Xarelto® Rivaroxaban
Brief Description of Significant Activities Undertaken by Applicant during the Regulatory Review Period

Date of FDA Contact	Brief Description of Contact/Activity
May 29, 2002	Submission of initial IND application
June 5, 2002	FDA acknowledged IND submission; **June 30, 2002 effective date of IND**
July 3, 2002	Submission of Protocol Amendment protocol 10850
July 29, 2002	FDA comments re: Protocol 10850
July 31, 2002	Request Type B Meeting
August 5, 2002	Submission of pharm/tox report PH-32076
August 26, 2002	FDA confirmed Type B meeting date
Sept. 4, 2002	Submission of pharm/tox report PH-32333
Sept. 6, 2002	Submission of Briefing Document
Sept. 20, 2002	Submission of Revised Questions in Briefing Document
Sept. 27, 2002	Submission of response to FDA comments received July 29, 2002
October 2, 2002	Submission of pharm/tox report PH-32303
October 10, 2002	FDA Meeting
November 1, 2002	Submission of 2 pharm/tox reports PH-32339 and PH-32348
November 18, 2002	Submission of pharm/tox report PH-32386
November 19, 2002	FDA comments/recommendations after pharmacology review
December 4, 2002	FDA Official Minutes of October 10, 2002 Meeting
December 13, 2002	Submitted Bayer Corporate Name Change
January 15, 2003	FDA acknowledgement of Bayer Corporate Name Change
March 6, 2003	Submission of Revised IB
April 17, 2003	Submission of CMC Amendment
May 23, 2003	Request Type C Meeting
May 29, 2003	Submission of 2 pharm/tox reports PH-32627 and R-8312
June 5, 2003	FDA confirmed by phone Type C meeting date
June 11, 2003	FDA confirmed by Fax Type C meeting date
June 24, 2003	Submission of Briefing Document
July 18, 2003	FDA sent responses to Meeting Request Questions
July 25, 2003	FDA Meeting
July 29, 2003	Submission of Annual Report
August 19, 2003	FDA Official Minutes of July 25, 2003 Meeting
October 15, 2003	Submission of Phase 3 protocol 10945
November 10, 2003	Submission of 6 pharm/tox reports PH-32735, PH-32791, PH-32792, PH-32793, PH-32794, and PH-32682.
November 24, 2003	Submission of CMC Amendment
December 11, 2003	Submission of 2 Clinical Reports: study 10848 and 10850
December 17, 2003	Submission of 7 pharm/tox reports PH-32948, PH-32946, PH-32846, PH-32913, PH-32914, PH-33015, and PH-33056.

January 9, 2004	Submission of Revised IB, version 7.1
January 19, 2004	Submission of Sub-study 10944/10945
March 1, 2004	Submission of Protocol Amendment study 10945
March 10, 2004	Submission of 5 pharm/tox reports PH-31969A, PH-31991A, PH-32966, PH-33092, and R-8340.
May 19, 2004	Informed FDA by phone that highest dose in study 10944 was discontinued
May 26, 2004	Informed FDA by letter that highest dose in study 10944 was discontinued
June 17, 2004	Submission of 4 pharm/tox reports PH-33250, PH-33256, PH-33273, and PH-33320. Submission of 8 new clinical reports: study 10842, study 10842 Amendment, study 10992, study 10847, study 10991, study 10993, study 11127, and PH-33230.
July 28, 2004	Submission of Annual Report
July 30, 2004	Submission of Revised IB, version 8
August 16, 2004	Submission of response to FDA question/comments received November 19, 2002 regarding pharm/tox review. Submission of pharm/tox report PH-33256
September 7, 2004	Submission of Protocol Amendment #2 study 10945
October 26, 2004	Submission of clinical report PH-33444; Submission of 5 pharm/tox reports PH-33368, PH-33380, PH-33395, PH-33414, and PH-33434.
December 2, 2004	Submission of pharm/tox report PH-33496
December 10, 2004	Submission of safety data
January 20, 2005	Submission of 4 pharm/tox reports PH-33561, PH-33582, PH-33609, and PH-33611; Submission of 4 clinical reports MRR-00081, MRR-00081A, PH-33003, PH-33308
February 15, 2005	Submission of Revised IB, version 9
March 17, 2005	Submission of 4 clinical reports PH-33320, PH-33582, PH-33599, and MRR-00086
March 18, 2005	Submission of 8 pharm/tox reports: PH-33320, PH-33582, PH-33599, PH-33623, PH-33681, PH-33718, PH-33719, PH-33780
March 23, 2005	Submission Request for Special Protocol Assessment, 2-yr carcinogenicity studies
April 19, 2005	Submission of 2 pharm/tox reports: PH-33051A, PH-33755; Submission of 5 clinical reports: PH-33730, PH-32952, PH-33775, PH-33776, PH-33800.
April 22, 2005	Request Type B End of Phase 2 Meeting
May 3, 2005	Type B End of Phase 2 Meeting Date Confirmed
May 4, 2005	FDA recommendations received regarding Request for Special Protocol Assessment, 2-yr carcinogenicity studies

May 25, 2005	Submission of clinical report MRR-00135
June 2, 2005	Submission of Briefing Document for Type B Meeting
June 30, 2005	Request Type A Meeting; carcinogenicity SPA request
July 5, 2005	Type B End of Phase 2 Meeting with FDA
July 14, 2005	Submission of Annual Report
July 20, 2005	FDA Official Minutes of Type B Meeting received
August 4, 2005	Submission of 9 pharm/tox reports: PH-33092A, PH-33230A, PH-33880, PH-33897, PH-33902, PH-33906, PH-33916, PH-33917, and PH-33918.
August 15, 2005	Request Type C Meeting
August 25, 2005	Submission of clinical report MRR-00161
August 29, 2005	FDA Confirmed Type C Meeting Date
September 22, 2005	Submission of clinical report PH-34050
October 3, 2005	Request Type B End of Phase 2 CMC Meeting
October 6, 2005	Submission of pharm/tox report PH-34016
October 19, 2005	Submission of Briefing Document for Type C Meeting
October 25, 2005	FDA confirmed Type B CMC meeting date
November 1, 2005	Submission of Revised IB, version 10
November 3, 2005	Submission of Briefing Document for Type B CMC Meeting
November 10, 2005	Submission 3 pharm/tox reports: PH-34045, PH-34088,and PH-34107
November 15, 2005	FDA Faxed partial responses to meeting questions
November 18, 2005	FDA Type C Meeting
November 30, 2005	FDA Official Minutes of Type C Meeting received
December 1, 2005	FDA Faxed responses to CMC Meeting questions
December 2, 2005	FDA Type B CMC Meeting cancelled; Submission 2 pharm/tox reports: PH-33395 and PH-34138
December 8, 2005	Submission 4 clinical reports: PH-33951, PH-34102, PH-34035, PH-33957
December 14, 2005	Submission of pharm/tox report: PH-34235; Submission of request for Special Protocol Assessment study 11354; Submission of request for Special Protocol Assessment study 11357.
December 22, 2005	Submission request for Special Protocol Assessment 2 year carcinogenicity studies; Submission of request for Special Protocol Assessment study 11356; Submission of request for Special Protocol Assessment study 11355.
January 19, 2006	Submission Operations Manual and DSMB Charter for Phase 3 studies; Submission of CMC information
January 27, 2006	FDA Comments received re: SPAs for studies 11354 and 11357
January 31, 2006	Bayer Agreed to accept FDA requested changes for SPAs for studies 11354 and 11357
February 3, 2006	FDA Comments received re: SPAs for studies 11355 and 11356
February 6, 2006	Submission 3 pharm/tox reports: PH-34189, PH-34198,and PH-34235

February 10, 2006	Confirmed date for FDA teleconference re: SPAs stat issues
February 15, 2006	FDA teleconference
March 2, 2006	FDA Faxed Official Minutes of Teleconference Feb. 15; FDA Faxed Official Minutes of Teleconference Feb. 23.
March 3, 2006	Re-submitted SPA request for study 11354
March 7, 2006	Re-submitted SPA request for study 11357
March 13, 2006	Re-submitted SPA request for study 11356
March 15, 2006	Re-submitted SPA request for study 11355
March 24, 2006	Submission 3 clinical reports: PH-34168, PH-34169, and PH-34140
April 7, 2006	Submission 2 pharm/tox reports: PH-34378 and PH-34379
April 20, 2006	FDA Approved SPAs for studies 11354 and 11357
April 25, 2006	FDA Approved SPA for study 11355
April 28, 2006	FDA Approved SPA for study 11356
May 15, 2006	Submission of Protocol 12090
May 22, 2006	Submission of Revised IB, version 11
June 1, 2006	FDA teleconference re: carcinogenicity protocols
June 2, 2006	FDA Faxed Official Minutes of teleconference re: carcinogenicity protocols
June 5, 2006	Submission of clinical report MRR 00174
June 9, 2006	Re-submitted SPA request for carcinogenicity studies; Submission of Revised IB, version 11 amend. 1
June 27, 2006	Re-submitted SPA request for carcinogenicity studies
June 30, 2006	FDA corrected Minutes of June 1, 2006 teleconference
July 26, 2006	Submission of Annual Report
August 8, 2006	FDA Fax regarding dosing in carcinogenicity studies received
August 10, 2006	Bayer agreed to FDA carcinogenicity dosing recommendation
August 23, 2006	Submission of ISS (Integrated Safety Summary)
August 29, 2006	Submission of Revised IB, version 11 amendments 2 and 3
October 13, 2006	Submission of CMC Information Amendment
October 24, 2006	Submission of Revised IB, version 12 amendment 1
November 7, 2006	Submission of 6 pharm/tox reports: PH-31969, PH-33092, PH-33230, PH-34897, PH-34610, and PH-34647
December 5, 2006	Discussed "rolling" NDA with FDA
December 15, 2006	Submission of CMC Information Amendment
January 10, 2007	Submission of a pharm/tox report: PH-34553
January 23, 2007	Request Type C Pre-clinical Meeting
February 7, 2007	FDA Letter Confirming Type C Pre-clinical Meeting
February 13, 2007	Submission of pharm/tox report: PH-34783
February 19, 2007	Submission of Briefing Document for Type C Pre-clinical Meeting
February 28, 2007	Request Type A Stat.-Clinical Meeting
March 9, 2007	FDA Letter Confirming Type A Stat.-Clinical Meeting
March 15, 2007	FDA Type A Teleconference Meeting
March 20, 2007	FDA Faxed Official Minutes of March 15 Type A Meeting
March 20, 2007	FDA Type C Pre-clinical Meeting

March 22, 2007	Submission of Revised Statistical Analysis Plan for RECORD 3 Study
March 22, 2007	FDA Faxed Official Minutes of March 20 Type C Meeting
May 21, 2007	Submission of CMC Information Amendment
May 29, 2007	Submission of Xarelto® Trade Name
June 13, 2007	Submission of REECORD 4 Protocol Amendment 1, ver. 2.1
June 22, 2007	Submission of RECORD 3 Abstract Prior to Public Release
June 27, 2007	Submission of 16 pharm/tox reports
June 29, 2007	Teleconference to Discuss Results of RECORD 1 and 3 Trials
July 19, 2007	Discuss 4 Separate Meetings with FDA Regarding NDA Filing
July 24, 2007	Request Type C Pre-NDA Meeting
July 27, 2007	FDA Confirmed Meeting Date for Type C Pre-NDA Meeting
August 21, 2007	Submit Carton Mock-up and Draft Brief Label
August 23, 2007	Brief Discussion of eCTD format for NDA
August 28, 2007	Submit Briefing Document for Type C Pre-NDA FDA Meeting; Submit Annual Report
September 10, 2007	Request Type B Pre-NDA CMC Meeting
September 14, 2007	Request Type B pre-NDA Meeting to Discuss eCTD
September 24, 2007	FDA Responses Received for Sept. 27 Pre-NDA Meeting
September 27, 2007	FDA Pre-NDA Meeting Long Term Safety Data and NDA Date
September 28, 2007	Confirmation of FDA Pre-NDA CMC Meeting Date
October 2, 2007	FDA Confirmed Date for Pre-NDA eCTD Meeting
October 3, 2007	Discussed Postponing 2 FDA Confirmed Meetings
October 11, 2007	Cancelled Pre-NDA Meeting Scheduled for Nov. 15
October 12, 2007	Submit Briefing Document for Type B CMC Pre-NDA Meeting
October 17, 2007	FDA Tentatively Scheduled Pre-NDA eCTD "demo" Meeting
October 19, 2007	Official FDA Minutes of September 27 FDA Meeting Received
October 22, 2007	FDA Confirmed re-scheduled Pre-NDA eCTD "demo" Meeting
November 8, 2007	FDA Responses Received for Nov. 16 CMC Pre-NDA Meeting
November 9, 2007	Submit Briefing Document for Type B Pre-NDA eCTD Meeting
November 15, 2007	Cancel CMC Pre-NDA Meeting; All Issues Resolved
December 7, 2007	Submission of CMC Information Amendment
December 7, 2007	FDA Sent Preliminary Responses re: Pre-NDA eCTD Meeting
December 10, 2007	Submit Clarifying Questions Prior to FDA Pre-NDA eCTD Meeting
December 12, 2007	Submit Clarifying Questions Prior to FDA Pre-NDA eCTD Meeting
December 13, 2007	Pre-NDA eCTD Meeting
December 20, 2007	Notify FDA of Bayer's New Corporate Name and NJ Address
January 11, 2008	FDA Official Minutes of Dec. 13 Pre-NDA eCTD Meeting
January 15, 2008	Discuss NDA Filing Date and NDA Number Request
January 23, 2008	Submit Reviewer's Guide for NDA Structure Prior to FDA Meeting
January 28, 2008	Submission of CMC Information Amendment
January 29, 2008	Meeting to Present eCTD NDA Format/Content Linking Structure
February 5, 2008	Submission of CMC Information Amendment
February 7, 2008	FDA Official Minutes of Jan. 29 eCTD NDA Format Meeting

February 14, 2008	Submit "Stat." Response F/U to Dec. 13 and Jan. 29 Meetings
February 15, 2008	Submit Interim Results of Mouse Carcinogenicity Study
March 5, 2008	FDA Response to Interim Mouse Carcinogenicity Results
March 17, 2008	Submission of CMC Information Amendment
March 20, 2008	FDA Response to CMC Proposal; FDA Requested a "Stat." Teleconference
March 24, 2008	Submission of CMC Information Amendment; FDA Acknowledged Receipt of Corporate Name Change
March 25, 2008	FDA "Stat." Teleconference
April 4, 2008	FDA Official Minutes of March 25 "Stat" Teleconfernece
April 15, 2008	Submit Response to "Stat." Teleconference
May 6, 2008	Submit IB Version 13 and Amend. 1 and 2
May 29, 2008	Submit Copy of RECORD 4 Press Release
July 16, 2008	Letter of Authorization: FDA to Refer to Bayer IND for J&J NDA
July 24, 2008	Submit 7 Clinical Study Reports
July 25, 2008	Submit 12 Clinical Study Reports
July 28, 2008	Submit 5 Clinical Study Reports
July 28, 2008	NDA Submitted
July 29, 2008	FDA Cover Letter receipt Acknowledgement of New NDA
August 4, 2008	Amendment to RECORD 4 Study Report
August 5, 2008	Letter from FDA: NDA Receipt Acknowledgement
August 6, 2008	Inform FDA of Intent to Transfer IND to J&J
August 7, 2008	Request for European Label for Rivaroxaban
August 7, 2008	NDA Introduction Meeting correspondence
August 11, 2008	European Final Summary Product Characteristics (SPC) & Amendment to the RECORD 4 MRR (AA41857) Study Report
August 13, 2008	Submit 29 Pre-Clinical Study Reports; Inform FDA that IND Transfer to J&J Effective Aug. 15.
September 3, 2008	SAE (Serious Adverse Event) Reporting Unblinding of Subjects
September 4, 2008	Request CP Electronic Datasets
September 4, 2008	NDA Introduction Meeting correspondence
September 18, 2008	NDA Introduction Meeting
October 3, 2008	MAGELLAN Study - FDA Request for Additional Information
October 6, 2008	CMC Request Page 3 of FDA Filing Letter
October 15, 2008	Submission of Clinical Pharmacology Sets Study Data
October 15, 2008	Call with FDA re: CMC and Labeling Comments in Filing Letter and Proposal for Two Meetings
October 22, 2008	FDA CMC Request for Information
October 31, 2008	Follow-up Call on CMC, NDA questions, Trade Name and Liver Meeting
November 4, 2008	Submission of Information on Multiple Bleeding Event Analysis
November 6, 2008	Provide ECG Datasets
November 6, 2008	Submission of Safety Data, including information on CMC, ISS, Unblinded SAEs
November 14, 2008	Submission of RECORD 4 Data with Dr. D. Craig Loucks

November 21, 2008	Submission in Response to Office of Compliance Request re: RECORD 4 Study ICFs
November 25, 2008	Submission of 4 Month Safety Update: Ongoing Clinical Studies
November 25, 2008	Submission of Chemistry and Manufacturing Information
November 25, 2008	Submission of Case Report Forms from Clinical Studies
December 1, 2008	Letter from FDA: November 17, 2008 Official Meeting Minutes
December 4, 2008	FDA sent Mid-Cycle Completed Review
December 4, 2008	Sponsor Monitor Inspections
December 5, 2008	Letter from FDA: Response Requested re: Statistical CMC Clinical Pharmacology Sections
December 8, 2008	Dr. Susan Thompson (FDA DSI) NDA Routine Sponsor Monitor Inspection
December 12, 2008	Letter from FDA: NDA Clinical Section Review: RFI
December 12, 2008	Follow-up on Mid-Cycle Questions, CMC Telecon Minutes, SSP, and Clinical Questions
December 16, 2008	Statistical Datasets; Response to Information Request Letter
December 16, 2008	December 12, 2008 IR Letter Clarification
December 16, 2008	IR Letter Clarification/Dataset Size Clarification
December 18, 2008	Information request: CRFs
December 19, 2008	Response to Information Request Letter: CMC, Stats, ClinPharm
December 24, 2008	Unblinded SAEs
December 30, 2008	Fax from FDA: Inspections in Shanghai, China
January 7, 2009	Response to Information Request Letter: Response to Statistics Question 2b
January 7, 2009	Fax from FDA: FDA Advisory Committee Meeting
January 9, 2009	eCRF Navigation Question
January 9, 2009	Response to the December 12, 2008 Clinical IR Letter
January 10, 2009	Safety Report SN 711
January 14, 2009	Responses to Information Request Letter (December 12, 2008)
January 16, 2009	Follow-up Call with FDA on IR Responses and 6 Month Safety Update Timeline
January 23, 2009	Letter from FDA: January 9, 2009 Official Meeting Minutes
January 23, 2009	Information Request dated January 21, 2009
January 23, 2009	Information Request dated January 12, 2009
January 23, 2009	February 2, 2009 Telecon and Information Request Clarifications
January 27, 2009	Response to Question 1c of Information Request Letter (December 12, 2008)
January 27, 2009	Telecon with Division Director Regarding FDA Advisory Committee Meeting March 19, 2009
January 28, 2009	Letter from FDA: January 16, 2009 Official Meeting (Teleconference) Minutes
January 28, 2009	Letter from FDA: January 23, 2009 Official Meeting (Teleconference) Minutes
January 29, 2009	Responses to Information Request Letter (December 12, 2008)

January 30, 2009	Response to Question 3 of Information Request Letter (January 12, 2009)
January 30, 2009	Follow-up on February 2, 2009 Telecon Attendees
February 2, 2009	Response to Questions 7, 8, and 9 of Information Request (January 21, 2009)
February 2, 2009	Submission of 6 Month Safety Update
February 2, 2009	FDA Telecon: February 2, 2009 Meeting Participants
February 5, 2009	Letter from FDA: Discipline Review Letter
February 11, 2009	FDA Correspondence - Letter from FDA: Clinical and Statistical Comments
February 12, 2009	FDA Advisory Committee Meeting March 19, 2009 Briefing Document
February 13, 2009	Email from FDA: Information Request
February 13, 2009	Letter from FDA: February 2, 2009 Official Meeting (Teleconference) Minutes
February 19, 2009	Letter from FDA: Information Request Letter
February 20, 2009	Responses to Information Request Letter (February 10, 2009)
February 23, 2009	Email/Attachment to FDA: Information Request February 13, 2009
February 24, 2009	Responses to Information Request (January 28, 2009)
February 25, 2009	Additional Response to Information Request (December 12, 2008)
February 25, 2009	Response to Question 1 of Discipline Review Letter (February 5, 2009)
March 2, 2009	Response to Information Request (February 11, 2009)
March 3, 2009	Responses to Information Request (February 13, 2009)
March 3, 2009	Sponsor Monitor Inspection - Raritan
March 4, 2009	Response to Information Request Letter (February 19, 2009) and Question 2 of Discipline Review Letter (February 5, 2009)
March 6, 2009	Letter from FDA: February 9, 2009 Official Meeting Minutes
March 6, 2009	Responses to Information Request (February 20, 2009)
March 11, 2009	Responses to Information Request (March 10, 2009)
March 11, 2009	Additional Information in Response to Q2 of Information Request Letter (February 19, 2009)
March 12, 2009	Clarification of Response to Information Request (February 13, 2009)
March 16, 2009	Response to March 4, 2009 Information Request
March 18, 2009	Letter from FDA: March 6, 2009 Official Meeting Minutes
March 18, 2009	Letter from FDA: March 13, 2009 Official Meeting Minutes
March 19, 2009	FDA Advisory Committee Meeting
March 25, 2009	Clarification of Response to Information Request (February 13, 2009 and March 4, 2009)
March 26, 2009	Follow-up Call re: Request from Biopharmaceutics Reviewer for Individual Dissolution Results
March 26, 2009	Email to FDA: Biopharmaceutics Request for Rivaroxaban Dissolution Information
March 26, 2009	Response to Information Request (March 6, 2009)

April 1, 2009	Biostatistics Meeting April 24, 2009 - Pre-Meeting Questions
April 1, 2009	Letter from FDA: March 9, 2009 Official Meeting Minutes
April 1, 2009	Letter from FDA: April 1, 2009 Official Meeting Minutes
April 7, 2009	Responses to Information Request (March 11, 2009)
April 9, 2009	Email/Attachments to FDA: Response to April 1, 2009 Information Request-Background Information for Record 4 Sites 14010, 14004, and 14045
April 17, 2009	Responses to Information Request (April 6, 2009)
April 24, 2009	Responses to CMC Information Request (April 17, 2009)
April 24, 2009	Letter from FDA: April 24, 2009 Official Meeting Minutes
April 28, 2009	Email to FDA: CMC Inspection
April 29, 2009	Follow-up Call re: CMC Inspection Scheduling (Wuppertal)
April 30, 2009	Letter from FDA: 21 Apr 2009 Official Meeting Minutes
May 1, 2009	Letter from FDA: CMC Section DMF Files 21580, 21581, and 21592 Inadequate to Support the NDA
May 5, 2009	Module 1 Financial Disclosure
May 11, 2009	Update on PDUFA Date
May 11, 2009	CMC Amendment for Trade Blister Packs
May 19, 2009	Additional Clarification to Response to Information Request 1 (20 Feb 2009)
May 20, 2009	Updated Investigator's Brochure
May 20, 2009	DMF Responses: DMF 21592, DMF 21580, DMF 21581
May 21, 2009	CMC Amendment for Trade Blister Packs
May 27, 2009	Letter from FDA complete response to NDA (Review with Comments and Recommendations)
May 28, 2009	FDA Complete Response Letter (27 May 2009) Proposed Clarifications Meeting
May 29, 2009	Request for Type A Telecon/Meeting
June 5, 2009	Follow-up Call re: Quality Items in Complete Response Letter
June 8, 2009	Complete Response Letter – Clarification Questions
June 10, 2009	Proposal for Addressing Complete Response Letter
June 11, 2009	Additional Clarification on Q2a Complete Response Proposal
June 16, 2009	Complete Response Letter Clarification
June 18, 2009	Complete Response Letter correspondence
June 18, 2009	Follow-up Call re: Clarification Responses from FDA to Telecon 19 Jun 3:00 to 4:30 PM EST
June 19, 2009	FDA Meeting Minutes Complete Response Clarifications Teleconference
June 22, 2009	NDA Complete Response Letter – Question 2(a) and IND 75,931 ACS SAP
July 2, 2009	Responses to Agency Recommendations and Revised Proposal for Q2a of the Complete Response Letter
July 8, 2009	Supplemental Audit Plan for Q1(c) of the Complete Response Letter
July 14, 2009	Letter from FDA: 19 Jun 2009 Official Meeting Minutes
July 14, 2009	FDA Recommendation for a New Liver Adjudication Panel (NDA

	22-406 Complete Response Clarification Meeting Minutes)
July 29, 2009	Email from FDA: Draft Comments on Proposed Supplemental Audit Plan
July 31, 2009	FDA teleconference minutes-clarification on FDA CR Letter
August 14, 2009	Letter from FDA: Feedback on Supplemental Audit Plan
August 28, 2009	Email with Attachment from FDA: Feedback from the ONDQA Project Manager on Questions about the CRL from CMC RA
August 28, 2009	Email from FDA: Response to FDA CRL Labeling
October 6, 2009	Updated Patent Information
October 13, 2009	Letter with Attachment from FDA: Memorandum of Teleconference Minutes of 31 Jul 2009
October 13, 2009	FDA Comments on the Proposed Liver Adjudication Panel Procedural Charter (NDA 22-406 Complete Response Clarification Meeting Minutes)
October 21, 2009	Patent Update
November 2, 2009	Email from FDA: eCTD File Question and Response
November 13, 2009	FDA Teleconference minutes on un-blinding of liver data LAP
December 10, 2009	Letter from FDA: 13 Nov 2009 Official Meeting Minutes
January 18, 2010	Type A Meeting Request
January 22, 2010	Letter from FDA: Meeting Granted 05 Mar 2010
February 4, 2010	FDA Type C Meeting – 05 Mar 2010 – To be Rescheduled
March 5, 2010	Type C Meeting Background Information 07 Apr 2010
March 8, 2010	Email to FDA: Meeting Background Package; FYI – 7 Apr Meeting
March 8, 2010	Email from FDA: Meeting Background Package; To Opt Out of Meeting
April 7, 2010	FDA Response to Rivaroxaban Cross Referencing Proposal in the NDA e-mail
April 7, 2010	FDA Meeting re: Falcon and Bayer Audits
April 19, 2010	J&J Submission of Falcon/Bayer Audits to FDA (DSI) (Follow-up to 7 Apr 2010 Meeting)
April 27, 2010	FDA Letter re: Warning Letter Issued by FDA to Craig Buettner regarding Conduct of a Study
April 29, 2010	Complete Response Timeframe Extension Request
April 30, 2010	FDA Letter re: "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" letter issued to Dr. David Craig Loucks
May 7, 2010	Official Meeting Minutes of 07 April 2010
May 10, 2010	FDA Letter Granting Extension until 27 May 2011 the Resubmission of a Complete Response to FDA Action Letter dated 27 May 2009
June 10, 2010	Complete Response – Record 4 Study Data Verification SAP (Study 11355)
August 2, 2010	Information Request – Written Response due on or before 30 August 2010
August 6, 2010	Email to FDA regarding DSI Feedback on the Falcon and Bayer

	audits – Clarification Requested
August 10, 2010	Email to FDA regarding Clarification for FDA DSI Requests for Additional Datasets
August 11, 2010	Email from FDA regarding Clarification for FDA DSI Requests for Additional Datasets; Responses Noted
August 23, 2010	Telecon Minutes –CR DSI Information Request of 02- Aug-2010
September 2, 2010	Type C Meeting Request to obtain guidance and concurrence from the Agency regarding the rivaroxaban exposures in special populations of interest and potential dose reduction
September 7, 2010	CR DSI IR Response Bayer and Falcon Audits for the RECORD Studies and Reference to the DSI Information Request Received 02 Aug 2010
September 13, 2010	CR Renal DDI Study Meeting Request (telecom) – FDA Meeting Granted Letter Attached – Type C Meeting Teleconference Scheduled for 14-Oct-10
September 24, 2010	J&J Response to DSI IR Q2 and Q3 of August 2, 2010 (cover letter)
October 14, 2010	Summary of FDA teleconference on Renal DDI Study Meeting from 14-Oct-10
October 15, 2010	Question on Resubmission of documents – Information may be linked no need to submit twice
October 15, 2010	Type C Meeting Minutes from 14-Oct-2010 Meeting
October 20, 2010	FDA Draft Label in Word Format Agreement
November 9, 2010	Foreign Labeling Question – Proposal is Acceptable
November 22, 2010	FDA Additional Analyses Request
December 30, 2010	Sponsor Complete Response filed 30-Dec-2010
January 4, 2011	Notification of Amendment to DMF 21592 which includes updated site specific stability data and stability evaluation, as well as updated container closure description information
January 13, 2011	Acknowledgement for Receipt of Complete Response CMC in pdf form
January 13, 2011	Screen Shot of Module 1 to Assist in location of Complete Response Document
January 13, 2011	Liver-related safety information from studies ROCKET AF 11630, J-ROCKET 12620, EINSTEIN 11702, EINSTEIN Extension 11899, EINSTEIN PE 11702
January 13, 2011	Call re: email request from ONDQA project manager for location of Bayer stability commitment as request in 27-May-2009 agency complete response letter
January 14, 2011	FDA in receipt of 30-Dec-2010 resubmission – complete Class 2 Response to 27-May-2009 action letter
January 27, 2011	Information request from the FDA Hematology division for clinical narratives in a SAS dataset
February 3, 2011	General Correspondence Response to IR 27-Jan-2011
February 4, 2011	Teleconference Scheduled to Discuss the Patient Narratives Provided in the Complete Response is cancelled

February 5, 2011	Clinical Pharmacology Section in Submission – Information Request
February 7, 2011	Clarification of a Typographical Error – for Rivaroxaban, not Section 505(b) for Heparin Sodium Injection
February 18, 2011	Response to Information Request IR dated 07-Feb-2011
February 25, 2011	Request for Proprietary Name Review: Primary Name: XARELTO (rivaroxaban) Alternate Name: Not Submitted
February 28, 2011	Copy of Cover Letter and Request for Proprietary Name Review Provided to the Division of Medication Error Prevention and Analysis
March 25, 2011	Response to Information Request of 16-Mar-2011
April 13, 2011	Request from ONDQA Project Manager for Updated 356h Establishment Information for NDA 22-406; Follow-up re: Timing for Dissolution Response
April 18, 2011	Establishment Update
April 21, 2011	Agency Information Request Relating to DMF 21580 CMC Section
April 25, 2011	Response to IR 14-Apr-2011
April 25, 2011	Updated Response to IR 14-Apr-2011
April 28, 2011	Response to CMC Information Request of 08-Apr-2011
May 3, 2011	Request for Bayer Pooled Adverse Events Analysis Dataset for EINSTEIN DVT – 11702, Extension – 11899, and EINSTEIN PE – 11702 with Cutoff Date of 31-Dec-2010
May 3, 2011	CMC Dissolution Specification for Rivaroxaban 15mg and 20mg Tablets
May 4, 2011	Drug Product Specification Update and DMF 21529 Update Notification
May 6, 2011	Response to Information Request of 27-Apr-2011 – Bayer Pooled Adverse Events Analysis Dataset for EINSTEIN DVT (11702) Extension (11899) and EINSTEIN PE (11702)
May 10, 2011	Updated 10mg Packaging Components
May 11, 2011	Copy of DMF 21592 Information Into Module 3 of NDA
May 11, 2011	Courtesy Copy of DMF 21592 Information Into Module 3 of NDA Submission – Cover Letter and CMC Information
May 12, 2011	Agency Notification That the Proposed Proprietary Name, XARELTO, is Conditionally Acceptable
May 17, 2011	Information Request Regarding the Label
May 19, 2011	Information Request Regarding Tables for SAEs, AEs, Bleeding Events, and Drug-Related AEs Based on an Integrated Safety Analysis for RECORD 1-3, Excluding RECORD 4
May 25, 2011	Response to Information Request of 17-May-2011 and 19-May-2011
June 8, 2011	Response to Information Request of 02-Jun-2011
June 8, 2011	FDA Sending Draft USPI Within a Few Days
June 13, 2011	Redlined Version of Label Provided for Review
June 13, 2011	FDA Label Review – Comments Regarding the Container Carton

	and Blister Pack Labels
June 14, 2011	Proposed Post Marketing Trial Request
June 16, 2011	Comments Regarding FDA Label Review Request and Change of Sponsor Name
June 16, 2011	Label Review with Comments
June 17, 2011	Response to Information Request – Hypersensitivity Cases
June 17, 2011	Final Version of the GPC Consulting Report and the RECORD 1-4 Justification Request
June 17, 2011	PMR – PMC Comments
June 20, 2011	Company Name Change and Updated Label Components Based on FDA Comments
June 21, 2011	FDA Minutes of Teleconference to Discuss Bleeding in Table 1 of the Label
June 21, 2011	Agreement to Teleconferences with FDA-Telecon with Clinical Pharmacology on 23-Jun-2011 and Telecon with Representatives of the Division of Scientific Investigations DRI and Clinical on 27-Jun-2011
June 22, 2011	Clarification on the Post Marketing Requirement
June 22, 2011	Final Proposed Post-marketing Request
June 23, 2011	Agency Comments to Sponsor Response to FDA Regarding Draft Label
June 24, 2011	Meeting Minutes from the 23-Jun-2011 Teleconference Regarding the Clinical Pharmacology Section of the Label
June 24, 2011	Background Material for the 27-Jun-2011 Meeting Regarding the RECORD 4 Study
June 24, 2011	PMR Clarification Request Extension for Submission of Timeline
June 28, 2011	Sponsor Response to FDA Label Comments
June 28, 2011	Agency Acknowledgement of Corporate Name Change from Ortho-McNeil-Janssen Pharmaceuticals, Inc. to Janssen Pharmaceuticals, Inc. for XARELTO
June 29, 2011	Two Issues from Review of Updates to the Carton and Label Containers
June 29, 2011	Updated PMC for Review With Request to Confirm Agreement and to Let Agency Know If Timelines Remain the Same
June 29, 2011	Updated Label with Updates and Comments Under Table 2 Footnote and in Section 12.3
June 29, 2011	Updated Labels for the Bottle, Carton, and HUD Blister
June 29, 2011	Notification that USPI for 30-Jun-2011 Meeting Will Be Sent
June 29, 2011	Final PI Provided
June 30, 2011	PMRs (Post-Marketing Reviews) and PMC (Post-Marketing Commitment) Provided for Review
July 1, 2011	Approval Letter for NDA 22-406

#4,425,062v2

Fee pd

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 7,157,456 B2

ISSUED: January 2, 2007

INVENTORS: Alexander Straub et al.

FOR: Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation

Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Enclosed is an application for the extension of U.S. Patent No. 7,157,456 under 35 U.S.C. §156.

Accompanying this Transmittal is authorization to charge the Application Fee of $1,120.00 prescribed by 37 C.F.R. §1.20(j)(1), as well as any additional fees which may be necessitated in connection with the filing of this Application for Patent Term Extension, to the undersigned's credit card. If any additional fees are due, the Commissioner is hereby authorized to charge to Deposit Account No. 03-2775.

Dated: August 25, 2011

Respectfully Submitted

Christine M. Hansen

Christine M. Hansen
Registration No. 40,634
Connolly Bove Lodge & Hutz LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, DE 19899
Attorney for Applicant

Enclosures: Patent Term Extension Application including Appendices

683632-1

PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

PATENT – POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS		
	Patent Number	7,157,456
	Issue Date	January 2, 2007
	First Named Inventor	Alexander Straub
	Title	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD...
	Attorney Docket No.	11987-00014-US

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 23416

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number	Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☐ The address associated with the above-mentioned Customer Number.

OR

☒ The address associated with Customer Number: 23416

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country		Telephone		Email	

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Inventor or Patent Owner

Signature	/ppa. Dorian Immler/ /Dr. Frank Burkert/	Date	July 21, 2011
Name	Dr. Dorian Immler/Dr. Frank Burkert	Telephone	
Title and Company	secretaries Bayer Pharma Aktiengesellschaft		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

#4,393,808

Electronic Acknowledgement Receipt

EFS ID:	10625481
Application Number:	10181051
International Application Number:	
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor/Applicant Name:	Alexander Straub
Customer Number:	23416
Filer:	Christine Hansen/Amy Hamm
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	29-JUL-2011
Filing Date:	24-JUN-2002
Time Stamp:	10:19:11
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		456_POA.pdf	147357 a9f1fee1b2912fe1402f1a3bb9ad1404b4cf8e73	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Assignee showing of ownership per 37 CFR 3.73(b).	1	2
	Power of Attorney	3	3
Warnings:			
Information:			
	Total Files Size (in bytes):	147357	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alexander Straub et al.

Application No./Patent No.: 7,157,456 Filed/Issue Date: January 2, 2007

Titled: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

Bayer Pharma Aktiengesellschaft (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [x] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. [x] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Alexander Straub et al. To: Bayer Aktiengesellschaft
The document was recorded in the United States Patent and Trademark Office at
Reel 013411, Frame 0223, or for which a copy thereof is attached.

2. From: Bayer Aktiengesellschaft To: Bayer Healthcare Aktiengesellschaft
The document was recorded in the United States Patent and Trademark Office at
Reel 015004, Frame 0466, or for which a copy thereof is attached.

3. From: Bayer Healthcare AG To: Bayer Schering Pharma Aktiengesellschaft
The document was recorded in the United States Patent and Trademark Office at
Reel 023769, Frame 0122, or for which a copy thereof is attached.

[x] Additional documents in the chain of title are listed on a supplemental sheet(s).

[x] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Christine M. Hansen/	July 29, 2011
Signature	Date
Christine M. Hansen	Attorney for Assignee
Printed or Typed Name	Title

4. From: Bayer Healthcare AG To: Bayer Schering Pharma AG
   The document was recorded in the United States Patent and Trademark Office at
   Reel 022520 , Frame 0150 , or for which a copy thereof is attached.
5. From: Bayer Healthcare AG To: Bayer Schering Pharma AG
   The document was recorded in the United States Patent and Trademark Office at
   Reel 022575 0337 , or for which a copy thereof is attached.
6. From: Bayer Schering Pharma AG To: Bayer Pharma Aktiengesellschaft
   The document was recorded in the United States Patent and Trademark Office at
   Reel 026661 , Frame 0406 , or for which a copy thereof is attached.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Patent No. : **7157456**
Ser. No. : **10/181051**
Inventor(s) : **STRAUB, ALEXANDER**
Issued : **01/02/2007**
Title : **SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION**
Docket No. : **LE A 34122**

Re: Request for Certificate of Correction

Consideration has been given your request for the issuance of a certificate of correction for the above-identified patent under the provisions of Rule(s) 1.322 and/or 1.323.

