m$, wherein m is 0-3, and each R^{12} can be the same or different, wherein $(R^{12})_2$ can also form a ring with C represented by C3-7 cycloalkyl,
- f) $R^2CH_2C(R^{12})_2(CH_2)_q$, wherein q is 0-2, and each R^{12} can be the same or different, wherein $(R^{12})_2$ can also form a ring with C represented by C3-7 cycloalkyl,
- 10 g) $(R^2)_2CH(CH_2)_r$, where r is 0-4 and each R^2 can be the same or different, and wherein $(R^2)_2$ can also form a ring with CH represented by C3-7 cycloalkyl, C7-12 bicyclic alkyl, C10-16 tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to three heteroatoms selected
- 15 from the group consisting of N, O and S,
- h) $R^2O(CH_2)_p$, wherein p is 1-4,
- i) $R^2CF_2C(R^{12})_2$,
- j) $(R^2CH_2)(R^2CH_2)CH$, or
- 20 k) $R^2(COOR^{13})(CH_2)_r$, where r is 1-4,
- 25 R^2 is
- a) phenyl, unsubstituted or substituted with one or more of C1-4 alkyl, C1-4 alkoxy, halogen, hydroxy, COOH, CONH₂, CH₂OH, CO₂R', where R' is C1-4 alkyl, or SO₂NH₂,
- b) naphthyl,
- c) biphenyl,
- 30 d) a 5- to 7- membered mono- or a 9- to 10-membered bicyclic heterocyclic ring or non-heterocyclic ring which can be saturated or unsaturated, wherein the heterocyclic ring contains from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the heterocyclic or non-

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heterocyclic ring is unsubstituted or substituted with halogen or hydroxy,

e) C₁₋₇ alkyl, unsubstituted or substituted with one or more of

hydroxy,

5

COOH,

amino,

aryl,

C₃₋₇ cycloalkyl,

CF₃,

10

N(CH₃)₂,

-C₁₋₃alkylaryl,

heteroaryl, or

heterocycloalkyl,

f) CF₃

15

g) C₃₋₇ cycloalkyl, unsubstituted or substituted with aryl,

h) C₇₋₁₂ bicyclic alkyl, or

i) C₁₀₋₁₆ tricyclic alkyl,

R³ is selected from the group consisting of

20

a) YR¹⁵ wherein

Y is O or S(O)_n, where n is 0, 1, or 2, and

f- R¹⁵ is H, C₁₋₄ alkyl or C₃₋₇ cycloalkyl, or

25

b) C₁₋₄ alkyl substituted with halogen, CN, N₃ or YR¹⁶, wherein

Y is O or S(O)_n, where n is 0, 1, or 2, and

R¹⁶ is H, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl,

R¹³ is selected from the group consisting of

30

hydrogen,

C₁₋₄ alkyl,

C₃₋₇ cycloalkyl, or

trifluoromethyl,

35

X is

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603

hydrogen, or
halogen, and

R¹² is

- 5 a) hydrogen,
b) phenyl, unsubstituted or substituted with one or more of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxy, COOH, CONH₂,
c) naphthyl,
d) biphenyl,
10 e) a 5- to 7- membered mono- or a 9- to 10-membered bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to four heteroatoms selected from the group consisting of N, O and S,
f) C₁₋₄ alkyl, unsubstituted or substituted with one or more of
15 hydroxy,
COOH,
amino,
aryl,
heteroaryl, or
20 heterocycloalkyl,
g) CF₃
h) C₃₋₇ cycloalkyl,
i) C₇₋₁₂ bicyclic alkyl, or
j) C₁₀₋₁₆ tricyclic alkyl

25

2 A compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein

W is

- 30 C₁₋₇ alkyl, unsubstituted or substituted with one or more of
hydroxy,
COOH,
amino,
aryl,
35 C₃₋₇ cycloalkyl,

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[54] PYRAZINONE THROMBIN INHIBITORS

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[21] Appl No 837,682

[22] Filed Apr 21, 1997

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[60] Provisional application No 60/016,041, Apr 23, 1996

[51] Int Cl⁶ .. A61K 31/495, C07D 401/12
C07D 403/12, C07D 413/12

[52] U.S. CL .. 514/235.8 514/252, 514/253,
514/255 544/120 544/405 544/408

[58] Field of Search .. 544/405, 408,
544/120 514/252 253, 235.8 255

[56] References Cited

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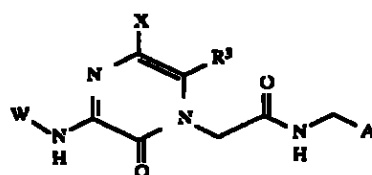
0 262 096 9/1987 European Pat Off

Primary Examiner—Emily Bernhardt

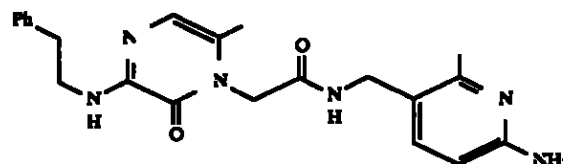
Attorney, Agent, or Firm—Richard S Parr Melvin Winokur

[57] ABSTRACT

Compounds of the invention are useful in inhibiting thrombin and associated thrombotic occlusions having the following structure



for example



18 Claims, No Drawings

Component	0.25 mg	2 mg	10 mg	50 mg
Active IV	0.500%	1.000%	5.000%	14.29%
mannitol	49.50%	49.25%	47.25%	42.61%
microcrystalline cellulose	49.50%	49.25%	47.25%	42.61%
magnesium stearate	0.500%	0.500%	0.500%	0.500%

2, 10 and 50 mg tablets were film-coated with an aqueous dispersion of hydroxypropyl cellulose hydroxypropyl methylcellulose and titanium dioxide, providing a nominal weight gain of 2.4%

Tablet Preparation Via Direct Compression

Active IV mannitol and microcrystalline cellulose were sieved through mesh screens of specified size (generally 250 to 750 μ m) and combined in a suitable blender. The mixture was subsequently blended (typically 15 to 30 min) until the drug was uniformly distributed in the resulting dry powder blend. Magnesium stearate was screened and added to the blender after which a precompression tablet blend was achieved upon additional mixing (typically 2 to 10 min). The precompression tablet blend was then compacted under an applied force typically ranging from 0.5 to 2.5 metric tons sufficient to yield tablets of suitable physical strength with acceptable disintegration times (specifications will vary with the size and potency of the compressed tablet). In the case of the 2, 10 and 50 mg potencies, the tablets were dedusted and film-coated with an aqueous dispersion of water-soluble polymers and pigment.

Tablet Preparation Via Dry Granulation

Alternatively a dry powder blend is compacted under modest forces and remilled to afford granules of specified particle size. The granules are then mixed with magnesium stearate and tableted as stated above.

EXAMPL LXXXVI

Intravenous Formulations

Intravenous formulations of 3 (2-Phenethylamino)-6 methyl-1 (2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl) pyrazinone dihydrochloride Type A monohydrate (Active IV) were prepared according to general intravenous formulation procedures.

Component	Estimated range
Active IV	0.12-0.61 mg
D-glucuronic acid*	0.5-5 mg
Mannitol NF	50-83 mg
1N Sodium Hydroxide	q.s. pH 3.9-4.1
Water for injection	q.s. 1.0 mL

Exemplary compositions A-C are as follows.

Component	A	B	C
Active IV	0.61 mg*	0.30**	0.15 **
D-glucuronic acid	1.94 mg	1.94 mg	1.94 mg
Mannitol NF	51.2 mg	51.2 mg	51.2 mg

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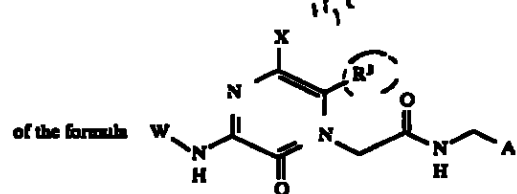
1N Sodium Hydroxide	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0
Water for injection	q.s. 1.0 mL	q.s. 1.0 mL	q.s. 1.0 mL

5 *0.50 mg free base
0.25 mg free base
**0.12 mg free base

10 Various other buffer acids, such as L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be substituted for glucuronic acid.

