Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Dr. Rall, Klaus, *24.06.1960, Leverkusen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 115. Salge, Andreas, *17.07.1958, Leverkusen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 116. Schmidt, Jens, *24.03.1969, Wuppertal Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 117. Dr. Schneider, Stephan, *26.03.1959, Wuppertal		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 118. Dr. Schöneseiffen, Josef, *24.09.1953, Wuppertal Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 119. Dr. Streicher-Saled, Ursula, *22.05.1957, Düsseldorf Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 120. Dr. von Keutz, Eckardt, *07.01.1956, Wuppertal Prokura gemeinsam mit einem Vor-		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				stand oder einem weiteren Prokuristen 121. Dr. Wild, Hanno, *23.06.1957, Wuppertal Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 122. Dr. Zimmermann, Jürgen, *13.12.1954, Odenthal Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen		
26				Änderung zu Nr. 94: von Amts wegen (Schreibfehlerberichtigung): Dr. Fischer, Horst, *10.07.1954, Köln		a) 13.03.2007 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 119: von Amts wegen (Schreibfehlerberichtigung): Dr. Streicher-Saied, Ursula, *22.05.1957, Düsseldorf Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen		
27			b) Vorstand: 12. Dr. Malik, Kemal, *29.09.1962, Berlin Nicht mehr Vorstandsmitglied: 6. Rubin, Marc			a) 19.03.2007 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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28			b) Vorstand: 13. Prof. Dr. Busch, Andreas, *26.08.1963, Wuppertal			a) 27.04.2007 Waligorski
29				123. Dr. Atzor, Michael, *31.05.1956, Leverkusen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 124. Berrang, Thomas, *29.04.1950, Leichlingen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 125. Dr. Bey, Alexander, *02.04.1962, Köln		a) 08.06.2007 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 126. Dr. Brill, Gisela, *18.11.1951, Düsseldorf Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 127. Dr. Große-Bley, Michael, *04.05.1958, Leverkusen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 128. Dr. Klotz, Rainer, *30.09.1953, Niederkassel Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuris-		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				ten 129. Dr. Königer, Ursula, *05.04.1969, Berlin Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 130. Meixner, Frank, *18.02.1966, Düsseldorf Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 131. Dr. Pintsch, Tanja, *03.06.1973, Berlin Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				132. Reinkober, Ingrid, *15.03.1960, Leverkusen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen 133. Dr. Thomaier, Jörg, *23.11.1966, Bergisch Gladbach Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Nicht mehr Prokurist: 23. Ünal, Kemalettin Nicht mehr Prokurist: 52. Dr. Förster, Jutta Nicht mehr Prokurist:		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				59. Schlosser, Harald Nicht mehr Prokurist: 80. Schumann, Arnd		
30					b) Auf Grund des Verschmelzungsvertrages vom 20.08.2007 und des Zustimmungsbeschlusses der übertragenden Gesellschaft vom selben Tage ist die IDF Institut für Diagnostikforschung GmbH mit Sitz in Berlin (Amtsgericht Charlottenburg, HRB 24843) durch Übertragung ihres Vermögens unter Auflösung ohne Abwicklung als Ganzes auf die Gesellschaft verschmolzen.	a) 30.08.2007 Schmidt
31				Nicht mehr Prokurist: 84. Prof. Dr. Busch, Andreas		a) 10.10.2007 Waligorski
32				Nicht mehr Prokurist: 114. Dr. Rall, Klaus		a) 14.11.2007 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Nicht mehr Prokurist: 122. Dr. Zimmermann, Jürgen		
33				134. Drescher, Günter, *22.08.1961, Nordwalde Einzelprokura		a) 04.12.2007 Waligorski