In regards to the alleged error(s) on the Title Page In Notice, left column, at (*), a Petition under 35 USC 154(b) is required to recalculate the Patent Term Adjustment.

In view of the foregoing, your request, in this matter, is hereby denied.

The Petition request under 35 USC 154 (b) should be directed to the attention of:

By mail: Mail Stop PETITIONS
Commissioner for Patents
Post Office Box 1450
Alexandria, VA 22313-1450

By hand: Customer Service Window
Mail Stop Petitions
Randolph Building
401 Dulany Street
Alexandria, VA 22314

By fax: (703) 872-9306
ATTN: Office of Petitions

Omega Lewis
For Mary Diggs
Decisions & Certificates
Of Correction Branch
(703)756-1575 or (703) 756-1814

Christine M. Hansen, J.D.
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

OL

Docket No.: 11987-00014-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Alexander Straub et al.

Application No.: 10/181,051 (Patent No. 7,157,456) Confirmation No.: 5850

Filed: June 24, 2002 Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION Examiner: R. L. Anderson

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 CFR 1.322

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted an error in the patent term adjustment which should be corrected.

On Page 1:

In Notice, left column, at (*) between items (73) and (21), "Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 59 days." should read -- Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 99 days. --

The error in patent term adjustment incurred through the fault of the Patent and Trademark Office for incorrectly interpreting the law pertaining to calculation of patent term adjustment. The Federal Circuit in *Wyeth v. Kappos*, 591 F.3d 1364, 93 USPQ2d 1257 (Fed. Cir. 2010) recently clarified the correct calculation and rejected the Patent Office's calculation method.

When the correct calculation as explained in *Wyeth v. Kappos* is used to determine the patent term adjustment for the present patent, the patent term adjustment is 99 days. The calculation is as follows.

Pursuant to 35 USC 154(b)(1), a patent term is adjusted based on guarantees of promptness found in section 154(b)(1) (A) (the "A" delay) and guarantees of no more than three year

pendency found in section 154(b)(1) (B) (the "B" delay). The A delay in the present patent is a 40 day delay for the late mailing of a first Office notification, plus a 36 day delay for late issuance of the patent after the issue fee was paid, for a total A delay of 76 days. The B delay is calculated according to Patent Office practice by the time exceeding three years from the filing date to the filing of a request for continued examination on November 22, 2005. The B delay was 151 days.

If the periods of delay under A and B overlap, the overlapping period is only counted once. As the court clearly explained in *Wyeth v. Kappos*, an overlap only occurs when the delay covers the very same calendar day or days. Here, the A delays occurred on different days than the B delays so Patentees are entitled to count both the A and the B delays. The A delays occurred from August 24, 2003 to October 3, 2003 and from November 27, 2006 to January 2, 2007. The B delays, in contrast, occurred June 24, 2005 to November 22, 2005. None of these periods encompasses the same days. Therefore, all the A and B delay should be included in the term adjustment. The Patent Office erred in failing to include the 40 day delay from the A delay.

The patent term adjustment is calculated as the A delay (40 days + 36 days) plus the B delay (151 days) minus the Applicants' delay (128 days) for a total of 99 days.

The error was not in the application as filed by Applicants. The correction does not involve new matter or require reexamination.

Transmitted herewith is a proposed Certificate of Correction. Patentee respectfully solicits the granting of the requested Certificate of Correction.

No fee is believed due. However, if a fee is due, the Director is hereby authorized to charge our Deposit Account No. 03-2775, under Order No. 11987-00014-US from which the undersigned is authorized to draw.

Dated: July 30, 2010

Respectfully submitted,

Electronic signature: /Christine M. Hansen/
Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

#759281

PTO/SB/44 (09-07)
Approved for use through 08/31/2010. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	7,157,456
APPLICATION NO.	:	10/181,051
ISSUE DATE	:	January 2, 2007
INVENTOR(S)	:	Alexander Straub et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Page 1:

In Notice, left column, at (*) between items (73) and (21), "Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 59 days." should read -- Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 99 days. --

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Christine M. Hansen, J.D.
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

759282_1

Electronic Acknowledgement Receipt

EFS ID:	8127188
Application Number:	10181051
International Application Number:	
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor/Applicant Name:	Alexander Straub
Customer Number:	23416
Filer:	Christine Hansen/Sara Maloney
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	30-JUL-2010
Filing Date:	24-JUN-2002
Time Stamp:	15:30:19
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	Req_Certificate_correction.pdf	103232 3449a5f50144cc5f4ef1ca90cfb61e778c2288e5	no	2

Warnings:	
Information:	

2	Request for Certificate of Correction	Certiciate_Correction.pdf	27397 b19f07a8ec3752746ca44d81c86fabc7b55f7776	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	130629

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

[X] Practitioners associated with the Customer Number: 23416

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name

Address					
City		State		Zip	
Country		Telephone		Email	

Assignee Name and Address:

Bayer Schering Pharma Aktiengesellschaft
Müllerstrasse 178
13353 Berlin
GERMANY

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	ppa. Dr. F. Köhler, ppa. Dr. F. Burkert	Date	April 08, 2009
Name	(secretaries)	Telephone	+49 214 30 81459
Title			

PTO/SB/96 (03-09)
Approved for use through 04/30/2009. OMB 0651-0031
U.S. Patent and Trad emark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alexander Straub, Thomas Lampe, Jens Pohlmann, Susanne Röhrig, Elisabeth Perzborn, Karl-Heinz Schlemmer, and Joseph Pernerstorfer

Application No./Patent No.: 7157456 Filed/Issue Date: January 2, 2007

Titled: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

Bayer Schering Pharma AG (Name of Assignee), a corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [x] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. [x] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Straub et al. To: Bayer AG
The document was recorded in the United States Patent and Trademark Office at
Reel 013411, Frame 0223, or for which a copy thereof is attached.

2. From: Bayer AG To: Bayer HealthCare AG
The document was recorded in the United States Patent and Trademark Office at
Reel 015004, Frame 0466, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[x] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Christine M. Hansen/	April 15, 2009
Signature	Date
Christine M. Hansen	Attorney for Assignee
Printed or Typed Name	Title

Docket No.: 11987-00014-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Alexander Straub et al.

Application No.: 10/181,051 (Patent No. 7,157,456) Confirmation No.: 5850

Filed: June 24, 2002 Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION Examiner: R. L. Anderson

TRANSMITTAL OF POWER OF ATTORNEY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Applicant encloses herewith an executed Power Of Attorney along with a Statement Under 37 CFR § 3.73(b) for the above-referenced application. Applicants request that all pertinent U.S. Patent and Trademark Office records relating to the subject application be updated accordingly.

Applicants believe no fee is due. However, if a fee is due, the Director is hereby authorized to charge or credit our Deposit Account No. 03-2775, under Order No. 11987-00014-US, from which the undersigned is authorized to draw.

Dated: April 15, 2009

Respectfully submitted,

By Christine Hansen

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

Electronic Acknowledgement Receipt

EFS ID:	5159002
Application Number:	10181051
International Application Number:	
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor/Applicant Name:	Alexander Straub
Customer Number:	23416
Filer:	Christine Hansen/Erica Liga
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	15-APR-2009
Filing Date:	24-JUN-2002
Time Stamp:	15:23:54
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	POA.pdf	49566 7e8db8f4752a29238b4760ce4cfe562917c363dc	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73(b).	Statement_Support.pdf	45799 0bc0d0bbc4e99fae10b21d3cbcab98c9e60bce5f	no	1
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	Transmittal_POA.pdf	28962 539486a56f1b50ed4af4445383733f6a4f5b6672	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	124327	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

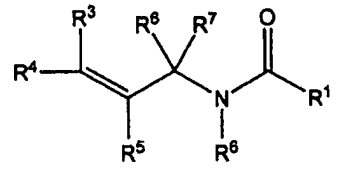
UNITED STATES PATENT AND TRADEMARK OFFICE

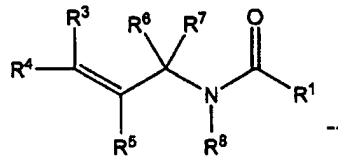
CERTIFICATE OF CORRECTION

PATENT NO. : 7,157,456 B2
APPLICATION NO. : 10/181051
DATED : January 2, 2007
INVENTOR(S) : Alexander Straub et al.

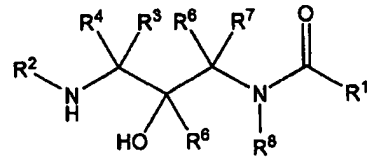
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

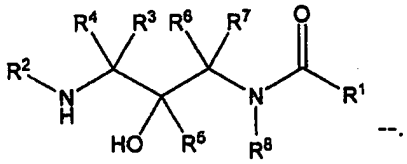
In Claim 7, at column 130, lines 25 - 30, Formula (IV),

“  ” should read

--  --.

In Claim 7, at column 130, lines 60 - 66, Formula (VII),

“  ” should read

--  --.

Signed and Sealed this

Nineteenth Day of February, 2008

JON W. DUDAS
Director of the United States Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Alexander Straub et al.

Patent No.: 7,157,456

Issued: January 2, 2007

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 CFR 1.322 OR ALTERNATIVELY 37 CFR 1.323

Attention: Decision & Certificates of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

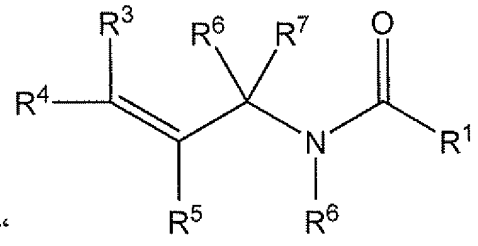
We reviewed the decision sent on May 21, 2007 denying a request for issuance of a Certificate of Correction pursuant to CFR 1.322. Applicants admit error in the Certificate of Correction submitted on May 3, 2007. The proposed Certificate of Correction effected no change at two sections although the Certificate indicated that a change should be made at those sections. Namely, Formula (IV) and Formula (VII) of claim 7 at col. 130, lines 25-30 and 60-66 required correction. However, the proposed correction was erroneously the same text as the original incorrect text in the issued patent. Nevertheless, Formula (IV) and Formula (VII) of claim 7 were correctly stated in Amendment in Response to Final Office Action dated March 31, 2006. The errors in the issued patent were thus the fault of the Patent Office; accordingly no fee is required.

Alternatively, if the Commissioner determines that the error was the mistake of Applicants, then Applicants request that a Certificate of Correction be issued pursuant to 37 CFR 1.323.

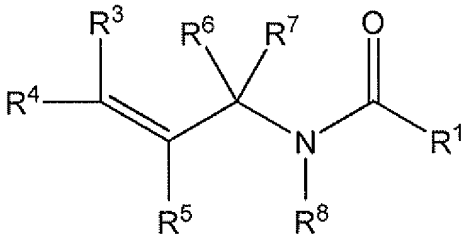
The following typographical errors should be corrected.

In the Claims:

In Claim 7, at column 130, lines 25 - 30, Formula (IV),

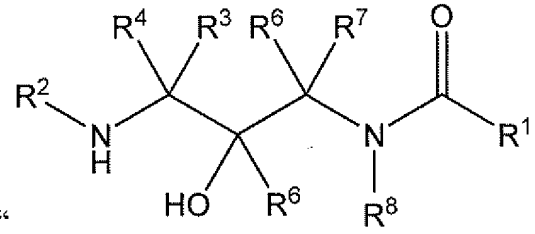


" should read

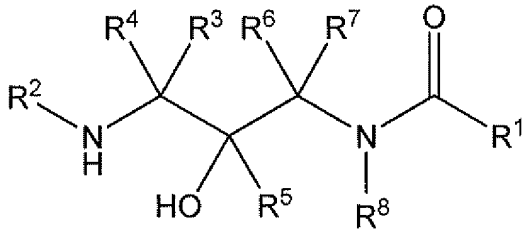


--.

In Claim 7, at column 130, lines 60 - 66, Formula (VII),



" should read



--.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Applicant believes no fee is due with this request. However, if a fee is due, including a fee under 37 CFR §1.20(a), please charge our Deposit Account No. 03-2775, under Order No. 11987-00014-US from which the undersigned is authorized to draw.

Dated: December 7, 2007

Respectfully submitted,

By Christine Hansen

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

580158_1

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,157,456

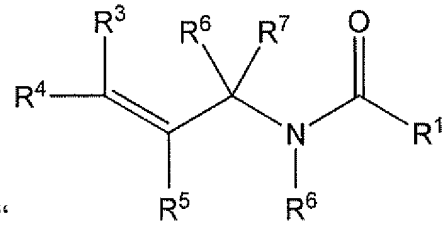
APPLICATION NO. : 10/181,051

ISSUE DATE : January 2, 2007

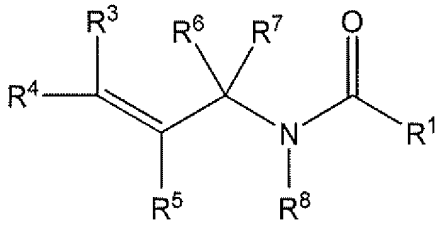
INVENTOR(S) : Alexander Straub et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 7, at column 130, lines 25 - 30, Formula (IV),



" should read



--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Christine M. Hansen
CONNOLLY BOVE LODGE & HUTZ LLP 1
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

536754

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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.
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

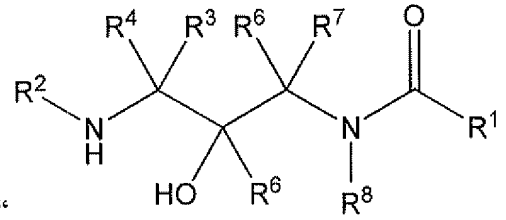
PATENT NO. : 7,157,456

APPLICATION NO. : 10/181,051

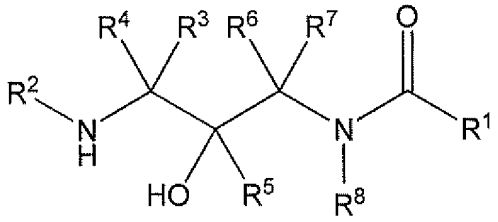
ISSUE DATE : January 2, 2007

INVENTOR(S) : Alexander Straub et al.

In Claim 7, at column 130, lines 60 - 66, Formula (VII),



" should read



--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Christine M. Hansen
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

2

536754

Electronic Acknowledgement Receipt

EFS ID:	2561170
Application Number:	10181051
International Application Number:	
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor/Applicant Name:	Alexander Straub
Customer Number:	23416
Filer:	Christine Hansen/Jean Marshall
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	07-DEC-2007
Filing Date:	24-JUN-2002
Time Stamp:	13:09:48
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	11987_14_Req.pdf	63291 a40a8bdd80812cb1d12aca383e78d584b3a8a8a5	no	3

Warnings:	
Information:	

2	Request for Certificate of Correction	11987_14_Cert.pdf	39270 de99e41850c277e576983578f4054c82813ce7bd	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	102561

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY OF COMMERCE AND
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

5/21/07

Patent No. :7157456
Inventor(s) : ALXANDER STRAUB ET AL.
Issued : 1/2/2007
Title : SUBSTITUTED OXAZOLIDINONES AND THEIR IN THE FIELD OF BLOOD COAGULATION
Atty.doc./File No.

Request for Certificates of Correction

Consideration has been given to your request for the issuance of a Certificate of Correction, for the above – identified patent under the provisions of CFR 1.322.

Inspection of the application for the patent reveals that claim 7, is printed in accordance with the record. Therefore being no fault on the Patent and Trademark Office, It has no authority to issue a certificate of correction under the provision of 1.322.

In view of the forgoing, your request in this matter, is hereby denied.

Future written correspondence concerning this matter should be filed and directed to Decisions & Certificates of Correction Branch.

Henry Randall
Cecelia Newman
Decisions & Certificates
of Correction Branch
(703) 308-9390 Ext. 108

CONNOLLY BOVE LODGE & HUTZ LLP
1007 NORTH ORANGE STREET
P.O. BOX 2207
WILMINGTON, DELAWARE 19899

HR/CBN

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Alexander Straub et al.

Patent No.: 7,157,456

Issued: January 2, 2007

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 CFR 1.322

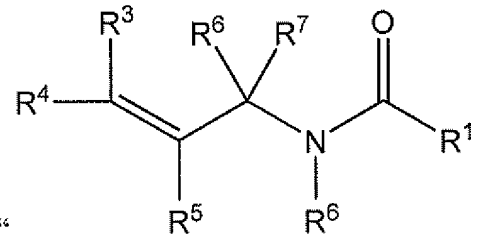
Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

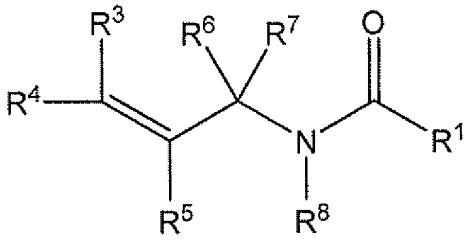
Upon reviewing the above-identified patent, Patentee noted typographical errors which should be corrected.

In the Claims:

In Claim 7, at column 130, lines 25 - 30, Formula (IV),

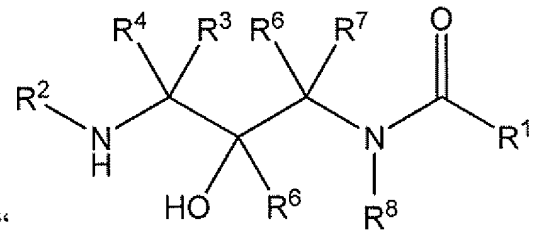


" should read

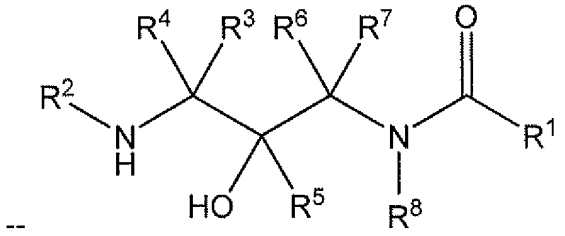


--.

In Claim 7, at column 130, lines 60 - 66, Formula (VII),



" should read



--.

The errors were not in the application as filed by applicant; accordingly no fee is required.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Applicant believes no fee is due with this request. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 11987-00014-US from which the undersigned is authorized to draw.

Dated: May 3, 2007

Respectfully submitted,

By Christine M. Hansen

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

536741_1.DOC

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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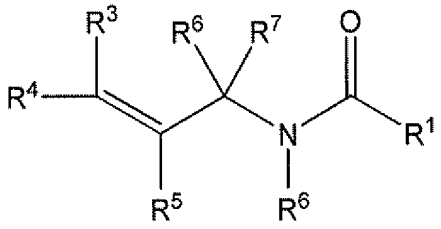
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

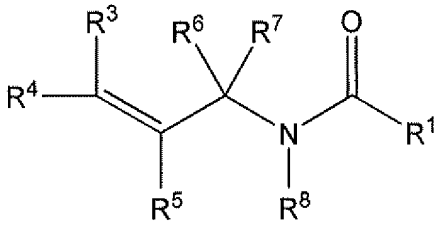
PATENT NO.	:	7,157,456
APPLICATION NO.	:	10/181,051
ISSUE DATE	:	January 2, 2007
INVENTOR(S)	:	Alexander Straub et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 7, at column 130, lines 25 - 30, Formula (IV),



" should read



--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Christine M. Hansen
CONNOLLY BOVE LODGE & HUTZ LLP 1
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

536754

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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.
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

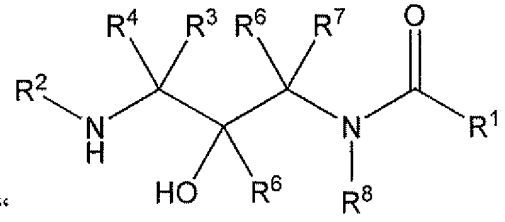
PATENT NO. : 7,157,456

APPLICATION NO. : 10/181,051

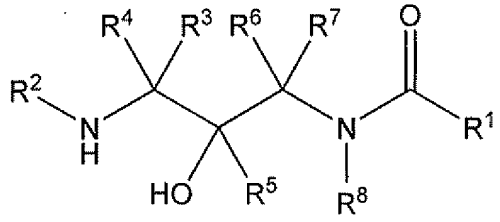
ISSUE DATE : January 2, 2007

INVENTOR(S) : Alexander Straub et al.

In Claim 7, at column 130, lines 60 - 66, Formula (VII),



" should read



--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Christine M. Hansen
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

2

536754

Electronic Acknowledgement Receipt

EFS ID:	1742277
Application Number:	10181051
International Application Number:	
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor/Applicant Name:	Alexander Straub
Customer Number:	23416
Filer:	Christine Hansen/Jean Marshall
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	03-MAY-2007
Filing Date:	24-JUN-2002
Time Stamp:	16:39:32
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	Req_Cert_Corr.pdf	41309	no	2
Warnings:					

Information:					
2	Request for Certificate of Correction	Cert_Corr.pdf	39648	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	80957	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

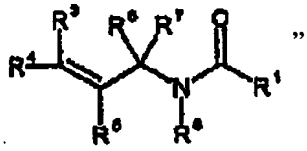
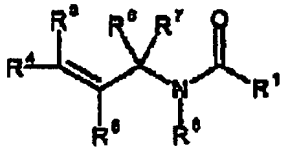
PATENT NO. : 7,157,456 B2
APPLICATION NO. : 10/181051
DATED : January 2, 2007
INVENTOR(S) : Alexander Straub et al.

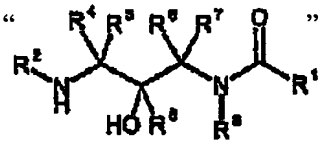
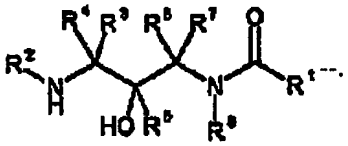
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 1, at column 125, line 50, "where  ; the radical "A" represents optionally substituted" should read --where the radical "A" represents optionally substituted  ;--.

In Claim 7, at column 129, lines 30 - 40, Formula (II), radical "R^9" should read -- R^8 --.

In Claim 7, at column 130, lines 5 - 15, Formula (I), radical "R^9" should read -- R^8 --.

In Claim 7, at column 130, lines 25 - 30, Formula (IV), "  " should read --  --.

In Claim 7, at column 130, lines 60 - 66, Formula (VII), "  " should read --  --.

In Claim 7, at column 131, lines 10 - 20, in Formula (I), radical "R^9" should read -- R^8 --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

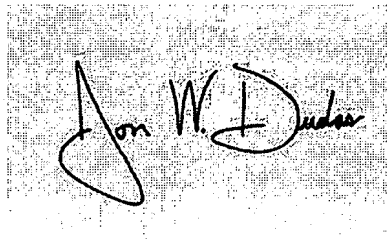
PATENT NO. : 7,157,456 B2
APPLICATION NO. : 10/181051
DATED : January 2, 2007
INVENTOR(S) : Alexander Straub et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 10, at column 132, line 4, "($_1$-C_8)-alkyl substituent is methyl, where the methyl radical" should read --"(C_1-C_8)-alkyl substituent is methyl, where the methyl radical --.

Signed and Sealed this

Seventeenth Day of April, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

Docket No.: 11987-00014-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Alexander Straub et al.

Patent No.: 7,157,456

Issued: January 2, 2007

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

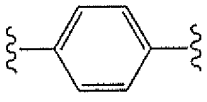
REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 CFR 1.322

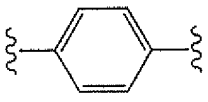
Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted typographical errors which should be corrected.

In the Claims:

In Claim 1, at column 125, line 50, "where  ; the radical "A" represents optionally substituted" should read -- where

the radical "A" represents optionally substituted  ; --.

In Claim 7, at column 129, lines 30 - 40, Formula (II), radical "R^{9}" should read -- R^{8} --.

In Claim 7, at column 130, lines 5 - 15, Formula (I), radical "R^{9}" should read -- R^{8} --.

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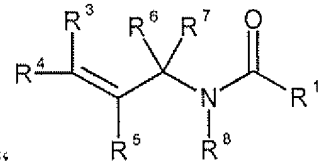
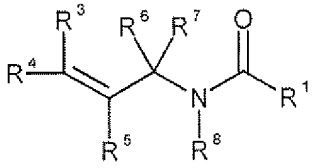
In Claim 7, at column 130, lines 25 - 30, Formula (IV), "



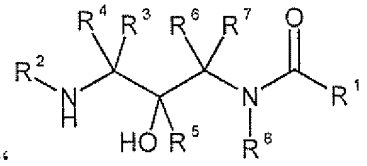
"

should read --



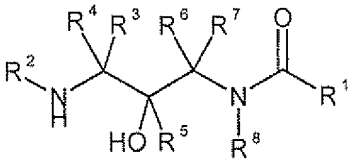
--.

In Claim 7, at column 130, lines 60 - 66, Formula (VII), "



"

should read --



--.

In Claim 7, at column 131, lines 10 - 20, in Formula (I), radical "R^{9}" should read -- R^{8} --.

In Claim 10, at column 132, line 4, "($_{1}$-C_{8})-alkyl substituent is methyl, where the methyl radical" should read -- "(C_1-C_8)-alkyl substituent is methyl, where the methyl radical --.

The errors were not in the application as filed by applicant; accordingly no fee is required.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Applicant believes no fee is due with this request. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 11987-00014-US from which the undersigned is authorized to draw.

Dated:

Respectfully submitted,

By CMH /Robert L. McCall/ 30,962

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,157,456

APPLICATION NO. : 10/181,051

ISSUE DATE : January 2, 2007

INVENTOR(S) : Alexander Straub et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 1, at column 125, line 50, "where  ; the radical "A" represents optionally substituted" should read -- where

the radical "A" represents optionally substituted  ; --.

In Claim 7, at column 129, lines 30 - 40, Formula (II), radical "R^9" should read -- R^8 --.

In Claim 7, at column 130, lines 5 - 15, Formula (I), radical "R^9" should read -- R^8 --.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Christine M. Hansen
CONNOLLY BOVE LODGE & HUTZ LLP 1
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

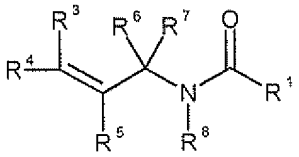
PATENT NO. : 7,157,456

APPLICATION NO. : 10/181,051

ISSUE DATE : January 2, 2007

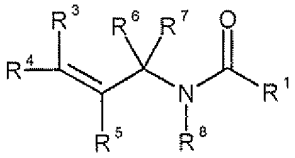
INVENTOR(S) : Alexander Straub et al.

In Claim 7, at column 130, lines 25 - 30, Formula (IV), "



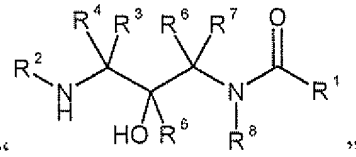
"

should read --



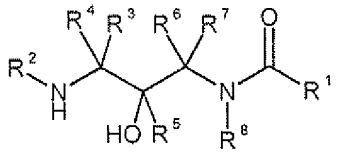
--.

In Claim 7, at column 130, lines 60 - 66, Formula (VII), "



"

should read --



--.

In Claim 7, at column 131, lines 10 - 20, in Formula (I), radical "R^9" should read -- R^8 --.

In Claim 10, at column 132, line 4, "(C_1-C_8)-alkyl substituent is methyl, where the methyl radical" should read -- "(C_1-C_8)-alkyl substituent is methyl, where the methyl radical --.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Christine M. Hansen
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899

Electronic Acknowledgement Receipt

EFS ID:	1607776
Application Number:	10181051
International Application Number:	
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor/Applicant Name:	Alexander Straub
Customer Number:	23416
Filer:	Christine Hansen/Jean Marshall
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	20-MAR-2007
Filing Date:	24-JUN-2002
Time Stamp:	15:30:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	Req_Cert_Corr.pdf	101813	no	5
Warnings:					

Information:	
Total Files Size (in bytes):	101813

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/181,051	01/02/2007	7157456	LE A 34122	5850

23416 7590 12/13/2006

CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 59 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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 (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Alexander Straub, Wuppertal, GERMANY;
Thomas Lampe, Wuppertal, GERMANY;
Jens Pohlmann, Wuppertal, GERMANY;
Susanne Rohrig, Essen, GERMANY;
Elisabeth Perzborn, Wuppertal, GERMANY;
Karl-Heinz Schlemmer, Wuppertal, GERMANY;
Joseph Pernerstorfer, Wuppertal, GERMANY;

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

BIBDATASHEET

Bib Data Sheet

CONFIRMATION NO. 5850

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/181,051	06/24/2002 RULE	514	1626	LE A 34122

APPLICANTS

Alexander Straub, Wuppertal, GERMANY;
Thomas Lampe, Wuppertal, GERMANY;
Jens Pohlmann, Wuppertal, GERMANY;
Susanne Rohrig, Essen, GERMANY;
Elisabeth Perzborn, Wuppertal, GERMANY;
Karl-Heinz Schlemmer, Wuppertal, GERMANY;
Joseph Pernerstorfer, Wuppertal, GERMANY;

** CONTINUING DATA **********

This application is a 371 of PCT/EP00/12492 12/11/2000

** FOREIGN APPLICATIONS **********

GERMANY 199 62 924.2 12/24/1999

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	GERMANY	0	15	2

35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance

Verified and Acknowledged _____ Examiner's Signature Initials

ADDRESS

23416

TITLE

SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2228	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/181,051	06/24/2002	Alexander Straub	LE A 34122

CONFIRMATION NO. 5850

OC000000019848438

OC000000019848438

35969
JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

Date Mailed: 08/01/2006

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/31/2006.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

for

MARQUITA MOORE
PATDACAP (571) 272-4200

OFFICE COPY

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/181,051	06/24/2002	Alexander Straub	LE A 34122

CONFIRMATION NO. 5850

23416
CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

OC000000019848454

OC000000019848454

Date Mailed: 08/01/2006

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/31/2006.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/for Lakisha Tennessee/

MARQUITA MOORE
PATDACAP (571) 272-4200

OFFICE COPY

PTO/SB/80 (04-05)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

[X] Practitioners associated with the Customer Number: 23416

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

[X] The address associated with Customer Number: 23416

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country		Telephone		Email	

Assignee Name and Address:

BAYER HEALTHCARE AKTIENGESELLSCHAFT
D-51368
Leverkusen, Germany

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	July 28, 2006
Name	Dr. F.Burkert Dr. D. Linken-	Telephone	++49-214-30-36819
Title	Secretaries heil		

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office, facsimile no. (571) 273-8300, on the date shown below.

Dated: _____ Signature: _____ (Barbara J. Miller)

PTO/SB/96 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alexander Straub et al.

Application No./Patent No.: 10/181,051 Filed/Issue Date: June 24, 2002

Entitled: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

Bayer Healthcare Aktiengesellschaft (Name of Assignee), a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [x] the assignee of the entire right, title, and interest; or

2. [ ] an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

in the patent application/patent identified above by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. [x] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: Alexander Straub et al. To: Bayer Aktiengesellschaft
The document was recorded in the United States Patent and Trademark Office at
Reel 013411, Frame 0223, or for which a copy thereof is attached.

2. From: Bayer Aktiengesellschaft To: Bayer Healthcare Aktiengesellschaft
The document was recorded in the United States Patent and Trademark Office at
Reel 015004, Frame 0466, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Christie M. Hansen — Signature
July 31, 2006 — Date

Christine M. Hansen — Printed or Typed Name
(302) 658-9141 — Telephone Number

Attorney – Reg. No. 40,634 — Title

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office, facsimile no. (571) 273-8300, on the date shown below.

Dated: _____ Signature: _____ (Barbara J. Miller)

Electronic Acknowledgement Receipt

EFS ID:	1134021
Application Number:	10181051
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor:	Alexander Straub
Customer Number:	35969
Filer:	Christine Hansen/Jean Marshall
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	31-JUL-2006
Filing Date:	24-JUN-2002
Time Stamp:	15:29:08
Application Type:	U.S. National Stage under 35 USC 371
International Application Number:	

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part	Pages
1	Power of Attorney (may include Associate POA)	Powerofattorney.pdf	58778	no	1

Warnings:					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73(b).	Statement.pdf	56847	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	115625	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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)

35969 7590 04/27/2006

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

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.

Jean M. Marshall	(Depositor's name)
	(Signature)
July 27, 2006	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/181,051	06/24/2002	Alexander Straub	LE A 34122	5850

TITLE OF INVENTION: SUBSTITUTED OXAZOLIDINONES AND THEIR IN THE FIELD OF BLOOD COAGULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	07/27/2006

EXAMINER	ART UNIT	CLASS-SUBCLASS
ANDERSON, REBECCA L	1626	514-236800

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

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/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 Connolly Bove Lodge & Hutz LLP
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 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Bayer HealthCare AG

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Leverkusen, Germany

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 enclosed:

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

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 03-2775 (enclose an extra copy of this form).

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

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Christine M. Hansen Date July 27, 2006

Typed or printed name Christine M. Hansen Registration No. 40,634

This collection of information 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.

Electronic Patent Application Fee Transmittal

Application Number:	10181051
Filing Date:	24-Jun-2002
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor:	Alexander Straub
Filer:	Christine Hansen/Jean Marshall
Attorney Docket Number:	LE A 34122

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1400	1400
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1700**

Electronic Acknowledgement Receipt

EFS ID:	1130463
Application Number:	10181051
Confirmation Number:	5850
Title of Invention:	SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION
First Named Inventor:	Alexander Straub
Customer Number:	35969
Filer:	Christine Hansen/Jean Marshall
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	LE A 34122
Receipt Date:	27-JUL-2006
Filing Date:	24-JUN-2002
Time Stamp:	16:04:51
Application Type:	U.S. National Stage under 35 USC 371
International Application Number:	

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1700
RAM confirmation Number	186
Deposit Account	032775

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part	Pages

1	Issue Fee Payment Recorded	issuefeetransmittal.pdf	85541	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	8341	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	93882		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

Issue Classification	Application/Control No. 10/181,051	Applicant(s)/Patent under Reexamination STRAUB ET AL.
	Examiner Rebecca L. Anderson	Art Unit 1626

ISSUE CLASSIFICATION

ORIGINAL		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
514	236.8	A	61	K	31	/5377					/
CROSS REFERENCES		C	07	D	409	/14					/
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					/					/
544	139					/					/
						/					/
						/					/
						/					/
						/					/

Rebecca Anderson 6/16/06
(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

Kamal A. Saeed, PH.D.
(Primary Examiner) (Date)
06/16/06

Total Claims Allowed: 30

O.G. Print Claim(s)	O.G. Print Fig.
1	---

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1	22	31		61		91		121		151		181
1	2		32		62		92		122		152		182
2	3		33		63		93		123		153		183
3	4	23	34		64		94		124		154		184
4	5	24	35		65		95		125		155		185
5	6		36		66		96		126		156		186
6	7		37		67		97		127		157		187
7	8		38		68		98		128		158		188
8	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
	11	25	41		71		101		131		161		191
	12	26	42		72		102		132		162		192
9	13		43		73		103		133		163		193
	14		44		74		104		134		164		194
	15		45		75		105		135		165		195
	16		46		76		106		136		166		196
10	17		47		77		107		137		167		197
11	18	29	48		78		108		138		168		198
12	19	30	49		79		109		139		169		199
13	20		50		80		110		140		170		200
14	21		51		81		111		141		171		201
	22		52		82		112		142		172		202
15	23	27	53		83		113		143		173		203
16	24		54		84		114		144		174		204
17	25		55		85		115		145		175		205
18	26		56		86		116		146		176		206
28	27		57		87		117		147		177		207
19	28		58		88		118		148		178		208
20	29		59		89		119		149		179		209
21	30		60		90		120		150		180		210

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

35969 7590 04/27/2006

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/27/2006

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/181,051	06/24/2002	Alexander Straub	LE A 34122	5850

TITLE OF INVENTION: SUBSTITUTED OXAZOLIDINONES AND THEIR IN THE FIELD OF BLOOD COAGULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	07/27/2006

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 REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. 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.

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.

PTOL-85 (Rev. 01/06) Approved for use through 04/30/2007.

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)

35969 7590 04/27/2006

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

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.
10/181,051	06/24/2002	Alexander Straub	LE A 34122	5850

TITLE OF INVENTION: SUBSTITUTED OXAZOLIDINONES AND THEIR IN THE FIELD OF BLOOD COAGULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	07/27/2006

EXAMINER	ART UNIT	CLASS-SUBCLASS
ANDERSON, REBECCA L	1626	514-236800

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

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/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 3.11. 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 enclosed:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

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.
10/181,051	06/24/2002	Alexander Straub	LE A 34122	5850

35969 7590 04/27/2006

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/27/2006

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

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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.

PTOL-85 (Rev. 01/06) Approved for use through 04/30/2007.

Notice of Allowability	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- 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 *to the amendment filed 31 march 2006*.

2. ☒ The allowed claim(s) is/are *2-9, 13, 17-21, 23-31, 34, 35, 41, 42, 48, 49 and 53, now renumbered as claims 1-30*.

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

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ 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)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

Claims 2-9, 13, 17-21, 23-31, 34, 35, 41, 42, 48, 49 and 53 are currently pending in the instant application, appear allowable over the prior art of record and have been renumbered as claims 1-30. The rejection of claims 34, 35, 41, 42, 48 and 49 under 35 USC 112 1st paragraph has been overcome by the amendment to the claims to delete "prevention" of the claimed diseases and disorders.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/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.