15 What is claimed is

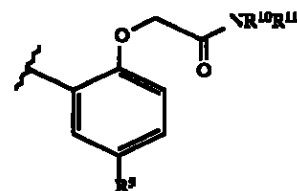
1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is

i)



wherein

R3 is H, fluoro, chloro and

R10 and R11 are independently selected from

H

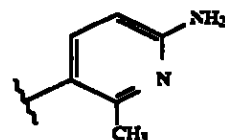
C2H5,

C3H7,

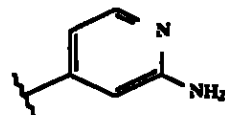
(CH2)2N(CH2)2

C3 cycloalkyl

ii)

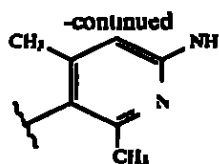


iii)

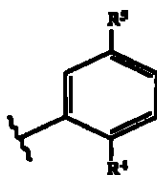


iv)

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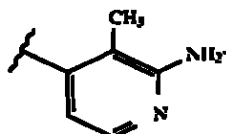


v)



wherein R^4 is OH, chloro, H, $-OCH_2CN$, fluoro, $-OCH_2COOH$, and R^5 is chloro or CF_3

vi)



R^3 is CH_3 , or CH_2CH_3 ,

X is H or chloro, and

W is

$PhCH_2CH_2$,

$(CH_3)_3C-$

$HOOCCH_2$

CF_3CH_2 ,

$(CH_3)_2N(CH_2)_2$

$PhCH_2O(CH_2)_2$

$PhCH(CH_3)$,

$PhCH_2CH(COOH)$

$CH_3(CH_2)_3$,

$PhCH_2-$

H

$CH_3(CH_2)_4$

$CH_3CH_2CH(CH_3)CH_2$

$(Ph)_2CHCH_2$

$PhCH_2CH(CH_3)$,

$PhCH_2C(CH_3)_2$

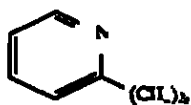
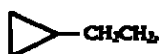
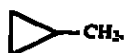
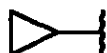
$PhCH(CH_3)CH_2$

$(CH_3)_2CH$

$PhCH(OH)CH_2$

$PhC(CH_3)CH_2$

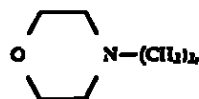
$(Ph)_2CHCH_2$



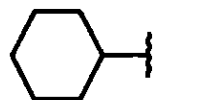
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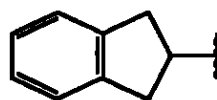
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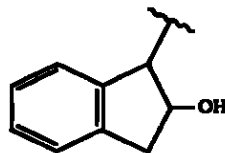
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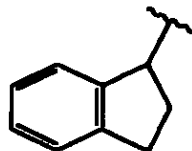
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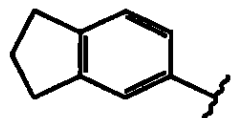
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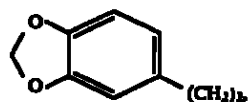
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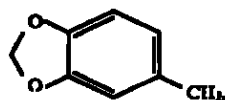
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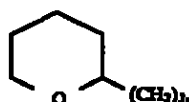
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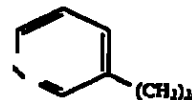
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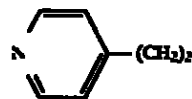
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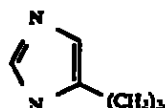
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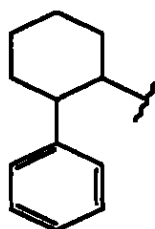
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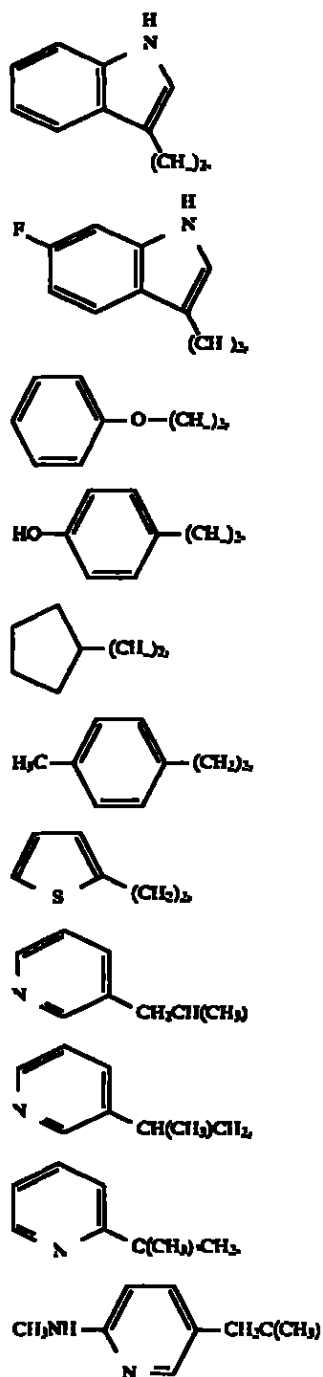
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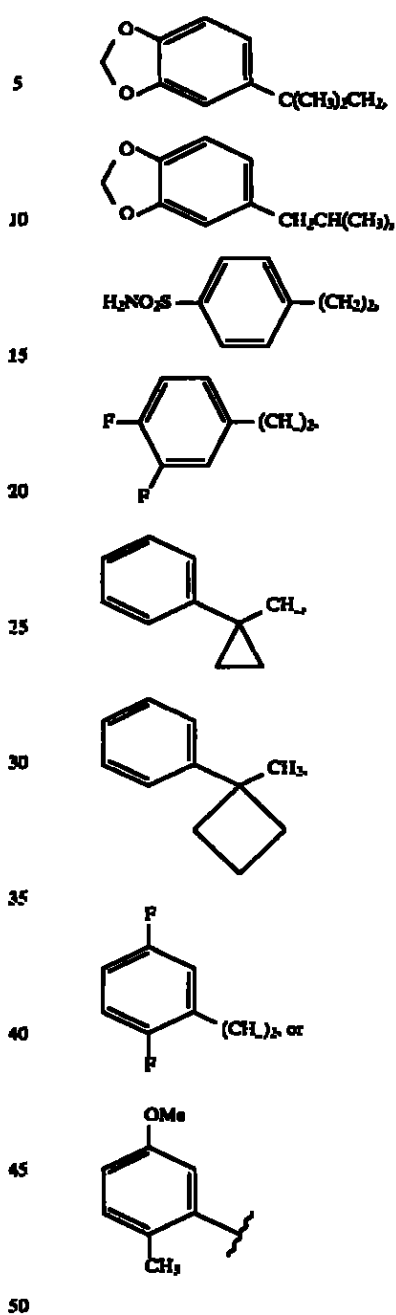
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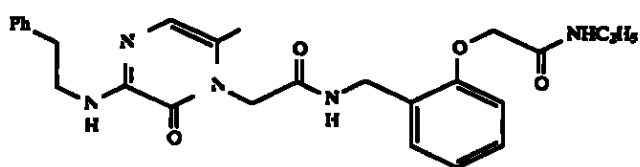
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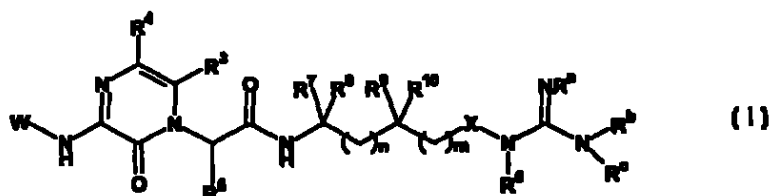


2 The compound of claim 1 or a pharmaceutically acceptable salt thereof selected from the group consisting of



(51) International Patent Classification ⁶ C07K 5/078, A61K 38/05, G01N 33/68		A1	(11) International Publication Number WO 99/64446
			(43) International Publication Date: 16 December 1999 (16.12.99)
(21) International Application Number PCT/US99/13228		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW	
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		Published With international search report Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments	

(54) Title. PYRAZINONE PROTEASE INHIBITORS

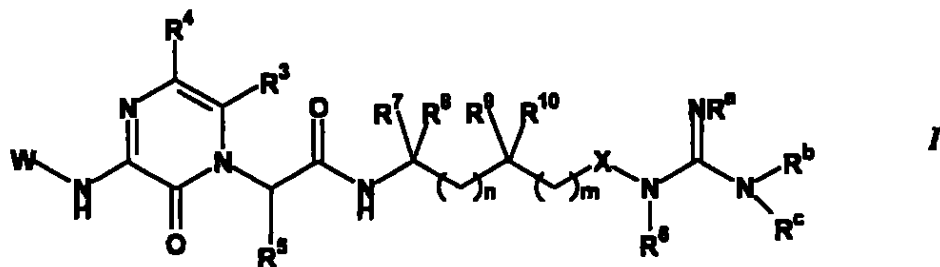


(57) Abstract

Pyrazinone compounds are described, including compounds of Formula (I) wherein X is O, NR¹¹ or CH=N, R³, R¹¹, R^a, R^b, R^c, W, m and n are set forth in the specification as well as hydrates, solvates or pharmaceutically acceptable salts thereof. The compounds of the invention are potent inhibitors of proteases, especially trypsin-like serine proteases, such as chymotrypsin, trypsin, thrombin, plasmin and factor Xa. Certain of the compounds exhibit antithrombotic activity *via* direct, selective inhibition of thrombin. Compositions for inhibiting loss of blood platelets, inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation are described. Other uses of compounds of the invention are as anticoagulants either embedded in or physically linked to materials used in the manufacture of devices used in blood collection, blood circulation and blood storage, such as catheters, blood dialysis machines, blood collection syringes and tubes, blood lines and stents. Additionally, the compounds can be detectably labeled and employed for *in vivo* imaging of thrombi.