34				135. Schalk, Christian, *23.05.1966, Leverkusen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Nicht mehr Prokurist: 8. Dr. Raack, Rainer Nicht mehr Prokurist: 35. Eierdanz, Angelika		a) 30.01.2008 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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35					b) Auf Grund des Verschmelzungsvertrages vom 04.06.2008 und des Zustimmungsbeschlusses der übertragenden Gesellschaft vom selben Tage ist die Schering-Forschungsgesellschaft mbH mit Sitz in Berlin (AG Charlottenburg, HRB 39650) durch Übertragung ihres Vermögens unter Auflösung ohne Abwicklung als Ganzes auf die Gesellschaft verschmolzen.	a) 10.06.2008 Schmidt
36				136. Dr. Beyreuther, Stefan, *04.06.1969, Düsseldorf Einzelprokura 137. Brill, Klaus, *14.02.1953, Berlin Einzelprokura 138.		a) 20.06.2008 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Devoy, Michael, *28.09.1962, Berlin Einzelprokura 139. Dr. Hausner, Thomas-Peter, *13.04.1959, Berlin Einzelprokura 140. Linder, Claudia, *05.04.1966, Solingen Einzelprokura 141. Yeomans, Michael, *08.06.1949, Berlin Einzelprokura Nicht mehr Prokurist: 19. Bernhardt, Wilfried		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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37				142. Bier, Bernd-Peter, *15.07.1966, Köln Einzelprokura 143. von Schmeling, Ulrike, *28.02.1954, Bergisch Gladbach Einzelprokura Änderung zu Nr. 108: infolge Namensänderung Lohkamp, Gudrun, *09.11.1957, Wuppertal Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Nicht mehr Prokurist: 14. Dr. Dohse, Knuth		a) 28.07.2008 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Nicht mehr Prokurist: 22. Dr. Papendieck, Hatto Nicht mehr Prokurist: 43. Fragner, Reinhard Nicht mehr Prokurist: 61. Göckel, Thomas		
38				Nicht mehr Prokurist: 70. Schmitt, Thomas		a) 31.07.2008 Waligorski
39				144. Mechelhoff, Ralf, *27.09.1953, Münster Einzelprokura 145. Prof. Dr. Schneider, Martin, *23.11.1951, Berlin		a) 08.08.2008 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Einzelprokura		
40					b) Die Hauptversammlung vom 17.01.2007 hat die Übertragung der Aktien der übrigen Aktionäre (Minderheitsaktionäre) auf den Hauptaktionär, die Bayer Schering GmbH mit Sitz in Leverkusen (AG Köln, HRB 52162) gegen Barabfindung beschlossen.	a) 25.09.2008 Schmidt
41			b) Vorstand: 14. Fibig, Andreas, *23.02.1962, Berlin Nicht mehr Vorstand: 9. Higgins, Arthur J.			a) 06.10.2008 Waligorski
42			b) Vorstand: 15. Dr. Bernd, Metzner, *13.10.1970, Hernau			a) 03.11.2008 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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43				146. Dr. Petry, Wolfgang, *01.08.1958, Berlin Einzelprokura 147. Schmitt, Thomas, *18.05.1970, Berlin Einzelprokura Nicht mehr Prokurist: 78. Gorski, Cornelia		a) 10.11.2008 Waligorski
44		194.001.000 EUR			a) Durch Beschluss der Hauptversammlung vom 04.12.2008 ist das Grundkapital zum Zwecke der Verschmelzung mit der Bayer HealthCare Aktiengesellschaft mit Sitz in Leverkusen (AG Köln, HRB 49694) um 1.000 EUR auf 194.001.000 EUR erhöht und die Satzung geän-	a) 09.12.2008 Schmidt

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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					dert in § 4 (Grundkapital, Aktien). Die Kapitalerhöhung ist durchgeführt. b) Der Beherrschungs- und Gewinnabführungsvertrag mit der Dritte BV GmbH (nunmehr: Bayer Schering GmbH) mit Sitz in Leverkusen besteht infolge Verschmelzung nunmehr mit der Bayer AG mit Sitz in Leverkusen (AG Köln, HRB 48248).	
45					a) Durch Beschluss der Hauptversammlung vom 11.12.2008 ist die Satzung geändert in § 13 (Vergütung des Aufsichtsrates). b) Auf Grund des Verschmelzungsvertrages vom 04.12.2008 und der Zustimmungsbeschlüsse vom selben Tage ist die Bayer HealthCare Aktiengesellschaft mit Sitz in Leverku-	a) 30.12.2008 Schmidt

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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					sen (AG Köln, HRB 49894) durch Übertragung ihres Vermögens unter Auflösung ohne Abwicklung als Ganzes auf die Gesellschaft verschmolzen.	