The application has been amended as follows:

1. Amend page 1 of the specification by inserting on the line following the title, the following sentence:

--This application is a 371 of PCT/EP00/12492 filed 11 December 2000.--

Reasons for Allowance

The following is an examiner's statement of reasons for allowance. This invention relates to the products of the formula (I), methods of treatment and methods of preparation. The novel and nonobvious aspect of this invention involves the substituents R1 and R2. The closest prior art of record, Hutchinson et al. (WO 97/09328), which discloses the phenyloxazolidinone compounds of the formula (I) wherein the position equivalent to applicants R2 is a phenyl substituted with a C-C bond

to a 4-8 membered heterocyclic ring and the position equivalent to applicants R1 is hydrogen, C1-12alkyl, C3-12 cycloalkyl or C1-6alkoxy, fails to teach or suggest applicants' instantly claimed invention wherein R1 is a phenyl substituted by a morpholinone and R2 is an optionally benzo-fused thiophene group. Furthermore, the tests found on pages 43-46 coupled with the prior art reference of Al-Obeidi et al. (vol. 3, No. 5, May 1998) wherein the inhibition of Factor Xa is shown to treat myocardial infarction, deep vein and pulmonary embolism and the Hauptmann et al. reference which discloses the relationship between the inhibition of Factor Xa and the treatment of atherosclerosis support the treatment of myocardial infarct, pulmonary embolism, deep venous thrombosis and atherosclerosis.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an 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. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600
4/19/06

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

for Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Issue Classification	Application/Control No. 10/181,051	Applicant(s)/Patent under Reexamination STRAUB ET AL.
	Examiner Rebecca L. Anderson	Art Unit 1626

ISSUE CLASSIFICATION

ORIGINAL		INTERNATIONAL CLASSIFICATION					
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED
514	236.8	A	61	K	31	/5377	/
CROSS REFERENCES		C	07	D	409	/14	/
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					/	/
544	139					/	/
						/	/
						/	/
						/	/

Rebecca Anderson 4/19/2006
(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER
(Primary Examiner) (Date) 04/24/06

Total Claims Allowed: 30

O.G. Print Claim(s)	O.G. Print Fig.
1	---

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1	22	31		61		91		121		151		181
1	2	23	32		62		92		122		152		182
2	3	24	33		63		93		123		153		183
3	4		34		64		94		124		154		184
4	5		35		65		95		125		155		185
5	6		36		66		96		126		156		186
6	7		37		67		97		127		157		187
7	8		38		68		98		128		158		188
8	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
	11	25	41		71		101		131		161		191
	12	26	42		72		102		132		162		192
9	13		43		73		103		133		163		193
	14		44		74		104		134		164		194
	15		45		75		105		135		165		195
	16		46		76		106		136		166		196
10	17		47		77		107		137		167		197
11	18	29	48		78		108		138		168		198
12	19	30	49		79		109		139		169		199
13	20		50		80		110		140		170		200
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17	25		55		85		115		145		175		205
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28	27		57		87		117		147		177		207
19	28		58		88		118		148		178		208
20	29		59		89		119		149		179		209
21	30		60		90		120		150		180		210

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/181,051	514STRAUB ET AL.	
Examiner	**Art Unit**	
Rebecca L. Anderson	1626	

SEARCHED			
Class	Subclass	Date	Examiner
514	236.8	4/19/2006	RA
544	139	4/19/2006	RA

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**236.8**	**4/19/2006**	**RA**
544	139	4/19/2006	RA

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor and STN update	4/19/2006	RA
EAST search notes and Interference search notes	4/19/2006	RA

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	275	(514/236.8).CCLS.	US-PGPUB; USPAT; EPO; DERWENT	OR	OFF	2006/04/19 10:01
L2	707	(544/139).CCLS.	US-PGPUB; USPAT; EPO; DERWENT	OR	OFF	2006/04/19 10:01
L5	2647	(oxazolone)".CLM"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/04/19 10:02
L6	22	l5 and (morpholinone)".CLM"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/04/19 10:03
L8	4	l6 and (thiophene)".CLM"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/04/19 10:03

PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

10/181,051

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	21 minus 20=	*
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐			OR	OTHER THAN SMALL ENTITY	
RATE	FEE			RATE	FEE
BASIC FEE	150.00		OR	BASIC FEE	300.00
X$ 25=			OR	X$50=	
X100=			OR	X200=	
+180=			OR	+360=	
TOTAL			OR	TOTAL	

CLAIMS AS AMENDED - PART II

03.31.06

AMENDMENT A

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	* 31	Minus	** 51	=
Independent	* 5	Minus	*** 5	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

2, 7, 23, 24, ~~25~~ 53

SMALL ENTITY			OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE			RATE	ADDITIONAL FEE
X$ 25=			OR	X$50=	
X100=			OR	X200=	
+180=			OR	+360=	
TOTAL ADDIT. FEE			OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FAX TRANSMISSION

DATE: March 31, 2006

PTO IDENTIFIER: **Application Number** 10/181,051-Conf. #5850
Patent Number
Inventor: Alexander Straub et al.

MESSAGE TO: US Patent and Trademark Office
FAX NUMBER: (571) 273-8300

FROM: CONNOLLY BOVE LODGE & HUTZ LLP
Christine M. Hansen
PHONE: (302) 658-9141
Attorney Dkt. #: 11987-00014-US

PAGES (Including Cover Sheet): 22

CONTENTS:
Amendment in Response to Final Office Action (20 pages)
Certificate of Transmission (1 page)

CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street, P.O. Box 2207, Wilmington, Delaware 19899
Telephone: (302) 658-9141 **Facsimile:** (302) 658-5614

Docket No.: 11987-00014-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Alexander Straub et al.

Application No.: 10/181,051 Confirmation No.: 5850

Filed: June 24, 2002 Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION Examiner: R. L. Anderson

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Introductory Comments

In response to the Final Office Action dated February 3, 2006, please amend the above-captioned U.S. patent application as follows:

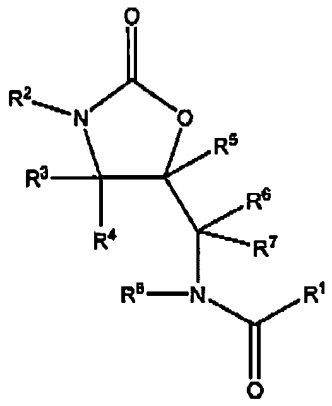
Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 19 of this paper.

Amendments to the Claims

1. (canceled)

2. (previously presented) A compound of the formula (I)



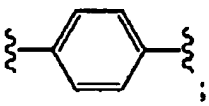
(I)

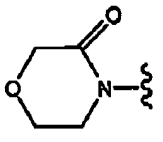
characterized in that

R^1 represents an optionally benzo-fused thiophene group which may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; cyano; nitro; amino; aminomethyl; (C_1-C_8)-alkyl which for its part may optionally be mono- or polysubstituted by halogen; (C_3-C_7)-cycloalkyl; (C_1-C_8)-alkoxy; imidazolinyl; $-C(=NH)NH_2$; carbamoyl; and mono- and di-(C_1-C_4)-alkyl-aminocarbonyl,

R^2 represents
D-M-A-,

where

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; (C_1-C_6)-alkanoyl; -OR^{30}; -$NR^{30}R^{31}$, and (C_1-C_6)-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, or $C(O)R^{33}$,

where

R^{33} represents (C_1-C_4)-aminoalkyl, or (C_1-C_8)-alkyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

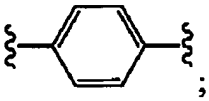
3. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

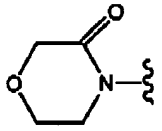
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen, amino, aminomethyl or (C_1-C_8)-alkyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

D-M-A-,

where

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; (C_1-C_6)-alkanoyl; $-OR^{30}$; $-NR^{30}R^{31}$, and (C_1-C_6)-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, or (C_1-C_4)-alkylaminocarbonyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

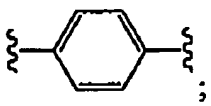
4. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

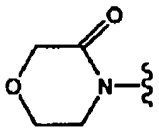
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen or by $(C_1$-$C_8)$-alkyl, where the $(C_1$-$C_8)$-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; $(C_1$-$C_3)$-alkanoyl; -OH; $-NR^{30}R^{31}$; and $(C_1$-$C_4)$-alkyl;

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or (C_1-C_3)-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

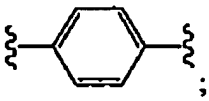
except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

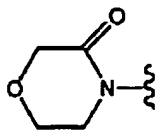
5. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

R^1 represents 2-thiophene which may optionally be substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents
D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; (C_1-C_3)-alkanoyl; -OH; -$NR^{30}R^{31}$; and (C_1-C_4)-alkyl;

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or (C_1-C_3)-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_4)-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

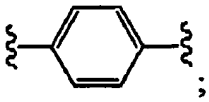
except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

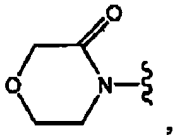
6. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

R^1 represents 2-thiophene which is substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents D-A-,

where:

the radical "A" represents  ;

the radical "D" represents  ,

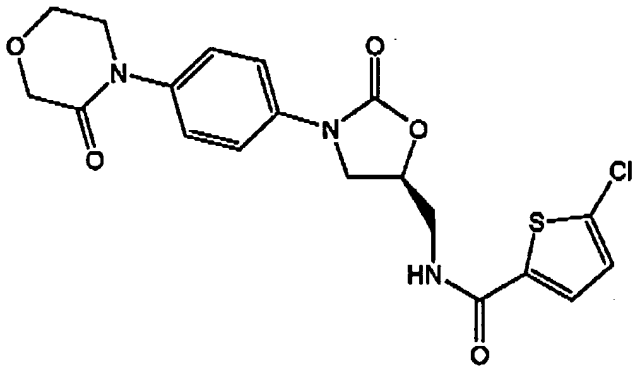
where

the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical selected from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen

or a pharmaceutically acceptable salt or hydrate thereof.

7. (previously presented) The compound having the following formula

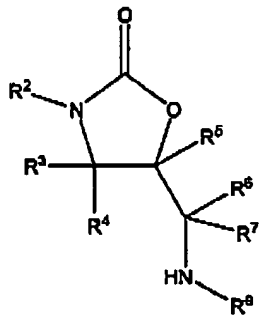


or a pharmaceutically acceptable salt or hydrate thereof.

8. (previously presented) Process for preparing the substituted oxazolidinone of claim 2, where

either according to a process alternative

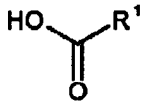
(A) a compound of the formula (II)



(II),

in which

the radicals R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2 is reacted with carboxylic acid of the formula (III)



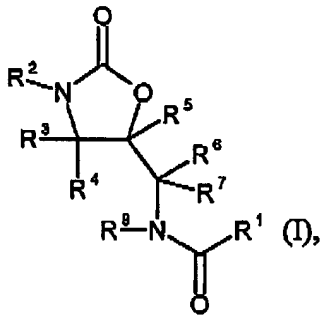
(III),

in which

the radical R^1 is as defined in Claim 2,

or else with a corresponding carbonyl halide, or else with a corresponding symmetric or mixed carboxylic anhydride of the carboxylic acid of the formula (III) defined above

in an inert solvent, if appropriate in the presence of an activating or coupling agent and/or a base, to give a compound of the formula (I)



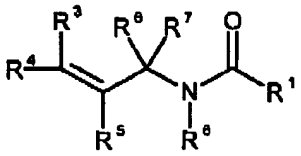
(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

or else according to a process alternative

(B) a compound of the formula (IV)

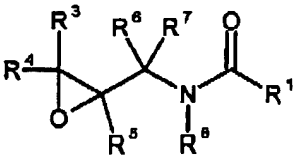


(IV),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the formula (V)



(V),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

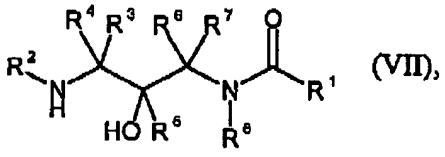
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the formula (VI)

$$R^2\text{-}NH_2 \qquad \text{(VI)},$$

in which

the radical R^2 is as defined in Claim 2,

a compound of the formula (VII)



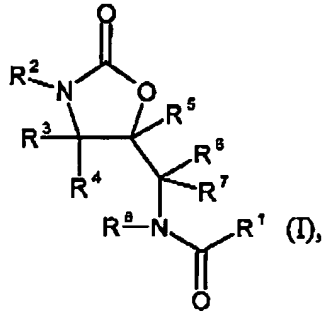
(VII),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is initially prepared and,

subsequently, in an inert solvent in the presence of phosgene or a phosgene equivalent, cyclized to give a compound of the formula (I)



(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

where - both for process alternative (A) and for process alternative (B) - in the case where R^2 contains a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical having one or more identical or different heteroatoms from the group consisting of N and S, an oxidation with a selective oxidizing agent to afford the corresponding sulphone, sulphoxide or N-oxide may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has a cyano group in the molecule, an amidination of this cyano group by customary methods may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has a BOC amino protective group in the molecule, removal of this BOC amino protective group by customary methods may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with a carboxylic acid, carboxylic anhydride, carbonyl chloride, isocyanate, sulphonyl chloride or alkyl halide to give the corresponding derivative may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with an amine to give the corresponding sulphonamide may follow.

9. (previously presented) A pharmaceutical composition comprising at least one compound of the formula (I) according to claim 2 and one or more pharmacologically acceptable auxiliaries or excipients.

10. (canceled)

11. (canceled)

12. (canceled)

13. (previously presented) A method for treatment of atherosclerosis comprising administering an effective amount of a compound of claim 2 to a patient in need thereof.

14. (canceled)

15. (canceled)

16. (canceled)

17. (previously presented) The compound of claim 3 or 4 wherein R^1 represents an optionally substituted 2-thiophene group, and wherein said halogen substituent is chlorine or bromine, and said (C_1-C_8)-alkyl substituent is methyl, where the methyl radical for its part optionally may be mono- or polysubstituted by fluorine.

18. (previously presented) The process of claim 8 wherein in process alternative "A", the corresponding carbonyl halide of carboxylic acid (III) is a carbonyl chloride.

19. (previously presented) The process of claim 8 wherein in process alternative "B", the phosgene equivalent employed in the cyclization of compound (VII) is carbonyldimidazole (CDI).

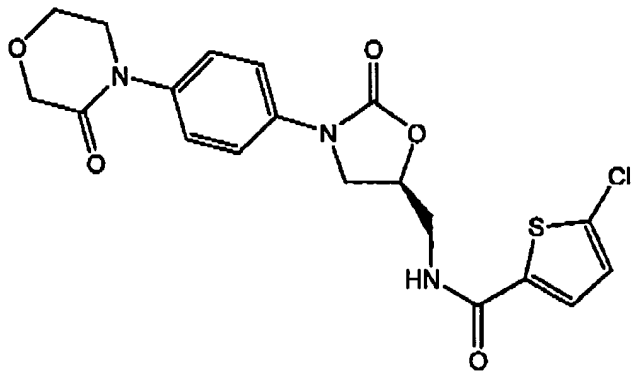
20. (previously presented) A method for treatment of a thromboembolic disorder comprising administering to a patient in need thereof an effective amount of a compound of claim 2,

wherein the thromboembolic disorder is myocardial infarct, pulmonary embolism or deep venous thrombosis.

21. (previously presented) The compound of claim 7 that is purified and isolated.

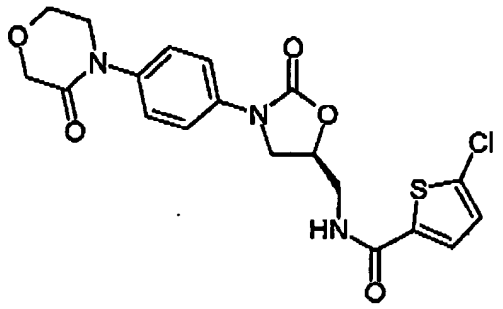
22. (canceled)

23. (previously presented) A racemic mixture of a compound having the following formula



and its enantiomer, or a pharmaceutically acceptable salt or hydrate thereof.

24. (previously presented) A compound having the following formula:



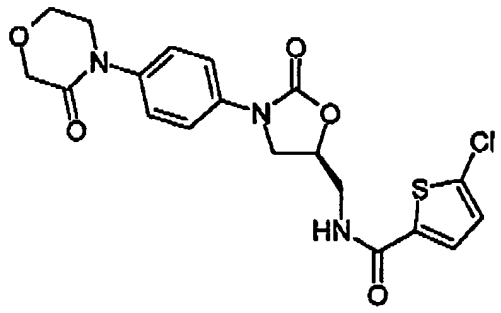
25. (previously presented) A pharmaceutical composition comprising the compound of claim 7 and one or more pharmacologically acceptable auxiliaries or excipients.

26. (previously presented) A pharmaceutical composition comprising the compound of claim 21 and one or more pharmacologically acceptable auxiliaries or excipients.

27. (previously presented) A pharmaceutical composition comprising the composition of claim 53 and one or more pharmacologically acceptable auxiliaries or excipients.

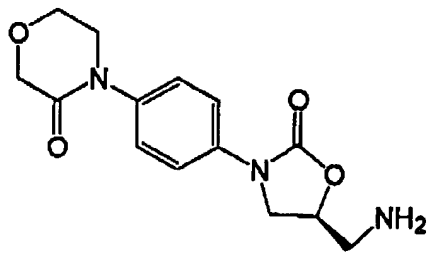
28. (previously presented) A pharmaceutical composition comprising the compound of claim 24 and one or more pharmacologically acceptable auxiliaries or excipients.

29. (previously presented) The process of claim 8 wherein the substituted oxazolidinone that is prepared is



or a pharmaceutically acceptable salt or hydrate thereof.

30. (previously presented) A process for the preparation of the compound of claim 7 comprising reacting a compound of the following formula



with 5-chlorothiophene-2-carbonyl chloride in an inert solvent to prepare the compound of claim 7.

31. (previously presented) The process of claim 30 wherein the inert solvent comprises pyridine.

32. (canceled)

33. (canceled)

34. (currently amended) A method for the ~~prevention or~~ treatment of atherosclerosis comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

35. (currently amended) A method for the ~~prevention or~~ treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

36. (canceled)

37. (canceled)

38. (canceled)

39. (canceled)

40. (canceled)

41. (currently amended) A method for the ~~prevention or~~ treatment of atherosclerosis comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

42. (currently amended) A method for the ~~prevention or~~ treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

43. (canceled)

44. (canceled)

45. (canceled)

46. (canceled)

47. (canceled)

48. (currently amended) A method for the ~~prevention or~~ treatment of atherosclerosis comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

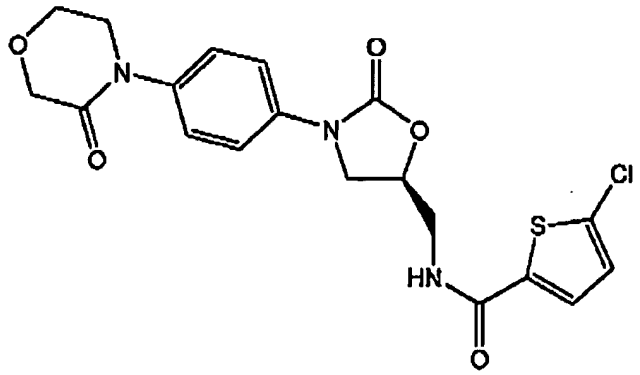
49. (currently amended) A method for the ~~prevention or~~ treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

50. (canceled)

51. (canceled)

52. (canceled)

53. (previously presented) A composition comprising a compound having formula (a):



(a)

or a pharmaceutically acceptable salt or hydrate thereof, wherein the composition is substantially free of the enantiomer of the compound of formula (a) and substantially free of the salts and hydrates of the enantiomer of the compound of formula (a).

Remarks

Claims 2-9, 13, 17-21, 23-31, 34, 35, 41, 42, 48, 49 and 53 are pending. Applicants respectfully request entry of the amendments to claims 34, 35, 41, 42, 48 and 49 as they are believed to put the claims in condition for allowance or, alternatively, in better form for consideration on appeal. Thus, entry under 37 CFR 1.116 is correct. The claims are amended without prejudice to or disclaimer of Applicants' right to pursue the canceled subject matter of these claims in a later application. No new matter has been added.

The Examiner has found that claims 2-9, 13, 17-21, 23-31 and 53 appear allowable over the art of record.

Claims 34, 35, 41, 42, 48 and 49 stand rejected for lack of enablement under 35 USC § 112, first paragraph. The Examiner asserts that the specification supports methods of treatment, but not prevention, of the disorders of atherosclerosis, pulmonary embolism, myocardial infarct and deep venous thrombosis. Applicants respectfully disagree. However, to expedite prosecution, the claims are amended to recite methods of treatment. The rejection is believed to be rendered moot.

In view of the foregoing, Applicants respectfully believe that the claims are in condition for allowance. The Examiner is invited to telephone the attorney listed below if there are any further issues before allowance.

No fee is believed due for the filing of this paper. Should any fees be required in connection with this Amendment, authorization is hereby made to charge any fees due or outstanding, including any extension fees, or credit any overpayment, to Deposit Account No.

03-2775.

Dated: March 31, 2006

Respectfully submitted,

By Christine M. Hansen

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Application No. (if known): 10/181,051 Attorney Docket No.: 11987-00014-US

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Amendment in Response to Final Office Action (20 pages)

Docket No.: 11987-00014-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Alexander Straub et al.

Application No.: 10/181,051 Confirmation No.: 5850

Filed: June 24, 2002 Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION Examiner: R. L. Anderson

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION

OK to enter
RL
3/26/06

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Introductory Comments

In response to the Final Office Action dated February 3, 2006, please amend the above-captioned U.S. patent application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 19 of this paper.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/181,051	06/24/2002	Alexander Straub	Le A 34122	5850

35969 7590 02/03/2006

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EXAMINER	
ANDERSON, REBECCA L	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9,13,17-21,23-31,34,35,41,42,48,49 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2-9,13,17-21,23-31 and 53* is/are allowed.

6)☒ Claim(s) *34,35,41,42,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-9, 13, 17-21, 23-31, 34, 35, 41, 42, 48, 49 and 53 are currently pending in the instant application. Claims 2-9, 13, 17-21, 23-31 and 53 appear allowable over the prior art of record and claims 34, 35, 41, 42, 48 and 49 are rejected.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 22 November 2005 have been entered.

Election/Restrictions

Applicants' have requested clarification of the restriction requirement. As the initial restriction requirement included groups corresponding to different R2 definitions in the compound of formula I as well as into groups corresponding to different types of claims (e.g., product, process of making, etc.)., the restriction requirement was not lifted for all the groups, but only for the groups drawn to processes of making or using the patentable product, i.e. groups IV, VII and X.

Claims 2-9, 17-19, 21, 23-31 and 53 are directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 13, 17, 34, 35, 41, 42, 48 and 49 directed to the process of making or using the patentable product wherein R2 is as found in the elected group I,

previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Process claims 13, 17, 34, 35, 41, 42, 48 and 49 are hereby rejoined and fully examined for patentability under 37 CFR 1.104. The withdrawn subject matter of product, process of making and process of using wherein R2 is other than as found in elected group I, that have previously been cancelled, are not directed to the process of making or using the patentable product and will not be rejoined.

Response to Arguments and Amendments

While applicants' traverse the 35 USC 112 1st paragraph rejection of the method claims and in order to expedite prosecution, have amended the claims to recite only the disorders of atherosclerosis, pulmonary embolism, myocardial infarct and deep venous thrombosis, it is noted that, as stated in the final rejection mailed 7/25/2005, only the method of treatment of myocardial infarct, atherosclerosis, pulmonary embolism and deep venous thrombosis finds support and enablement in applicants' disclosure. No support is found for the prevention of myocardial infarct, arherosclerosis, pulmonary embolism and deep venous thrombosis and the rejection of claims 34, 35, 41, 42, 48 and 49 is therefore maintained under 35 USC 112 1st paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 35, 41, 42, 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of

myocardial infarct, atherosclerosis, pulmonary embolism or deep venous thrombosis does not reasonably provide enablement for the prevention of myocardial infarct, atherosclerosis, pulmonary embolism or deep venous thrombosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The nature of the invention

Applicants' instant claims 34, 35, 41, 42, 48 and 49 are claiming the treatment and prevention of atherosclerosis, myocardial infarct, pulmonary embolism or deep venous thrombosis.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant

case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects of the above listed diseases, whether or not the disease is effected by the inhibition of factor Xa would make a difference.

Applicants claims are directed to the treatment and prevention of myocardial infarct, pulmonary embolism or deep venous thrombosis or artherosclerosis. Applicants' disclosure fails to enable the skilled artisan to use the compounds of the formula to prevent myocardial infarct, atherosclerosis, pulmonary embolism or deep venous thrombosis. In addition, there is no proof that the claimed compounds have ever been administered to a human.

The lack of predictability in the art of applicants' invention can be seen for example, in that only the treatment of diseases with the inhibition of factor Xa is found in the prior art, in the role of the inhibition of the factor Xa in the treatment of certain disorders. It is the state of the art that data on the metabolism of factor Xa inhibitors has not been published yet (Hauptmann et al., page 223, 1449 of 12/9/02) and at the time of the publication, no published reports on the clinical use of factor Xa inhibitors existed. Furthermore, as seen in Kaiser (1449 of 12/9/02, page 431), Most of the specific factor Xa inhibitors known at the time of publication are still in the phase of preclinical development or are being investigated in first clinical studies, and while many treatment possibilities are discussed as possibilities, the real potential of factor Xa inhibitors has still to be validated in comprehensive clinical trials. Furthermore, an important point is that factor Xa inhibitors cannot interrupt thrombotic processes which

are caused by generated thrombin. Page 432 of Kaiser states that Despite major progress in the development of antifactor Xa agents, there are still some unresolved issues such as that they are expected to be much less antithrombotically effective when sufficient amounts of thrombin have already been generated. Kaiser also discloses on page 433 that A particular factor Xa inhibitor might be useful for only a specific clinical indication, and it is likely that one drug might not be the optimum treatment for all thrombotic situations.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of prevention by the inhibition of factor Xa, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of the inhibition of factor Xa

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as influenced positively by inhibitionof factor Xa, see the list of diseases on page 38. Page 39 states that the compounds of the invention act as selective inhibitors of the blood coagulation factor Xa and do not inhibit, or only inhibit at considerably higher concentrations, other serine proteases as well. Assay data for the determination of the factor Xa inhibition, determination of the selectivity and determination of the anticoagulant action is found on pages 42 and 43. Pages 43-46 give antithrombotic activity (in vivo) with the arteriovenous shunt model, the arterial thrombosis model and the venous thrombosis model. The tests found on pages 43-46

coupled with the prior art reference of Al-Obeidi et al. (vol. 3, NO. 5, May 1998) wherein the inhibition of Factor Xa is shown to treat myocardial infarction, deep vein and pulmonary embolism and the Hauptmann et al. reference which discloses the relationship between the inhibition of factor Xa and the treatment of atherosclerosis support the treatment of myocardial infarct, pulmonary embolism, deep venous thrombosis and atherosclerosis with applicants compound of claim 2. There are no working examples present for the treatment, let alone the prevention of any disorder. There are no examples for the prevention of any disease in the specification, nor is there any direction or guidance as to the prevention of any disease. Furthermore, there are no working examples present for the prevention of any disease.

The breadth of the claims

The breadth of the claims is that Applicants' instant claims 34, 35, 41, 42, 48 and 49 is the treatment and prevention of myocardial infarct, atherosclerosis, pulmonary embolism or deep venous thrombosis.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited (prevented) by the inhibition of factor Xa and would furthermore then have to determine which of the claimed compounds would provide prevention of which disease, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be

individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the prevention of myocardial infarct, atherosclerosis, pulmonary embolism or deep venous thrombosis as found in the claims. As a result necessitating one of skill to perform an exhaustive search for which diseases can be prevented by what compounds of the instant claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the

grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an 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. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600
2/1/06

for Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

PTO/SB/08a/b (07-05)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete If Known	
Application Number	10/181,051-Conf. #5850
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
RL	CA	Bono, F., et al., "Human Umbilical Vein Endothelial Cells Express High Affinity Receptors for Factor Xa," Journal of Cellular Physiology; Vol. 172; pp 36-43; (July 1997).	
RL	CB	Cocks, T., et al., "Protease-activated receptors: sentries for inflammation?" TiPS; Vol. 21; pp. 103-108; (March 2000).	
RL	CC	Ross, R., Ph.D, "Atherosclerosis -- An Inflammatory Disease," The New England Journal of Medicine; Vol. 340, no. 2; pp. 115-126; (January 14, 1999).	
RL	CD	Nakata, M., et al.; "DX9065a, an Xa inhibitor, inhibits prothrombin-induced A549 lung adenocarcinoma cell proliferation," Cancer Letters; Vol. 122; pp. 127-133; (January 9, 1998).	
RL	CE	Cirino, G., et al., "Inflammation-coagulation network: are serine protease receptors the knot?" TiPS; Vol. 21; pp. 170-172; (May 2000).	
RL	CF	Kaiser, B., et al., "A Synthetic Inhibitor of Factor Xa, DX-9065a, Reduces Proliferation of Vascular Smooth Muscle Cells in Vivo in Rats," Thrombosis Research; Vol. 98; pp. 175-185; (April 15, 2000).	
RL	CG	Altieri, D., et al., "Identification of Effector Cell Protease Receptor-1: A Leukocyte-Distributed Receptor for the Serine Protease Factor Xa," The Journal of Immunology; Vol. 145, no. 1; pp. 246-253; (July 1, 1990).	
RL	CH	Coughlin, Shaun R., "Thrombin signalling and protease-activated receptors," Nature; Vol. 407; pp. 258-264; (September 14, 2000).	
RL	CI	Ornstein, D., MD, et al., "Cancer, thrombosis, and anticoagulants," Current Opinion in Pulmonary Medicine; Vol. 6; pp. 301-308; (July 2000).	
RL	CJ	Dabbagh, K., et al., "Thrombin Stimulates Smooth Muscle Cell Procollagen Synthesis and mRNA Levels via a PAR-1 Mediated Mechanism," Thrombosis and Haemostatis; Vol. 79, No. 2; pp. 405-409; (Feb. 1997).	
RL	CK	Herault, J., et al., "Activation of Human Vascular Endothelial Cells by Factor Xa: Effect of Specific Inhibitors," Biochemical Pharmacology; Vol. 57; pp. 603-610; (March 1999).	
RL	CL	Leveugle, B., et al., "Heparin Oligosaccharides that Pass the Blood -- Brain Barrier Inhibit β-Amyloid Precursor Protein Secretion and Heparin Binding to β-Amyloid Peptide," Journal of Neurochemistry; Vol. 70, No. 2; pp. 736-744; (Feb. 1998).	

Examiner Signature		Date Considered	2/1/06

PTO/SB/08a/b (07-05)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 3

	Complete if Known
Application Number	10/181,051-Conf. #5850
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

RL	CM	Molino, M., et al., "Differential Expression of Functional Protease-Activated Receptor-2 (PAR-2) in Human Vascular Smooth Muscle Cells," Arteriosclerosis, Thrombosis, and Vascular Biology; Vol. 18, No. 5; pp. 825-832; (May 1997).	
RL	CN	Plescia, J., et al., "Activation of Mac-1 (CD11b/CD18)-bound factor X by released cathepsin G defines an alternative pathway of leucocyte initiation of coagulation," Biochemical Journal; Vol. 319; pp. 873-879; (November 1, 1996).	
RL	CO	Howells, G., et al., "Proteinase-activated receptor-2: expression by human neutrophils," Journal of Cell Science; Vol. 110; pp. 881-887; (April 1, 1997).	
RL	CP	Herbert, J.-M., et al., "Effector Protease Receptor 1 Mediates the Mitogenic Activity of Factor Xa for Vascular Smooth Muscle Cells In Vitro and In Vivo," Journal of Clinical Investigation; Vol. 101, No. 5; pp. 993-1000; (March 1998).	
RL	CQ	Donnelly, K., et al., "Ancylostoma caninum Anticoagulant Peptide Blocks Metastasis In Vivo and Inhibits Factor Xa Binding to Melanoma Cells In Vitro," Thrombosis and Haemostasis; Vol. 79; pp. 1041-1047 (May 1998).	
RL	CR	Ragosta, M., MD, et al., "Specific Factor Xa Inhibition Reduces Restenosis After Balloon Angioplasty of Atherosclerotic Femoral Arteries in Rabbits," Circulation; Vol. 89, No. 3; pp. 1262 – 1271; (March 1994).	
RL	CS	Lindner, J., et al., "Delayed Onset of Inflammation in Protease-Activated Receptor-2-Deficient Mice," The Journal of Immunology; Vol. 165; pp. 6504-6510 (December 1, 2000).	
RL	CT	Zhang, Y., et al., "Tissue Factor Controls the Balance of Angiogenic and Antiangiogenic Properties of Tumor Cells in Mice," Journal of Clinical Investigation; Vol. 94; pp. 1320-1327; (Sept. 1994).	
RL	CU	Green, D., et al., "Lower mortality in cancer patients treated with low-molecular-weight versus standard heparin," Letters to the Editor, The Lancet; Vol. 339; p. 1476; (June 13, 1992).	
RL	CV	Ko, F., et al., "Coagulation Factor Xa Stimulates Platelet-derived Growth Factor Release and Mitogenesis in Cultured Vascular Smooth Muscle Cells of Rat," Journal of Clinical Investigation; Vol. 98, No. 6; pp. 1493-1501; (Sept. 1996).	
RL	CW	Kakkar, A., et al., "Antithrombotic therapy in cancer," British Medical Journal; Vol. 318; pp. 1571-1572; (June 12, 1999).	
RL	CX	Gasic, G., et al., "Coagulation factors X, Xa, and protein S as potent mitogens of cultured aortic smooth muscle cells," Proceedings of the National Academy of Sciences; Vol. 89; pp. 2317-2320; (March 1992).	
RL	CY	Cirino, G., et al., "Factor Xa as an Interface Between Coagulation and Inflammation," Journal of Clinical Investigation; Vol. 99, No. 10; pp. 2446-2451; (May 1997).	
RL	CZ	Senden, N., et al., "Factor Xa Induces Cytokine Production and Expression of Adhesion Molecules by Human Umbilical Vein Endothelial Cells," The Journal of Immunology; Vol. 161; pp. 4318-4324; (October 15, 1998)	
RL	CA1	Papapetropoulos, A., et al., "Hypotension and inflammatory cytokine gene expression triggered by factor Xa-nitric oxide signaling," Proceedings of the National Academy of Sciences; Vol. 95; pp. 4738-4742; (April 1998).	
RL	CB1	Camerer, E., et al., "Tissue factor- and factor X-dependent activation of protease-activated receptor 2 by factor VIIa," Proceedings of the National Academy of Sciences; Vol. 97, No. 10; pp. 5255-5260; (May 9, 2000).	
RL	CC1	Donovan, F., et al., "Thrombin Induces Apoptosis in Cultured Neurons and Astrocytes via a Pathway Requiring Tyrosine Kinase and RhoA Activities," The Journal of Neuroscience; Vol. 17, No. 14; pp. 5316-5326; (July 15, 1997).	
RL	CD1	Bouchard, B., et al., "Effector Cell Protease Receptor-1, a Platelet Activation-dependent Membrane Protein, Regulates Prothrombinase-catalyzed Thrombin Generation," The Journal of Biological Chemistry; Vol. 272, No. 14; pp. 9244-9251; (April 4, 1997).	
RL	CE1	Molino, M., et al., "Endothelial Cell Thrombin Receptors and PAR-2," The Journal of Biological Chemistry; Vol. 272, No. 17; pp. 11133-11141; (April 25, 1997).	

Examiner Signature		Date Considered	2/1/06

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PTO/SB/08a/b (07-05)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 3

Complete If Known	
Application Number	10/181,051-Conf. #5850
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

RL	CF1	Nicholson, A., et al., "Effector Cell Protease Receptor-1 Is a Vascular Receptor for Coagulation Factor Xa," The Journal of Biological Chemistry; Vol. 271, No. 45; pp. 28407-28413; (Nov. 8, 1996).	
RL	CG1	Watson, D., et al., "Heparin-binding Properties of the Amyloidogenic Peptides Aβ and Amylin," The Journal of Biological Chemistry; Vol. 272, No. 50; pp. 31617-31624; (Dec. 12, 1997).	
RL	CH1	Tuszynski, G., et al., "Isolation and Characterization of Antistasin," The Journal of Biological Chemistry; Vol. 262, No. 20; pp. 9718-9723; (July 15, 1987).	
RL	CI1	Kranzhöfer, R., et al., "Thrombin Potently Stimulates Cytokine Production in Human Vascular Smooth Muscle Cells but Not in Mononuclear Phagocytes," Circulation Research; Vol. 79, No. 2; pp. 286-294; (August 1996).	
RL	CJ1	Schwartz, R., MD, et al., "Neointimal Thickening After Severe Coronary Artery Injury Is Limited by Short-term Administration of a Factor Xa Inhibitor," Circulation; Vol. 93, No. 8; pp. 1542-1548; (April 15, 1996).	
RL	CK1	Abendschein, D., Ph.D. et al., "Inhibition of Thrombin Attenuates Stenosis After Arterial Injury in Minipigs," Journal of the American College of Cardiology; Vol. 28, No.7; pp. 1849-1855; (Dec. 1996).	
RL	CL1	Carmeliet, P., MD, Ph.D. et al., "Gene Manipulation and Transfer of the Plasminogen and Coagulation System in Mice," Seminars in Thrombosis and Hemostatis; Vol. 22, No. 6; pp. 525-542; (1996).	
RL	CM1	Stouffer, G., MD, et al., "The Role of Secondary Growth Factor Production in Thrombin-Induced Proliferation of Vascular Smooth Muscle Cells," Seminars in Thrombosis and Hemostasis; Vol. 24, No. 2; pp. 145-150; (1998).	
RL	CN1	Bevilacqua, M., MD, Ph.D., et al., "Inducible Endothelial Functions in Inflammation and Coagulation," Seminars in Thrombosis and Hemostasis; Vol. 13, No. 4; pp. 425-433; (1987).	
RL	CO1	Bots, M., et al., "Coagulation and Fibrinolysis Markers and Risk of Dementia," Haemostasis; Vol. 28; pp. 216-222; (May-Aug. 1998).	
RL	CP1	Benzakour, O., et al., "Cellular and molecular events in atherogenesis: basis for pharmocological and gene therapy approaches to restenosis," Cellular Pharmacology; Vol. 3; pp. 7-22; (1996).	
RL	CQ1	Kanthou, C., et al., "Cellular effects of thrombin and their signalling pathways," Cellular Pharmacology; Vol. 2; pp. 293-302; (1995).	
RL	CR1	Kaiser, B., et al., "Antiproliferative Action of Factor Xa Inhibitors in a Rat Model of Chronic Restenosis," Abstracts of the XVIIth Congress of the International Society on Thrombosis and Haemostasis; p. 144; (August 1999).	
RL	CS1	Tyrrell, D., et al., "Heparin in Inflammation: Potential Therapeutic Applications beyond Anticoagulation," Advances in Pharmacology; Vol. 46; pp. 151-208; (May 1999).	
RL	CT1	Smirnova, I., et al., "Thrombin Is an Extracellular Signal that Activates Intracellular Death Protease Pathways Inducing Apoptosis in Model Motor Neurons," Journal of Neurobiology; Vol. 36; pp. 64-80; (July 1998).	
RL	CU1	Bono, F., et al., "Factor Xa Activates Endothelial Cells by a Receptor Cascade Between EPR-1 and PAR-2," Arteriosclerosis, Thrombosis, and Vascular Biology; pp 1-6; (Nov. 2000).	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	2/1/06

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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/181,051	STRAUB ET AL.
Examiner	**Art Unit**
Rebecca L. Anderson	1626

SEARCHED			
Class	Subclass	Date	Examiner
544	139	2/1/2006	RA
514	236.8	2/1/2006	RA

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor and STN update	2/1/2006	RA

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/181,051	STRAUB ET AL.
Examiner	**Art Unit**
Rebecca L. Anderson	1626

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

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Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	701	(544/139).CCLS.	US-PGPUB; USPAT; EPO; DERWENT	OR	OFF	2006/02/01 10:15
L2	274	(514/236.8).CCLS.	US-PGPUB; USPAT; EPO; DERWENT	OR	OFF	2006/02/01 10:15

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: 10/181051

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	21 minus 20=	* 1
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☒

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	890
X$ 9=		OR	X$18=	18
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	1188

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 30	Minus	** 21	=
Independent	* 3	Minus	*** 2	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 51	Minus	** 21	= 30
Independent	* 3	Minus	*** 3	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	540
X42=		OR	X84=	—
+140=		OR	+280=	—
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	540

11/22/10

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 30	Minus	** 51	= /
Independent	* 5	Minus	*** 3	= /
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

AMENDMENT TRANSMITTAL LETTER

Docket No. 11987-00014-US

Application No.	Filing Date	Examiner	Art Unit
10/181,051	June 24, 2002	R. L. Anderson	1626

Applicant(s): Alexander Straub et al.