611
609**What Is Claimed Is**

1 A compound of Formula I



or a solvate, hydrate or pharmaceutically acceptable salt thereof, wherein

5 W is hydrogen, R¹, R¹OCO, R¹CO, R¹(CH₂)_sNHCO, or (R¹)₂CH(CH₂)_sNHCO
wherein s is 0-4,

R¹ isR²

10 R²(CH₂)_tC(R¹²)₂, wherein t is 0-3 and each R¹² is the same or different,

(R²)(OR¹²)CH(CH₂)_p, wherein p is 1-4,(R²)₂(OR¹²)C(CH₂)_p, wherein p is 1-4

R²C(R¹²)₂(CH₂)_t, wherein t is 0-3, and each R¹² is the same or different, and
wherein (R¹²)₂ together with the C to which they are attached can
also form a 3- to 7-membered cycloalkyl ring,

15 R²CH₂C(R¹²)₂(CH₂)_q, wherein q is 0-2, and each R¹² is the same or different,
and wherein (R¹²)₂, together with the C to which they are attached,
can also form a 3- to 7-membered cycloalkyl ring,

20 R²CF₂C(R¹²)₂(CH₂)_q, wherein q is 0-2, and each R¹² is the same or different,
and wherein (R¹²)₂, together with the C to which they are attached
can also form a 3- to 7-membered cycloalkyl ring,

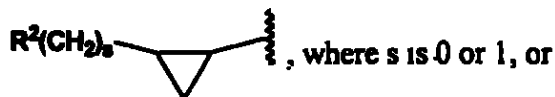
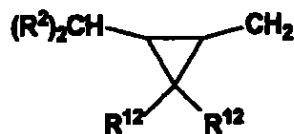
(R²)₂CH(CH₂)_r, wherein r is 0-4, and each R² is the same or different, and
wherein (R²)₂, together with the C to which they are attached, can
also form a C₃₋₇ cycloalkyl, C₇₋₁₂ bicyclic alkyl, C₁₀₋₁₆ tricyclic alkyl,
or a 5- to 7-membered, saturated or unsaturated mono- or bi-cyclic

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510

heterocyclic ring, having from one to three heteroatoms selected from N, O, and S,

$R^2O(CH_2)_p$, wherein p is 2-4,

$(R^{12})_2CF(CH_2)_r$, wherein r is 0-4 and each R^{12} is the same or different, and wherein $(R^{12})_2$, together with the C to which they are attached, can also form a 3- to 7-membered cycloalkyl, C_{7-12} bicyclic alkyl, C_{10-16} tricyclic alkyl, or a 5- to 7-membered mono- or bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to three heteroatoms selected from the group consisting of N, O and S,



$R^2CF_2C(R^{12})_2$,

R^2 is

phenyl, naphthyl or biphenyl, each of which is optionally substituted with one or more of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, CF_3 , OCF_3 , $COOH$, $CONH_2$, or SO_2NH_2 ,

a 5- to 7-membered, saturated or unsaturated, mono- or a 9- to 10-membered bi-cyclic ring optionally having from one to four heteroatoms selected from N, O, or S, and optionally substituted with halogen or hydroxy,

C_{1-7} alkyl, optionally substituted with one or more of hydroxy, $COOH$, amino, aryl, C_{2-7} cycloalkyl, CF_3 , $N(CH_3)_3$, $-C_{1-3}$ alkylaryl, heteroaryl, or heterocycloalkyl,

CF_3

C_{3-7} cycloalkyl, optionally substituted with aryl,

C_{7-12} bicyclic alkyl or

613
611

C_{10-16} tricyclic alkyl,

R^3 is

hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl,
optionally substituted aralkyl optionally substituted heteroaryl,
5 trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamido,
-CO₂R^x, -CH₂OR^x, or OR^x wherein R^x, in each instance is
independently one of hydrogen, optionally unsaturated alkyl, or
optionally unsaturated cycloalkyl,

R^4 is

10 hydrogen or halogen,

R^{12} is

hydrogen,

phenyl naphthyl or biphenyl, each of which is optionally substituted with
one or more of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxy, CF₃, OCF₃,
15 COOH, or CONH₂,

a 5- to 7-membered mono- or a 9- to 10-membered bi-cyclic, saturated or
unsaturated, heterocyclic ring having from one to four heteroatoms
selected from N, O, or S,

C₁₋₄ alkyl, optionally substituted with one or more of hydroxy, COOH,
20 amino, aryl, heteroaryl, or heterocycloalkyl,

CF₃,

C₃₋₇ cycloalkyl,

C₇₋₁₂ bicyclic alkyl, or

C₁₀₋₁₆ tricyclic alkyl,

25 R^5 is hydrogen, C₁₋₄ alkyl, or C₂₋₄ alkenyl,

R^6 is hydrogen, alkyl alkenyl, aralkyl aryl, hydroxyalkyl aminoalkyl,
monoalkylamino(C₂₋₁₀)alkyl, dialkylamino(C₂₋₁₀)alkyl, or carboxyalkyl,

R^7 , R^8 , R^9 , R^{10} are independently hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl,
aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, or carboxyalkyl,

30 or R^7 and R^8 , together with the C to which they are attached, form a 3- to 8-
membered cycloalkyl group, and R^9 and R^{10} are as defined above,

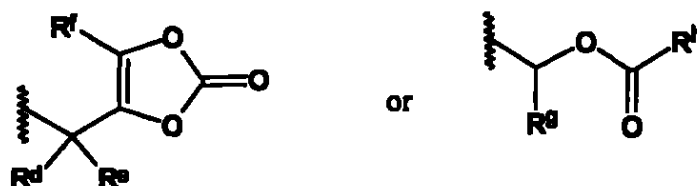
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or R^9 and R^{10} , together with the C to which they are attached, form a 3- to 8-membered cycloalkyl group, and R^7 and R^8 are as defined above,
 or R^7 and R^9 , together with the C to which they are attached, form a 3- to 8-membered cycloalkyl group, and R^8 and R^{10} are as defined above,

5 X is oxygen, $-NR^{11}-$, or $-CH=N-$, wherein R^{11} is hydrogen, alkyl, cycloalkyl, or aryl and said alkyl, cycloalkyl and aryl are optionally substituted with amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, carboxy, alkoxycarbonyl, aryloxy, aralkoxycarbonyl, aryl, heteroaryl, acylamino, cyano, or trifluoromethyl,

10 R^a , R^b and R^c are independently hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbonyl, cyano, or $-CO_2R^w$, wherein

R^w is alkyl, cycloalkyl, phenyl, benzyl



15 where R^d and R^e are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^f is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^g is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, and R^h is aralkyl or C_{1-6} alkyl,

n is zero to 8, and

m is zero to 6

20 2 A compound of claim 1, wherein
 R^3 is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or CF_3 ,
 m is from zero to 4, and
 n is from zero to 4

3 A compound of claim 2, wherein R^3 is C_{1-4} alkyl

25 4 A compound of claim 2, wherein R^4 is hydrogen or halogen

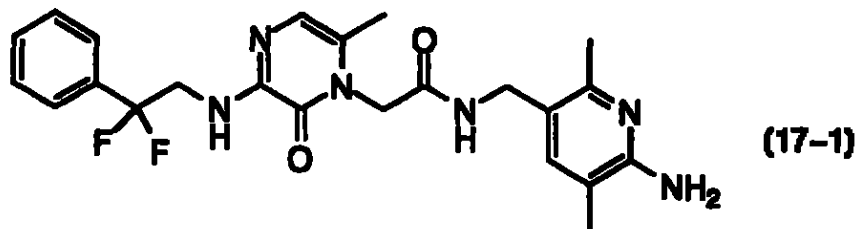
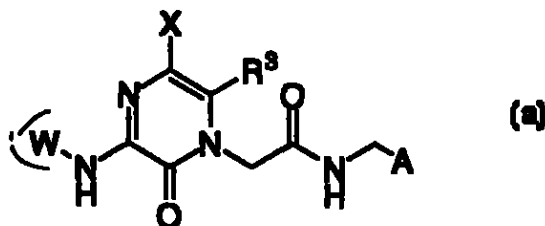
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ A61K 31/495, C07D 241/20, 401/12, 401/14, 405/12, 405/14	A1	(11) International Publication Number WO 99/11267 (43) International Publication Date: 11 March 1999 (11.03.99)
(21) International Application Number: PCT/US98/18417 (22) International Filing Date: 3 September 1998 (03.09.98) (30) Priority Data: 60/058,058 5 September 1997 (05.09.97) US 9801005 1 16 January 1998 (16.01.98) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SANDERSON, Philip E. [GB/US], 126 East Lincoln Avenue, Rahway NJ 07065 (US). LYLE, Terry A. [US/US] 126 East Lincoln Avenue, Rahway, NJ 07065 (US). DORSEY, Bruce, D. [US/US], 126 East Lincoln Avenue, Rahway, NJ 07065 (US) (74) Common Representative: MERCK & CO., INC., 126 East Lincoln Avenue, Rahway NJ 07065 (US).	(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: **PYRAZINONE THROMBIN INHIBITORS**