Invention: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims	30	- 51 =		x	
Independent Claims	5	- 36 =		x	
Multiple Dependent Claims (check if applicable)			[x]		
Other fee (please specify):	Extension for response within first month; Request for continued examination (RCE) (see 37 CFR 1.114)				910.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					910.00

[x] Large Entity [ ] Small Entity

[x] No additional fee is required for this amendment.

[x] Please charge Deposit Account No. 03-2775 in the amount of $ 910.00. A duplicate copy of this sheet is enclosed.

[ ] A check in the amount of $ _____ to cover the filing fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[x] The Director is hereby authorized to charge and credit Deposit Account No. 03-2775 as described below. A duplicate copy of this sheet is enclosed.

[x] Credit any overpayment.

[x] Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.

Christine M. Hansen

Dated: November 23, 2005

Christine M. Hansen
Attorney Reg. No.: 40,634

CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141

Express Mail Label No. EV 622756994 US Dated: 11/23/2005

Docket No.: 11987-00014-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Alexander Straub et al.

Application No.: 10/181,051

Confirmation No.: 5850

Filed: June 24, 2002

Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

Examiner: R. L. Anderson

Express Mail Label No. EV 622756994 US Dated: 11/23/2005

REQUEST FOR CONTINUED EXAMINATION AND AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION

MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Introductory Comments

In response to the Final Office Action dated July 25, 2005, the period of response having been extended to November 25, 2004 by a petition for a one-month extension of time and fee filed concurrently with this Amendment, and prior to examining the present RCE application, please amend the above-captioned U.S. patent application as follows:

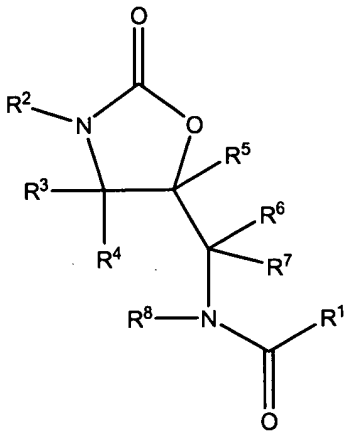
Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 19 of this paper.

Amendments to the Claims

1. (canceled)

2. (previously presented) A compound of the formula (I)



(I)

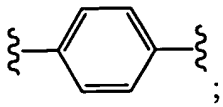
characterized in that

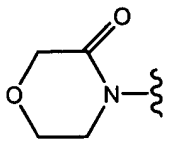
R^1 represents an optionally benzo-fused thiophene group which may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; cyano; nitro; amino; aminomethyl; $(C_1\text{-}C_8)$-alkyl which for its part may optionally be mono- or polysubstituted by halogen; $(C_3\text{-}C_7)$-cycloalkyl; $(C_1\text{-}C_8)$-alkoxy; imidazolinyl; $-C(=NH)NH_2$; carbamoyl; and mono- and di-$(C_1\text{-}C_4)$-alkyl-aminocarbonyl,

R^2 represents

D-M-A-,

where

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; $(C_1\text{-}C_6)$-alkanoyl; $-OR^{30}$; $-NR^{30}R^{31}$, and $(C_1\text{-}C_6)$-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1\text{-}C_4)$-alkyl, or $C(O)R^{33}$,

where

R^{33} represents $(C_1\text{-}C_4)$-aminoalkyl, or $(C_1\text{-}C_8)$-alkyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents $(C_1\text{-}C_6)$-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

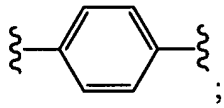
3. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

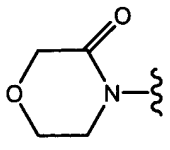
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen, amino, aminomethyl or (C_1-C_8)-alkyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

D-M-A-,

where

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; (C_1-C_6)-alkanoyl; -OR^{30}; -$NR^{30}R^{31}$, and (C_1-C_6)-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, or (C_1-C_4)-alkylaminocarbonyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

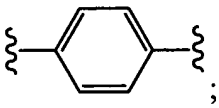
4. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

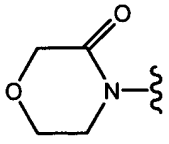
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen or by (C_1-C_8)-alkyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; (C_1-C_3)-alkanoyl; -OH; $-NR^{30}R^{31}$; and (C_1-C_4)-alkyl;

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or (C_1-C_3)-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

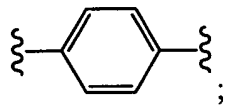
except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

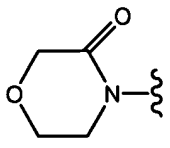
5. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

R^1 represents 2-thiophene which may optionally be substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents
D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; $(C_1$-$C_3)$-alkanoyl; -OH; $-NR^{30}R^{31}$; and $(C_1$-$C_4)$-alkyl;

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl or $(C_1$-$C_3)$-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents $(C_1$-$C_4)$-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

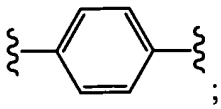
except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

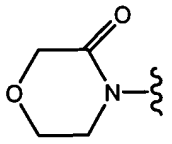
6. (previously presented) The compound of the formula (I) according to claim 2, characterized in that

R^1 represents 2-thiophene which is substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents D-A-,

where:

the radical "A" represents  ;

the radical "D" represents  ,

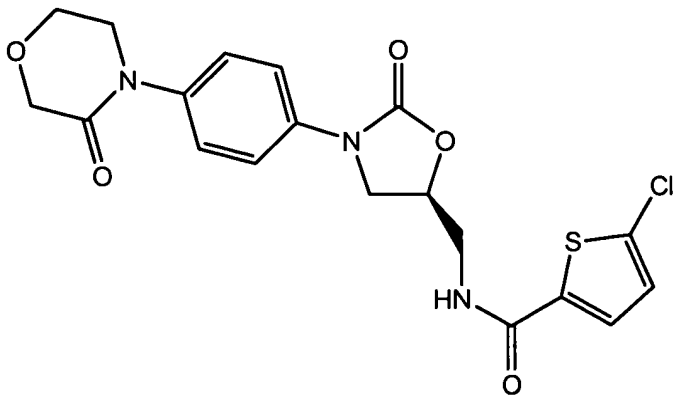
where

the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical selected from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen

or a pharmaceutically acceptable salt or hydrate thereof.

7. (previously presented) The compound having the following formula

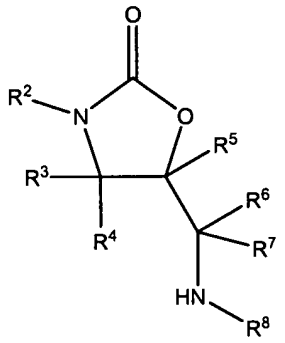


or a pharmaceutically acceptable salt or hydrate thereof.

8. (previously presented) Process for preparing the substituted oxazolidinone of claim 2, where

either according to a process alternative

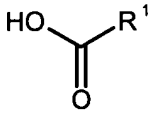
(A) a compound of the formula (II)



(II),

in which

the radicals R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2 is reacted with carboxylic acid of the formula (III)



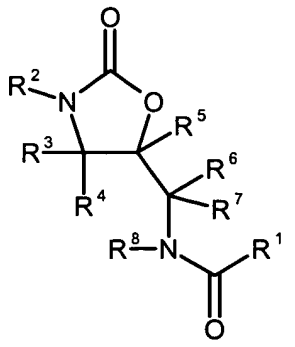
(III),

in which

the radical R^1 is as defined in Claim 2,

or else with a corresponding carbonyl halide, or else with a corresponding symmetric or mixed carboxylic anhydride of the carboxylic acid of the formula (III) defined above

in an inert solvent, if appropriate in the presence of an activating or coupling agent and/or a base, to give a compound of the formula (I)



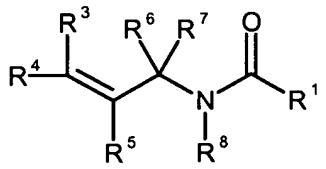
(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

or else according to a process alternative

(B) a compound of the formula (IV)

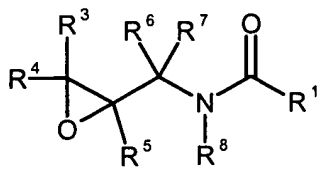


(IV),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the formula (V)



(V),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

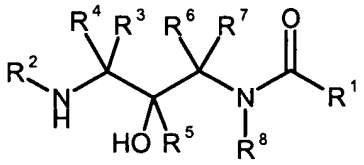
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the formula (VI)

$$R^2\text{-}NH_2 \qquad \text{(VI)},$$

in which

the radical R^2 is as defined in Claim 2,

a compound of the formula (VII)



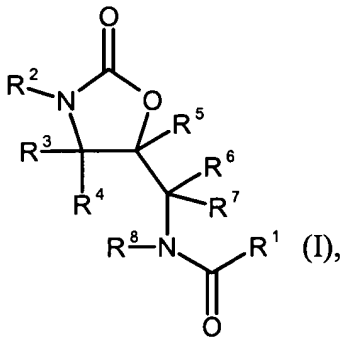
(VII),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is initially prepared and,

subsequently, in an inert solvent in the presence of phosgene or a phosgene equivalent, cyclized to give a compound of the formula (I)



(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

where - both for process alternative (A) and for process alternative (B) - in the case where R^2 contains a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical having one or more identical or different heteroatoms from the group consisting of N and S, an oxidation with a selective oxidizing agent to afford the corresponding sulphone, sulphoxide or N-oxide may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has a cyano group in the molecule, an amidination of this cyano group by customary methods may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has a BOC amino protective group in the molecule, removal of this BOC amino protective group by customary methods may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with a carboxylic acid, carboxylic anhydride, carbonyl chloride, isocyanate, sulphonyl chloride or alkyl halide to give the corresponding derivative may follow

and/or

where - both for process alternative (A) and for process alternative (B) - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with an amine to give the corresponding sulphonamide may follow.

9. (previously presented) A pharmaceutical composition comprising at least one compound of the formula (I) according to claim 2 and one or more pharmacologically acceptable auxiliaries or excipients.

10. (canceled)

11. (canceled)

12. (canceled)

13. (currently amended) A method for treatment of atherosclerosis~~, arthritis, Alzheimer's disease or cancer~~ comprising administering an effective amount of a compound of claim 2 to a patient in need thereof.

14. (canceled)

15. (canceled)

16. (canceled)

17. (previously presented) The compound of claim 3 or 4 wherein R^1 represents an optionally substituted 2-thiophene group, and wherein said halogen substituent is chlorine or bromine, and said (C_1-C_8)-alkyl substituent is methyl, where the methyl radical for its part optionally may be mono- or polysubstituted by fluorine.

18. (previously presented) The process of claim 8 wherein in process alternative "A", the corresponding carbonyl halide of carboxylic acid (III) is a carbonyl chloride.

19. (previously presented) The process of claim 8 wherein in process alternative "B", the phosgene equivalent employed in the cyclization of compound (VII) is carbonyldimidazole (CDI).

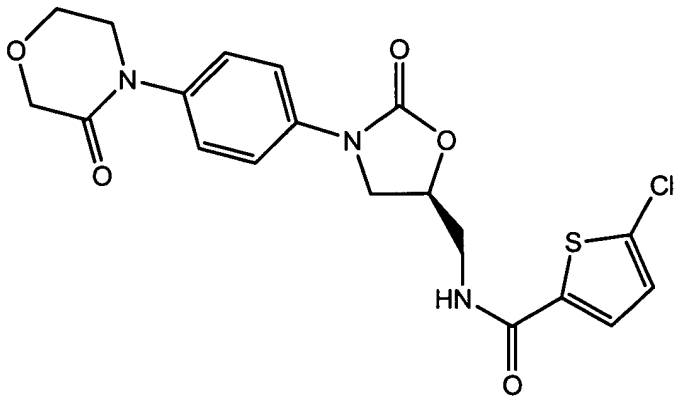
20. (currently amended) ~~The method of claim 10~~ A method for treatment of a thromboembolic disorder comprising administering to a patient in need thereof an

effective amount of a compound of claim 2, wherein the thromboembolic disorder is myocardial infarct, ~~angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive disease,~~ pulmonary embolism or deep venous thrombosis.

21. (previously presented) The compound of claim 7 that is purified and isolated.

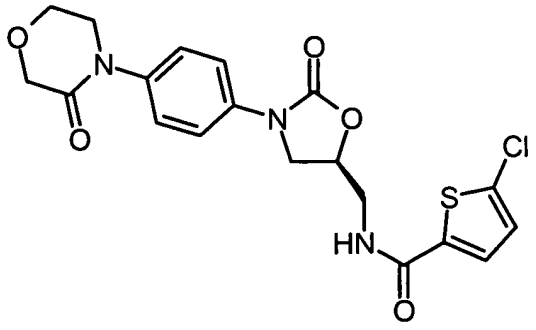
22. (canceled)

23. (previously presented) A racemic mixture of a compound having the following formula



and its enantiomer, or a pharmaceutically acceptable salt or hydrate thereof.

24. (previously presented) A compound having the following formula:



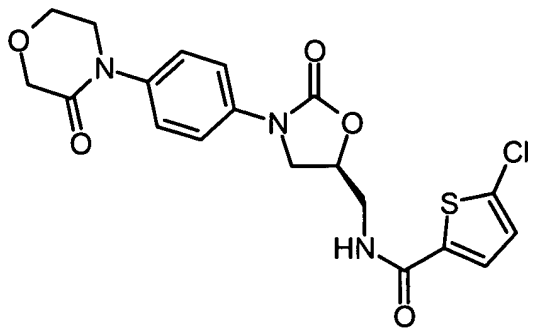
25. (currently amended) A pharmaceutical composition comprising the compound of claim 7 and ~~a pharmacologically acceptable auxiliary or excipient~~ one or more pharmacologically acceptable auxiliaries or excipients.

26. (currently amended) A pharmaceutical composition comprising the compound of claim 21 and ~~a pharmacologically acceptable auxiliary or excipient~~ one or more pharmacologically acceptable auxiliaries or excipients.

27. (currently amended) A pharmaceutical composition comprising the composition of claim 53 and ~~a pharmacologically acceptable auxiliary or excipient~~ one or more pharmacologically acceptable auxiliaries or excipients.

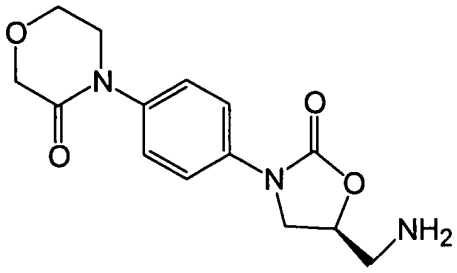
28. (currently amended) A pharmaceutical composition comprising the compound of claim 24 and ~~a pharmacologically acceptable auxiliary or excipient~~ one or more pharmacologically acceptable auxiliaries or excipients.

29. (previously presented) The process of claim 8 wherein the substituted oxazolidinone that is prepared is



or a pharmaceutically acceptable salt or hydrate thereof.

30. (previously presented) A process for the preparation of the compound of claim 7 comprising reacting a compound of the following formula



with 5-chlorothiophene-2-carbonyl chloride in an inert solvent to prepare the compound of claim 7.

31. (previously presented) The process of claim 30 wherein the inert solvent comprises pyridine.

32. (canceled)

33. (canceled)

34. (currently amended) A method for the prevention or treatment of atherosclerosis~~, arthritis, Alzheimer's disease or cancer~~ comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

35. (currently amended) A method for the prevention or treatment of myocardial infarct, ~~angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases,~~ pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

36. (canceled)

37. (canceled)

38. (canceled)

39. (canceled)

40. (canceled)

41. (currently amended) A method for the prevention or treatment of atherosclerosis~~, arthritis, Alzheimer's disease or cancer~~ comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

42. (currently amended) A method for the prevention or treatment of myocardial infarct, ~~angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases,~~ pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

43. (canceled)

44. (canceled)

45. (canceled)

46. (canceled)

47. (canceled)

48. (currently amended) A method for the prevention or treatment of atherosclerosis~~, arthritis, Alzheimer's disease or cancer~~ comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

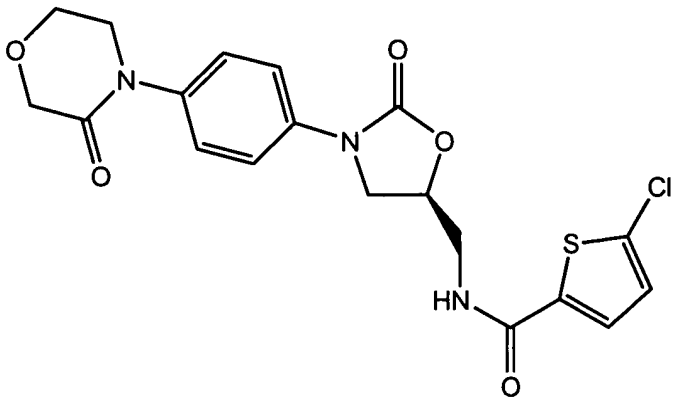
49. (currently amended) A method for the prevention or treatment of myocardial infarct, ~~angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases,~~ pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

50. (canceled)

51. (canceled)

52. (canceled)

53. (previously presented) A composition comprising a compound having formula (a):



(a)

or a pharmaceutically acceptable salt or hydrate thereof, wherein the composition is substantially free of the enantiomer of the compound of formula (a) and substantially free of the salts and hydrates of the enantiomer of the compound of formula (a).

Remarks

After entry of this amendment, claims 2-9, 13, 17-21, 23-31, 34, 35, 41, 42, 48, 49 and 53 are pending. In the present Amendment, claims 10-12, 14-16, 32, 33, 36-40, 43-47 and 50-52 are canceled without prejudice to or disclaimer of Applicants' right to pursue the subject matter of these claims in a later application. Claims 13, 20, 25-28, 34, 35, 41, 42, 48 and 49 are amended without prejudice or disclaimer to pursuing the subject matter omitted in a later application. Support is found in the original claims and at page 39, lines 26-29. No new matter has been added.

Applicants appreciatively acknowledge that the Examiner has found product claims 2-9, 17-19, 21, 23-31 and 53 allowable. Applicants also appreciate that the Examiner has rejoined the claims of restriction groups IV, VII and X, all of which share the same R^2 in the compound of formula I. Applicants, however, respectfully disagree with the statement in the Office Action that all claims have been rejoined and that the restriction requirement made on October 3, 2003 is withdrawn. It is respectfully submitted that not all claims were rejoined. The restriction requirement divided the claims into groups corresponding to different R^2 in the compound of formula I as well as into groups corresponding to different types of claims (e.g., product, process of making, etc.). Accordingly, although the rejoinder of certain restricted groups is much appreciated, it is requested that the Examiner clarify that the restriction requirement was not lifted for all the groups and, therefore, that future divisional applications that may be directed to the subject matter of those restriction groups not rejoined are entitled to the protection available under 35 USC 121.

Method claims 10-16, 20 and 32-52 were rejected. Reconsideration of these rejections is respectfully requested in view of the foregoing amendments and following remarks.

Rejection Under 35 U.S.C. § 112, 1st Paragraph

Claims 10-16, 20 and 32-52 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner found that the specification enables the treatment of the factor Xa-related disorders of myocardial infarct, atherosclerosis, pulmonary embolism and deep venous thrombosis and further enables the method of preventing coagulation in banked blood containing factor Xa or in a biological sample containing factor Xa. However, the Examiner found that the other treatment and preventative methods recited in the claims were not enabled by the specification. Applicants respectfully traverse. However, to expedite prosecution, the rejected method of treatment claims have either been canceled or narrowed such that the current claims recite methods of treating disorders that the Examiner has indicated are enabled. Namely, claims 13, 20, 34, 35, 41, 42, 48, and 49 are amended to recite methods for the prevention or treatment of disorders within the group that the Examiner found enabled. For this reason, reconsideration of the rejection and allowance of these claims is requested.

In addition, Applicants note an inconsistency in the Final Office Action regarding the allowability of claim 53. In the first paragraph on page 2 of the Office Action, claim 53 is included both in the lists of allowable claims and rejected claims. Based on the arguments supporting the rejections, it appears that product claim 53 is allowable, as the enablement rejections concerned method claims, not product claims. Also, claim 53 is not listed with the rejected claims in either the discussion of claim rejections on page 3 or in the Office Action Summary. Accordingly, Applicants respectfully request that the Examiner clarify the allowability of claim 53.

In view of the foregoing, Applicants respectfully request that the rejections be reconsidered and withdrawn and that the claims be allowed to issue.

Enclosed is a Petition for a One-Month Extension of Time Pursuant to 37 CFR 1.136. The Director is authorized to charge $120.00 to Deposit Account No. 03-2775, under Order No. 11987-00014-US, to cover the fee under 37 CFR 1.17 for this extension. Should any other fees be required in connection with this Amendment, authorization is hereby made to charge any fees

due or outstanding, including any extension fees, or credit any overpayment, to Deposit Account No. 03-2775. Also enclosed for the Examiner's consideration is an Information Disclosure Statement.

Dated: November 23, 2005

Respectfully submitted,

By Christine M. Hansen

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11-28-05

RCE

PTO/SB/30 (04-05)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request For Continued Examination (RCE) Transmittal

Address to:
MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. [ ] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. [ ] Other _____

   b. [X] Enclosed

      i. [X] Amendment/Reply

      ii. [ ] Affidavit(s)/Declaration(s)

      iii. [X] Information Disclosure Statement (IDS)

      iv. [ ] Other _____

2. Miscellaneous

   a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. [ ] Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. [X] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments to Deposit Account No. 03-2775 . I have enclosed a duplicate copy of this sheet.

      i. [X] RCE fee required under 37 CFR 1.17(e)

      ii. [X] Extension of time fee (37 CFR 1.136 and 1.17)

      iii. [ ] Other _____

   b. [ ] Check in the amount of $ _____ enclosed

   c. [ ] Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	Christine M. Hansen	Date	November 23, 2005
Name (Print/Type)	Christine M. Hansen	Registration No.	40,634

Express Mail Label No. EV 622756994 US Dated: 11/23/2005

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PTO/SB/92 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application No. (if known): 10/181,051 Attorney Docket No.: 11987-00014-US

Certificate of Mailing under 37 CFR 1.8

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on November 23, 2005 .
Date

Barbara J. Miller
Signature

Barbara J. Miller
Typed or printed name of person signing Certificate

Registration Number, if applicable

Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Request for Continued Examination Transmittal (1 page)
One Month Request for Extension of Time Under 37 CFR 1.136(a) (1 page)
Amendment Transmittal (1 page)
Amendment (21 pages)
Information Disclosure Statement (2 pages)
IDS (Citation) by Applicant (3 pages, 47 References)
Fee Transmittal (1 page)
Transmittal Form (1 page)
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PTO/SB/21 (09-04)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Request for Continued Examination Transmittal (PTO/SB/30)

Amendment Transmittal Letter

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	CONNOLLY BOVE LODGE & HUTZ LLP		
Signature	Christine M. Hansen		
Printed name	Christine M. Hansen		
Date	November 23, 2005	Reg. No.	40,634

Express Mail Label No. EV 622756994 US Dated: 11/23/2005

PTO/SB/17 (12-04v2)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 910.00

Complete if Known	
Application Number	10/181,051-Conf. #5850
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Examiner Name	R. L. Anderson
Art Unit	1626
Attorney Docket No.	11987-00014-US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 03-2775 Deposit Account Name: Connolly Bove Lodge & Hutz LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fees Paid ($)**
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	**Fee ($)**	**Small Entity Fee ($)**
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
30 - 51 =		x	=

Multiple Dependent Claims

Fee ($)	**Fee Paid ($)**

Indep. Claims	**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
5 - 36 =		x	=

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	**Extra Sheets**	**Number of each additional 50 or fraction thereof**	**Fee ($)**	**Fee Paid ($)**
- 100 =	/50	(round up to a whole number) x		=

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): 1251 Extension for response within first month	120.00
1801 Request for continued examination (RCE) (see 37 ...	790.00

SUBMITTED BY					
Signature	Christine M. Hansen	Registration No. (Attorney/Agent)	40,634	Telephone	(302) 658-9141
Name (Print/Type)	Christine M. Hansen			Date	November 23, 2005

Express Mail Label No. EV 622756994 US Dated: 11/23/2005

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 (Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)	Docket Number (Optional) 11987-00014-US
Application Number 10/181,051	Filed June 24, 2002
For SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION	
Art Unit 1626	Examiner R. L. Anderson

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
[x]	One month (37 CFR 1.17(a)(1))	$120	$60	$ 120.00
[ ]	Two months (37 CFR 1.17(a)(2))	$450	$225	$
[ ]	Three months (37 CFR 1.17(a)(3))	$1020	$510	$
[ ]	Four months (37 CFR 1.17(a)(4))	$1590	$795	$
[ ]	Five months (37 CFR 1.17(a)(5))	$2160	$1080	$

[ ] Applicant claims small entity status. See 37 CFR 1.27.

[ ] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[x] The Director has already been authorized to charge fees in this application to a Deposit Account.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 03-2775 . I have enclosed a duplicate copy of this sheet.

I am the

[ ] applicant/inventor.

[ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

[ ] attorney or agent of record. Registration Number _____

[x] attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 40,634 .

Christine M. Hansen
Signature

November 23, 2005
Date

Christine M. Hansen
Typed or printed name

(302) 658-9141
Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

[ ] Total of 1 forms are submitted.

Express Mail Label No. EV 622756994 US Dated: 11/23/2005

11/29/2005 EAREGAY1 00000059 032775 10181051

02 FC:1251 120.00 DA

Docket No.: 11987-00014-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Alexander Straub et al.

Application No.: 10/181,051 | Confirmation No.: 5850

Filed: June 24, 2002 | Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION | Examiner: R. L. Anderson

Express Mail Label No. EV 622756994 US Dated: 11/23/05

INFORMATION DISCLOSURE STATEMENT

MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed concurrently and in connection with a Request for Continued Examination of the above-captioned U.S. patent application. Applicants hereby request that the Information Disclosure Statement be considered by the Examiner.

A copy of each non-patent reference on the PTO/SB/08 is attached in accordance with 37 CFR 1.98(a)(2).

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

Applicants believe that no fees are due with this Information Disclosure Statement. However, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 03-2775, under Order No. 11987-00014-US. A duplicate copy of this paper is enclosed.

Dated: November 23, 2005

Respectfully submitted,

By Christine M. Hansen

Christine M. Hansen
Registration No.: 40,634
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Attorney for Applicant

PTO/SB/08a/b (07-05)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	10/181,051-Conf. #5850
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Bono, F., et al., "Human Umbilical Vein Endothelial Cells Express High Affinity Receptors for Factor Xa," Journal of Cellular Physiology; Vol. 172; pp 36-43; (July 1997).	
	CB	Cocks, T., et al., "Protease-activated receptors: sentries for inflammation?" TiPS; Vol. 21; pp. 103-108; (March 2000).	
	CC	Ross, R., Ph.D, "Atherosclerosis -- An Inflammatory Disease," The New England Journal of Medicine; Vol. 340, no. 2; pp. 115-126; (January 14, 1999).	
	CD	Nakata, M., et al.; "DX9065a, an Xa inhibitor, inhibits prothrombin-induced A549 lung adenocarcinoma cell proliferation," Cancer Letters; Vol. 122; pp. 127-133; (January 9, 1998).	
	CE	Cirino, G., et al., "Inflammation-coagulation network: are serine protease receptors the knot?" TiPS; Vol. 21; pp. 170-172; (May 2000).	
	CF	Kaiser, B., et al., "A Synthetic Inhibitor of Factor Xa, DX-9065a, Reduces Proliferation of Vascular Smooth Muscle Cells in Vivo in Rats," Thrombosis Research; Vol. 98; pp. 175-185; (April 15, 2000).	
	CG	Altieri, D., et al., "Identification of Effector Cell Protease Receptor-1: A Leukocyte-Distributed Receptor for the Serine Protease Factor Xa," The Journal of Immunology; Vol. 145, no. 1; pp. 246-253; (July 1, 1990).	
	CH	Coughlin, Shaun R., "Thrombin signalling and protease-activated receptors," Nature; Vol. 407; pp. 258-264; (September 14, 2000).	
	CI	Ornstein, D., MD, et al., "Cancer, thrombosis, and anticoagulants," Current Opinion in Pulmonary Medicine; Vol. 6; pp. 301-308; (July 2000).	
	CJ	Dabbagh, K., et al., "Thrombin Stimulates Smooth Muscle Cell Procollagen Synthesis and mRNA Levels via a PAR-1 Mediated Mechanism," Thrombosis and Haemostatis; Vol. 79, No. 2; pp. 405-409; (Feb. 1997).	
	CK	Herault, J., et al., "Activation of Human Vascular Endothelial Cells by Factor Xa: Effect of Specific Inhibitors," Biochemical Pharmacology; Vol. 57; pp. 603-610; (March 1999).	
	CL	Leveugle, B., et al., "Heparin Oligosaccharides that Pass the Blood -- Brain Barrier Inhibit β-Amyloid Precursor Protein Secretion and Heparin Binding to β-Amyloid Peptide," Journal of Neurochemistry; Vol. 70, No. 2; pp. 736-744; (Feb. 1998).	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 3

Complete if Known	
Application Number	10/181,051-Conf. #5850
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

	CM	Molino, M., et al., "Differential Expression of Functional Protease-Activated Receptor-2 (PAR-2) in Human Vascular Smooth Muscle Cells," Arteriosclerosis, Thrombosis, and Vascular Biology; Vol. 18, No. 5; pp. 825-832; (May 1997).	
	CN	Plescia, J., et al., "Activation of Mac-1 (CD11b/CD18)-bound factor X by released cathepsin G defines an alternative pathway of leucocyte initiation of coagulation," Biochemical Journal; Vol. 319; pp. 873-879; (November 1, 1996).	
	CO	Howells, G., et al., "Proteinase-activated receptor-2: expression by human neutrophils," Journal of Cell Science; Vol. 110; pp. 881-887; (April 1, 1997).	
	CP	Herbert, J.-M., et al., "Effector Protease Receptor 1 Mediates the Mitogenic Activity of Factor Xa for Vascular Smooth Muscle Cells In Vitro and In Vivo," Journal of Clinical Investigation; Vol. 101, No. 5; pp. 993-1000; (March 1998).	
	CQ	Donnelly, K., et al., "Ancylostoma caninum Anticoagulant Peptide Blocks Metastasis In Vivo and Inhibits Factor Xa Binding to Melanoma Cells In Vitro," Thrombosis and Haemostasis; Vol. 79; pp. 1041-1047 (May 1998).	
	CR	Ragosta, M., MD, et al., "Specific Factor Xa Inhibition Reduces Restenosis After Balloon Angioplasty of Atherosclerotic Femoral Arteries in Rabbits," Circulation; Vol. 89, No. 3; pp. 1262 – 1271; (March 1994).	
	CS	Lindner, J., et al., "Delayed Onset of Inflammation in Protease-Activated Receptor-2-Deficient Mice," The Journal of Immunology; Vol. 165; pp. 6504-6510 (December 1, 2000).	
	CT	Zhang, Y., et al., "Tissue Factor Controls the Balance of Angiogenic and Antiangiogenic Properties of Tumor Cells in Mice," Journal of Clinical Investigation; Vol. 94; pp. 1320-1327; (Sept. 1994).	
	CU	Green, D., et al., "Lower mortality in cancer patients treated with low-molecular-weight versus standard heparin," Letters to the Editor, The Lancet; Vol. 339; p. 1476; (June 13, 1992).	
	CV	Ko, F., et al., "Coagulation Factor Xa Stimulates Platelet-derived Growth Factor Release and Mitogenesis in Cultured Vascular Smooth Muscle Cells of Rat," Journal of Clinical Investigation; Vol. 98, No. 6; pp. 1493-1501; (Sept. 1996).	
	CW	Kakkar, A., et al., "Antithrombotic therapy in cancer," British Medical Journal; Vol. 318; pp. 1571-1572; (June 12, 1999).	
	CX	Gasic, G., et al., "Coagulation factors X, Xa, and protein S as potent mitogens of cultured aortic smooth muscle cells," Proceedings of the National Academy of Sciences; Vol. 89; pp. 2317-2320; (March 1992).	
	CY	Cirino, G., et al., "Factor Xa as an Interface Between Coagulation and Inflammation," Journal of Clinical Investigation; Vol. 99, No. 10; pp. 2446-2451; (May 1997).	
	CZ	Senden, N., et al., "Factor Xa Induces Cytokine Production and Expression of Adhesion Molecules by Human Umbilical Vein Endothelial Cells," The Journal of Immunology; Vol. 161; pp. 4318-4324; (October 15, 1998)	
	CA1	Papapetropoulos, A., et al., "Hypotension and inflammatory cytokine gene expression triggered by factor Xa-nitric oxide signaling," Proceedings of the National Academy of Sciences; Vol. 95; pp. 4738-4742; (April 1998).	
	CB1	Camerer, E., et al., "Tissue factor- and factor X-dependent activation of protease-activated receptor 2 by factor VIIa," Proceedings of the National Academy of Sciences; Vol. 97, No. 10; pp. 5255-5260; (May 9, 2000).	
	CC1	Donovan, F., et al., "Thrombin Induces Apoptosis in Cultured Neurons and Astrocytes via a Pathway Requiring Tyrosine Kinase and RhoA Activities," The Journal of Neuroscience; Vol. 17, No. 14; pp. 5316-5326; (July 15, 1997).	
	CD1	Bouchard, B., et al., "Effector Cell Protease Receptor-1, a Platelet Activation-dependent Membrane Protein, Regulates Prothrombinase-catalyzed Thrombin Generation," The Journal of Biological Chemistry; Vol. 272, No. 14; pp. 9244-9251; (April 4, 1997).	
	CE1	Molino, M., et al., "Endothelial Cell Thrombin Receptors and PAR-2," The Journal of Biological Chemistry; Vol. 272, No. 17; pp. 11133-11141; (April 25, 1997).	