(57) Abstract

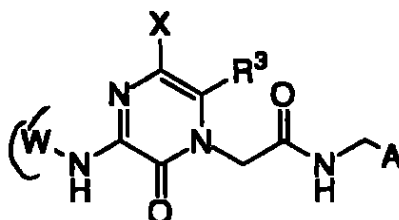
Compounds of the invention are useful in inhibiting thrombin and associated thrombotic occlusions having structure (a), for example, structure (17-1)



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WHAT IS CLAIMED IS

1 A compound having the formula



5 wherein

W is

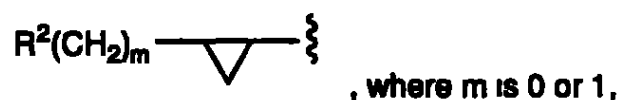
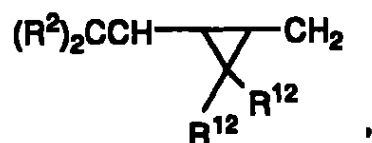
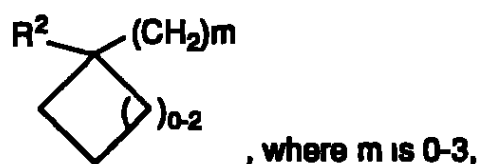
hydrogen,
 R^1 ,
 10 R^1OCO ,
 R^1CO ,
 $R^1(CH_2)_nNHCO$, or
 $(R^1)_2CH(CH_2)_nNHCO$,
 wherein n is 0-4,

15

 R^1 is

R^2 ,
 $R^2(CH_2)_mC(R^{12})_2$, where m is 0-3, and each R^{12} can be the same
 or different,
 20 $(R^2)(OR^2)CH(CH_2)_p$, where p is 1-4,

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615


$$\text{R}^2\text{CCCH}_2,$$

$R^2C(R^{12})_2(CH_2)_m$, wherein m is 0-3, and each R^{12} can be the same or different, wherein $(R^{12})_2$ can also form a ring with C represented by C₃₋₇ cycloalkyl.

$R^2CH_2C(R^{12})_2(CH_2)_q$, wherein q is 0-2, and each R^{12} can be the same or different, wherein $(R^{12})_2$ can also form a ring with C represented by C3-7 cycloalkyl.

$(R^2)_2CH(CH_2)_r$, where r is 0-4 and each R^2 can be the same or different, and wherein $(R^2)_2$ can also form a ring with CH represented by C₃₋₇ cycloalkyl, C₇₋₁₂ bicyclic alkyl, C₁₀₋₁₆ tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to three heteroatoms selected from the group consisting of N, O and S.

$$R^2O(CH_2)_p$$
, wherein p is 1-4,
$$R^2CF_2C(R^{12})_2,$$
$$(R^2CH_2)(R^2CH_2)CH, \text{ or}$$
$$R^2(COOR^3)(CH_2)_r, \text{ where } r \text{ is } 1-4,$$

**R² and R¹⁴ are independently
phenyl, unsubstituted or substituted with one or more of C₁₋₄
alkyl, C₁₋₄ alkoxy, halogen, hydroxy, COOH, CONH₂,
CH₂OH, CO₂R', where R' is C₁₋₄ alkyl, or SO₂NH₂.**

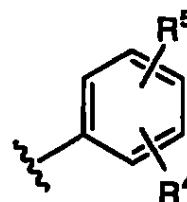
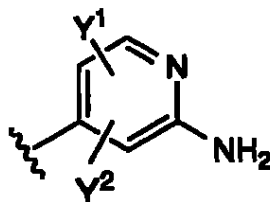
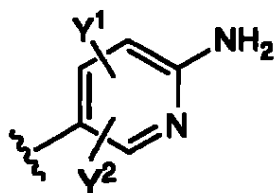
naphthyl,

biphenyl,

- a 5- to 7- membered mono- or a 9- to 10-membered bicyclic heterocyclic ring or non-heterocyclic ring which can be saturated or unsaturated, wherein the heterocyclic ring contains from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the heterocyclic or non-heterocyclic ring is unsubstituted or substituted with halogen, C₁₋₄ alkyl, or hydroxy,
- 5 C₁₋₇ alkyl, unsubstituted or substituted with one or more of
- hydroxy,
- 10 COOH,
- halogen,
- amino,
- aryl,
- C₃₋₇ cycloalkyl,
- 15 CF₃,
- N(CH₃)₂,
- C₁₋₃alkylaryl,
- heteroaryl, or
- heterocycloalkyl,
- 20 CF₃
- C₃₋₇ cycloalkyl, unsubstituted, monosubstituted with halogen or aryl, or disubstituted with halogen,
- C₇₋₁₂ bicyclic alkyl, or
- C₁₀₋₁₆ tricyclic alkyl,
- 25 R³₁₈
- hydrogen,
- C₁₋₄ alkyl,
- C₃₋₇ cycloalkyl, or
- trifluoromethyl,
- 30 X is hydrogen or halogen,

A is chosen from one of the following radicals

6A



wherein Y¹ and Y² are independently
hydrogen,
C₁₋₄ alkyl,
C₁₋₄ alkoxy,
C₃₋₇ cycloalkyl,
halogen, or
trifluoromethyl,

10 R⁴ is

hydrogen,
C₁₋₄ alkyl,
C₁₋₄ alkoxy,
halogen,
-OCH₂CF₃,
-OCH₂CN,
-COOH,
-OH,
-COOR⁶, where R⁶ is C₁₋₄alkyl,
-CONR⁷R⁸, where R⁷ and R⁸ are independently
hydrogen or C₁₋₄alkyl,
-(CH₂)₁₋₄OH,
-CH₂NHC(O)CH₃,
-CH₂NHC(O)CF₃,
-CH₂NHSO₂CH₃,
-SO₂NH₂,
-(CH₂)₁₋₄SO₂NR⁷R⁸,
-(CH₂)₁₋₄SO₂R⁶,

a 5- to 7- membered mono- or a 9- to 10-membered bicyclic

heterocyclic ring which can be saturated or unsaturated, and
which contains from one to four heteroatoms selected from the
group consisting of N, O and S,

-ZCH₂CO₂H,

5 -ZCH₂CO₂CH₃,

-ZCH₂R¹⁴,

-ZCH₂NHR¹⁴,

-ZCH₂CO₂(CH₂)₁₋₃CH₃,

-Z(CHR⁹)₁₋₃C(O)NR¹⁰R¹¹,

10 wherein

R⁹ is H or C₁₋₄ alkyl,

R¹⁰ and R¹¹ are independently

hydrogen,

C₃₋₇ cycloalkyl,

15 aryl,

heteroaryl,

heterocycloalkyl,

-(CH₂)₁₋₂NCH₂CH₃,

C₁₋₄ alkyl unsubstituted or substituted with one or more

20 of

hydroxy,

COOH,

amino,

aryl,

25 heteroaryl, or

heterocycloalkyl, or

R¹⁰ and R¹¹ are joined to form a four to seven membered
cycloalkyl or heterocycloalkyl ring unsubstituted or

substituted with hydroxy, amino or aryl or

30 disubstituted with hydroxy,

wherein Z is O, S or CH₂,

621
- 6P1

- R⁵₁₈**
hydrogen,
halogen,
C1-4 alkyl,
5 C1-4 alkoxy,
CF₃,
CN, or
CO₂NH₂, and
- 10 **R¹²₁₈**
hydrogen,
phenyl, unsubstituted or substituted with one or more of C1-4
alkyl, C1-4 alkoxy, halogen, hydroxy, COOH, CONH₂,
naphthyl,
15 biphenyl,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
which contains from one to four heteroatoms selected from the
group consisting of N, O and S,
20 C1-4 alkyl, unsubstituted or substituted with one or more of
hydroxy,
COOH,
amino,
aryl,
25 heteroaryl, or
heterocycloalkyl,
CF₃,
C3-7 cycloalkyl,
C7-12 bicyclic alkyl, or
30 C10-16 tricyclic alkyl,

or a pharmaceutically acceptable salt thereof

United States Patent [19]

Sanderson et al.

[11] Patent Number. 5,792,779

[45] Date of Patent Aug 11, 1998

[54] PYRIDINONE THROMBIN INHIBITORS

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[21] Appl. No. 882,370

[22] Filed Feb 19, 1997

[51] Int. Cl.⁶ C07D 213/64 C07D 213/75
C07D 213/70 A61K 31/44

[52] U.S. Cl. 514/382, 546/291 546/292

[58] Field of Search 546/292 291
514/352

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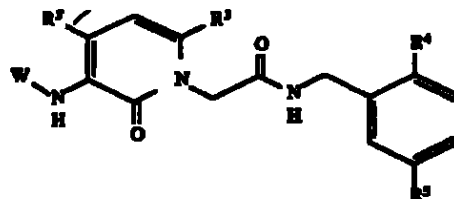
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Primary Examiner—Alan L. Rotman

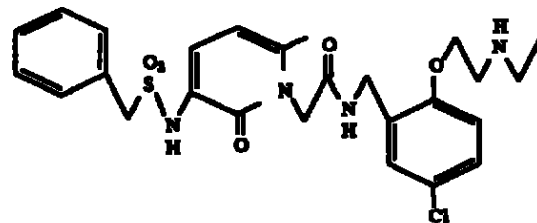
Attorney, Agent, or Firm—Richard S Parr, Mel Winokur

[57] ABSTRACT

Compounds of the invention are useful in inhibiting throm-
bin and associated thrombotic occlusions and have the
following structure



for example

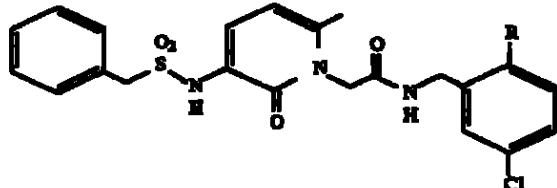


15 Claims, No Drawings

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TABLE 1

	
R	H Cl OH OCH ₂ CONHC(=O)CH ₃ OCH ₂ CONHC(=O)CH ₂ CH ₃ OCH ₂ CONHC(=O)CH ₂ CH ₂ CH ₃ OCH ₂ CF ₃

EXAMPLE 9

In Vivo Studies To Measure Thrombotic Occlusions

Applicants have conducted in vivo studies of the compounds claimed herein using the following rat ferric chloride assay substantially as described in *Thrombosis Research*, No. 60, page 269(1990) by Kurtz et al.

In the assay used to determine in vivo activity of the thrombin inhibitors or the invention Male Sprague-Dawley rats (body weights 200-350 grams) were anesthetized with dial-urethane solution (0.1 ml/100 gm body weight i.p.), and a lateral tail vein was cannulated with a 23 gauge needle connected to a 12 inch length of PE50 tubing. The tubing was attached to a 3-way valve by a tubing adapter. Saline (control) or test compound, as appropriate was administered via the tail vein catheter. A tracheostomy was performed with a 0.75 inch length of PE205 tubing. The right carotid artery was exposed and a 1.3 mm diameter Doppler flow probe was placed on the vessel. Body temperature was maintained at 37° C. using a heat lamp.

Rats (8-10/group) were randomized to continuous intravenous infusions of saline or test compound administered via the tail vein at a rate of 0.028 ml/min. Treatment infusions were initiated 60 min before the placement of a 3 mm square piece of Whatman No. 1 filter paper saturated with 35% FeCl₃ onto the exposed carotid artery distal to the flow probe. Treatment infusions were continued for an additional 90 minutes after the application of FeCl₃ (total infusion duration 150 minutes) if thrombotic occlusions did not occur or were terminated 30 minutes after thrombotic occlusion of the vessel. Time to occlusion was defined as the time from application of FeCl₃ to thrombotic occlusion of the vessel. At the termination of the study (90 minutes after application of FeCl₃ in animals which did not occlude, or at 30 minutes after thrombotic occlusion), 3 ml blood samples were drawn by cardiac puncture into 0.3 ml of 3.8% sodium citrate.

The results show that the compounds of the invention are effective in preventing thrombotic occlusions.

24

EXAMPLE 10

Tablet Preparation

Tablets containing 25.0 50.0, and 100.0 mg respectively of the following active compounds are prepared as illustrated below

- 3-Benzylsulfonylamino-6-methyl-1-(methylenecarboxamidomethyl 2,5-dichlorophenyl)-2-pyridinone.
- 3-Benzylsulfonylamino-6-methyl-1-[Ethyl-(2-methylenecarboxamidomethyl-4-chlorophenoxy)-acetamido]-2-pyridinone.
- 3-Benzylsulfonylamino-6-methyl-1-[cyclopropyl-(2-Methylenecarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyridinone.
- 3-Benzylsulfonylamino-6-methyl-1-(2-Methylenecarboxamidomethyl-4-Chlorophenoxyacetamido)-2-Pyridinone

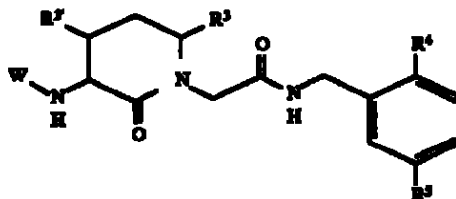
TABLE FOR DOSES CONTAINING FROM 25-100 MG OF THE ACTIVE COMPOUND

Active Compound	Amount-mg		
	25.0	50.0	100.0
Mecrocrystalline cellulose	37.25	100.0	200.0
Modified food corn starch	37.25	4.25	8.5
Magnesium stearate	0.50	0.75	1.5

All of the active compound, cellulose and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0 50.0 and 100.0 mg. respectively of active ingredient per tablet.

What is claimed is

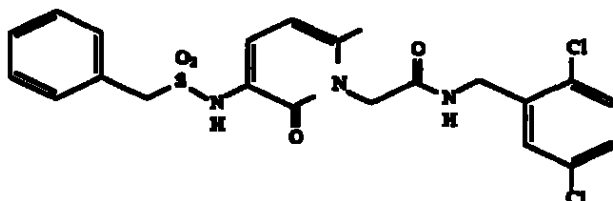
1 A compound having the formula.



wherein

W is

- hydrogen.
- R¹—,
- R¹OC(O)—,
- R¹C(O)—,
- R¹SO₂—,
- R¹NHSO₂—,
- (R¹)₂NSO₂—,
- R¹(CH₂)_nNHC(O)—,
- (R¹)₂CH(CH₂)_nNHC(O)—, or wherein n is 0-4,
- R¹ is
- R²(CH₂)_r—, where r is 0-4,
- (R²)₂CH(CH₂)_p—, where p is 1-4,
- (R²)₂CH(CH₂)_r—, where r is 0-4 and each R² can be the same or different, and wherein (R²)₂ can also form a ring with CH represented by C₂₋₇ cycloalkyl, C₇₋₁₂ bicyclic alkyl, or C₁₀₋₁₆ tricyclic alkyl,
- R²O(CH₂)_p—, wherein p is 1-4, or

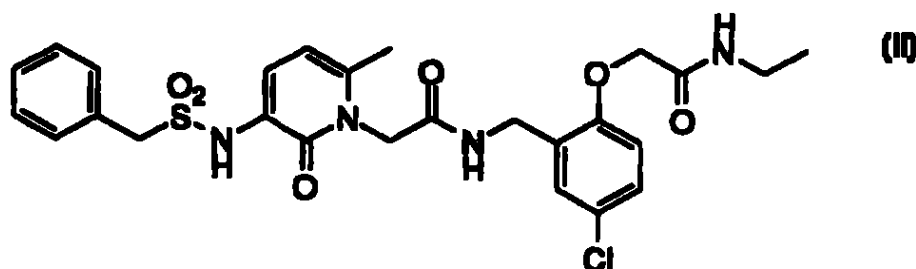
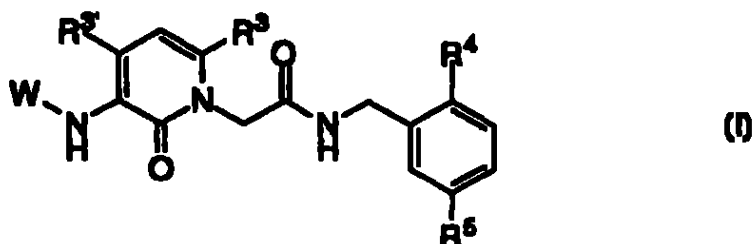