Examiner Signature		Date Considered	

PTO/SB/08a/b (07-05)
Approved for use through 07/31/2006. OMB 0651-0031
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(Use as many sheets as necessary)

Sheet 3 of 3

Complete if Known	
Application Number	10/181,051-Conf. #5850
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	11987-00014-US

	CF1	Nicholson, A., et al., "Effector Cell Protease Receptor-1 Is a Vascular Receptor for Coagulation Factor Xa," The Journal of Biological Chemistry; Vol. 271, No. 45; pp. 28407-28413; (Nov. 8, 1996).	
	CG1	Watson, D., et al., "Heparin-binding Properties of the Amyloidogenic Peptides Aβ and Amylin," The Journal of Biological Chemistry; Vol. 272, No. 50; pp. 31617-31624; (Dec. 12, 1997).	
	CH1	Tuszynski, G., et al., "Isolation and Characterization of Antistasin," The Journal of Biological Chemistry; Vol. 262, No. 20; pp. 9718-9723; (July 15, 1987).	
	CI1	Kranzhöfer, R., et al., "Thrombin Potently Stimulates Cytokine Production in Human Vascular Smooth Muscle Cells but Not in Mononuclear Phagocytes," Circulation Research; Vol. 79, No. 2; pp. 286-294; (August 1996).	
	CJ1	Schwartz, R., MD, et al., "Neointimal Thickening After Severe Coronary Artery Injury Is Limited by Short-term Administration of a Factor Xa Inhibitor," Circulation; Vol. 93, No. 8; pp. 1542-1548; (April 15, 1996).	
	CK1	Abendschein, D., Ph.D. et al., "Inhibition of Thrombin Attenuates Stenosis After Arterial Injury in Minipigs," Journal of the American College of Cardiology; Vol. 28, No.7; pp. 1849-1855; (Dec. 1996).	
	CL1	Carmeliet, P., MD, Ph.D. et al., "Gene Manipulation and Transfer of the Plasminogen and Coagulation System in Mice," Seminars in Thrombosis and Hemostatis; Vol. 22, No. 6; pp. 525-542; (1996).	
	CM1	Stouffer, G., MD, et al., "The Role of Secondary Growth Factor Production in Thrombin-Induced Proliferation of Vascular Smooth Muscle Cells," Seminars in Thrombosis and Hemostasis; Vol. 24, No. 2; pp. 145-150; (1998).	
	CN1	Bevilacqua, M., MD, Ph.D., et al., "Inducible Endothelial Functions in Inflammation and Coagulation," Seminars in Thrombosis and Hemostasis; Vol. 13, No. 4; pp. 425-433; (1987).	
	CO1	Bots, M., et al., "Coagulation and Fibrinolysis Markers and Risk of Dementia," Haemostasis; Vol. 28; pp. 216-222; (May-Aug. 1998).	
	CP1	Benzakour, O., et al., "Cellular and molecular events in atherogenesis: basis for pharmocological and gene therapy approaches to restenosis," Cellular Pharmacology; Vol. 3; pp. 7-22; (1996).	
	CQ1	Kanthou, C., et al., "Cellular effects of thrombin and their signalling pathways," Cellular Pharmacology; Vol. 2; pp. 293-302; (1995).	
	CR1	Kaiser, B., et al., "Antiproliferative Action of Factor Xa Inhibitors in a Rat Model of Chronic Restenosis," Abstracts of the XVIIth Congress of the International Society on Thrombosis and Haemostasis; p. 144; (August 1999).	
	CS1	Tyrrell, D., et al., "Heparin in Inflammation: Potential Therapeutic Applications beyond Anticoagulation," Advances in Pharmacology; Vol. 46; pp. 151-208; (May 1999).	
	CT1	Smirnova, I., et al., "Thrombin Is an Extracellular Signal that Activates Intracellular Death Protease Pathways Inducing Apoptosis in Model Motor Neurons," Journal of Neurobiology; Vol. 36; pp. 64-80; (July 1998).	
	CU1	Bono, F., et al., "Factor Xa Activates Endothelial Cells by a Receptor Cascade Between EPR-1 and PAR-2," Arteriosclerosis, Thrombosis, and Vascular Biology; pp 1-6; (Nov. 2000).	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	

ARTIFACT SHEET

Enter artifact number below. Artifact number is application number + artifact type code (see list below) + sequential letter (A, B, C ...). The first artifact folder for an artifact type receives the letter A, the second B, etc..
Examples: 59123456PA, 59123456PB, 59123456ZA, 59123456ZB

10181051ZA

Indicate quantity of a single type of artifact received but not scanned. Create individual artifact folder/box and artifact number for each Artifact Type.

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pages of specification and/or sequence listing and/or table ☐
Doc Code: Artifact Artifact Type Code: S
content unspecified or combined ☐
Doc Code: Artifact Artifact Type Code: U

☐ Stapled Set(s) Color Documents or B/W Photographs
Doc Code: Artifact Artifact Type Code: C

☐ Microfilm(s)
Doc Code: Artifact Artifact Type Code: F

☐ Video tape(s)
Doc Code: Artifact Artifact Type Code: V

☐ Model(s)
Doc Code: Artifact Artifact Type Code: M

☐ Bound Document(s)
Doc Code: Artifact Artifact Type Code: B

☐ Confidential Information Disclosure Statement or Other Documents marked Proprietary, Trade Secrets, Subject to Protective Order, Material Submitted under MPEP 724.02, etc.
Doc Code: Artifact Artifact Type Code X

☒ Other, description: NPL
Doc Code: Artifact Artifact Type Code: Z

March 8, 2004

10/198,081

Practice and Procedures

Allowance and Issue Check List

EXAMINER'S ISSUE CHECKLIST

When passing an application to issue, each of the following items should be checked:

1. CLAIMS

- ☑ Single sentence, starting with a capital letter and ending with a period (beware of claims ending with chemical structure and no period).
- ☑ Claim text should not be missing or contain duplicate or additional text.
- ☑ Make sure that there is a complete claim listing, and that the status identifier for each claim is correct.
- ☑ Claim numbering:
  - ☑ If needed, Examiner should renumber both the independent and dependent claims, properly using Issue Classification form (IFW).
  - ☐ No two claims are numbered the same.
- ☑ Dependent claims:
  - ☐ No claim depends from the wrong claim or a higher-numbered claim, as renumbered. If claims are renumbered in other than the order presented by applicant, amend numbering by Examiner's amendment (no attorney authorization).
  - ☑ Dependent claims narrow the scope of the claim from which they depend.
  - ☐ No improper multiple dependent claims

2. SPECIFICATION

- ☑ Abstract:
  - ☐ Abstract is present, and gives an adequate and clear statement of the disclosed invention (M.P.E.P. 608.01(b)).
  - ☐ No more than 150 words.
  - ☐ Single paragraph -no legal phraseology such as "said" or "means".
- ☑ Continuing data is mentioned in first paragraph, including §371 data, if any, and agrees with the Continuing Data on Bibliographic Data Sheet. **NOTE:** If application data sheet (ADS) has been filed and contains continuity data, continuing data do NOT need to be mentioned in first paragraph; however, the Bibliographic Data Sheet (BDS) must agree with the most recent ADS- correct BDS if necessary.
- ☐ U.S. applications referred to by Attorney Docket Number should be changed to U.S. Application Numbers. (Examiner's amendment, no attorney authorization required.)

SPECIFICATION, continued

- ☒ Update status of referenced U.S. applications (e.g. "now abandoned", or "issued as US Patent No.:" (Examiner's amendment, no attorney authorization required.)
- ☐ Recheck for Brief Description of Drawings of each figure. Note that if figures have multiple parts (e.g. Fig. 1A, Fig. 1B, etc.) Each individual part must be referred to in the brief description of the drawings. (Examiner's amendment, no attorney authorization required.)
- ☐ Recheck Brief Summary & Description to see if in harmony with the claims. If not, require applicant to modify, using FP 1307 (M.P.E.P. 1302.01).
- ☐ No blanks or missing text (e.g. "Serial Number _____").
- ☐ No unclear or missing words because of HOLES at top of page or poor copy quality.
- ☐ No missing pages or page numbers, no duplicate pages, page numbers are consecutive.
- ☒ Examples, tables, etc. numbered/lettered consecutively.
- ☐ Text and tables/charts legible.
- ☒ No non-initialed alterations.
- ☒ Minor, obvious errors in spelling, grammar, punctuation corrected by Examiner (Examiner's amendment, no attorney authorization required).
- ☐ CD-ROM submissions (e.g. large tables, computer programs) are in compliance with M.P.E.P. 608.05.

Biotech only:

- ☐ Complies with sequence rules:
  - ☐ CRF (computer readable form) filed and approved by STIC or generated from parent (M.P.E.P. 2422.05)
  - ☐ Raw sequence listing entered in IFW (STIC printout).
  - ☐ Sequence listing in IFW (copy provided by applicant).
  - ☐ Sequence listing matches CRF.
- ☐ All requirements for Deposit of Biological Materials have been fulfilled (See M.P.E.P. 2411: 37 C.F.R. §1.809).

3. OATH OR DECLARATION

- ☑ Original, first and sole/joint inventor(s) clause.
- ☑ Contains "reviewed and understands" and "duty of disclosure" statements, CIP oath states duty to disclose intervening art.
- ☑ Names of applicants on bibliographic data sheet same as in oath/declaration, unless there has been a request under 37 C.F.R. §1.48 to delete one or more inventors, and that request has been granted.
- ☑ Full given name for each applicant (M.P.E.P. 605.04(b)).
- ☑ Signature, Address and Citizenship for each inventor. (Address may be found on Application Data Sheet, see M.P.E.P. 601.05).
- ☑ Any alterations initialed and dated.
- ☑ Foreign priority includes country, serial number and filing date (check against bibliographic data sheet). (May be found on Application Data Sheet, see M.P.E.P. 601.05).
- ☑ Continuing data, if any, should be mentioned in the first sentences of the specification or ADS (not the oath or declaration). Especially in cases where an oath or declaration from a prior application is used, the continuity data may differ, and no objection should be made to the inclusion or lack or inclusion of continuity data in the oath. Benefit under 35 U.S.C. §120 should only be given if the application is mentioned in the first sentences of the specification, or on the ADS. See M.P.E.P. 601.05.

4. APPLICATION DATA SHEET

- ☐ If more than one Application Data Sheet is present, only the most recent one is considered.
- ☐ If present, must be compared with Oath/Declaration. If any discrepancies, a notice of defective oath or declaration should be sent. (M.P.E.P. 601.05)

5. PTO/SB/08 (former PTO-1449): INFORMATION DISCLOSURE STATEMENT (M.P.E.P 609)

- ☑ U.S. Patents-identified by patent number, patent date (Month-Year), and patentees.
- ☐ Foreign published applications and patents-identified by document number, publication date (Month-Year) and country or office.
- ☐ Printed publications-identified by author (if any), title, publication date (Month-Year), volume and issue number (if known), and pages relied on.

PTO/SB/08, con't.

- ☑ Examiner should initial all citations considered.
- ☐ Examiner should draw a line through each citation not considered.
- ☐ For each US patent considered, Examiner should insert the relevant classification or draw a line in the space provided for classification information.
- ☐ Sign and date each page.

6. PTO-892 NOTICE OF REFERENCES CITED (M.P.E.P 707.05)

- ☐ If applicants have not filed an information disclosure statement, the Examiner must cite references using a PTO-892, and the references must be appropriately addressed in an office action or in the notice of allowability. References cited at the time of allowance should be scanned into e-DAN, but do not need to be sent to applicants.
- ☐ U.S. Patents-identified by patent number, patent date (Month-Year), and patentees. If class/subclass not provided, line through appropriate boxes.
- ☑ Foreign published applications and patents-identified by document number, publication date (Month-Year) and country or office. If classification not provided, line through appropriate boxes.
- ☐ Printed publications-identified by author (if any), title, publication date (Month-Year), volume and issue number (if known), and pages relied on.

7. DRAWINGS

- ☐ Figure selected for printing must be consistent with claim selected for printing, and must be referred to in the abstract. If no figure is to be printed, write "none" in the appropriate box on the Issue Classification Sheet (IFW form).
- ☐ Do not select a figure labeled as "prior art" for printing.
- ☐ If color photographs or drawings are present, check M.P.E.P. 608.02 for requirements.

8. IFW SEARCH NOTES FORM:

- ☑ Update and complete Searched Box, Search Notes Box and Interference Searched Box.
- ☑ Search Notes Box:
  - ☑ Parent files checked
  - ☑ Record consultations with other examiners, primaries, SPEs, SPREs and TQASs.
  - ☑ Database searches recorded, with "printout attached" indicated, or search strategy set forth; specific vendors and files listed (e.g. Dialog, files 5, 55).
  - ☑ Inventor/assignee search noted for possible double patenting issues.
- ☐ Interference Searched Box:
  - ☑ Lists both original class and subclass and all cross-referenced classes and subclasses.
  - ☑ Indicates interference search of claimed sequences (Biotech).
  - ☑ Search the broadest claims on EAST or WEST for all original and cross-referenced classes and subclasses. Make sure PG-PUB file is searched.
  - ☐ Provide copies of search results in case.

9. IFW ISSUE CLASSIFICATION FORM:

- ☑ Assistant Examiner and Primary Examiner spaces should be completed.
- ☑ Primary Examiner must SIGN above their typewritten name.
- ☑ Update FINAL classification
- ☑ Complete classification cross-references.
- ☑ Complete INTERNATIONAL CLASSIFICATION- available on PTO intranet.
- ☑ Print claim should be the most comprehensive independent claim that conveys the nature of the invention. If dependent claim is printed, independent claim from which it depends must also be printed.
- ☐ If only one claim is being allowed, write "the" in the "print claim" box instead of "1".
- ☐ If there is a Terminal Disclaimer print IFW terminal disclaimer sheet.
- ☐ Index of Claims no longer required upon allowance, issue classification form is sufficient.

10. BIBLIOGRAPHIC DATA SHEET:

☑ TITLE-should reflect claimed invention-Rewrite if necessary (Examiner's amendment, no attorney authorization required; print Bib Data Sheet, correct, initial and date- give to LIE to be entered into PALM/IFW).

☑ Check that continuing data agrees with first paragraph of specification or Application Data Sheet (ADS). If continuity data has been omitted, print Bibliographic Data Sheet, correct, and have corrected document scanned into IFW. Additionally, have your LIE correct the data in PALM.

☑ Recheck Foreign-PCT application with oath or declaration. If in error, print Bibliographic Data sheet and correct in black ink, have LIE correct in PALM (See M.P.E.P. 202.03).

☑ Foreign priority claim should be verified and acknowledged.

☑ Check to see if certified copy of priority document is present and acknowledged.

11. MISCELLANEOUS

☑ Ensure that all amendments were timely filed and the application is not abandoned (all necessary extensions of time have been purchased or authorized).

☑ All foreign patents and publications cited during the prosecution should be scanned into eDAN.

☑ Papers pertaining to computer searches, e.g. PTO-1041, computer generated search reports, computer generated logic statements, sequence searches should scanned into eDAN (be sure to remove interference search).

☑ Check to ensure the substance of all interviews is of record.

☑ In cases filed under 35 U.S.C. §371, a PCT form 903 is present in IFW authorizing the filing under 371 and stating the priority dates. A photocopy of the ribboned priority document must also be in IFW.

☑ Double check that the claims are statutory under 35 U.S.C. §101

12. ITEMS TO BE PLACED IN RED FOLDER

LEFT SIDE OF FOLDER:

(Papers to be scanned but not mailed)

- ☑ PTO-1472 Case Action Worksheet (Count Sheet)
- ☑ Issue Classification form (IFW)
- ☑ IFW-Application Number
- ☑ IFW-Search Notes including Interference search in PG-PUBs
- ☑ IFW-Terminal Disclaimer, if applicable
- ☑ Initial and update Bibliographic Data Sheet

RIGHT SIDE OF FOLDER:

(Papers to be mailed to applicant)

- ☑ PTO-37 Notice of Allowability
- ☑ Examiner's Amendment (if applicable)
- ☑ Reasons for Allowance (if applicable)
- ☑ PTO-892 and/or PTO-1449 (if applicable)
- ☑ Any newly cited NPL or Foreign Patent or publication cited on PTO-892

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/181,051	06/24/2002	Alexander Straub	Le A 34122	5850

35969 7590 07/25/2005

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 07/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-21 and 23-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2-9, 17-19, 21, 23-31 and 53* is/are allowed.

6)☒ Claim(s) *10-16,20 and 32-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-21 and 23-53 are currently pending in the instant application. Claims 2-9, 17-19, 21, 23-31 and 53 appear allowable over the prior art of record and claims 10-16, 20 and 32-53 are rejected.

Election/Restrictions

Claims 2-9, 17-19, 21, 23-31 and 53 are directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 1-16, 20 and 32-52 directed to the process of making or using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Claims 1-16, 20 and 32-52 are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Since all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, the restriction requirement made in the Office action mailed on 3 October 2003 is hereby withdrawn.

Response to Amendment and Arguments

Applicants' amendment filed 27 April 2005 has overcome the objection to claims 22, and 23, has overcome the 35 USC 112 1st paragraph rejection of claims 2-7 and has overcome the 35 USC 112 2nd paragraph rejection of claims 2-6, 9, 17, 22 and 23.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-16, 20 and 32-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of myocardial infarct, atherosclerosis, pulmonary embolism or deep venous thrombosis and for the prevention of the coagulation of banked blood or a biological sample containing factor Xa does not reasonably provide enablement for the treatment of any disease applicant considers influenced positively by the inhibition of factor Xa, such as, thromboembolic disorders (excluding myocardial infarct, pulmonary embolism or deep venous thrombosis), Alzheimer's disease, arthritis, cancer, DIC, or for the prevention of any disease applicant considers influenced positively by the inhibition of factor Xa, such as any thromboembolic disorder (including myocardial infarct, pulmonary embolism or deep venous thrombosis), artherosclerosis, Alzheimer's disease, arthritis, cancer, DIC, or for the prevention of the coagulation of blood wherein the biological sample does not contain factor Xa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The nature of the invention

Applicants' instant claims 10, 20, 32, 35, 39, 42, 46 and 49 are claiming the treatment and prevention of thromboembolic disorders, such as myocardial infarct, angina pectoris, reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis. Applicants' instant claim 11 claims the treatment of disorders influenced positively by inhibition of factor Xa (which as found in the

specification on page 3, includes, for example, the thromboembolic disorders). Applicants' claims 12, 33, 40 and 47 claim the treatment and prevention of disseminated intravascular coagulation (DIC). Claims 13, 34, 41 and 48 claim the treatment and prevention of artherosclerosis, arthritis, Alzheimer's disease or cancer. Claims 14, 36, 43 and 50 claim the inhibition of factor Xa (which, by referring back to the originally filed specification is for the treatment and prevention of, for example, thromboembolic disorders, Alzheimer's disease, cancer and the prevention of the coagulation of blood). Claims 15, 16, 37, 38, 44, 45, 51 and 52 are claiming the prevention of the coagulation of blood in, for example, banked blood and biological samples containing factor Xa.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant

case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects of the above listed diseases, whether or not the disease is effected by the inhibition of factor Xa would make a difference.

Applicants claims are directed to the treatment and prevention of various diseases, such as DIC, Alzheimer's disease, various thromboembolic disorders, cancer, and the prevention of the coagulation of blood. As such, the specification fails to enable the skilled artisan to use the compounds of the formula (I) to treat any disease other than myocardial infarct, pulmonary embolism or deep venous thrombosis or artherosclerosis, fails to enable the skilled artisan to use the compounds of the formula to prevent the coagulation of blood in biological samples that do not contain factor Xa. In addition, there is no proof that the claimed compounds have ever been administered to a human.

The lack of predictability in the art of applicants' invention can be seen for example, in the treatment and prevention of cancer. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment or preventive protocol. It is known that the challenge of cancer treatment and prevention has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different

responses to therapy (Golub et al. page 531). Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

The lack of predictability in the art of applicants' invention can also be seen for example, in the treatment and prevention of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html

Finally, the lack of predictability in the art of applicants' invention can be seen for example, in the role of the inhibition of the factor Xa in the treatment of certain disorders. It is the state of the art that data on the metabolism of factor Xa inhibitors

has not been published yet (Hauptmann et al., page 223, 1449 of 12/9/02) and at the time of the publication , no published reports on the clinical use of factor Xa inhibitors existed. Furthermore, as seen in Kaiser (1449 of 12/9/02, page 431), Most of the specific factor Xa inhibitors known at the time of publication are still in the phase of preclinical development or are being investigated in first clinical studies, and while many treatment possibilities are discussed as possibilities, the real potential of factor Xa inhibitors has still to be validated in comprehensive clinical trials. Furthermore, an important point is that factor Xa inhibitors cannot interrupt thrombotic processes which are caused by generated thrombin. Page 432 of Kaiser states that Despite major progress in the development of antifactor Xa agents, there are still some unresolved issues such as that they are expected to be much less antithrombotically effective when sufficient amounts of thrombin have already been generated. Kaiser also discloses on page 433 that A particular factor Xa inhibitor might be useful for only a specific clinical indication, and it is likely that one drug might not be the optimum treatment for all thrombotic situations.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment or prevention by the inhibition of factor Xa, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of the inhibition of factor Xa, since various types of cancers have different causative agents, involve different cellular mechanisms and differ in treatment protocol and since it is known that there is

no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as influenced positively by inhibitionof factor Xa, see the list of diseases on page 38. Page 39 states that the compounds of the invention act as selective inhibitors of the blood coagulation factor Xa and do not inhibit, or only inhibit at considerably higher concentrations, other serine proteases as well. Assay data for the determination of the factor Xa inhibition , determination of the selectivity and determination of the anticoagulant action is found on pages 42 and 43. Pages 43-46 give antithrombotic activity (in vivo) with the arteriovenous shunt model, the arterial thrombosis model and the venous thrombosis model. The tests found on pages 43-46 coupled with the prior art reference of Al-Obeidi et al. (vol. 3, NO. 5, May 1998) wherein the inhibition of Factor Xa is shown to treat myocardial infarction, deep vein and pulmonary embolism and the Hauptmann et al. reference which discloses the relationship between the inhibition of factor Xa and the treatment of atherosclerosis support the treatment of myocardial infarct, pulmonary embolism, deep venous thrombosis and atherosclerosis with applicants compound of claim 2. There are no working examples present for the treatment or prevention of any disorder. Applicants' instant specification states on page 39 that the compounds of the invention are selective inhibitors of the blood coagulation factor and these compounds can be used for the

prevention of coagulation in banked blood or biological samples which contain factor Xa. There is no mention of the prevention of coagulation in blood samples which do not contain factor Xa.

The breadth of the claims

The breadth of the claims is that Applicants' instant claims 10, 20, 32, 35, 39, 42, 46 and 49 are claiming the treatment and prevention of thromboembolic disorders, such as myocardial infarct, angina pectoris, reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis. Applicants' instant claim 11 claims the treatment of disorders influenced positively by inhibition of factor Xa (which as found in the specification on page 3, includes, for example, the thromboembolic disorders). Applicants' claims 12, 33, 40 and 47 claim the treatment and prevention of disseminated intravascular coagulation (DIC). Claims 13, 34, 41 and 48 claim the treatment and prevention of artherosclerosis, arthritis, Alzheimer's disease or cancer. Claims 14, 36, 43 and 50 claim the inhibition of factor Xa (which, by referring back to the originally filed specification is for the treatment and prevention of, for example, thromboembolic disorders, Alzheimer's disease, cancer and the prevention of the coagulation of blood). Claims 15, 16, 37, 38, 44, 45, 51 and 52 are claiming the prevention of the coagulation of blood in, for example, banked blood and biological samples containing factor Xa.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited (treated or prevented) by the inhibition of factor Xa and would furthermore then have to determine which of the claimed compounds would provide treatment or prevention of which disease, if any Furthermore, undue experimentation would be needed to determine how to prevent coagulation of biological samples not containing factor Xa as the compounds of the present invention are stated to act as selective factor Xa inhibitors.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment or prevention of any disease or disorder as found in the claims except for the treatment of myocardial infarct, atherosclerosis, pulmonary embolism and deep venous thrombosis. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated or prevented by what compounds of the instant claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an 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. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600
6/30/05

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER
Kamal Saeed

for Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Notice of References Cited	Application/Control No. 10/181,051	Applicant(s)/Patent Under Reexamination STRAUB ET AL.	
	Examiner Rebecca L. Anderson	Art Unit 1626	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-			
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	K	US-			
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	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	Cancer and Metastasis Review, Vol. 17, pages 91-106, (1998).
	V	Science (1999), Vol. 286, 531-537.
	W	FDA mulls drug to slow late-stage Alzheimers's [online[, [retrieved on 2003-09-23]. Retrieved from the internet, URL;http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>.
	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.

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/181,051	STRAUB ET AL.	
Examiner	**Art Unit**	
Rebecca L. Anderson	1626	

SEARCHED

Class	Subclass	Date	Examiner
544	139	6/30/2005	RA
514	236.8	6/30/2005	RA

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
Inventor and STN update	6/30/2005	RA

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/181,051	STRAUB ET AL.
Examiner	**Art Unit**
Rebecca L. Anderson	1626

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	6/30/05
	1	-
	2	=
	3	=
	4	=
	5	=
	6	=
	7	=
	8	=
	9	=
	10	√
	11	√
	12	√
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	15	√
	16	√
	17	=
	18	=
	19	=
	20	√
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	50	√

Claim		Date
Final	Original	6/30/05
	51	√
	52	√
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Claim		Date
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Attorney's Docket No. LeA 34 122

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Straub, et al.

Serial No.: 10/181,051

Filed: 06/24/02

For: Substituted Oxazolidinones and Their Use in the field of Blood Coagulation

MAIL STOP AMENDMENT
COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that the *attached* correspondence comprising:

- Transmittal Letter to the United States Patent and Trademark Office
- Amendment In Response to Non-Final Office Action
- Fee Transmittal Form For FY 2005
- Return Receipt Post Card.

is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

April 25, 2005
Date

William F. Gray
Signature of Person Certifying /William F. Gray

PTO/SB/21 (02-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Straub, et al.
Art Unit	1626
Examiner Name	Anderson, Rebecca L.
Total Number of Pages in This Submission: 26	Attorney Docket Number: Le A 34 122

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance communication to Technology Center (TC)
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  1). Return Receipt Postcard
  2). Fee Transmittal for FY 2005

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	William F. Gray
Signature	William F. Gray
Date	April 25, 2005

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	William F. Gray		
Signature	William F. Gray	Date	April 25, 2005

This collection of information is required by 37 CFR 1.5. 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 2 hours 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, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Docket No.: LeA 34122
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Alexander Straub et al.

Application No.: 10/181,051 | Confirmation No.: 5850

Filed: June 24, 2002 | Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION | Examiner: R. L. Anderson

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

This is in response to the Official Action dated 01/25/2005.

Authorization for payment of extra claims fees

According to the applicants' calculations, a) when this application was filed, payment was authorized for 5 independent claims, 10 dependent claims, and 20 total claims; b) in the response dated 4 January 2004, the amendment resulted in 10 independent claims, 10 dependent claims, 1 multiply dependent claim, and a total of 20 claims, and authorization was given to charge the applicants' deposit account for all necessary claims fees; c) in the response dated 19 October 2004, the amendment resulted in 35 independent claims, 17 dependent claims, 1 multiply dependent claim, and a total of 51 claims, and authorization was given to charge the applicants' deposit account for all necessary claims fees; d) in the present response, the amendment results in 36 independent claims, 16 dependent claims, 1 multiply dependent claim,

and a total of 51 claims. Accordingly, it is believed that a fee of $200 for one additional independent claim should be due with in connection with this response, and authorization to charge our deposit account No. 13-3372 in the amount of $200 is hereby given. If any additional fees are due with respect to this application, please charge our Deposit Account No. 13-3372, from which the undersigned is authorized to draw.

In response to the Office Action dated January 25, 2005, please amend the above-identified U.S. patent application as follows:

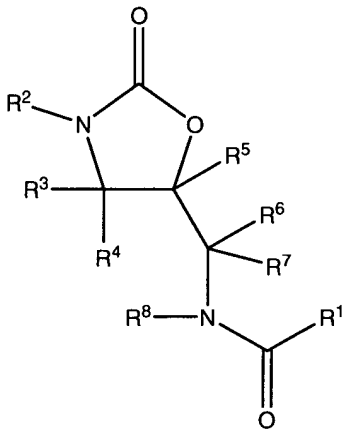
Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 21 of this paper.

AMENDMENTS TO THE CLAIMS

1. (canceled)

2. (currently amended) A compound of the ~~general~~ formula (I)



(I)

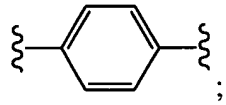
characterized in that

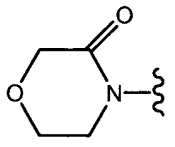
R^1 represents an optionally benzo-fused thiophene group which may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; cyano; nitro; amino; aminomethyl; (C_1-C_8)-alkyl which for its part may optionally be mono- or polysubstituted by halogen; (C_3-C_7)-cycloalkyl; (C_1-C_8)-alkoxy; imidazolinyl; -C(=NH)NH_2; carbamoyl; and mono- and di-(C_1-C_4)-alkyl-aminocarbonyl,

R^2 represents

D-M-A-,

where

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; (C_1-C_6)-alkanoyl; $-OR^{30}$; $-NR^{30}R^{31}$, and (C_1-C_6)-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, or $C(O)R^{33}$,

where

R^{33} represents (C_1-C_4)-aminoalkyl, or (C_1-C_8)-alkyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable ~~salt, hydrate, or prodrug~~ salt or hydrate thereof

except for compounds of the ~~general~~ formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

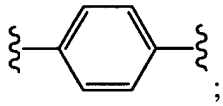
3. (currently amended) The compound of the ~~general~~ formula (I) according to claim 2, characterized in that

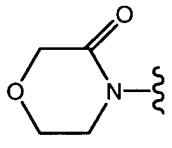
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen, amino, aminomethyl or (C_1-C_8)-alkyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

D-M-A-,

where

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; (C_1-C_6)-alkanoyl; $-OR^{30}$; $-NR^{30}R^{31}$, and (C_1-C_6)-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, or (C_1-C_4)-alkylaminocarbonyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable ~~salt, hydrate, or prodrug~~ salt or hydrate thereof

except for compounds of the ~~general~~ formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

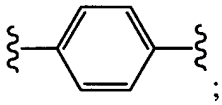
4. (currently amended) The compound of the ~~general~~ formula (I) according to claim 2, characterized in that

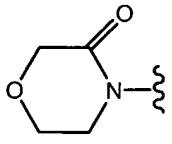
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen or by $(C_1$-$C_8)$-alkyl, where the $(C_1$-$C_8)$-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; $(C_1$-$C_3)$-alkanoyl; -OH; $-NR^{30}R^{31}$; and $(C_1$-$C_4)$-alkyl;

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or (C_1-C_3)-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable ~~salt, hydrate, or prodrug~~ salt or hydrate thereof

except for compounds of the ~~general~~ formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

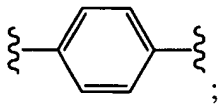
5. (currently amended) The compound of the ~~general~~ formula (I) according to claim 2, characterized in that

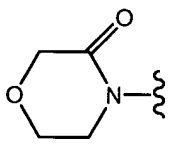
R^1 represents 2-thiophene which may optionally be substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents

D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; $(C_1$-$C_3)$-alkanoyl; -OH; $-NR^{30}R^{31}$; and $(C_1$-$C_4)$-alkyl;

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl or $(C_1$-$C_3)$-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents $(C_1$-$C_4)$-alkyl

or a pharmaceutically acceptable ~~salt, hydrate, or prodrug~~ salt or hydrate thereof

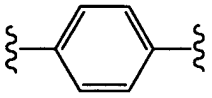
except for compounds of the ~~general~~ formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

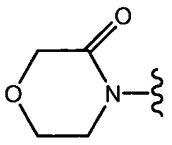
6. (currently amended) The compound of the ~~general~~ formula (I) according to claim 2, characterized in that

R^1 represents 2-thiophene which is substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents D-A-,

where:

the radical "A" represents  ;

the radical "D" represents  ,

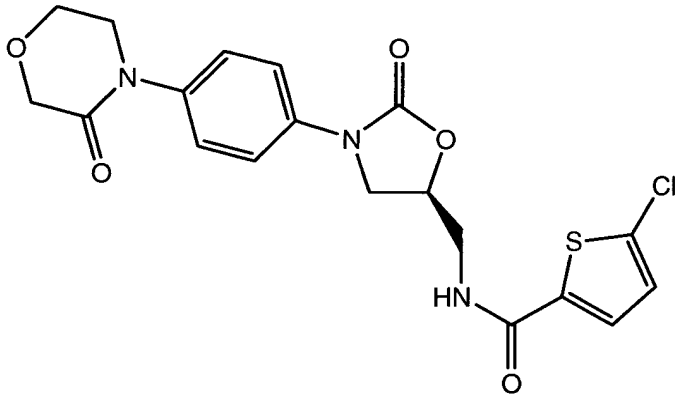
where

the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical selected from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen

or a pharmaceutically acceptable ~~salt, hydrate, or prodrug~~ salt or hydrate thereof.

7. (currently amended) The compound having the following formula

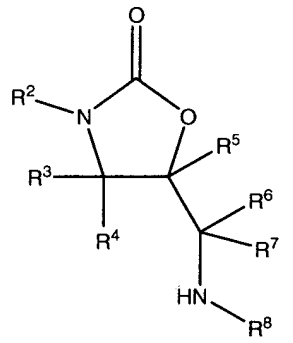


or a pharmaceutically acceptable ~~salt, hydrate, or prodrug~~ salt or hydrate thereof.

8. (withdrawn-currently amended) Process for preparing the substituted oxazolidinone of claim 2, where

either according to a process alternative

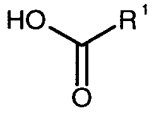
~~[A]~~ (A) a compound of the ~~general~~ formula (II)



(II),

in which

the radicals R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2 is reacted with carboxylic acid of the ~~general~~ formula (III)



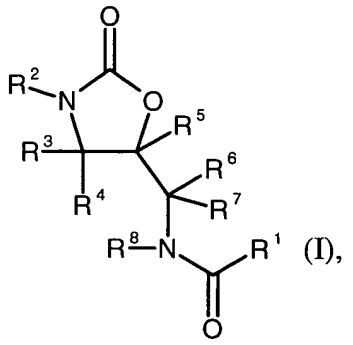
(III),

in which

the radical R^1 is as defined in Claim 2,

or else with a corresponding carbonyl halide, or else with a corresponding symmetric or mixed carboxylic anhydride of the carboxylic acid of the ~~general~~ formula (III) defined above

in an inert solvent, if appropriate in the presence of an activating or coupling agent and/or a base, to give a compound of the ~~general~~ formula (I)



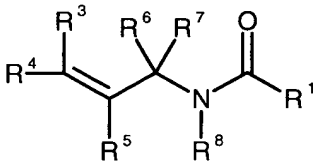
(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

or else according to a process alternative

~~[B]~~ (B) a compound of the ~~general~~ formula (IV)

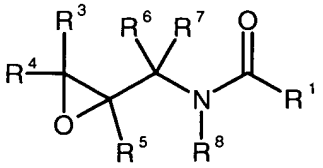


(IV),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the ~~general~~ formula (V)



(V),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

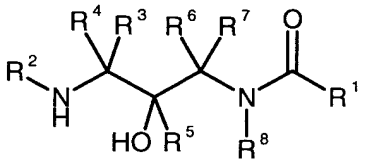
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the ~~general~~ formula (VI)

$$R^2\text{-}NH_2 \qquad \text{(VI)},$$

in which

the radical R^2 is as defined in Claim 2,

a compound of the ~~general~~ formula (VII)



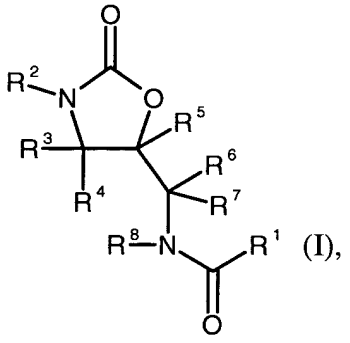
(VII),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is initially prepared and,

subsequently, in an inert solvent in the presence of phosgene or a phosgene equivalent, cyclized to give a compound of the ~~general~~ formula (I)



(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

where - both for process alternative ~~[A]~~ (A) and for process alternative ~~[B]~~ (B) - in the case where R^2 contains a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical having one or more identical or different heteroatoms from the group consisting of N and S, an oxidation with a selective oxidizing agent to afford the corresponding sulphone, sulphoxide or N-oxide may follow

and/or

where - both for process alternative ~~[A]~~ (A) and for process alternative ~~[B]~~ (B) - in the case where the compound prepared in this manner has a cyano group in the molecule, an amidination of this cyano group by customary methods may follow

and/or

where - both for process alternative ~~[A]~~ (A) and for process alternative ~~[B]~~ (B) - in the case where the compound prepared in this manner has a BOC amino protective group in the molecule, removal of this BOC amino protective group by customary methods may follow

and/or

where - both for process alternative ~~[A]~~ (A) and for process alternative ~~[B]~~ (B) - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with a carboxylic acid, carboxylic anhydride, carbonyl chloride, isocyanate, sulphonyl chloride or alkyl halide to give the corresponding derivative may follow

and/or

where - both for process alternative ~~[A]~~ (A) and for process alternative ~~[B]~~ (B) - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with an amine to give the corresponding sulphonamide may follow.

9. (currently amended) A pharmaceutical composition comprising at least one compound of the ~~general~~ formula (I) according to claim 2 and one or more pharmacologically acceptable auxiliaries or excipients.

10. (withdrawn) A method for treatment of a thromboembolic disorder, comprising administering an effective amount of a compound of claim 2.

11. (withdrawn) A method for treatment of disorders which are influenced positively by inhibition of factor Xa comprising adminstering an effective amount of a compound of claim 2.

12. (withdrawn) A method for treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of a compound of claim 2.

13. (withdrawn) A method for treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of a compound of claim 2.

14. (withdrawn) A method for the inhibition of factor Xa comprising administering an effective amount of a compound of claim 2.

15. (withdrawn) Method for preventing the coagulation of blood in vitro, comprising adding to said blood a compound of claim 2.

16. (withdrawn) The method of claim 15 wherein said blood is banked blood or a biological sample containing factor Xa.

17. (previously presented) The compound of claim 3 or 4 wherein R^1 represents an optionally substituted 2-thiophene group, and wherein said halogen substituent is chlorine or bromine, and said (C_1-C_8)-alkyl substituent is methyl, where the methyl radical for its part optionally may be mono- or polysubstituted by fluorine.

18. (withdrawn) The process of claim 8 wherein in process alternative "A", the corresponding carbonyl halide of carboxylic acid (III) is a carbonyl chloride.

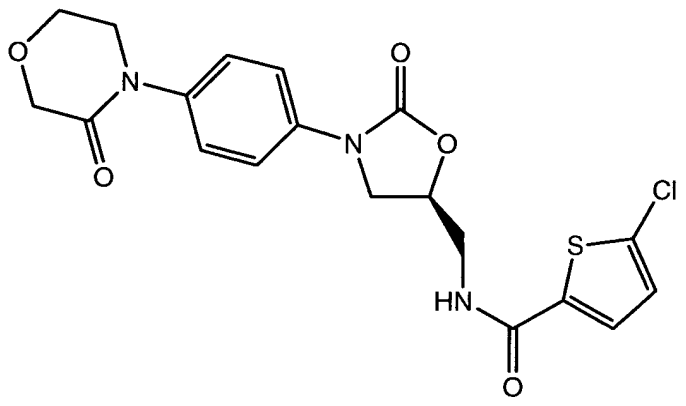
19. (withdrawn) The process of claim 8 wherein in process alternative "B", the phosgene equivalent employed in the cyclization of compound (VII) is carbonyldimidazole (CDI).

20. (withdrawn) The method of claim 10 wherein the thromboembolic disorder is myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive disease, pulmonary embolism or deep venous thrombosis.

21. (previously presented) The compound of claim 7 that is purified and isolated.