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ A61K 31/44, C07D 213/72		A1	(11) International Publication Number WO 97/30708
			(43) International Publication Date 28 August 1997 (28.08.97)
(21) International Application Number PCT/US97/02408		(81) Designated States AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date 18 February 1997 (18.02.97)			
(30) Priority Data 60/012,058 22 February 1996 (22.02.96) US 9605643 7 18 March 1996 (18.03.96) GB			
(71) Applicant (for all designated States except US) MERCK & CO., INC. [US/US] 126 East Lincoln Avenue Rahway NJ 07065 (US)		Published With international search report	
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(54) Title: PYRIDINONE THROMBIN INHIBITORS



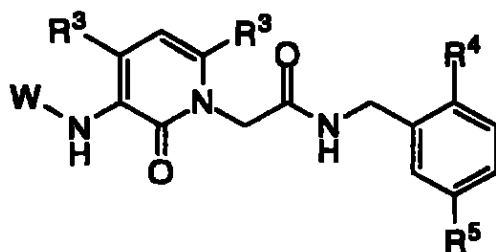
(57) Abstract

Compounds of the invention are useful in inhibiting thrombin and associated thrombotic occlusions and have structure (I), for example (II)

626
- 624

WHAT IS CLAIMED IS

1 A compound having the formula



5 wherein

W is

hydrogen,
R¹-,
10 R¹OC(O)-,
R¹C(O)-,
R¹SO₂-,
R¹NHSO₂-,
(R¹)₂NSO₂-,
15 R¹(CH₂)ₙNHC(O)-,
(R¹)₂CH(CH₂)ₙNHC(O)-, or
wherein n is 0-4,

R¹ is

20 R²(CH₂)ᵣ-, where r is 0-4,
(R²)(OR²)CH(CH₂)ₚ-, where p is 1-4,
(R²)₂CH(CH₂)ᵣ-, where r is 0-4 and each R² can be the same or
different, and wherein (R²)₂ can also form a ring with CH
represented by C3-7 cycloalkyl, C7-12 bicyclic alkyl, C10-16
25 tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic
heterocyclic ring which can be saturated or unsaturated, and
which contains from one to three heteroatoms selected from the
group consisting of N, O and S,
R²O(CH₂)ₚ-, wherein p is 1-4, or

627
- 625

$R^2(COOR^3)(CH_2)_r$ -, where r is 1-4,

R^2 and R^{14} are independently selected from
-phenyl, unsubstituted or substituted with one or more of
5 C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, $COOH$, or $CONH_2$,
naphthyl,
biphenyl,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
10 which contains from one to four heteroatoms selected from the
group consisting of N, O and S,
 C_{1-4} alkyl,
 C_{3-7} cycloalkyl,
 C_{7-12} bicyclic alkyl, or
15 C_{10-16} tricyclic alkyl,

R^3 and $R^{3'}$ are independently
 C_{1-4} alkyl,
 C_{3-7} cycloalkyl, or
20 trifluoromethyl,

R^4 is
hydrogen,
 C_{1-4} alkyl,
25 C_{1-4} alkoxy,
halogen,
 $-OCH_2CF_3$,
 $-COOH$,
 $-OH$,
30 $-COOR^6$, where R^6 is C_{1-4} alkyl,
 $-CONR^7R^8$, where R^7 and R^8 are independently
hydrogen or C_{1-4} alkyl,
 $-(CH_2)_{1-4}OH$,
 $-CH_2NHC(O)CH_3$,

- CH₂NHC(O)CF₃,
- CH₂NHSO₂CH₃,
- SO₂NH₂,
- 5 -(CH₂)₁₋₄SO₂NR⁷R⁸,
- (CH₂)₁₋₄SO₂R⁶,
- a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
 heterocyclic ring which can be saturated or unsaturated, and
 which contains from one to four heteroatoms selected from the
 group consisting of N, O and S,
- 10 -XCH₂CO₂H,
- XCH₂CO₂CH₃,
- XCH₂CO₂(CH₂)₁₋₃CH₃,
- X(CHR⁹)₁₋₃C(O)NR¹⁰R¹¹,
- wherein
- 15 R⁹ is H or C₁₋₄ alkyl,
- R¹⁰ and R¹¹ are independently
 hydrogen,
 C₃₋₇ cycloalkyl,
 aryl,
- 20 heteroaryl,
 heterocycloalkyl,
 C₁₋₄ alkyl unsubstituted or substituted with one or more of
 hydroxy,
 COOH,
- 25 amino,
 dialkylamino,
 aryl,
 heteroaryl, or
 heterocycloalkyl, or
- 30 R¹⁰ and R¹¹ are joined to form a four to seven
 membered cycloalkyl ring unsubstituted or
 substituted with hydroxy, amino or aryl, or
- XCH₂R¹⁴,

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- 62A

wherein X is O, S or CH₂,

R⁵ is

hydrogen,
5 halogen,
C₁₋₄ alkyl,
C₁₋₄ alkoxy,
CN, or
CO₂NH₂,

10 and pharmaceutically acceptable salts thereof

2 A compound of Claim 1, and pharmaceutically
acceptable salts thereof, wherein W is R¹ or R¹SO₂

15 3 A compound of Claim 2, and pharmaceutically
acceptable salts thereof, wherein R¹ is R²(CH₂)_r, or (R²)₂CH(CH₂)_r,
phenyl-CH₂SO₂, or diphenyl-CHSO₂

20 4 A compound of Claim 3, and pharmaceutically
acceptable salts thereof, wherein R¹ is phenyl-CH₂SO₂, or diphenyl-
CHSO₂

5 A compound of Claim 4, and pharmaceutically
acceptable salts thereof, wherein R³ is C₁₋₄ alkyl

25

6 A compound of Claim 5, and pharmaceutically
acceptable salts thereof, wherein R³ is methyl and R^{3'} is hydrogen

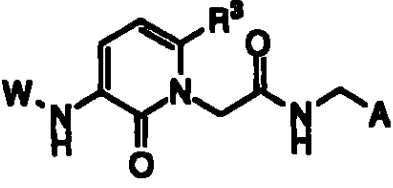
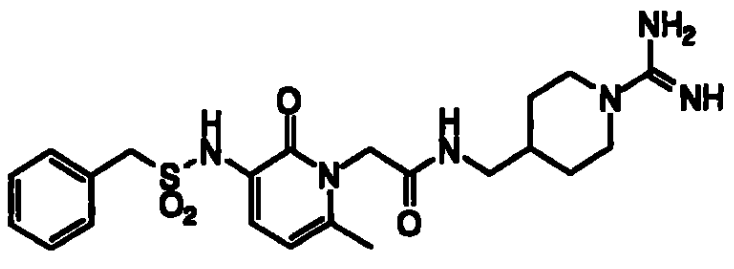
30 7 A compound of claim 6, and pharmaceutically
acceptable salts thereof, wherein

R⁴ is

hydrogen,
chlorine,

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT).

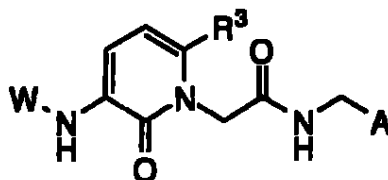
(51) International Patent Classification ⁶ A61K 31/445, C07D 213/02		A1	(11) International Publication Number WO 97/01338
			(43) International Publication Date: 16 January 1997 (16.01.97)
(21) International Application Number PCT/US96/10778		(74) Common Representative: MERCK & CO., INC., 126 East Lincoln Avenue, Rahway, NJ 07065 (US)	
(22) International Filing Date: 24 June 1996 (24.06.96)			
(30) Priority Data 60/000,560 27 June 1995 (27.06.95) US 60/003,818 15 September 1995 (15.09.95) US 9603430.9 19 February 1996 (19.02.96) GB		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, DE, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US).		Published With international search report.	
(72) Inventors; and (73) Inventors/Applicants (for US only): SANDERSON Philip, E. [GB/US], 126 East Lincoln Avenue, Rahway NJ 07065 (US). NAYLOR-OLSEN, Adel, M. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US). DYER Dona, L. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US). VACCA, Joseph, P. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US). ISAACS Richard C. A. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US). DORSEY Bruce, D. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US). FRALEY Mark, E. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US).			
(34) Title: PYRIDINONE-THROMBIN INHIBITORS			
(57) Abstract			
Compounds of the invention are useful in inhibiting thrombin and associated thrombotic occlusions and have structure (I), for example (a).			
 (I)			
 (a)			

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- 94 -

WHAT IS CLAIMED IS.