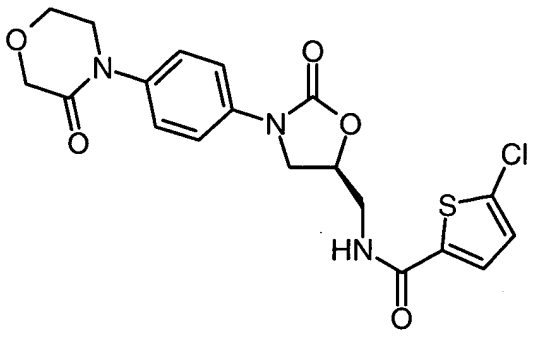
22. (canceled)

23. (currently amended) A racemic mixture of ~~the compound of claim 7~~ a compound having the following formula



and its enantiomer, or a pharmaceutically acceptable salt or hydrate thereof.

24. (previously presented) A compound having the following formula:



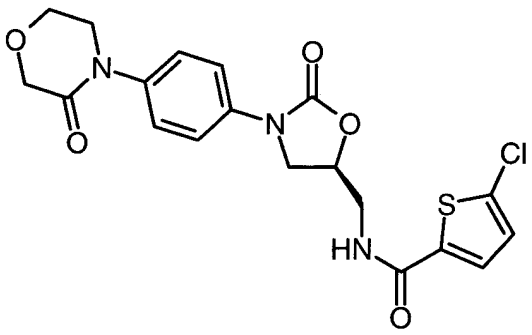
25. (previously presented) A pharmaceutical composition comprising the compound of claim 7 and a pharmacologically acceptable auxiliary or excipient.

26. (previously presented) A pharmaceutical composition comprising the compound of claim 21 and a pharmacologically acceptable auxiliary or excipient.

27. (withdrawn-currently amended) A pharmaceutical composition comprising the ~~compound of claim 22~~ composition of claim 53 and a pharmacologically acceptable auxiliary or excipient.

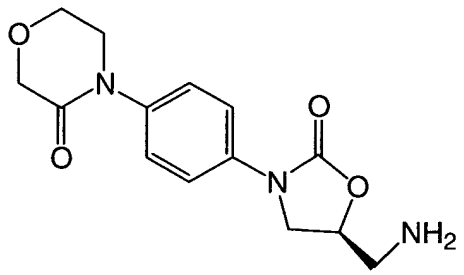
28. (previously presented) A pharmaceutical composition comprising the compound of claim 24 and a pharmacologically acceptable auxiliary or excipient.

29. (withdrawn-currently amended) The process of claim 8 wherein the substituted oxazolidinone that is prepared is



or a pharmaceutically acceptable ~~salt, hydrate, or prodrug~~ salt or hydrate thereof.

30. (withdrawn) A process for the preparation of the compound of claim 7 comprising reacting a compound of the following formula



with 5-chlorothiophene-2-carbonyl chloride in an inert solvent to prepare the compound of claim 7.

31. (withdrawn) The process of claim 30 wherein the inert solvent comprises pyridine.

32. (withdrawn) A method for the prevention or treatment of thromboembolic disorders comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

33. (withdrawn) A method for the prevention or treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

34. (withdrawn) A method for the prevention or treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

35. (withdrawn) A method for the prevention or treatment of myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

36. (withdrawn) A method for the inhibition of factor Xa comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

37. (withdrawn) A method for preventing the coagulation of blood in vitro comprising adding to said blood an effective amount of the compound of claim 7.

38. (withdrawn) The method of claim 37 wherein said blood is banked blood or a biological sample containing factor Xa.

39. (withdrawn) A method for the prevention or treatment of thromboembolic disorders comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

40. (withdrawn) A method for the prevention or treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

41. (withdrawn) A method for the prevention or treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

42. (withdrawn) A method for the prevention or treatment of myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

43. (withdrawn) A method for the inhibition of factor Xa comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

44. (withdrawn) A method for preventing the coagulation of blood in vitro comprising adding to said blood an effective amount of the compound of claim 21.

45. (withdrawn) The method of claim 44 wherein said blood is banked blood or a biological sample containing factor Xa.

46. (withdrawn) A method for the prevention or treatment of thromboembolic disorders comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

47. (withdrawn) A method for the prevention or treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

48. (withdrawn) A method for the prevention or treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

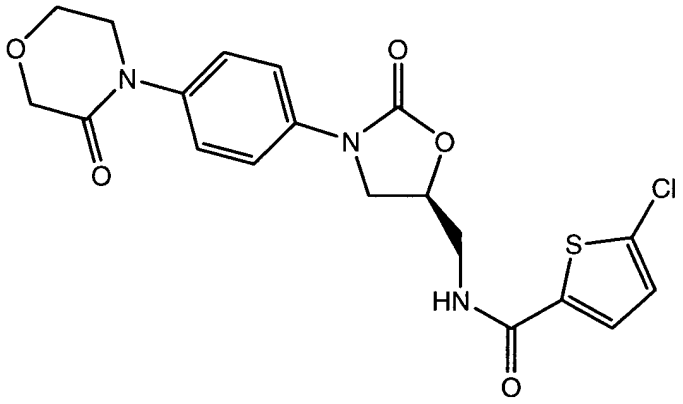
49. (withdrawn) A method for the prevention or treatment of myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

50. (withdrawn) A method for the inhibition of factor Xa comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

51. (withdrawn-currently amended) A method for preventing the coagulation of blood in vitro comprising adding to said blood an effective amount of the ~~compound of claim 22~~ composition of claim 53.

52. (withdrawn) The method of claim 51 wherein said blood is banked blood or a biological sample containing factor Xa.

53. (new) A composition comprising a compound having formula (a):



(a)

or a pharmaceutically acceptable salt or hydrate thereof, wherein the composition is substantially free of the enantiomer of the compound of formula (a) and substantially free of the salts and hydrates of the enantiomer of the compound of formula (a).

REMARKS

After entry of this amendment, claims 2-21 and 23-53 will be pending. Claims 8, 10-16, 18-20 and 29-52 have been withdrawn from consideration as being for non-elected subject matter. Claim 22 has been canceled without prejudice or disclaimer to resubmission in a later application. Claim 22 has been replaced by new claim 53, which has similar scope to claim 22. Thus, claim 53 is believed to be within the elected subject matter. Pending claims 2-7, 9 and 23 and withdrawn claims 8, 27, 29 and 51 have been amended without prejudice or disclaimer. Support for the amendments is found in the original claims and at page 27, lines 1-2 and example 97 on page 88 (claim 23) and at page 26, line 29 to page 27, line 2 and example 44 at page 69, line 3 to page 71, line 17 (claim 53).

Applicants respectfully thank the Examiner for the indication that claims 24 and 28 appear allowable over the prior art of record.

Response to Claim Objections

The Patent Office has objected to claim 22 as being of improper dependent form. The Office Action states that a claim to a specific stereoisomer not substantially free of its enantiomer would be a claim to a racemic mixture, and that is not claimed in claim 7. Applicants respectfully disagree that such a claim necessarily would be a racemic mixture. Nevertheless, to advance prosecution, claim 22 has been canceled and rewritten in independent form in new claim 53 as a composition comprising the identified stereoisomer, wherein the composition is substantially free of the enantiomer, its salts and hydrates. Accordingly, the objection is believed to be rendered moot.

The Examiner has suggested for clarity that the compound name be inserted into claim 7 in addition to the structure. Applicants respectfully submit that having the same compound identified in two different ways in one claim provides an opportunity for dispute and that defining it only by structure is the clearest option. Accordingly, Applicants have not amended claim 7. Reconsideration of this suggestion is respectfully requested.

Claim 23 was objected to as being of improper dependent form. Applicants respectfully disagree, and argue that claim 23 was always an independent claim. However, to expedite prosecution, Applicants have amended claim 23 to delete the reference to claim 7 and insert the structure from claim 7 in its place. The objection is believed to be overcome.

Response to Rejections under 35 U.S.C. § 112

Claims 2-7 and their dependent claims 9, 17, 21-23 and 25-27 were rejected under 35 U.S.C. § 112, first paragraph on the grounds that the specification does not enable one to make and use prodrugs. Applicants respectfully disagree. Nevertheless, to further prosecution, pending claims 2-7 and withdrawn claim 29 have been amended to remove reference to prodrugs. Thus, the rejection is rendered moot as to these claims. Claim 23 has been amended to delete the reference to claim 7, and claim 27 has been amended to refer to new claim 53. Because claims 9, 17, 21-22 and 25-26 refer to or depend from one or more of claims 2-7, the amendments to claims 2-7 are believed to obviate the rejection as to these dependent claims as well. Therefore, reconsideration and withdrawal of the enablement rejection is respectfully requested.

Claims 2-6, 9 and 17 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for using the term "general" in the phrase " a compound of the general formula (I)." Applicants respectfully disagree. A general formula is a generic formula that provides for a group of compounds to be encompassed within it. The "general formula" of the claims is specifically defined by the definite structure and description of allowed substituents that follows the term in the claims. Nevertheless, to expedite prosecution, claims 2-6 and 9 have been amended to remove "general." As claim 17 depends from claim 3 or 4, this amendment is believed to render moot the rejection for indefiniteness of claims 2-6, 9 and 17. Furthermore, reference to "general formula" has been replaced with "formula" where it appears in the withdrawn claims also.

Claim 22 stands rejected under 35 U.S.C. § 112, second paragraph as indefinite. The Office Action states that if claim 22 is properly dependent from claim 7, then claim 22 would be directed to a racemic mixture of the compound of claim 7. Applicants respectfully disagree.

However, to further prosecution, claim 22 has been canceled and replaced with new claim 53. Claim 53 is believed to avoid definiteness issues by specifically reciting a composition comprising the specific stereoisomer described, wherein the composition is substantially free of the enantiomer. Accordingly, the rejection is believed to be rendered moot.

Claim 23 stands rejected under 35 U.S.C. § 112, second paragraph as indefinite. To further prosecution, claim 23 has been rewritten to remove the reference to claim 7. Accordingly, the rejection for indefiniteness is believed to be overcome.

Conclusion

The objections and rejections of the claims are believed to be overcome by the amendments and the reasons discussed above. Accordingly, the claims are believed to be in condition for allowance. If any issues remain outstanding, a telephone conference with the undersigned representative for the Applicants would be welcomed to resolve them.

Applicants also respectfully urge that if the product claims are found allowable, then the withdrawn process claims to methods of making the products (claims 8, 18, 19 and 29-31) and methods of using the products (claims 10-16, 20, and 32-52) be rejoined. These method claims depend from or otherwise include all the limitations of the product claims now pending. Thus, pursuant to MPEP 821.04, rejoinder would appear to be appropriate. Furthermore, the withdrawn claims have been amended to obviate any grounds for rejection based on 35 U.S.C. § 112 that arose with the pending claims.

In view of the above amendments, Applicants believes the pending application is in condition for allowance.

Dated: 4/25/05

Respectfully submitted,

By William F. Gray

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10/181,051	06/24/2002	Alexander Straub	Lc A 34122	5850

35969 7590 01/25/2005

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-52* is/are pending in the application.

4a) Of the above claim(s) *8,10-16,18-20 and 29-52* is/are withdrawn from consideration.

5)☒ Claim(s) *24 and 28* is/are allowed.

6)☒ Claim(s) *2-7,9,17,21-23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-52 are currently pending in the instant application. Claims 8, 10-16, 18-20 and 29-52 are withdrawn from consideration as being for non-elected subject matter. Claims 2-7, 9, 17, 21-23 and 25-27 are rejected, claims 22 and 23 are objected and claims 24 and 28 appear allowable over the prior art of record.

Response to Arguments and Amendments

Applicants amendments and arguments filed 21 October 2004 have been entered into the application and considered. Applicants amendment to claims 2-5 to include the proviso which excludes the compounds of the formula (I) wherein R1 is an unsubstitued 2-thiophene radical, R2 simultaneously is a mono- or polysubstituted phenyl radical and R3-R8 are each simultaneously hydrogen from the claimed invention has overcome the rejection of claims 2-7, 9 and 17 under 35 USC 112 1st paragraph as failing to comply with the written description requirement. Applicants new claims 29-52, are directed to inventions of Groups IV, VII and X (process and method groups) of the restriction requirement mailed 3 October 2003. Therefore, these claims 29-52 are also withdrawn from consideration as being for non-elected subject matter along with the claims 8, 10-16 and 18-20.

Claim Objections

Claims 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7, from which claim

22 depends is claiming the specific stereoisomer as depicted in the claim (it is suggested that the compound name, 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, be inserted into the claim 7 for clarity). Claim 7 is therefore already claiming the depicted compound substantially free of its enantiomer, since a claim to a specific stereoisomer not substantially free of its enantiomer would be a claim to a racemic mixture, which is not what is claimed in claim 7. Therefore, claim 22 fails to further limit claim 7 since claim 22 is providing no further limitations than are already present in claim 7.

Claims 23 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7, from which claim 23 depends is claiming the specific stereoisomer, 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. Therefore, a claim to a racemic mixture of the compound of claim 7 is an improper dependent claim since it is broadening the claim 7 by adding an additional enantiomer instead of further limiting the specific stereoisomer of claim 7.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-7 and there dependent claims 9, 17, 21-23 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound of the formula (I), its pharmaceutically acceptable salts and hydrates thereof does not reasonably provide enablement for any prodrug of the formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

In the instant case, claims 2-7 and their dependent claims 9, 17, 21-23 and 25-27 are claiming products of the formula (I) or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

The state of the prior art

The state of the prior art is that prodrugs are inactive substances that are converted to a drug within the body by enzymes or other chemicals. Prodrugs can be formed by various mechanisms and vary depending on the functional groups present in the parent compound, i.e. different prodrugs would arise from parent compounds containing varying functional groups, such as a carboxylic acid, an alcohol or an amine, all of which would require differing mechanisms.

The predictability or lack thereof in the art and the amount of direction or guidance present

The only direction or guidance present in the instant specification is for the compounds of the formula I and their pharmaceutically acceptable salts and hydrates thereof. There is no data present in the instant specification as to what prodrugs of the compound of the formula (I) can be made nor for the preparation of prodrugs of the instant compounds of the formula I.

The breadth of the claims

The breadth of the claims is the products of the formula (I) or a pharmaceutically acceptable salt, hydrate, or any prodrug of the product of the formula (I).

The quantity of experimentation needed and the level of skill in the art

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any prodrug of the formula I as instantly claimed since it would require undue experimentation to prepare any covalently bonded compound that would release the active parent drug since

prodrugs are formed by varying mechanisms and depend on the functional groups of the parent compound. The only guidance present in the instant specification is for the compounds of the formula I and pharmaceutically acceptable salts and hydrates thereof. There is no guidance or working examples present for prodrugs of the formula I. Therefore, the claims lack enablement for prodrugs of the compounds of the formula I. This rejection can be overcome by deleting the term "prodrug" from the instant claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-6, 9 and the dependent claim 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the term "general" renders the claims indefinite. The use of the term "general" in the phrase "A compound of the general formula" renders the claims indefinite since the term general is defined as, for example, as involving only the main features and not limited in scope (Webster's II New Riverside University Dictionary, 1984). Therefore, it is unclear what compounds are encompassed by the instant claims since the claims are directed to the general formula I, which is not limited to the compound described as formula I but also includes other compounds outside the scope of the compounds of the formula I. It is suggested that the term "general" be deleted from all instances in the claims to overcome this rejection.

Claim 22 and its dependent claim 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 has been objected to as failing to further limit the claim from which it depends, claim 7. However, if claim 22 is to be considered a proper dependent claim, it is indefinite. If claim 7 is not substantially free of its enantiomer, than claim 22 would be directed to a racemic mixture of the compound of claim 7. A racemic mixture substantially free of its enantiomer is indefinite because it is unclear which enantiomer is being claimed and which enantiomer is being excluded from the claim 22.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. While claim 23 is failing to further limit the claim from which it depends, it is also considered indefinite. A racemic mixture is a mixture of the enantiomers of a chemical formula. It is unclear then, what is being claimed by claiming a racemic mixture of the compound of claim 7, which is a mixture of the enantiomers, and its (the racemic mixtures) enantiomer. By definition a racemic mixture is a mixture of the enantiomers of a compound, therefore it is unclear what an enantiomer of the enantiomer mixture is that is being included with the racemic mixture of claim 23.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571)

272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an 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. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RA

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600
1/19/05

for Kamal Saeed

Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

PTO/SB/08a/b (08-03)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	LeA 34 122

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
RL	AA	US-2,811,555	10-29-1957	Larive et al.	
RL	AB	US-3,279,880	10-18-1966	Straley et al.	
RL	AC	US-4,500,519	02-19-1985	Lormeau et al.	
RL	AD	US-4,705,779	11-10-1987	Madi-Szabo et al.	
RL	AE	US-5,254,577	10-19-1993	Carlson et al.	
RL	AF	US-5,349,045	09-20-1994	Ying Jiang	
RL	AG	US-5,532,255	07-02-1996	Raddatz et al.	
RL	AH	US-5,688,792	11-18-1997	Barbachyn et al.	
RL	AI	US-5,792,765	08-11-1998	Riedl et al.	
RL	AJ	US-5,827,857	10-27-1998	Riedl et al.	
RL	AK	US-5,910,504	06-08-1999	Hutchinson et al.	
RL	AL	US-5,922,708	07-13-1999	Riedl et al.	
RL	AM	US-5,972,947	10-26-1999	Tsaklakidis et al.	
RL	AN	US-6,069,160	05-30-2000	Stolle et al.	
RL	AO	US-6,251,869	06-26-2001	Michael J. Bohanon	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
RL	BA	EP-0 127 902	12-12-1984	E.I. Du Pont de Nemours and Co.		
RL	BB	EP-0 316 594	05-24-1989	The Du Pont Merck Pharmaceutical Co.		
RL	BC	EP-0 352 781	01-31-1990	E.I. Du Pont De Nemours and Co.		
RL	BD	WO-93/09103	05-13-1993	The Upjohn Company		
RL	BE	WO-93/23384	11-25-1993	The Upjohn Company		
RL	BF	EP-0 623 615	11-09-1994	Merck Patent GmbH		*
RL	BG	EP-0 738 726	10-23-1996	Bayer AG		*1
RL	BH	WO-97/03072	01-30-1997	Boehringer Mannheim GmbH		*2
RL	BI	WO-97/09328	03-13-1997	Pharmacia & Upjohn Company		
RL	BJ	WO-97/10223	03-20-1997	Pharmacia & Upjohn Company		
RL	BK	EP-0 785 200	07-23-1997	Bayer AG		*3
RL	BL	DE-196 04 223	08-07-1997	Bayer AG		*4
RL	BM	WO-98/01446	01-15-1998	Zeneca Limited		
RL	BN	WO-98/54161	12-03-1998	Pharmacia & Upjohn Company		
RL	BO	WO-99/02525	01-21-1999	Pharmacia & Upjohn Company		
RL	BP	WO-99/03846	01-28-1999	Bayer Aktiengesellschaft		
RL	BQ	WO-99/24428	05-20-1999	Pharmacia & Upjohn Company		

Examiner Signature		Date Considered	1/19/05

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Sheet 2 of 3

Complete if Known	
Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	LeA 34 122

	BR	WO-99/29688	06-17-1999	Pharmacia & Upjohn Company		
	BS	WO-99/37630	07-29-1999	Versicor, Inc.		
	BT	WO-99/37641	07-29-1999	Bayer Aktiengesellschaft		
	BU	WO-99/40094	08-12-1999	Bayer Aktiengesellschaft		
	BV	WO-99/59616	11-25-1999	Pharmacia & Upjohn Company		
	BW	WO-01/44212	06-21-2001	Pharmacia & Upjohn Company		
	BX	WO-01/46185	06-28-2001	Pharmacia & Upjohn Company		
	BY	WO-02/064575	08-22-2002	Bayer Aktiengesellschaft		*5
	BZ	CA-2 437 587	08-22-2002	Bayer Aktiengesellschaft		
	BA1	WO-03/000256	01-03-2003	Bayer Aktiengesellschaft		*6
	BB1	CA-2 451 258	01-03-2003	Bayer HealthCare AG		
	BC1	WO-03/035133	05-01-2003	Bayer Aktiengesellschaft		*7
	BD1	CA-2 464 290	05-01-2003	Bayer HealthCare AG		
	BE1	WO-01/42242	06-14-2001	Ortho-McNeil Pharmaceuticals Inc.		

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	ADAMS et al., Sulfanilamide Derivatives, J. Am. Chem. Soc. 1939, vol. 61, pp. 2342-2349	
	CB	AEBISCHER et al., Synthesis of N-Arylrolipram Derivatives – Potent and Selective Phosphodiesterase-IV Inhibitors – By Copper Catalyzed Lactam-Aryl Halide Coupling, Hetercycles. 1998, vol. 48, pp. 2225-2229	
	CC	ARTICO et al., Research on Compounds with Antiblastic Activity, Farmaco Ed. Sci. 1969, vol. 24, pp. 179-190	
	CD	BARBACHYN et al., Identification of a Novel Oxazolidinone (U-100480) with Potent Antimycobacterial Activity, J. Med. Chem. 1996, vol. 39, pp. 680-685	
	CE	BARTOLI et al., Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Reaction by Phenoxides as Nucleophiles in Dimethyl Sulfoxide, J. Org. Chem. 1975, vol. 40, pp. 872-874	
	CF	BERRY et al., Antithrombotic Actions of Argatroban in Rat Models of Venous, 'Mixed' and Arterial Thrombosis, and its Effects on the Tail Transection Bleeding Time, Br. J. Pharmacol. 1994, vol. 113, pp. 1209-1214	
	CG	BOUCHET et al., σ Values of N-Substituted Azoles, J. Chem. Soc. Perkin Trans. 1974, vol. 2, pp. 449-451	
	CH	BRICKNER et al., Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections, J. Med. Chem. 1996, vol. 39, pp. 673	
	CI	CHERN et al., Studies on Quinazolines IX : Fluorination versus 1,2-Migration in the Reaction of 1,3-Bifunctionalized amino-2-propanol with DAST, Tetrahedron Lett. 1998, vol. 39, pp. 8483-8486	

Examiner Signature		Date Considered	1/19/05

PTO/SB/08a/b (08-03)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 3

Complete if Known	
Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	LeA 34 122

	CJ	DANKWARDT et al., Nonpeptide Bradykinin Antagonist Analogs Based on a Model of a Sterling-Winthrop Nonpeptide Bradykinin Antagonist Overlapped with Cyclic Hexapeptide Bradykinin Antagonist Peptides, Bioorg. Med. Chem. Lett. 1997, vol. 7, no. 14, pp. 1921-1926
	CK	DOSTERT et al., 5-Hydroxymethyl-2-oxazolidinones, Chem. Abstr. 1979, vol. 90, pp. 186926
	CL	GREGORY et al., Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidines. 1. The "B" Group, J. Med. Chem. 1989, vol. 32, pp. 1673-1681
	CM	GRELL et al., Repaglinide and Related Hypoglycemic Benzoic Acid Derivatives, J. Med. Chem. 1998, vol. 41, pp. 5219-5246
	CN	GUTCAIT et al., Studies on Quinazolines. 6. Asymmetric Synthesis of (S)-(+)- and (R)-(-)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-5-methylthio-2,3-dihydroimidazo[1,2-c]quinazolines, Tetrahedron Asym. 1996, vol. 7, pp. 1641-1648
	CO	KHANNA et al., 1,2-Diarylpyrroles as Potent and Selective Inhibitors of Cyclooxygenase-2, J. Med. Chem. 1997, vol. 40, pp. 1619-1633
	CP	LUVALLE et al., Oxidation Processes. XXI. The Autoxidation of the p-Phenylenediamines, J. Am. Chem. Soc. 1948, vol. 70, pp. 2223-2233
	CQ	MENG et al., Effect of Acetylsalicylic Acid on Experimentally Induced Arterial Thrombosis in Rats, Naunyn-Schmiedeberg's Arch. Pharmacol. 1977, vol. 301, pp. 115-119
	CR	PFEIL et al., Synthese von Oxalactamen aus Aziridinium-tetrafluoroborat und Hydroxysäureestern, Agnew. Chem. 1967, vol. 79, p. 188
	CS	RENGER, Direct N-Arylation of Amides : An Improvement of the Goldberg-Reaction, Synthesis, September 1985, pp. 856-860
	CT	REPPE et al., Justus Liebigs Ann. Chem. 1955, vol. 596, pp. 204
	CU	REPPE et al., Justus Liebigs Ann. Chem. 1955, vol. 596, pp. 209
	CV	RIEDL et al., Recent Developments with Oxazolidinone Antibiotics, Exp. Opin. Ther. Patents 1999, vol. 9 (5), pp. 625-633
	CW	SHAKESPEARE, Palladium-Catalyzed Coupling of Lactams with Bromobenzenes, Tetrahedron Lett. 1999, vol. 40, pp. 2035-2038
	CX	SNYDER et al., Imidazo[4,5-f]quinolines III : Antibacterial 7-Methyl-9-(substituted Arylamino)imidazo[4,5-f]quinolines, J. Pharm. Sci. 1977, vol. 66, pp. 1204-1206
	CY	SURREY et al., The Preparation of N-Benzyl-3-morpholones and N-Benzyl-3-homomorpholones from N-(Hydroxyalkyl)-chloroacetamides, J. Amer. Chem. Soc. 1955, vol. 77, pp. 633-636
	CZ	TONG et al., The Mechanism of Dye Formation in Color Photography. VII. Intermediate Bases in the Deamination of Quinonediimines, J. Amer. Chem. Soc. 1960, vol. 82, pp. 1988-2001
	CA1	TUCKER et al., Piperazinyl Oxazolidinone Antibacterial Agents Containing a Pyridine, Diazene, or Triazene Heteroaromatic Ring, J. Med. Chem. 1998, vol. 41, pp. 3727-3735
	CB1	ZIEGLER et al., Synthesis of Some Novel 7-Substituted Quinolonecarboxylic Acids *via* Nitroso and Nitrone Cycloadditions, J. Hetercycl. Chem., May-June 1988, vol. 25 (2), pp. 719-723

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

* English language equivalent US 5532255 attached
*1 English language equivalent US 6069160 attached
*2 English language equivalent US 5972947 attached
*3 English language equivalent US 5827857 attached
*4 English language equivalent US 5792765 attached
*5 English language equivalent CA 2437587 attached
*6 English language equivalent CA 2451258 attached
*7 English language equivalent CA 2464290 attached

Examiner Signature		Date Considered	1/19/06

Index of Claims

Application No.	Applicant(s)	
10/181,051	STRAUB ET AL.	
Examiner	**Art Unit**	
Rebecca L Anderson	1626	

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date								
Final	Original	1/18/05								
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Claim		Date								
Final	Original	1/18/05								
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Search Notes	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

SEARCHED			
Class	Subclass	Date	Examiner
544	139	1/18/2005	RA

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor Name Search Update	1/18/2005	RA
STN structure search update	1/18/2005	RA

DW 1626 6

In the United States Patent and Trademark Office

Appl. No.:	10/181,051	Confirmation No. 5850
Applicant(s):	Straub, et al.	
Filed:	June 24, 2002	
TC/A.U.:	1626	
Examiner:	Anderson, Rebecca L.	
Docket No.:	LeA 34 122	
Customer No.:	35969	

CERTIFICATION OF MAILING UNDER 37 C.F.R. 1.8(a)

I hereby certify that this correspondence and any papers referred to as attached are being deposited, on the date shown below, with the United States Postal Service, with sufficient postage, as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: 19 Oct. '04 William F. Gray

William F. Gray

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

AMENDMENT

Sir:

This is in response to the Official Action dated 04/19/2004. Please amend the above-identified application as follows:

Amendments to the specification begin on page 2 of this paper.

Amendments to the claims are reflected in the listing of claims which begins on page 5 of this paper.

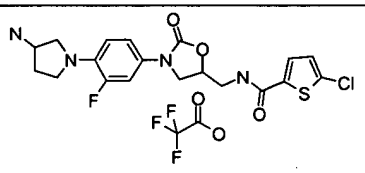
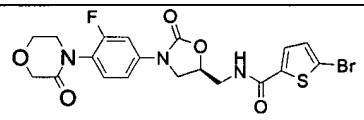
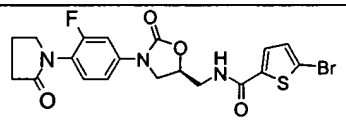
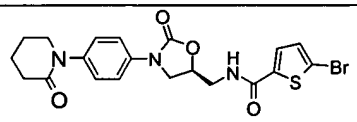
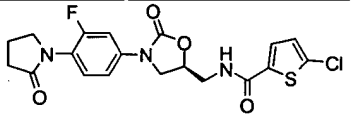
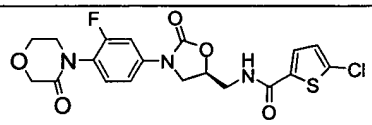
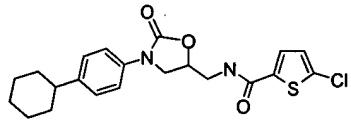
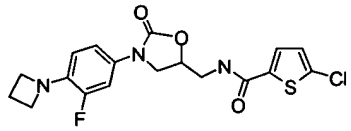
Remarks begin on page 23 of this paper.

Amendments to the specification:

Please replace the one-line paragraph beginning and ending at page 31, line 18, with the following amended one-line paragraph:

the radicals R^2, R^3, R^4, R^5, R^6, ~~and~~ R^7 and R^8 are each as defined above,

Please replace the table on page 94, starting at line 11, with the following amended version:

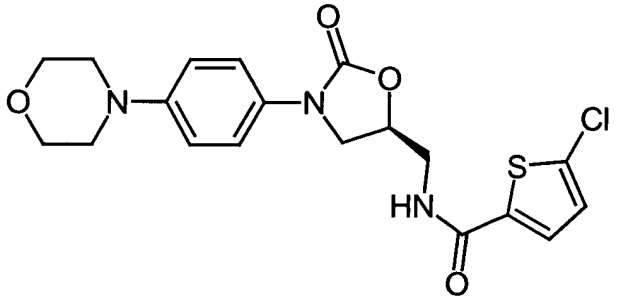
Example No.	Structure	M.p. [°C]	IC_{50} [µM]
126		229Z	0.013
127		159	0.0007
128		198	0.002
129		196	0.001
130		206	0.0033
130a		194	
131		195	0.85
132		206	0.12

Please replace the paragraph beginning on page 30, line 30 and ending on page 31, line3, with the following amended paragraph (note that the underlining in the first three lines is in the original text and does not indicate an addition to the text):

A 3- to 9-membered saturated or partially unsaturated, mono- or bicyclic, optionally benzo-fused heterocycle having up to 3 heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O represents a heterocycle which may contain one or more double bonds, which may be mono- or bicyclic, to which a benzene ring may be fused to two adjacent carbon ring atoms and which is attached via a carbon ring atom or a nitrogen ring atom. Examples which may be mentioned are: tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, piperidinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, piperazinyl, morpholinyl, morpholinyl N-oxide, thiomorpholinyl, azepinyl, and 1,4-diazepinyl ~~and cyclohexyl~~. Preference is given to piperidinyl, morpholinyl and pyrrolidinyl.

Please replace the paragraph beginning on page 56, line3 and ending on page 56, line 8, with the following amended paragraph:

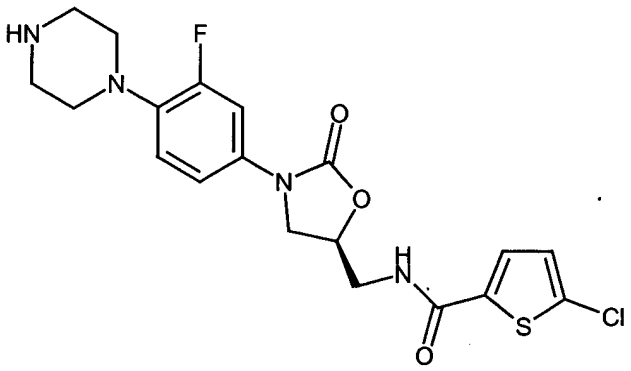
5-Chloro-N-{[(5S)-3-(4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



is obtained analogously from benzyl 4-morpholinophenylcarbamate via the (5S)-5-(aminomethyl)-3-(~~3-fluoro-~~ 4-morpholinophenyl)-1,3-oxazolidin-2-one intermediate (see Example 1).

Please replace the paragraph beginning on page 60, line 15 and ending on page 60, line 20, with the following revised paragraph:

5-Chloro-N-({(5S)-3-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



is obtained by reacting Example ~~12~~ 10 with trifluoroacetic acid in methylene chloride.
IC_{50} value = 140 nM;

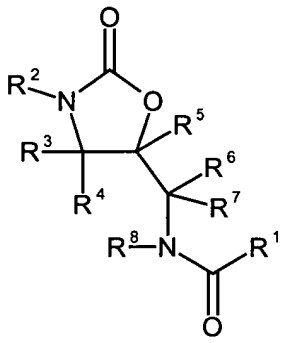
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Canceled)

2. (Currently amended) A compound of the general formula (I)



(I)

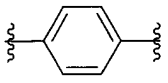
characterized in that

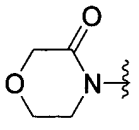
R^1 represents an optionally benzo-fused thiophene group which may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; cyano; nitro; amino; aminomethyl; $(C_1\text{-}C_8)$-alkyl which for its part may optionally be mono- or polysubstituted by halogen; $(C_3\text{-}C_7)$-cycloalkyl; $(C_1\text{-}C_8)$-alkoxy; imidazolinyl; $-C(=NH)NH_2$; carbamoyl; and mono- and di-$(C_1\text{-}C_4)$-alkyl-aminocarbonyl,

R^2 represents

D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; $(C_1\text{-}C_6)$-alkanoyl; $-OR^{30}$; $-NR^{30}R^{31}$, and $(C_1\text{-}C_6)$-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1\text{-}C_4)$-alkyl, or $C(O)R^{33}$,

where

R^{33} represents $(C_1\text{-}C_4)$-aminoalkyl, or $(C_1\text{-}C_8)$-alkyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents $(C_1\text{-}C_6)$-alkyl

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof

except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen .

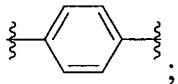
3. (Currently amended) The compound of the general formula (I) according to Claim 2, characterized in that

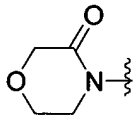
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen, amino, aminomethyl or (C_1-C_8)-alkyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; (C_1-C_6)-alkanoyl; -OR^{30}; -$NR^{30}R^{31}$, and (C_1-C_6)-alkyl,

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, or (C_1-C_4)-alkylaminocarbonyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and
each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof

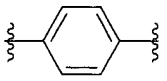
except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen .

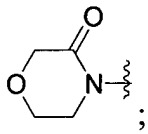
4. (Currently amended) The compound of the general formula (I) according to Claim 2, characterized in that

R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen or by (C_1-C_8)-alkyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents
D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; $(C_1\text{-}C_3)$-alkanoyl; -OH; $-NR^{30}R^{31}$; and $(C_1\text{-}C_4)$-alkyl;

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1\text{-}C_4)$-alkyl, or $(C_1\text{-}C_3)$-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and
each represents hydrogen or represents $(C_1\text{-}C_6)$-alkyl

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof

except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen .

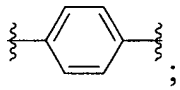
5. (Currently amended) The compound of the general formula (I) according to Claim 2, characterized in that

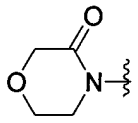
R^1 represents 2-thiophene which may optionally be substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents

D-M-A-,

where:

the radical "A" represents optionally substituted  ;

the radical "D" represents  ; and

the radical "M represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; cyano; $(C_1\text{-}C_3)$-alkanoyl; -OH; $-NR^{30}R^{31}$; and $(C_1\text{-}C_4)$-alkyl;

where:

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1\text{-}C_4)$-alkyl, or $(C_1\text{-}C_3)$-alkanoyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and

each represents hydrogen or represents $(C_1$-$C_4)$-alkyl

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof

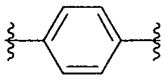
except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen .

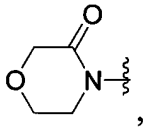
6. (Previously presented) The compound of the general formula (I) according to Claim 2, characterized in that

R^1 represents 2-thiophene which is substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents D-A-:

where:

the radical "A" represents  ;

the radical "D" represents  ,

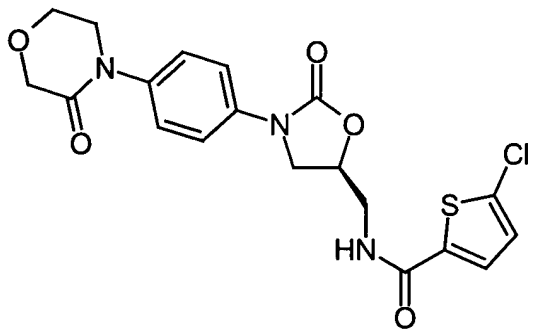
where

the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical selected from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

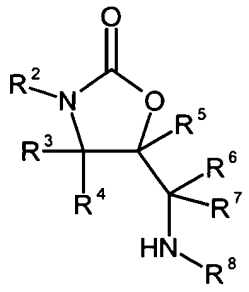
7. (Previously presented) The compound having the following formula



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

8. (Withdrawn-currently amended) Process for preparing the substituted oxazolidinone of claim 2, where
either according to a process alternative

[A] a compound of the general formula (II)

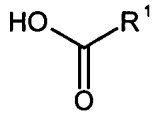


(II),

in which

the radicals R^2, R^3, R^4, R^5, R^6, ~~and~~ R^7, and R^8 are each as defined in Claim 2

is reacted with a carboxylic acid of the general formula (III)



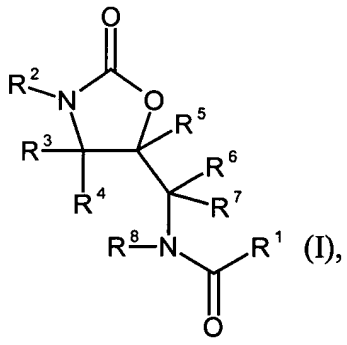
(III),

in which

the radical R^1 is as defined in Claim 2,

or else with a corresponding carbonyl halide, or else with a corresponding symmetric or mixed carboxylic anhydride of the carboxylic acid of the general formula (III) defined above

in an inert solvent, if appropriate in the presence of an activating or coupling agent and/or a base, to give a compound of the general formula (I)



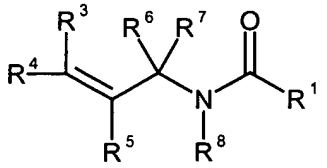
(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

or else according to a process alternative

[B] a compound of the general formula (IV)

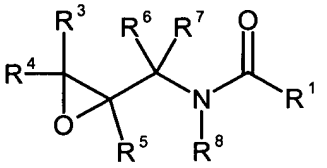


(IV),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the general formula (V)



(V),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

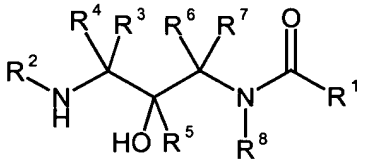
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the general formula (VI)

$$R^2\text{-}NH_2 \qquad \text{(VI)},$$

in which

the radical R^2 is as defined in Claim 2,

a compound of the general formula (VII)



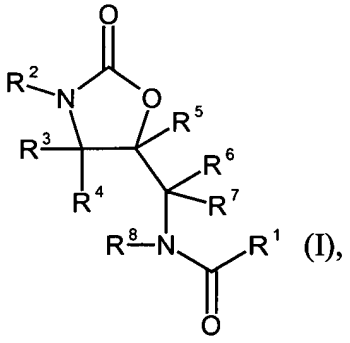
(VII),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

is initially prepared and,

subsequently, in an inert solvent in the presence of phosgene or a phosgene equivalent, cyclized to give ~~the~~ a compound of the general formula (I)



(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 2,

where - both for process alternative [A] and for process alternative [B] - in the case where R^2 contains a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical having one or more identical or different heteroatoms from the group consisting of N and S, an oxidation with a selective oxidizing agent to afford the corresponding sulphone, sulphoxide or N-oxide may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a cyano group in the molecule, an amidination of this cyano group by customary methods may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a BOC amino protective group in the molecule, removal of this BOC amino protective group by customary methods may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with a carboxylic acid, carboxylic anhydride, carbonyl chloride, isocyanate, sulphonyl chloride or alkyl halide to give the corresponding derivative may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with an amine to give the corresponding sulfonamide may follow.