1 A compound having the formula



5

I

wherein W is

10 R^1 ,
 R^1OCO ,
 R^1CO ,
 R^1SO_2 ,
 $(R^1)_m(CH_2)_nNH_qCO$,
 where n is 0-4, m is 1 or 2, and q is 0 or 1, with the proviso
 that where n is 1-4, q is 1 and m is 1, and where n is 0, m is
 15 1 or 2, and q is 0 or 1, and where n is 0, m is 2 and q is 0, R^1
 can be the same or different,

 R^1 is

20 $R^2(CH_2)_n$, where n is 0-4,
 $(R^2)(OR^2)CH(CH_2)_p$, where p is 1-4,
 $(R^2)_2CH(CH_2)_n$, where n is 0-4 and R^2 can be the same or
 different, and wherein $(R^2)_2$ can also be a ring
 25 substituent on CH represented by C3-7 cycloalkyl, C7-
 12 bicyclic alkyl, or a 5- to 7- membered mono- or
 bicyclic heterocyclic ring which can be saturated or
 unsaturated, and which contains from one to three
 heteroatoms selected from the group consisting of N, O
 and S, and
 30 $R^2O(CH_2)_p$, wherein p is 1-4,

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- 95 -

 R^2 is

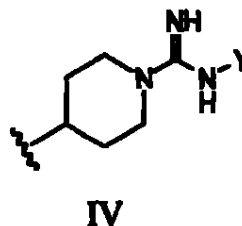
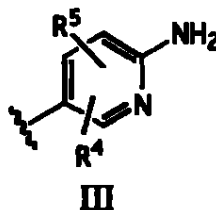
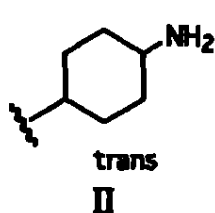
- hydrogen,
 phenyl, unsubstituted or substituted with one or more of C₁-
 4 linear or branched alkyl, C₁-4 linear or branched
 5 alkoxy, halogen, trifluoromethyl, hydroxy, COOH, or
 CONH₂,
 naphthyl,
 biphenyl,
 a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
 10 heterocyclic ring which can be saturated or unsaturated,
 and which contains from one to three heteroatoms
 selected from the group consisting of N, O and S,
 COOR⁶,
 C₁-4 linear or branched alkyl,
 15 C₃-7 cycloalkyl, or
 C₇-12 bicyclic alkyl,

 R^3 is

- hydrogen,
 20 C₁-4 linear or branched alkyl,
 C₃-7 cycloalkyl, or
 trifluoromethyl,

A is

- 25 chosen from one of the following Radicals



- wherein R^4 and R^5 are independently H, C₁-4 linear or
 30 branched alkyl or alkoxy, C₃-C₇ cycloalkyl, halogen, or trifluoromethyl,

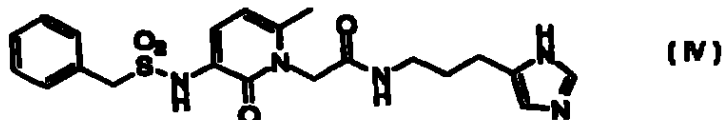
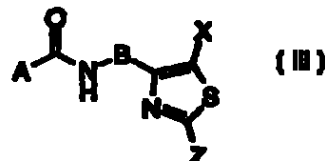
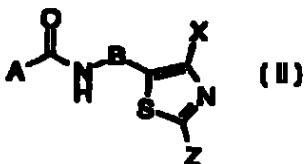
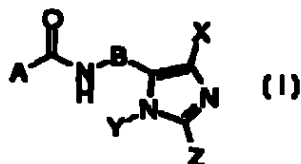
- 96 -

- Y is
hydrogen,
hydroxy, or
CN,
- 5 R⁶ is
hydrogen, or
C₁₋₄ linear or branched alkyl,
- 10 and pharmaceutically acceptable salts thereof
- 2 The compound of Claim 1 wherein W is R¹ or
R¹SO₂, and pharmaceutically acceptable salts thereof
- 15 3 The compound of Claim 2 wherein R¹, by itself or in
R¹SO₂, is R²(CH₂)_n, or (R²)₂CH(CH₂)_n, phenyl, or (phenyl)₂-CH, and
pharmaceutically acceptable salts thereof
- 20 4 The compound of Claim 1 wherein R³ is C₁₋₄ linear
or branched alkyl, and pharmaceutically acceptable salts thereof
- 5 The compound of Claim 4 wherein R³ is methyl, and
pharmaceutically acceptable salts thereof
- 25 6 The compound of Claim 1 wherein R⁴ is C₁₋₄ linear
or branched alkyl and R⁵ is methyl or hydrogen, and pharmaceutically
acceptable salts thereof
- 30 7 The compound of Claim 6 wherein R⁴ is methyl and
R⁵ is methyl or hydrogen, and pharmaceutically acceptable salts thereof
- 8 The compound of Claim 7 wherein R⁴ is methyl and
R⁵ is hydrogen, and pharmaceutically acceptable salts thereof

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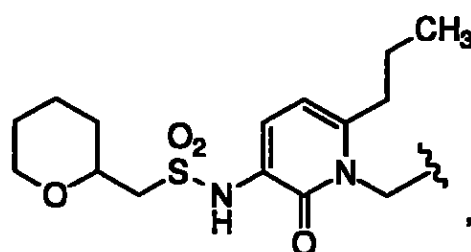
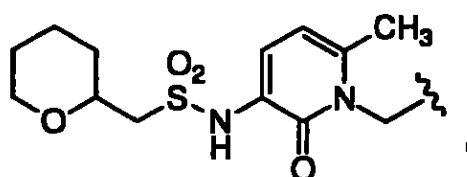
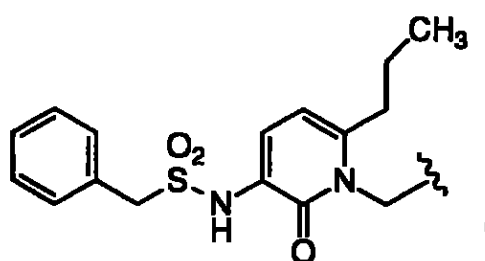
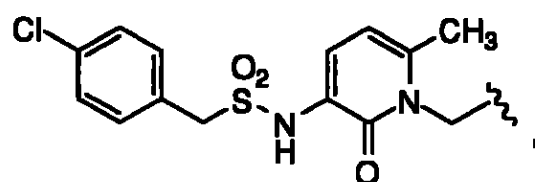
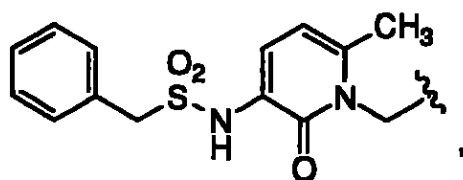
(51) International Patent Classification ⁶ A61K 31/495, 31/535, C07D 401/14, 403/12, 413/06		A1	(11) International Publication Number WO 98/42342
			(43) International Publication Date: 1 October 1998 (01.10.98)
(21) International Application Number PCT/US98/05486		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date 20 March 1998 (20.03.98)		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments	
(30) Priority Data			
60/041,543 24 March 1997 (24.03.97) US 60/047,561 22 May 1997 (22.05.97) US 9716872.8 8 August 1997 (08.08.97) GB 9800214.0 6 January 1998 (06.01.98) GB			
(71) Applicant (for all designated States except US) MERCK & CO., INC. [US/US], 126 East Lincoln Avenue, Rahway NJ 07065 (US)			
(72) Inventors; and (75) Inventors/Applicants (for US only): ISAACS Richard C. A. [US/US], 126 East Lincoln Avenue, Rahway NJ 07065 (US); NAYLOR-OLSEN, Adel M. [US/US], 126 East Lincoln Avenue, Rahway, NJ 07065 (US); DORSEY, Bruce, D. [US/US], 126 East Lincoln Avenue, Rahway, NJ 07065 (US); NEWTON, Christina, L. [US/US], 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			
(74) Common Representative MERCK & CO., INC., 126 East Lincoln Avenue, Rahway NJ 07065 (US)			

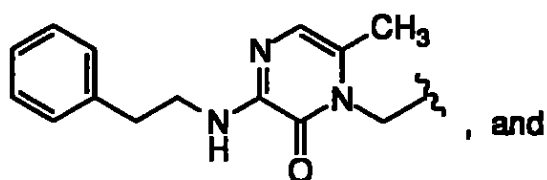
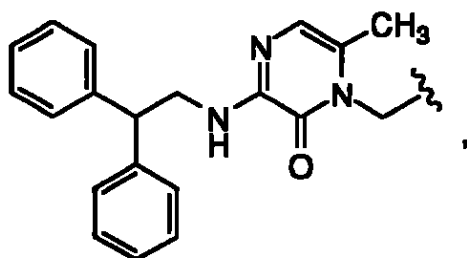
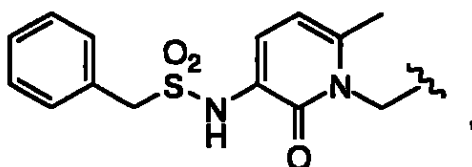
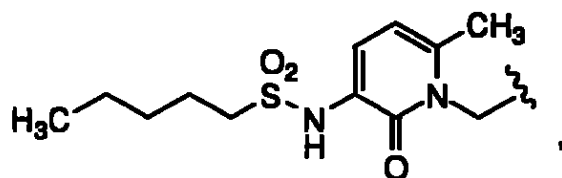
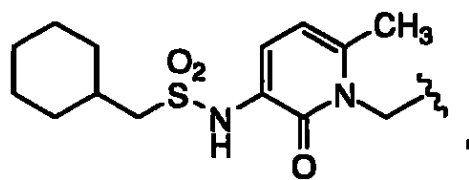
(54) Title: THROMBIN INHIBITORS



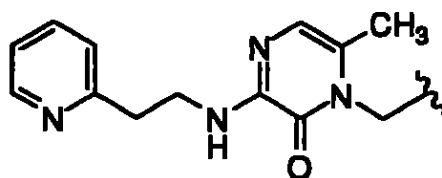
(57) Abstract

A compound which inhibits human thrombin and has structure (I) or (II) or (III) and pharmaceutically acceptable salts thereof wherein compounds such as (IV) are useful for inhibiting formation of blood platelet aggregates in blood in a mammal.

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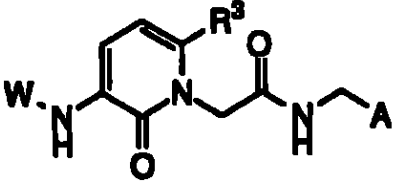
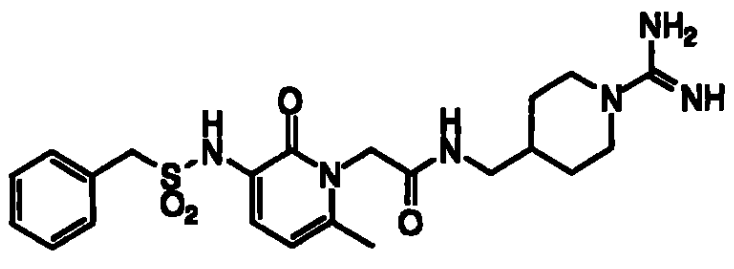


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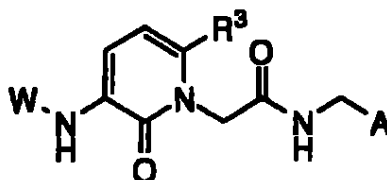
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ A61K 31/445, C07D 213/02	A1	(11) International Publication Number WO 97/01338 (43) International Publication Date: 16 January 1997 (16.01.97)									
(21) International Application Number PCT/US96/10778 (22) International Filing Date 24 June 1996 (24.06.96) (30) Priority Data <table border="0"><tr><td>60/000,560</td><td>27 June 1995 (27.06.95)</td><td>US</td></tr><tr><td>60/003,818</td><td>15 September 1995 (15.09.95)</td><td>US</td></tr><tr><td>9603450.9</td><td>19 February 1996 (19.02.96)</td><td>GB</td></tr></table> (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US], 126 East Lincoln Avenue, Rahway NJ 07065 (US) (72) Inventors; and (73) Inventor/Applicants (for US only): SANDERSON, Philip, E. [GB/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US) NAYLOR-OLSEN Adel, M [US/US] 126 East Lincoln Avenue Rahway NJ 07065 (US) DYER, Dona, L. [US/US], 126 East Lincoln Avenue, Rahway NJ 07065 (US) VACCA, Joseph P [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US). ISAACS Richard, C., A [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US) DORSEY, Bruce, D [US/US], 126 East Lincoln Avenue, Rahway NJ 07065 (US). FRALEY Mark, E. [US/US] 126 East Lincoln Avenue, Rahway NJ 07065 (US).		60/000,560	27 June 1995 (27.06.95)	US	60/003,818	15 September 1995 (15.09.95)	US	9603450.9	19 February 1996 (19.02.96)	GB	(74) Common Representative: MERCK & CO., INC., 126 East Lincoln Avenue, Rahway NJ 07065 (US). (81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, DE, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report
60/000,560	27 June 1995 (27.06.95)	US									
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9603450.9	19 February 1996 (19.02.96)	GB									
(54) Title: PYRIDINONE-THROMBIN INHIBITORS (57) Abstract Compounds of the invention are useful in inhibiting thrombin and associated thrombotic occlusions and have structure (I), for example (a).  (I)  (a)											

- 94 -

WHAT IS CLAIMED IS.

1 A compound having the formula



5

I

wherein W is

R¹,
 R¹OCO,
 10 R¹CO,
 R¹SO₂,
 (R¹)_m(CH₂)_nNHqCO,
 where n is 0-4, m is 1 or 2, and q is 0 or 1, with the proviso
 that where n is 1-4, q is 1 and m is 1, and where n is 0, m is
 15 1 or 2, and q is 0 or 1, and where n is 0, m is 2 and q is 0, R¹
 can be the same or different,

R¹ is

20 R²(CH₂)_n, where n is 0-4,
 (R²)(OR²)CH(CH₂)_p, where p is 1-4,
 (R²)₂CH(CH₂)_n, where n is 0-4 and R² can be the same or
 different, and wherein (R²)₂ can also be a ring
 substituent on CH represented by C₃-7 cycloalkyl, C₇-
 25 12 bicyclic alkyl, or a 5- to 7- membered mono- or
 bicyclic heterocyclic ring which can be saturated or
 unsaturated, and which contains from one to three
 heteroatoms selected from the group consisting of N, O
 and S, and
 30 R²O(CH₂)_p, wherein p is 1-4,

- 95 -

R² is

hydrogen,
 phenyl, unsubstituted or substituted with one or more of C₁-
 4 linear or branched alkyl, C₁-4 linear or branched
 5 alkoxy, halogen, trifluoromethyl, hydroxy, COOH, or
 CONH₂,
 naphthyl,
 biphenyl,
 a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
 10 heterocyclic ring which can be saturated or unsaturated,
 and which contains from one to three heteroatoms
 selected from the group consisting of N, O and S,
 COOR⁶,
 C₁-4 linear or branched alkyl,
 15 C₃-7 cycloalkyl, or
 C₇-12 bicyclic alkyl,

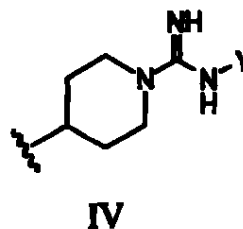
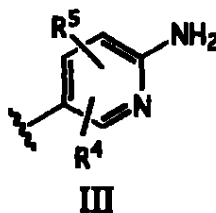
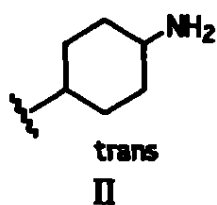
R³ is

hydrogen,
 20 C₁-4 linear or branched alkyl,
 C₃-7 cycloalkyl, or
 trifluoromethyl,

A is

chosen from one of the following Radicals

25



wherein R⁴ and R⁵ are independently H, C₁-4 linear or
 30 branched alkyl or alkoxy, C₃-C₇ cycloalkyl, halogen, or trifluoromethyl,

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- 96 -

- Y is
hydrogen,
hydroxy, or
CN,
- 5 R⁶ is
hydrogen, or
C₁₋₄ linear or branched alkyl,
- 10 and pharmaceutically acceptable salts thereof
- 2 The compound of Claim 1 wherein W is R¹ or
R¹SO₂, and pharmaceutically acceptable salts thereof
- 15 3 The compound of Claim 2 wherein R¹, by itself or in
R¹SO₂, is R²(CH₂)_n, or (R²)₂CH(CH₂)_n, phenyl, or (phenyl)₂-CH, and
pharmaceutically acceptable salts thereof
- 20 4 The compound of Claim 1 wherein R³ is C₁₋₄ linear
or branched alkyl, and pharmaceutically acceptable salts thereof
- 5 The compound of Claim 4 wherein R³ is methyl, and
pharmaceutically acceptable salts thereof
- 25 6 The compound of Claim 1 wherein R⁴ is C₁₋₄ linear
or branched alkyl and R⁵ is methyl or hydrogen, and pharmaceutically
acceptable salts thereof
- 30 7 The compound of Claim 6 wherein R⁴ is methyl and
R⁵ is methyl or hydrogen, and pharmaceutically acceptable salts thereof
- 8 The compound of Claim 7 wherein R⁴ is methyl and
R⁵ is hydrogen, and pharmaceutically acceptable salts thereof