9. (Previously presented) A pharmaceutical composition comprising at least one compound of the general formula (I) according to claim 2 and one or more pharmacologically acceptable auxiliaries or excipients.

10. (Withdrawn) A method for treatment of a thromboembolic disorder, comprising administering an effective amount of a compound of claim 2.

11. (Withdrawn) A method for treatment of disorders which are influenced positively by inhibition of factor Xa comprising administering an effective amount of a compound of claim 2.

12. (Withdrawn) A method for treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of a compound of claim 2.

13. (Withdrawn) A method for treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of a compound of claim 2.

14. (Withdrawn) A method for the inhibition of factor Xa comprising administering an effective amount of a compound of claim 2.

15. (Withdrawn) Method for preventing the coagulation of blood in vitro, comprising adding to said blood a compound of claim 2.

16. (Withdrawn) The method of claim 15 wherein said blood is banked blood or a biological sample containing factor Xa.

17. (Previously presented) The compound of claim 3 or 4 wherein R^1 represents an optionally substituted 2-thiophene group, and wherein said halogen substituent is chlorine or bromine, and said (C_1-C_8)-alkyl substituent is methyl, where the methyl radical for its part optionally may be mono- or polysubstituted by fluorine.

18. (Withdrawn) The process of claim 8 wherein in process alternative "A", the corresponding carbonyl halide of carboxylic acid (III) is a carbonyl chloride.

19. (Withdrawn) The process of claim 8 wherein in process alternative "B", the phosgene equivalent employed in the cyclization of compound (VII) is carbonyldiimidazole (CDI).

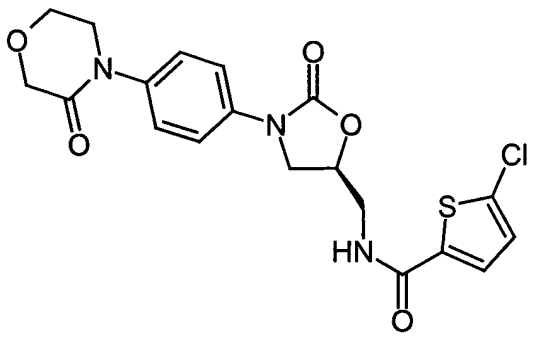
20. (Withdrawn) The method of claim 10 wherein the thromboembolic disorder is myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive disease, pulmonary embolism or deep venous thrombosis.

21. (New) The compound of claim 7 that is purified and isolated.

22. (New) The compound of claim 7 that is substantially free of its enantiomer.

23. (New) A racemic mixture of the compound of claim 7 and its enantiomer.

24. (New) A compound having the following formula:



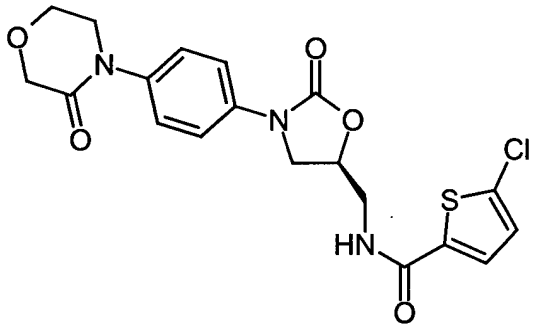
25. (New) A pharmaceutical composition comprising the compound of claim 7 and a pharmacologically acceptable auxiliary or excipient.

26. (New) A pharmaceutical composition comprising the compound of claim 21 and a pharmacologically acceptable auxiliary or excipient.

27. (New) A pharmaceutical composition comprising the compound of claim 22 and a pharmacologically acceptable auxiliary or excipient.

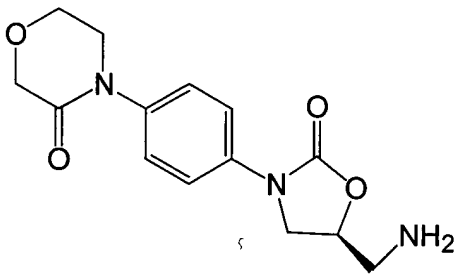
28. (New) A pharmaceutical composition comprising the compound of claim 24 and a pharmacologically acceptable auxiliary or excipient.

29. (New) The process of claim 8 wherein the substituted oxazolidinone that is prepared is



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

30. (New) A process for the preparation of the compound of claim 7 comprising reacting a compound of the following formula



with 5-chlorothiophene-2-carbonyl chloride in an inert solvent to prepare the compound of claim 7.

31. (New) The process of claim 30 wherein the inert solvent comprises pyridine.

32. (New) A method for the prevention or treatment of thromboembolic disorders comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

33. (New) A method for the prevention or treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

34. (New) A method for the prevention or treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

35. (New) A method for the prevention or treatment of myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

36. (New) A method for the inhibition of factor Xa comprising administering an effective amount of the composition of claim 25 to a patient in need thereof.

37. (New) A method for preventing the coagulation of blood in vitro comprising adding to said blood an effective amount of the compound of claim 7.

38. (New) The method of claim 37 wherein said blood is banked blood or a biological sample containing factor Xa.

39. (New) A method for the prevention or treatment of thromboembolic disorders comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

40. (New) A method for the prevention or treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

41. (New) A method for the prevention or treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

42. (New) A method for the prevention or treatment of myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

43. (New) A method for the inhibition of factor Xa comprising administering an effective amount of the composition of claim 26 to a patient in need thereof.

44. (New) A method for preventing the coagulation of blood in vitro comprising adding to said blood an effective amount of the compound of claim 21.

45. (New) The method of claim 44 wherein said blood is banked blood or a biological sample containing factor Xa.

46. (New) A method for the prevention or treatment of thromboembolic disorders comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

47. (New) A method for the prevention or treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

48. (New) A method for the prevention or treatment of atherosclerosis, arthritis, Alzheimer's disease or cancer comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

49. (New) A method for the prevention or treatment of myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive diseases, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

50. (New) A method for the inhibition of factor Xa comprising administering an effective amount of the composition of claim 27 to a patient in need thereof.

51. (New) A method for preventing the coagulation of blood in vitro comprising adding to said blood an effective amount of the compound of claim 22.

52. (New) The method of claim 51 wherein said blood is banked blood or a biological sample containing factor Xa.

Remarks

Claims 2-52 are pending in this application. Claim 1 has been canceled previously. Claims 2-5 and 8 have been amended. Claims 8, 10-16, 18-20 have been withdrawn. New claims 21-52 have been added. No new matter has been added.

Rejection under §112, first paragraph, on written description grounds.

The examiner maintains that the deletion of the exclusionary language "except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen" constitutes addition of new matter, as this subject matter had originally been excluded. Applicants respectfully traverse, but to advance prosecution of the application, have re-introduced this exclusionary language into the claims from which it was deleted. The examiner has stated that deleting the new subject matter (by re-introducing the exclusionary clause) should overcome the rejection.

Corrections

Process claim 8 has now been corrected to include R^8 in the definition of the radicals relating to structure (II). This group R^8 was omitted from the English translation of the application through a translation error. It is shown on page 37, line 1 of the published PCT application, WO 01/047919. Page 31 of the specification has been amended accordingly.

The revisions made to the text on pages 30, 56, 60, and 94 are to correct obvious errors. They are deemed not to constitute introduction of new matter.

New claims

New claims 21-52 are being introduced to claim the compound of example 44, pharmaceutical compositions containing it, methods of making it, and methods of using it more specifically. Support in the specification for new claims 21-52 is to be found at the locations listed below:

Claim 21: in example 44 at p. 69, line 3 to p. 71, line 17.

Claim 22: at p. 26, line 29 to p. 27, line 2 and example 44 at p. 69, line 3 to p. 71, line 17.

Claim 23: at p. 27, lines 1-2 and example 97 at p. 89, lines 1-5.

Claim 24: at example 44 at p. 69, line 3 to p. 71, line 17.

Claim 25: at p. 39, lines 26-30.

Claim 26: at p. 39, lines 26-30.

Claim 27: at p. 39, lines 26-30.

Claim 28: at p. 39, lines 26-30.

Claim 29: at p. 14, line 29 to p. 15, line 3 and at example 44 at p. 69, line 3 to p. 71, line 17.

Claim 30: at example 44 at p. 69, line 3 to p. 71, line 17 and original claim 8.

Claim 31: at p. 71, lines 1-2.

Claim 32: at p. 38, lines 17-21.

Claim 33: at p. 38, lines 27-30.

Claim 34: at p. 38, lines 32-36.

Claim 35: at p. 38, lines 17-25.

Claim 36: at p. 39, lines 2-6.

Claim 37: at p. 39, lines 16-19.

Claim 38: at p. 39, lines 16-19.

Claim 39: at p. 38, lines 17-21.

Claim 40: at p. 38, lines 27-30.

Claim 41: at p. 38, lines 32-36.

Claim 42: at p. 38, lines 17-25.

Claim 43: at p. 39, lines 2-6.

Claim 44: at p. 39, lines 16-19.

Claim 45: at p. 39, lines 16-19.

Claim 46: at p. 38, lines 17-21.

Claim 47: at p. 38, lines 27-30.

Claim 48: at p. 38, lines 32-36.

Claim 49: at p. 38, lines 17-25.

Claim 50: at p. 39, lines 2-6.

Claim 51: at p. 39, lines 16-19.

Claim 52: at p. 39, lines 16-19.

Method of treatment claims

The examiner's attention is drawn to the specification at pages 43-46, wherein applicants set forth standard *in vivo* models b.1), b.2), and b.3) for the prevention of thrombus formation. In particular, see the results from the b.1) arteriovenous shunt model (rat) shown in Table 1 on page 45. In Table 1, the ED_{50} headings stand for "Effective Dose to reduce the thrombus size by 50% relative to the controls" , and the data show that the test compounds were effective to reduce the size of the thrombus relative to controls, thus demonstrating the prophylactic effect of the compounds of the invention.

In view of the above amendments, the rejection under §112 is deemed to be overcome. Reconsideration and further examination are requested.

Respectfully submitted,

William F. Gray

Reg. No.: 31018
Phone: (203) 812-2712
Date: 19 Oct. 04

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional) **Le A 34 122**

In re Application of **Straub, et al.**

Application Number **10/181, 051** Filed **June 24, 2002**

For **Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation.**

Art Unit **1626** Examiner **Anderson, Rebecca L.**

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $ _____
- ☐ Two months (37 CFR 1.17(a)(2)) $ _____
- ☒ Three months (37 CFR 1.17(a)(3)) $ 980.00
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Typed or printed name: William F. Gray

Signature: William F. Gray

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $_____.

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NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

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Date

William F. Gray
Signature

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Telephone Number

William F. Gray
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of **1** forms are submitted.

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Docket No.: LeA 34 122
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Alexander Straub et al.

Application No.: 10/181,051 Confirmation No.: 5850

Filed: June 24, 2002 Art Unit: 1626

For: SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION Examiner: R. L. Anderson

INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed more than three months after the U.S. filing date, OR more than three months after the date of entry of the national stage of a PCT application, AND after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of a Final Office Action or Notice of Allowance (37 CFR 1.97(c)).

A copy of each reference on the PTO/SB/08 is attached.

References WO 99/03846, WO 99/37641, and WO 99/40094, are in the German language, however, have English language abstracts that describe their relevancy to the present invention. Reference E. Pfiel and U. Harder, Angew. Chem., vol. 79, no. 4, p. 188 (1967) is also in the German language. This reference discloses synthetic methods for preparing oxylactams. The present specification refers to the Pfiel and Harder article for preparation of morpholinones on pages 47 and 54. German language publication Reppe et al., Justis Liebigs Ann. Chem., vol. 596, p. 209 (1955) provides an analogous synthesis for the preparation of 1-(4-aminophenyl)pyrrolidin-2-one as discussed on page 62 of the instant specification. The same Reppe et al. article at page 204 provides a synthesis for N-p-aminophenyl-pyrrolidinone as discussed on page 78 of the instant specification.

Applicants would like to make clear for the Examiner the relationship between two previously cited references, AU 199919647 and WO 99/31092 (Dorsch et al.). WO 99/31092 was cited in the International Search Report, a copy of which was received by the U.S. Receiving Office. Because this reference is in the German language, Applicants cited the English language equivalent, AU 199919647, in their Information Disclosure Statement ("IDS") filed June 24, 2002. The Examiner then cited WO 99/31092 on October 10, 2003 in a Form 892 accompanying the restriction requirement. Subsequently, Applicants' IDS listing AU 199919647 was initialed by the Examiner on April 16, 2004. Thus, the Examiner has considered both the PCT publication and its English-language equivalent. Applicants wanted to point out clearly the relationship between the two references so that the Examiner would understand that the relevance of the AU 199919647 patent is similar if not the same as WO 99/31092, which was cited in the International Search Report and discussed in the International Preliminary Examination Report.

The instant specification refers to WO 99/31092 as disclosing benzamidine-containing oxazolidinones as synthetic intermediates in the synthesis of factor Xa inhibitors (p. 26, ll. 25-27). WO 99/31092 discloses such compounds as active factor Xa inhibitors also.

Please charge the $180.00 filing fee for this paper to Deposit Account No. 13-3372. The Commissioner is hereby authorized to charge any fees that may have been overlooked but that are required to Deposit Account 13-3372. Additionally, please credit any overpayment to the same account.

Dated: 19 October 2004

Respectfully submitted,

By William F. Gray

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Sheet 1 of 3

Complete if Known	
Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	LeA 34 122

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-2,811,555	10-29-1957	Larive et al.	
	AB	US-3,279,880	10-18-1966	Straley et al.	
	AC	US-4,500,519	02-19-1985	Lormeau et al.	
	AD	US-4,705,779	11-10-1987	Madi-Szabo et al.	
	AE	US-5,254,577	10-19-1993	Carlson et al.	
	AF	US-5,349,045	09-20-1994	Ying Jiang	
	AG	US-5,532,255	07-02-1996	Raddatz et al.	
	AH	US-5,688,792	11-18-1997	Barbachyn et al.	
	AI	US-5,792,765	08-11-1998	Riedl et al.	
	AJ	US-5,827,857	10-27-1998	Riedl et al.	
	AK	US-5,910,504	06-08-1999	Hutchinson et al.	
	AL	US-5,922,708	07-13-1999	Riedl et al.	
	AM	US-5,972,947	10-26-1999	Tsaklakidis et al.	
	AN	US-6,069,160	05-30-2000	Stolle et al.	
	AO	US-6,251,869	06-26-2001	Michael J. Bohanon	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	BA	EP-0 127 902	12-12-1984	E.I. Du Pont de Nemours and Co.		
	BB	EP-0 316 594	05-24-1989	The Du Pont Merck Pharmaceutical Co.		
	BC	EP-0 352 781	01-31-1990	E.I. Du Pont De Nemours and Co.		
	BD	WO-93/09103	05-13-1993	The Upjohn Company		
	BE	WO-93/23384	11-25-1993	The Upjohn Company		
	BF	EP-0 623 615	11-09-1994	Merck Patent GmbH		*
	BG	EP-0 738 726	10-23-1996	Bayer AG		*1
	BH	WO-97/03072	01-30-1997	Boehringer Mannheim GmbH		*2
	BI	WO-97/09328	03-13-1997	Pharmacia & Upjohn Company		
	BJ	WO-97/10223	03-20-1997	Pharmacia & Upjohn Company		
	BK	EP-0 785 200	07-23-1997	Bayer AG		*3
	BL	DE-196 04 223	08-07-1997	Bayer AG		*4
	BM	WO-98/01446	01-15-1998	Zeneca Limited		
	BN	WO-98/54161	12-03-1998	Pharmacia & Upjohn Company		
	BO	WO-99/02525	01-21-1999	Pharmacia & Upjohn Company		
	BP	WO-99/03846	01-28-1999	Bayer Aktiengesellschaft		
	BQ	WO-99/24428	05-20-1999	Pharmacia & Upjohn Company		

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Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	LeA 34 122

	BR	WO-99/29688	06-17-1999	Pharmacia & Upjohn Company		
	BS	WO-99/37630	07-29-1999	Versicor, Inc.		
	BT	WO-99/37641	07-29-1999	Bayer Aktiengesellschaft		
	BU	WO-99/40094	08-12-1999	Bayer Aktiengesellschaft		
	BV	WO-99/59616	11-25-1999	Pharmacia & Upjohn Company		
	BW	WO-01/44212	06-21-2001	Pharmacia & Upjohn Company		
	BX	WO-01/46185	06-28-2001	Pharmacia & Upjohn Company		
	BY	WO-02/064575	08-22-2002	Bayer Aktiengesellschaft		*5
	BZ	CA-2 437 587	08-22-2002	Bayer Aktiengesellschaft		
	BA1	WO-03/000256	01-03-2003	Bayer Aktiengesellschaft		*6
	BB1	CA-2 451 258	01-03-2003	Bayer HealthCare AG		
	BC1	WO-03/035133	05-01-2003	Bayer Aktiengesellschaft		*7
	BD1	CA-2 464 290	05-01-2003	Bayer HealthCare AG		
	BE1	WO-01/42242	06-14-2001	Ortho-McNeil Pharmaceuticals Inc.		

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	ADAMS et al., Sulfanilamide Derivatives, J. Am. Chem. Soc. 1939, vol. 61, pp. 2342-2349	
	CB	AEBISCHER et al., Synthesis of N-Arylrolipram Derivatives – Potent and Selective Phosphodiesterase-IV Inhibitors – By Copper Catalyzed Lactam-Aryl Halide Coupling, Hetercycles. 1998, vol. 48, pp. 2225-2229	
	CC	ARTICO et al., Research on Compounds with Antiblastic Activity, Farmaco Ed. Sci. 1969, vol. 24, pp. 179-190	
	CD	BARBACHYN et al., Identification of a Novel Oxazolidinone (U-100480) with Potent Antimycobacterial Activity, J. Med. Chem. 1996, vol. 39, pp. 680-685	
	CE	BARTOLI et al., Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Reaction by Phenoxides as Nucleophiles in Dimethyl Sulfoxide, J. Org. Chem. 1975, vol. 40, pp. 872-874	
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Examiner Signature		Date Considered	

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Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	R. L. Anderson
Attorney Docket Number	LeA 34 122

	CJ	DANKWARDT et al., Nonpeptide Bradykinin Antagonist Analogs Based on a Model of a Sterling-Winthrop Nonpeptide Bradykinin Antagonist Overlapped with Cyclic Hexapeptide Bradykinin Antagonist Peptides, Bioorg. Med. Chem. Lett. 1997, vol. 7, no. 14, pp. 1921-1926	
	CK	DOSTERT et al., 5-Hydroxymethyl-2-oxazolidinones, Chem. Abstr. 1979, vol. 90, pp. 186926	
	CL	GREGORY et al., Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidines. 1. The "B" Group, J. Med. Chem. 1989, vol. 32, pp. 1673-1681	
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	CO	KHANNA et al., 1,2-Diarylpyrroles as Potent and Selective Inhibitors of Cyclooxygenase-2, J. Med. Chem. 1997, vol. 40, pp. 1619-1633	
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	CR	PFEIL et al., Synthese von Oxalactamen aus Aziridinium-tetrafluoroborat und Hydroxysäureestern, Agnew. Chem. 1967, vol. 79, p. 188	
	CS	RENGER, Direct N-Arylation of Amides : An Improvement of the Goldberg-Reaction, Synthesis, September 1985, pp. 856-860	
	CT	REPPE et al., Justus Liebigs Ann. Chem. 1955, vol. 596, pp. 204	
	CU	REPPE et al., Justus Liebigs Ann. Chem. 1955, vol. 596, pp. 209	
	CV	RIEDL et al., Recent Developments with Oxazolidinone Antiboiotics, Exp. Opin. Ther. Patents 1999, vol. 9 (5), pp. 625-633	
	CW	SHAKESPEARE, Palladium-Catalyzed Coupling of Lactams with Bromobenzenes, Tetrahedron Lett. 1999, vol. 40, pp. 2035-2038	
	CX	SNYDER et al., Imidazo[4,5-f]quinolines III : Antibacterial 7-Methyl-9-(substituted Arylamino)imidazo[4,5-f]quinolines, J. Pharm. Sci. 1977, vol. 66, pp. 1204-1206	
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	CA1	TUCKER et al., Piperazinyl Oxazolidinone Antibacterial Agents Containing a Pyridine, Diazene, or Triazene Heteroaromatic Ring, J. Med. Chem. 1998, vol. 41, pp. 3727-3735	
	CB1	ZIEGLER et al., Synthesis of Some Novel 7-Substituted Quinolonecarboxylic Acids *via* Nitroso and Nitrone Cycloadditions, J. Hetercycl. Chem., May-June 1988, vol. 25 (2), pp. 719-723	

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* English language equivalent US 5532255 attached
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*2 English language equivalent US 5972947 attached
*3 English language equivalent US 5827857 attached
*4 English language equivalent US 5792765 attached
*5 English language equivalent CA 2437587 attached
*6 English language equivalent CA 2451258 attached
*7 English language equivalent CA 2464290 attached

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European Patent Office
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(11) Publication number: **0 127 902**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 84106400.9

(22) Date of filing: 05.06.84

(51) Int. Cl.³: C 07 D 263/20
C 07 D 263/24, A 61 K 31/42

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14.02.84 US 578332

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(84) Designated Contracting States:
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Patentanwälte Von Kreisler-Schönwald-Fues-Keller
Selting-Werner Deichmannhaus am Hauptbahnhof
D-5000 Köln 1(DE)

(54) Aminomethyl oxooxazolidinyl benzene derivatives useful as antibacterial agents.

(57) Novel aminomethyl oxooxazolidinyl benzene derivatives, including the sulfides, sulfoxides, sulfones and sulfonamides, such as (l)-N-[3-[4- (methylsulfonyl) phenyl] -2-oxooxazolidin -5- ylmethyl] carbamic acid, methyl ester possess useful antibacterial activity.

EP 0 127 902 A2

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0127902

Title BP-6244-A

AMINOMETHYL OXOOXAZOLIDINYL BENZENE DERIVATIVES USEFUL AS ANTIBACTERIAL AGENTS

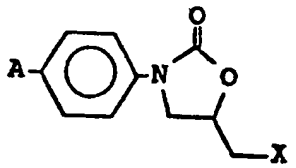
Technical Field

This invention relates to novel aminomethyl oxooxazolidinyl benzene derivatives, including the sulfides, sulfoxides, sulfones and sulfonamides, to pharmaceutical compositions containing them, and to methods of using them to alleviate bacterial infections.

Background of the Invention

At the present time, no existing antibacterial product provides all features deemed advantageous. There is continual development of resistance by bacterial strains. A reduction of allergic reactions and of irritation at the site of injection, and greater biological half-life (i.e., longer *in vivo* activity) are currently desirable features for antibacterial products.

U.S. Patent 4,128,654 issued to Fugitt et al. on December 5, 1978, discloses, among others, compounds of the formula:



where

A = $RS(O)_n$;

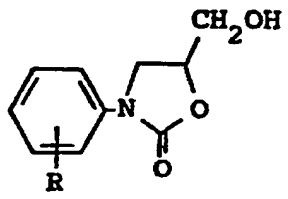
X = Cl, Br or F;

R = C_1-C_3 alkyl; and

n = 0, 1 or 2.

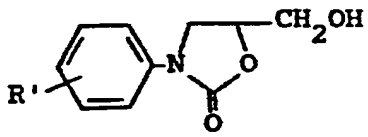
The compounds are disclosed as being useful in controlling fungal and bacterial diseases of plants.

U.S. Reissue Patent 29,607 reissued April 11, 1978 discloses derivatives of 5-hydroxymethyl-3-substituted-2-oxazolidinones of the formula:



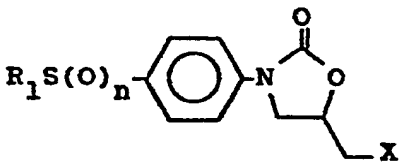
where R is H, F, CH_3, or CF_3. Such compounds are described as having antidepressive, tranquilizing, sedative, and antiinflammatory properties.

U.S. Patent 4,250,318, which was issued on February 10, 1981, discloses antidepressant compounds of the formula:



where R' can be, among others, a <u>para</u>-<u>n</u>-pentylamino group, an SR_1 group where R_1 is C_1-C_5 alkyl, or an acetylmethylthio group.

U.S. Patent 4,340,606, issued to Fugitt et al. on July 20, 1982, discloses antibacterial agents of the general formula:

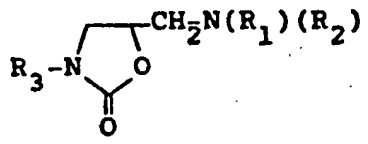


where

R_1 = CH_3, C_2H_5, CF_2H, CF_3 or CF_2CF_2H; and

X = OR_2 (R_2 = H or various acyl moieties).

U.S. Patent 3,687,965, issued to Fauran et al. on August 29, 1972, discloses compounds of the formula:



where

$-N(R_1)(R_2)$ represents either dialkylamino radical in which the alkyl portions have one to five carbon atoms, or a heterocyclic amino radical which may be substituted by an alkyl radical having one to five carbon atoms or by a pyrrolidinocarbonylmethyl radical, and

R_3 represents a phenyl radical which may be substituted by one or more of the following radicals:

an alkoxy radical having one to five carbon atoms;

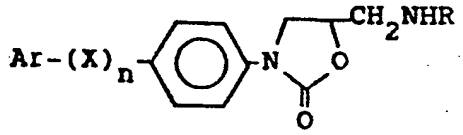
a halogen atom;

a trifluoromethyl radical, or

a carboxyl radical which may be esterified.

The patent states that these compounds possess hypotensive, vasodilatatory, spasmolytic, sedative, myorelaxant, analgesic and antiinflammatory properties. There is no mention of antibacterial properties.

Belgian Patent 892,270, published August 25, 1982, discloses monoamine oxidase inhibitors of the formula



where

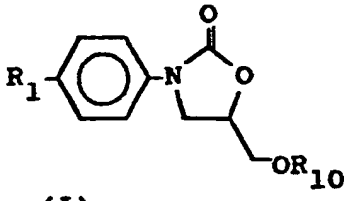
R is H, C_1-C_4 alkyl or propargyl;

Ar is phenyl, optionally substituted by halo or trifluoromethyl;

n is 0 or 1; and

X is $-CH_2CH_2-$, $-CH=CH-$, an acetylene group or $-CH_2O-$.

Pending U.S. Patent Appln. Serial No. 567,411, filed January 5, 1984, a continuation-in-part of U.S. Patent Application 417,569 filed September 15, 1982 by W. A. Gregory discloses antibacterial agents of the formula



(I)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

R_1 is R_2SO_2, $R_3R_4NC(=O)$, or $R_3C(=NR_5)$;

R_2 is $-NR_3R_4$, $-N(OR_3)R_4$, $-N_3$, $-NHNH_2$, $-NX_2$, $-NR_6X$, $-NXZ$, $-NHCR_7(=O)$, $-NZCR_7(=O)$ or $-N=S(O)_nR_8R_9$;

R_3 and R_4 are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

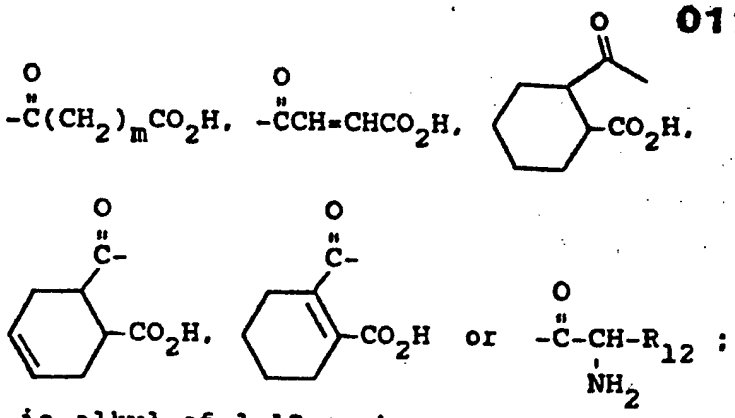
R_5 is NR_3R_4 or OR_3;

R_6 is alkyl of 1-4 carbons;

R_7 is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

R_8 and R_9 are independently alkyl of 1-4 carbons or, taken together are $-(CH_2)_p-$;

R_{10} is H, alkyl of 1-3 carbons, $-CR_{11}(=O)$.



R_{11} is alkyl of 1-12 carbons;

R_{12} is H, alkyl of 1-5 carbons, CH_2OH or CH_2SH;

X is Cl, Br or I;

Z is a physiologically acceptable cation;

m is 2 or 3;

n is 0 or 1; and

p is 3, 4 or 5;

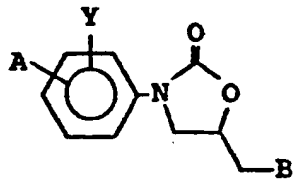
and when R_{10} is alkyl of 1-3 carbons, R_1 can also be $CH_3S(O)_q$ where q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

None of the cited references nor any known references suggest the novel antibacterial compounds of this invention.

Summary of the Invention

The novel compounds of the instant invention possess useful antibacterial activity in both *in vitro* and *in vivo* tests. Specifically, one aspect of this invention relates to compounds having the formula:



(I)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

A is $-NO_2$, $-S(O)_nR_1$, $-S(O)_2-N=S(O)_pR_2R_3$, $-SH$, $-S\overset{O}{\overset{\|}{C}}R_4$, $-COR_5$, $-CONR_5R_6$, $-\overset{NR_7}{\overset{\|}{C}}-R_5$, $-CN$, $-OR_5$, $-NR_5R_6$, $-\overset{R_5}{\overset{|}{N}}COR_4$, $-\overset{R_5}{\overset{|}{N}}S(O)_nR_4$, alkyl of 1 to 5 carbons, optionally substituted with one or more halogen atoms, alkenyl of 2-5 carbons or cycloalkyl of 3-8 carbons;

R_1 is C_1-C_4 alkyl, optionally substituted with one or more halogen atoms, CN, NR_5R_6 or CO_2R_8; C_2-C_4 alkenyl; $-NR_9R_{10}$; $-N_3$; $-NH\overset{O}{\overset{\|}{C}}R_4$; $-NZ\overset{O}{\overset{\|}{C}}R_4$; $-NX_2$-; NR_9X $-^{-}NXZ^{+}$;

R_2 and R_3 are independently C_1-C_2 alkyl or, taken together, are $-(CH_2)_q-$;

R_4 is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

R_5 and R_6 are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

R_7 is $-NR_5R_6$ or $-OR_5$;

R_8 is H or alkyl of 1-4 carbons;

R_9 is H, C_1-C_4 alkyl or C_3-C_8 cycloalkyl;

R_{10} is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_3-C_4 cycloalkyl, $-OR_8$ or $-NR_{11}R_{11a}$

R_{11} and R_{11a} are independently H or C_1-C_4 alkyl, or taken together, are $-(CH_2)_r-$;

X is Cl, Br or I;

Y is H, F, Cl, Br or NO_2, or A and Y taken together can be $-O-(CH_2)_tO-$;

Z is a physiologically acceptable cation;

n is 0, 1 or 2;

p is 0 or 1;

q is 3, 4 or 5;

r is 4 or 5;

t is 1, 2 or 3;

B is $-NH_2$, $-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-R_{13}$, $-\overset{R_{12}}{\underset{|}{N}}-S(O)_uR_{14}$ or N_3;

R_{12} is H, C_1-C_{10} alkyl or C_3-C_8 cycloalkyl;

R_{13} is H; C_1-C_4 alkyl optionally substituted with one or more halogen atoms; C_2-C_4 alkenyl; C_3-C_4 cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and O-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$;

R_{14} is C_1-C_4 alkyl, optionally substituted with one or more halogen atoms;

R_{15} is H or C_1-C_4 alkyl, optionally substituted with one or more halogen atoms;

R_{16} and R_{17} are independently C_1-C_4 alkyl or, taken together, are $-(CH_2)_m-$;

R_{18} is C_1-C_4 alkyl or C_7-C_{11} aralkyl;

R_{19} and R_{20} are independently H or C_1-C_4 alkyl;

R_{21} and R_{22} are independently H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl or, taken together, are $-(CH_2)_s$;

u is 1 or 2;

v is 0, 1 or 2;

m is 2 or 3; and

s is 2, 3, 4 or 5;

or a pharmaceutically suitable salt thereof;

provided that:

1) when A is CH_3S-, then B is not $-\overset{CH_3}{\overset{|}{N}}-CO_2CH_3$;

2) when A is CH_3SO_2-, then B is not $-\overset{CH_3}{\overset{|}{N}}-COCH_3$ or $-\overset{CH_3}{\overset{|}{N}}-COCF_3$;

3) when A is H_2NSO_2- and B is $-\overset{R_{12}}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}R_{13}$, then R_{12} is H;

4) when A is -CN, B is not $-N_3$;

5) when A is $(CH_3)_2CH$, B is not $NHCOCH_2Cl$.

Preferred, for their high antibacterial activity or ease of synthesis, or both, are compounds of formula I where:

(1) Y is H;

A, substituted in the para position, is $-S(O)_nR_1$, NO_2, $-\overset{O}{\overset{\|}{C}}-CH_3$, or $-CH(CH_3)_2$;

R_1 is C_1-C_2 alkyl optionally substituted with one or more halogen atoms or NR_5R_6;

R_5 is H or CH_3;

R_6 is H or CH_3;

n is 0, 1 or 2 when R_1 is alkyl or substituted alkyl; n is 2 when R_1 is NR_5R_6;

or

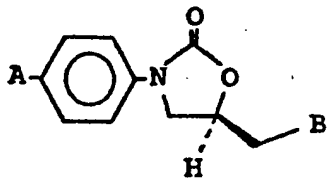
(2) B is $-NH-\overset{O}{\overset{\|}{C}}-R_{13}$;

R_{13} is H, CH_3, OR_{18}, $CHCl_2$, CH_2Cl or CH_2OR_{15};

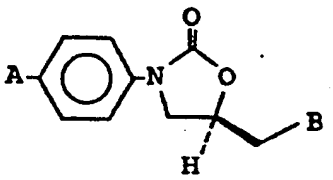
R_{15} is H or C_1-C_4 alkyl; and

R_{18} is C_1-C_4 alkyl.

Preferred because of high antibacterial activity are compounds of formula I having the absolute configuration depicted:



More preferred because of high antibacterial activity are compounds of formula I having the absolute configuration depicted:



and where A is $S(O)CH_3$, SCH_3, $S(O)_2CH_3$, SO_2NH_2, $COCH_3$ or $CH(CH_3)_2$; and

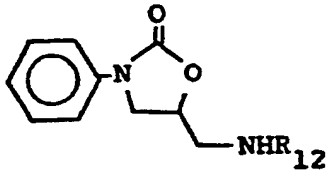
where B is $-NHCOCH_3$, $-NHCO_2CH_3$ or $-NHCOCHCl_2$.

Specifically preferred for their high antibacterial activity are the following compounds:

- (ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester;
- (ℓ)-N-[3-[4-(methylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester;
- (ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]formamide;

- (ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(methylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(aminosulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(methylsulfinyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-2,2-dichloro-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-isopropylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide; and
- (ℓ)-N-[3-(4-acetylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

Another aspect of this invention relates to novel intermediates having the formula:

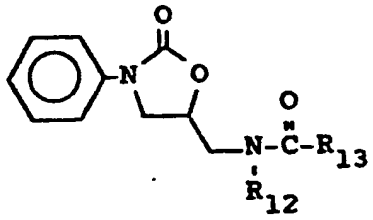


(Ia)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

R_{12} is H, C_1-C_{10} alkyl or C_3-C_8 cycloalkyl.

Another aspect of this invention relates to novel intermediates having the formula:



(Ib)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

R_{12} is H, C_1-C_{10} alkyl or C_3-C_8 cycloalkyl;

R_{13} is H; C_1-C_4 alkyl optionally substituted with one or more halogen atoms; C_2-C_4 alkenyl; C_3-C_4 cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $-\overset{O}{\overset{\|}{C}}R_{15}$; $-OR_{18}$; $-SR_{14}$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$;

R_{14} is C_1-C_4 alkyl, optionally substituted with one or more halogen atoms;

R_{15} is H or C_1-C_4 alkyl, optionally substituted with one or more halogen atoms;

R_{16} and R_{17} are independently C_1-C_4 alkyl or, taken together, are $-(CH_2)_m-$;

R_{18} is C_1-C_4 alkyl or C_7-C_{11} aralkyl;

R_{19} and R_{20} are independently H or C_1-C_4 alkyl;

R_{21} and R_{22} are independently H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;

m is 2 or 3; and

v is 0, 1 or 2; and

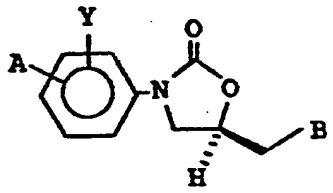
s is 2, 3, 4 or 5.

Another aspect of this invention relates to a pharmaceutical composition comprising a suitable pharmaceutical carrier and an antibacterially effective amount of a compound of formula I. Yet another aspect of the invention relates to a method for alleviating bacterial infection in a mammal which comprises administering to the mammal an antibacterially effective amount of a compound of formula I.

Detailed Description

The compounds of formulae I, Ia, and Ib contain at least one chiral center, and as such exist as two individual isomers or as a mixture of both. This invention relates to the levorotatory isomer (ℓ), as well as mixtures containing both the d and the ℓ isomers. An additional chiral center is present when A is $R_1S(O)_n$ and n is 1 and this invention relates to both of the possible isomers at that center. Additional chiral centers may be present in the group B and this invention relates to all possible stereoisomers in the group B.

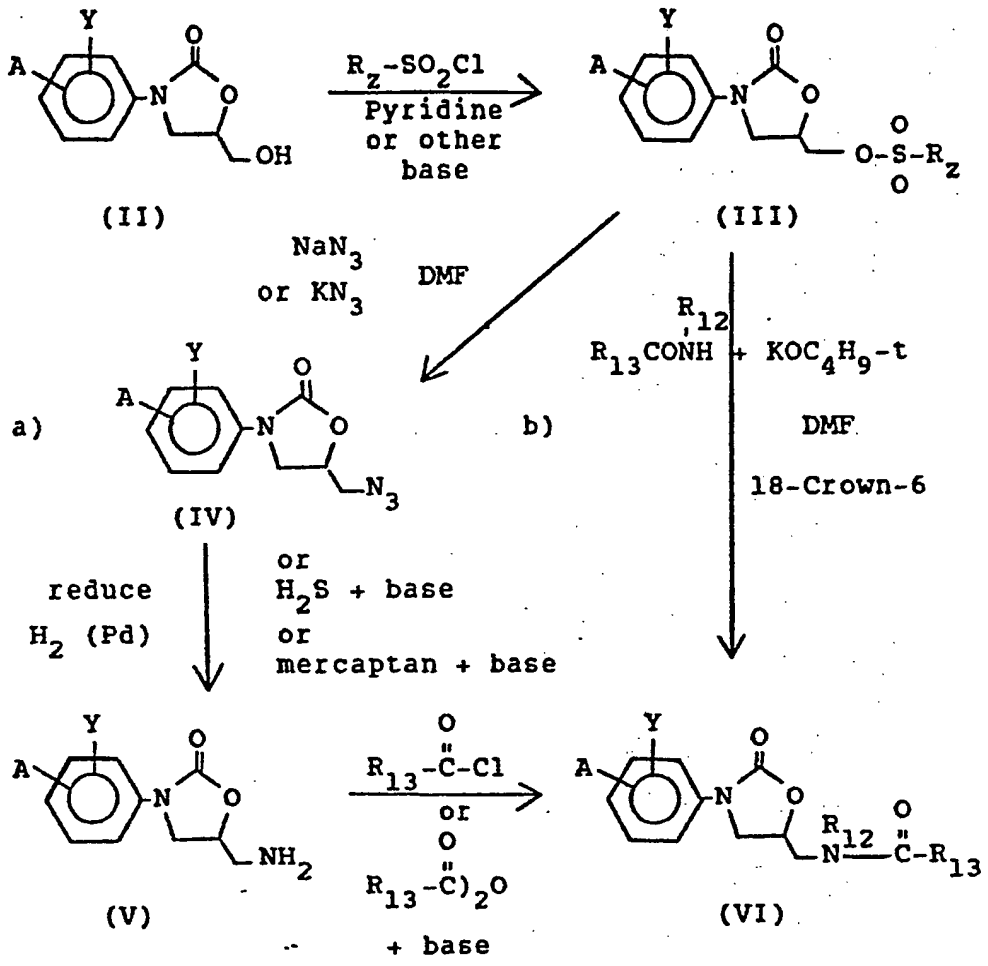
For the purposes of this invention, the ℓ-isomer of compounds of formulae I, Ia, and Ib is intended to mean compounds of the configuration depicted:



Synthesis

Compounds of Formula (I) can be prepared as follows:

Scheme 1:



Where R_z may be 4-tolyl, phenyl, 4-chlorophenyl, C_1-C_4 alkyl or haloalkyl, such as trifluoromethyl.

When the synthetic path a) is used, the group A may be -H or any of the groups previously shown except where R_1 is $-N_3$, $-NX_2$, $-NR_9X$, $-\bar{N}XZ^+$. When the synthetic path b) is used the group A may be -H or any of the groups previously shown except when A is $R_1S(O)_n$ and R_1 is NR_9R_{10}, R_9, R_{10}, R_{11}, and R_{11a} cannot be H.

Compounds of Formula (II) may be converted to sulfonate esters (III) by reaction with the appropriate sulfonyl halide or sulfonic anhydride in a solvent plus a base or in a basic organic solvent such as pyridine. It is desirable when the A group has a sulfonamide hydrogen to use pyridine or other mildly basic solvents such as the picolines or collidines. As solvents, 1,2-dimethoxyethane, dioxane, bis-(2-methoxyethyl)ether, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), acetonitrile, or tetramethylenesulfone may be used. As a base, triethylamine, N-methylmorpholine, tributylamine or one of the heterocyclic bases can be used.

Compounds (III) may be reacted with sodium, potassium, lithium, cesium or rubidium azides in a dipolar aprotic solvent such as DMF, N-methylpyrrolidone, DMAc, sulfolane, dimethylsulfoxide, tetramethylurea, hexamethylphosphoramide (HMPA), etc. along with the appropriate catalyst such as 18-crown-6 for sodium and potassium azide and 12-crown-4 for lithium azide. This reaction is carried out from about 60° to 125°C, with the preferred temperatures being 70° to 90°C. The products are azides of structure (IV).

The azides (IV) may be reduced by any of several methods, including hydrogenation over palladium-on-charcoal. It is also possible to reduce the azides by treating with 1,3-propanedithiol and a base such as triethylamine. Azides may also be reduced to amines by hydrogen sulfide and by trivalent phosphorous compounds such as trimethylphosphine and trimethylphosphite, and by mercaptans such as mercaptoacetic acid. Reduction with hydrogen can best be used where A is hydrogen, but it will work where A is a hexavalent sulfur containing group. The reduction is carried out using a solvent such as ethanol, methanol, 1,2-dime-

thoxyethane, acetic acid, trifluoroacetic acid, or isopropanol. A solution may be stirred at ambient temperature with palladium-on-charcoal catalyst present and the hydrogen introduced at atmospheric pressure through a glass frit. In some instances the reduction is exothermic.

The reduction using 1,3-propanedithiol is carried out in methanol or other alcohol solvents containing an equivalent of triethylamine, by warming until N_2 evolution occurs. At ambient temperatures, slow reduction occurs. Temperatures of 20° to 100°C may be used; temperatures of 40° to 60°C are preferred. Warming an azide (IV) with trimethylphosphine causes a rapid evolution of N_2. The reaction may be carried out in 1,2-dimethoxyethane or bis-(2-methoxyethyl)ether and the crude intermediate, when hydrolyzed with water or acid, gives the desired amine (V).

The aminomethyl compounds (V) are acylated by reaction of the amine with an acid chloride or anhydride in a basic solvent such as pyridine or by reaction in a water miscible solvent such as THF or 1,2-dimethoxyethane in the presence of an aqueous base such as sodium hydroxide or potassium hydroxide, sodium bicarbonate or sodium carbonate. When pyridine is used as solvent for the reaction, the acid chloride or anhydride is added to the mixture at 0° to 10°C. The reaction may be carried out between -30° and 50°C. With very reactive acid chlorides or anhydrides such as trifluoromethanesulfonyl chloride or anhydride the reaction is preferably carried out at -60° to -40°C. The acylations using aqueous bases are done by stirring the amine (V) in a water miscible solvent such as tetrahydrofuran (THF), 1,2-dimethoxyethane, or dioxane and adding 1-5 N NaOH to keep the mixture basic as the acid chloride or anhydride is added, while

keeping the temperature between -5° and 20°C. The compounds (V) can also be acylated by any of the standard peptide synthesis methods where the free acid is reacted with the amine using N,N-dicyclohexylcarbodiimide, or where a mixed anhydride is first formed from the acid using a chloroformate ester and a tertiary base such as triethylamine, followed by reaction with the amine. In the mixed anhydride procedure, the acid to be used is allowed to react with a chloroformate such as ethyl chloroformate or isobutyl chloroformate in a solvent such as THF, DMF or 1,2-dimethoxyethane, in the presence of a tertiary base such as triethylamine or N-methylmorpholine at -30° to 10°C. To this mixture the amine (V) is added and the mixture stirred at -10°C for 1-5 hours. When N,N-dicyclohexylcarbodiimide is used as the condensing agent, the conditions and solvents may be the same but it is often advantageous to add N-hydroxyphthalimide or N-hydroxysuccinimide.

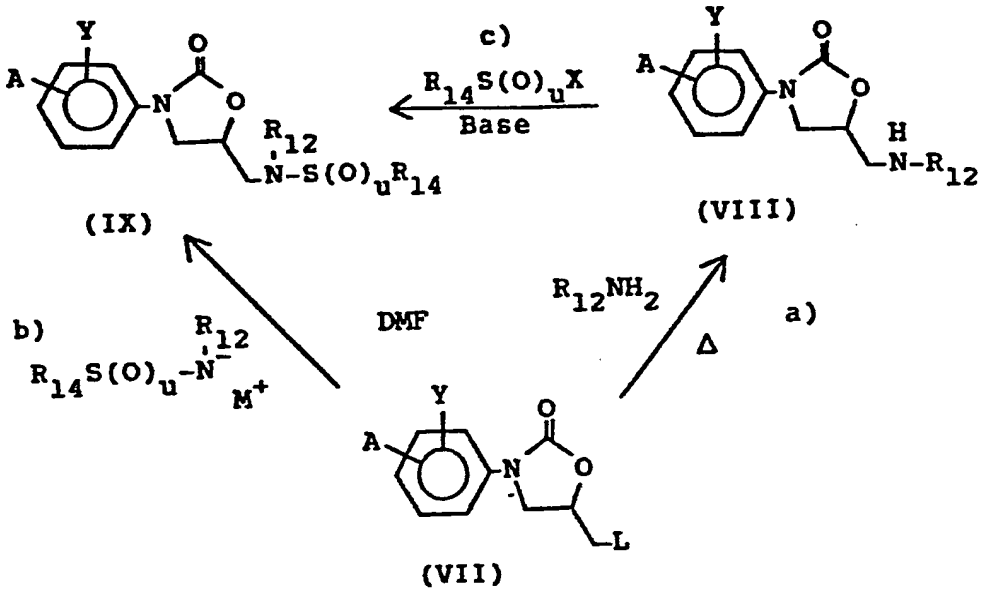
Further, these amines may be acylated by reaction with esters such as methyl dichloroacetate, ethyl trifluoroacetate or n-butyl formate. In this method, the amine (V) is combined with the ester and a solvent such as 1,2-dimethoxyethane, bis-(2-methoxyethyl)ether, or toluene (in some cases the ester may be used as the solvent) and the mixture is heated at reflux until the reaction is shown to be complete by an assay such as thin-layer chromatography. More reactive esters such as p-nitrophenyl esters, pentafluorophenyl esters, thio esters, enol esters, N-hydroxyphthalimide esters, N-hydroxysuccinimide esters, 1-hydroxybenzotriazole esters, 2,4,5-trichlorophenyl esters, and pentachlorophenyl esters, may be used. Further, other acylating agents such as acyl azides, acyl imidazoles and acyl phosphates, may be used.

When synthetic path b) is used, the sulfonate ester (III) is allowed to react with an amide in the form of its sodium or potassium salt, generated using NaH, KH or KOC_4H_9-t in a dipolar aprotic solvent such as DMF, DMAc, HMPA, N-methylpyrrolidinone, or tetramethylenesulfone. To the salt preparation is added the sulfonate ester (III) and the mixture is heated to 30° to 150°C. A catalyst such as 18-crown-6 may be used. Heating is continued for 3-50 hours.

In Scheme 1, the starting compound (II) may be dℓ- (the racemate) or the ℓ-isomer. The ℓ-isomer is a precursor for the preferred ℓ-amides (VI).

When the acylating group is derived from an α-amino acid and R_{13} contains an amino function it is necessary to protect that amino function with one of the commonly used protective groups such as benzyloxycarbonyl, t-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, or phthaloyl. Following the acylation, the protective group is removed by one of the standard methods to which the oxazolidinone ring is inert. The benzyloxycarbonyl group may be removed by hydrogenation in a solvent such as methanol, DMF, acetic acid, or mixtures of these solvents, using a catalyst such as 10% palladium-on-carbon or palladium black (100 to 500 mg of catalyst per mmole of compound). Alternatively the benzyloxycarbonyl group may be removed by dissolving the compound in acetic acid, adding an equal volume of 4 N HBr in acetic acid, and keeping the solution at room temperature for 1 to 5 hours. The N^{α}-t-butyloxycarbonyl groups are removed by hydrolysis with trifluoroacetic acid at room temperature.

Scheme 2:



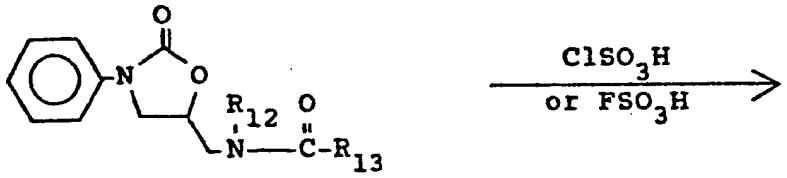
Compounds of formula (I) which may be made using the procedures of Scheme 2 are those where A is H or any of the groups previously shown except that when A is $R_1S(O)_n$ and R_1 is NR_9R_{10}. R_9. R_{10}. R_{11} and R_{11a} cannot be H. L may be any suitable leaving group such as I, Br, Cl, benzenesulfonyloxy, 4-toluenesulfonyloxy, methanesulfonyloxy or trifluoromethanesulfonyloxy. In route a) the compound (VII) is allowed to react with ammonia or an amine in a solvent such as ethanol at temperatures of 50° to 150°C. Where the amine or solvent is low-boiling, the reaction is carried out in a sealed vessel to allow the desired temperature to be reached. The solvent may be ethanol, DMF, DMAc, N-methylpyrrolidinone, tetramethylenesulfone, or HMPA. The reaction time may be 1 to 24 hours. Where (VII) is optically active (i.e., the ℓ-isomer) the product is optically active. The acylation of product VIII is carried out as described for Scheme 1, Path a).

The reaction of (VII) with the anion of a sulfonamide shown in Scheme 2, Path b) is carried out in a polar solvent such as DMF, DMAc, N-methylpyrrolidinone, tetramethylenesulfone, or HMPA. In some cases the use of a catalyst such as 18-crown-6 may improve the reaction. Temperatures of 50° to 150°C are employed; the time for the reaction can vary between 2 to 48 hours.

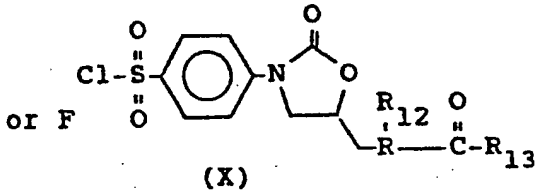
Alternatively, the sulfonamides (IX) can be prepared by reaction of the amine (VIII) with a sulfonyl halide in the presence of a base such as triethylamine or a basic solvent such as pyridine [Path c)].

Scheme 3:

a)

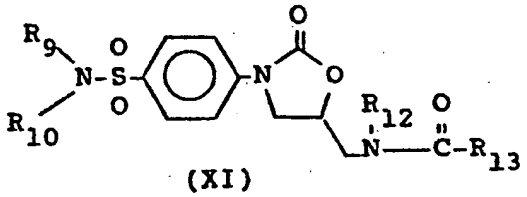


(VI; A=H)



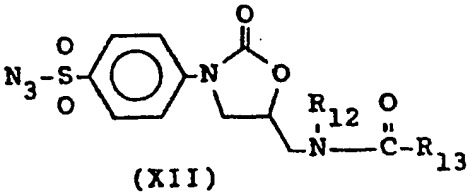
(X)

b) (X) $\xrightarrow{R_9R_{10}NH}$

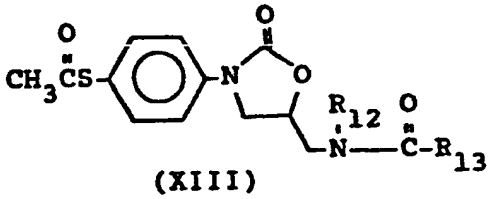


(XI)

c) (X) $\xrightarrow{NaN_3}$



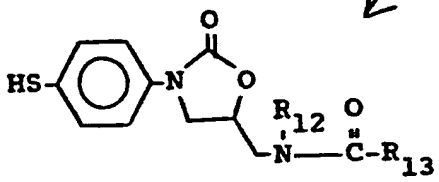
(XII)

d) (X) —Zn, acetic acid / acetic anhydride→ 

(XIII)

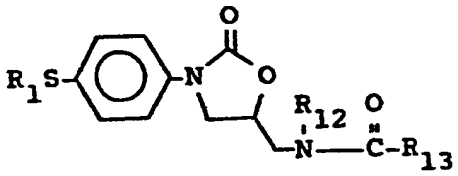
Zn, acetic acid

1) base
2) H^+



(XIV)

R_1-L / base →



(XV)

Compounds of Formula I, where B is $-N(R_{12})-C(=O)-R_{13}$ wherein R_{13} is not $CH(OR_{16})OR_{17}$ or CH_2N_3 can be prepared as shown in Scheme 3. The halosulfonation (particularly, chlorosulfonation) shown in Scheme 3, Path a), can be carried out by adding the compound of formula VI where A is H to chlorosulfonic acid or fluorosulfonic acid at room temperature in the absence of solvent. The temperature may be 10° to 100°C; preferred temperatures are 15° to 35°C. A solvent inert to chlorosulfonic acid or fluorosulfonic acid may be employed (examples include carbon tetrachloride, nitrobenzene, or a fluorocarbon) but using neat chlorosulfonic acid or fluorosulfonic acid is preferred.

The sulfonyl chloride or fluoride (X) may then be reacted by the procedure of Scheme 3, Path b), with ammonia, a mono- or disubstituted amine, a hydroxylamine or a hydrazine in a solvent such as THF, 1,2-dimethoxyethane, dioxane, bis-(2-methoxyethyl)ether or DMF. The reaction may be run at temperatures of -20° to 40°C; temperatures of -10° to 10°C are preferred.

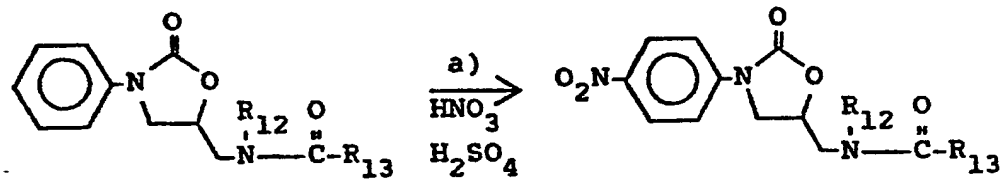
The sulfonyl chloride or fluoride (X), may be reacted with sodium azide or potassium azide in a mixture of acetone and water to give the sulfonyl azide (XII) as shown in Scheme 3, Path c). Other water-miscible solvents such as acetonitrile, DMF, 1,2-dimethoxyethane, THF, or dimethylsulfoxide may be used in place of acetone. An aqueous solution of sodium azide is added to acetone, the mixture is cooled in an ice-bath, the sulfonyl halide (X) is added, and the mixture is allowed to come to room temperature. The reaction may be carried out at -10° to 20°C. Preferred temperatures are -5° to 10°C.

The sulfonyl chlorides (X) may be reduced by several methods, as shown in Scheme 3, path a). The use of zinc metal added to a hot mixture of acetic acid, acetic anhydride and sodium acetate gives the S-acetates (XIII) in good yield. This is carried out at reflux temperature of the mixture, but may be carried out between 50°C to 120°C. Alternatively, the sulfonyl halides may be reduced by using zinc in acetic acid to give the mercaptans (XIV). The reduction may also be carried out using an iodide such as trimethylsilyl iodide or mixtures of trimethylsilyl chloride and sodium iodide in an inert solvent such as dichloromethane, benzene or toluene; stirring in the temperature range of 0°C to 50°C with the preferred temperature 20-30°C. This reduction gives the disulfide which is then reduced by sodium borohydride in an

alcohol solvent such as methanol. The disulfide may also be reduced by dithiothreitol or by zinc and acid. The product is the mercaptans (XIV). If desired the mercaptans may be alkylated with the halides R_1-L to give the sulfides (XV). This reaction may be carried out using base such as potassium carbonate, sodium methoxide, sodium ethoxide or potassium t-butoxide. The alkylation can be done using sodium hydroxide in dimethylsulfoxide.

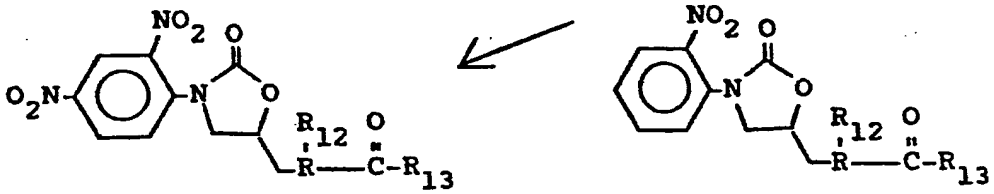
The reactions of Scheme 3 may be carried out starting with the ℓ-isomer of (VI) where A = H to give products of the preferred ℓ-form (the preferred configuration shown above).

Scheme 4:

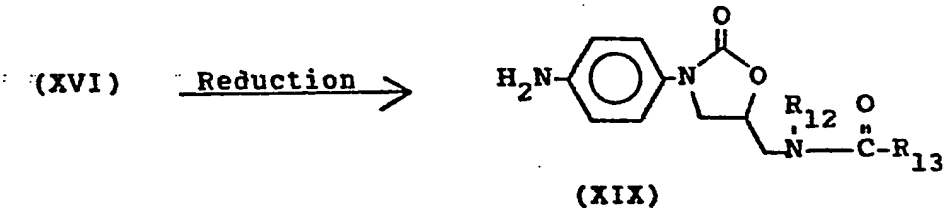


(VI; where A=H) (XVI)

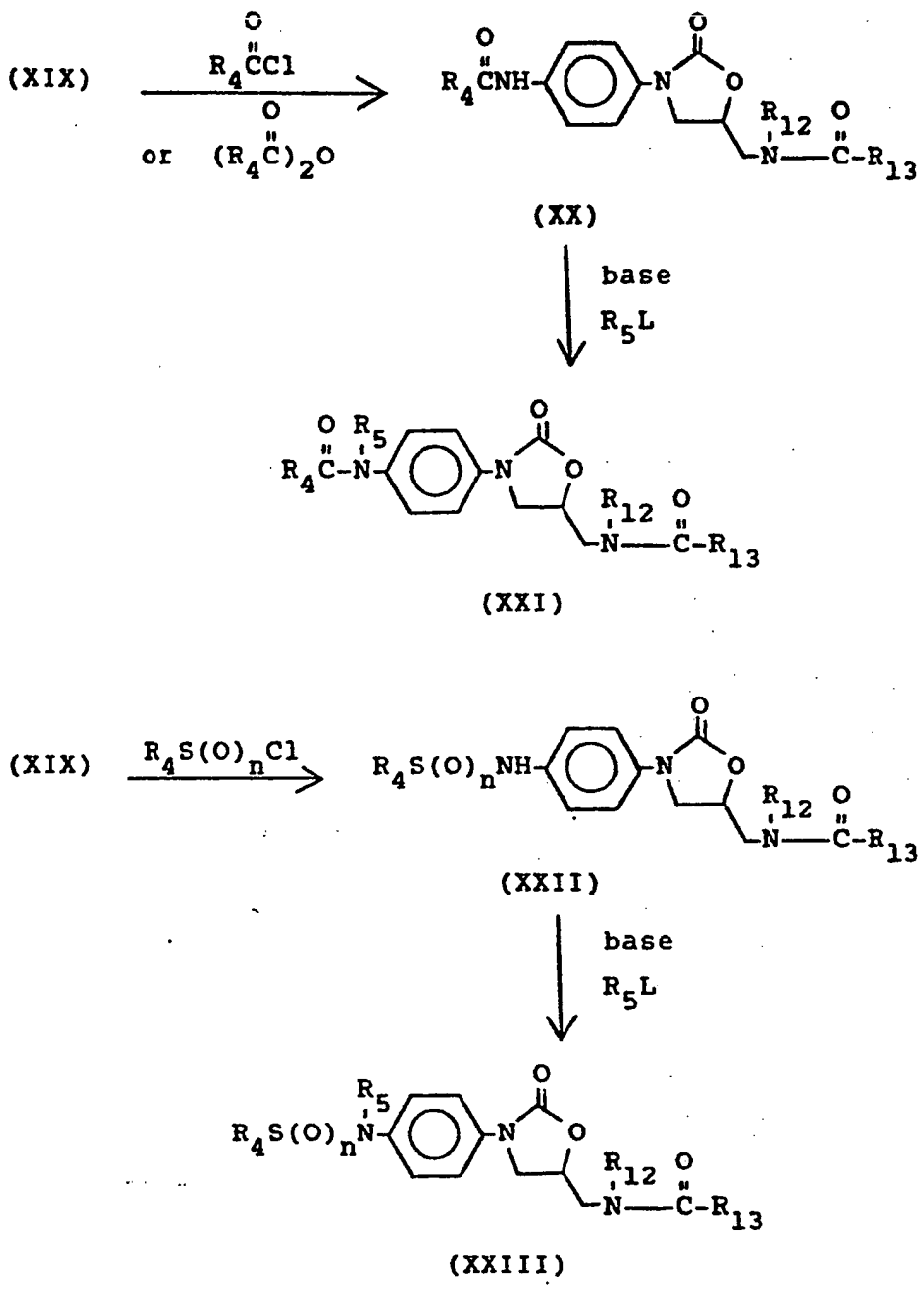
+



(XVIII) (XVII)



(XIX)


(XIX)
R_4CCl
or $(R_4C)_2O$
(XX)
base
R_5L
(XXI)
(XIX)
$R_4S(O)_nCl$
(XXII)
base
R_5L
(XXIII)

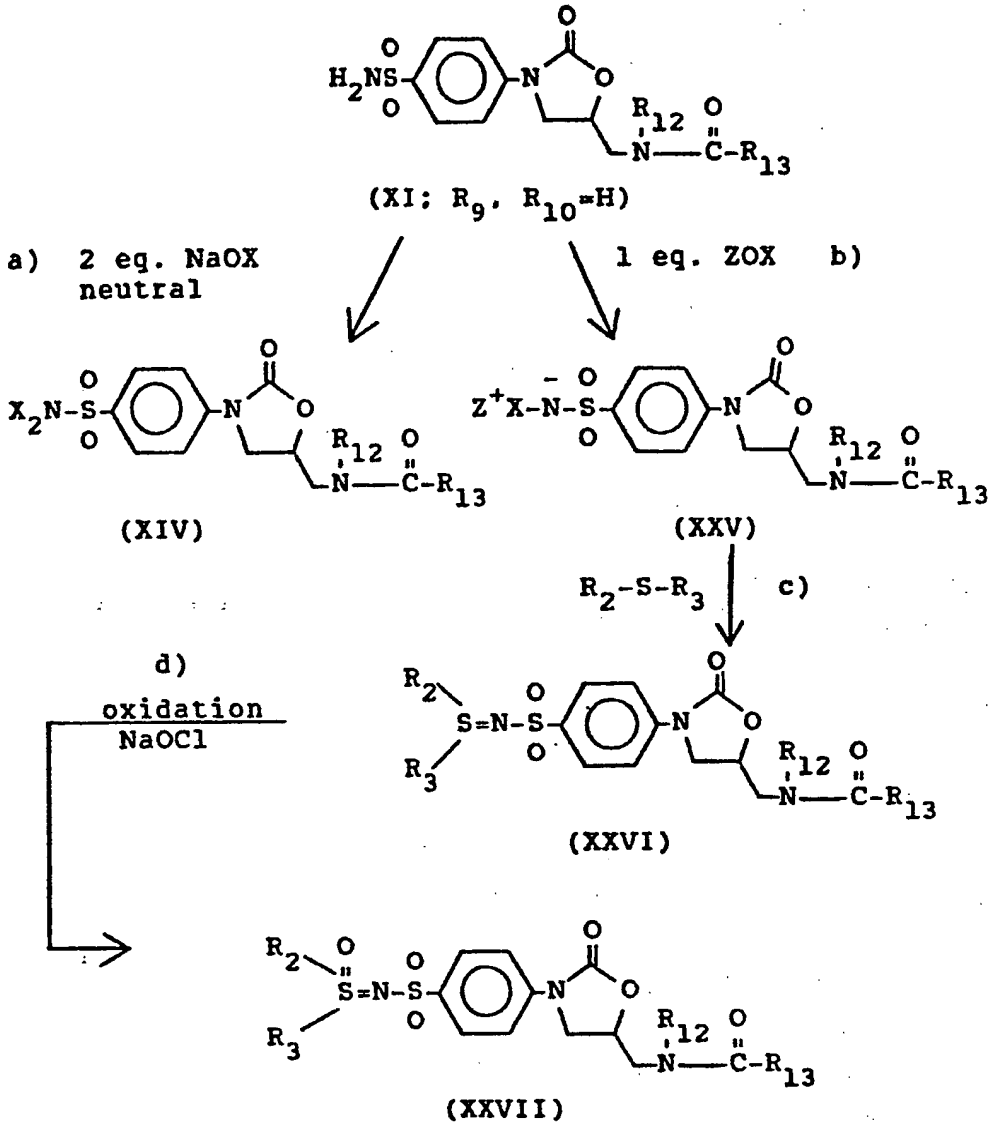
The nitration of Scheme 4, Path a) is carried out by adding the compound of formula (VI) (A=H) to concentrated sulfuric acid containing one equivalent of nitric acid. Nitrate may be added in the form of a salt such as potassium nitrate. The nitration mixture is cooled to about -5°C, kept below 0°C during the addition, and then allowed to warm to room temperature. The nitration may be carried out at temperatures of -20° to 15°C, over time periods of 30 to 180 minutes.

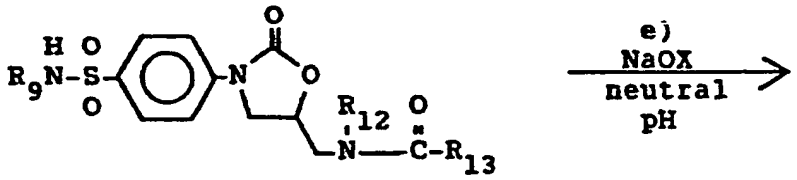
In the nitration shown in Scheme 4 it has been found that some ortho nitration occurs as well as the formation of 2,4-dinitro-compound. These products may be isolated by use of preparative chromography, and/or crystallization. The ortho nitro compound may be made in higher amounts by nitration in acetic acid by generating acetyl nitrate. The dinitro-compound can easily be made by using a higher molar ratio of nitrating agent.

The nitro-compounds (XVI, XVII, XVIII) can be reduced by using Raney nickel catalyst and hydrazine or by catalytic hydrogenation in a Parr shaker under 10-50 lbs. of hydrogen using palladium-on-charcoal as the catalyst. The products are the anilines (XIX). The anilines (XIX) may be acylated using an acyl halide or an acyl anhydride in the presence of an organic base such as pyridine or triethylamine or N-methylmorpholine; or using aqueous sodium hydroxide in an organic solvent such as tetrahydrofuran, 1,2-dimethoxyethane or DMF. A catalyst such as 4-dimethylaminopyridine may be used. In a similar way the anilines may be reacted with a sulfonyl halide to give the sulfonamides. In turn, the amides (XX) and sulfonamides (XXII) may be alkylated using base and the appropriate alkyl halide, alkyl sulfonate or sulfate ester.

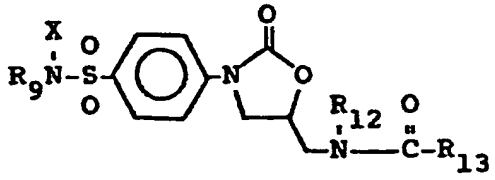
Compounds where R_1 is $-NX_2$, $-NR_4X$, $-NXZ$ or $-N=S(O)_pR_2R_3$ may be made as shown in Scheme 5.

Scheme 5:





(Xi: R_{10}=H)



(XXVIII)

Part a) of Scheme 5 is carried out by adding the sulfonamide (XI; R_9, R_{10}=H) to 1.3-2 N sodium or other hypohalite (2 equivalents) while keeping the pH between 6 and 7 by adding a dilute acid solution or acetic acid. This reaction may be carried out at -20° to 50°C; it goes well at room temperatures of 20° to 30°C. The reaction is complete in 30 minutes to 2 hours. To make the metal salts of the haloamide (XXV), Scheme 5, Path b), one keeps the solution basic and uses approximately an equivalent amount of the hypohalite.

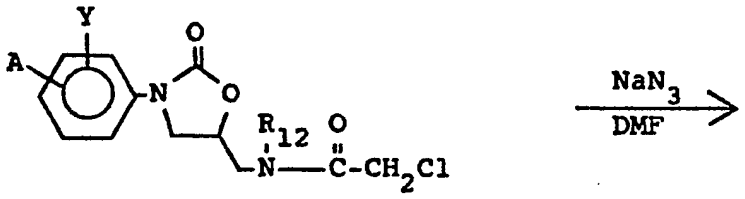
The sulfilimines (XXVI) are made by reacting the haloamide (XXV) with the appropriate sulfide in an alcohol-water mixture at 50° to 70°C. These products may be converted to the sulfoximines by oxidation using an oxidant such as hypochlorite anion in a phase transfer catalyzed system. This oxidation is carried out by stirring (XXVI) in a mixed solvent (ethyl acetate and dichloromethane) with tetra-n-butylammonium bromide while a two-fold excess of aqueous NaOCl are added at room temperature.

The preparation of N-alkyl haloamides (XXVIII) (Scheme 5, step e)) is carried out using the procedure

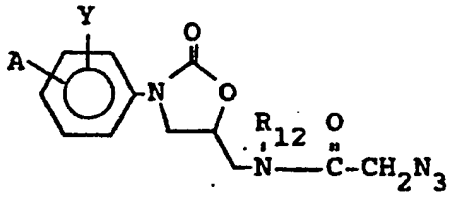
of Scheme 5, Path a), except employing one equivalent of hypohalite.

An alternative synthesis of the glycinamides of Formula I where B is $\overset{R_{12}}{\underset{|}{N}}\!\!-\!\!\overset{O}{\overset{\|}{C}}\!-R_{13}$ wherein R_{13} is CH_2NH_2 as well as compounds where R_{13} is CH_2N_3 is shown in Scheme 6.

Scheme 6:

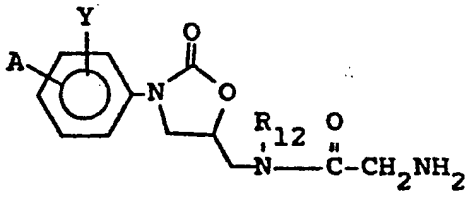


(XXIX)



(XXX)

reduction



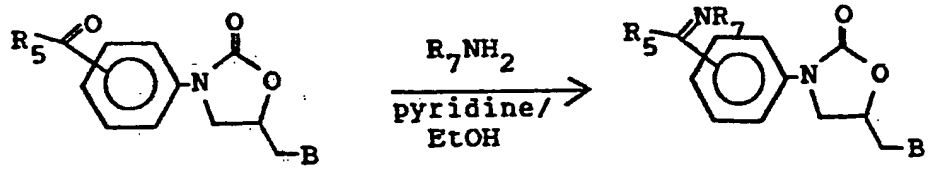
(XXXI)

Glycine amides (XXXI) may be prepared by making the chloroacetyl or bromoacetyl or iodoacetyl compounds (XXIX) followed by reacting these with sodium azide in dimethylsulfoxide or other dipolar aprotic solvents to give the azidoacetyl compounds (XXX). The azidoacetyl compounds then may be reduced by hydrogen

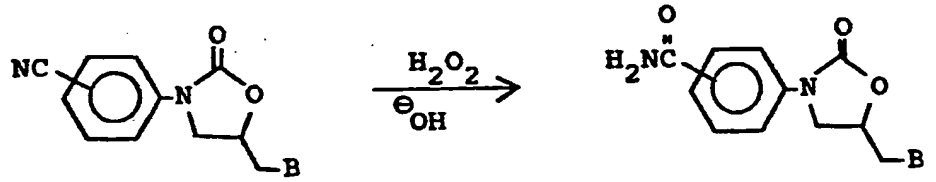
using a palladium catalyst or by any of the other reduction methods such as 1,3-propanedithiol and triethylamine, thioglycolic acid or hydrogen sulfide. The products are the glycine amides (XXXI).

The compounds of Formula I where A is $-\overset{\overset{NR_7}{\|}}{C}-R_5$ or $-\overset{\overset{O}{\|}}{C}NR_5R_6$ are obtained as shown in Scheme 7.

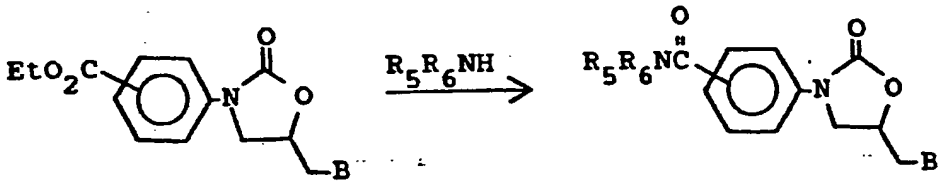
Scheme 7:



(XXXII) (XXXIII)



(XXXIV) (XXXV)



(XXXVI) (XXXVII)