46	b) Geschäftsanschrift: Müllerstraße 178, 13353 Berlin			148. Dr. Bechem, Martin, *07.08.1954, Wuppertal Einzelprokura 149. Dr. Binda, Maria Luisa, *28.05.1956, Leverkusen Einzelprokura 150. Dr. Brehm, Oliver, *18.01.1965, Langenfeld Einzelprokura 151. Dr. Burkert, Frank, *31.01.1950,		a) 22.01.2009 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Odenthal Einzelprokura 152. Dr. Groß, Dietmar, *31.08.1962, Teltow Einzelprokura 153. Dr. Gunkel, Frank-Andreas, *31.03.1959, Bergisch Gladbach Einzelprokura 154. Dr. Harenberg, Horst-Eberhard, *08.01.1950, Berlin Einzelprokura 155. Dr. Hörlein, Hans-Dietrich, *25.05.1949, Wuppertal		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Einzelprokura 156. Dr. Jacke, Jürgen, *11.11.1960, Unna Einzelprokura 157. Dr. Jelich, Klaus, *02.03.1953, Wuppertal Einzelprokura 158. Klotzki, Volker, *23.06.1959, Langenfeld Einzelprokura 159. Dr. Köhler, Ferdinand, *15.11.1954, Düsseldorf Einzelprokura		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				160. Dr. Kraemer, Hans-Peter, *03.03.1949, Mettmann Einzelprokura 161. Krokowski, Reinhard, *21.03.1967, Köln Einzelprokura 162. Dr. Kubin, Maria, *25.07.1962, Langenfeld Einzelprokura 163. Dr. Linkenheil, Dieter, *30.08.1955, Mönchengladbach Einzelprokura 164. Mohr, Thomas, *30.07.1956, Berlin		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Einzelprokura 165. Dr. Mohrs, Klaus-Helmut, *16.12.1952, Wuppertal Einzelprokura 166. Richartz, André, *30.03.1962, Haan Einzelprokura 167. Dr. Schultz, Michael, *27.03.1957, Berlin Einzelprokura 168. Dr. Smits, Philip, *02.06.1959, Berlin Einzelprokura		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				169. Staunton, Angela, *27.06.1959, Berlin Einzelprokura 170. Talmage, Ian, *11.02.1950, Düsseldorf Einzelprokura 171. Wernecke, Knut, *13.12.1958, Leichlingen Einzelprokura Nicht mehr Prokurist: 76. Dr. Wozniewski, Thomas		
47			b) Änderung zu Nr. 15: infolge Berichtigung Vorstand:	Änderung zu Nr. 92: infolge Berichtigung		a) 12.02.2009 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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			Dr. Metzner, Bernd, *13.10.1970, Hernau	Dr. de Jonge, Maarten, *13.02.1958, Hohen Neuendorf Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Nicht mehr Prokurist: 79. Grohé, Ulrich		
48				172. Franzen, Reinhard, *30.03.1962, Haan Einzelprokura 173. Dr. Raubach, Hans-Joachim, *31.10.1969, Bonn Einzelprokura 174. Renner, Oliver, *06.12.1965, Leverkusen		a) 06.03.2009 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Einzelprokura 175. Schmidt, Joachim, *15.04.1967, Leverkusen Einzelprokura		
49					b) Auf Grund des Verschmelzungsvertrages vom 17.03.2009 und der Zustimmungsbeschlüsse vom selben Tage ist die DIREVO Biotech Aktiengesellschaft mit Sitz in Köln (AG Köln, HRB 35249) durch Übertragung ihres Vermögens unter Auflösung ohne Abwicklung als Ganzes auf die Gesellschaft verschmolzen.	a) 31.03.2009 Schmidt
50					b) Auf Grund des Verschmelzungsvertrages vom 17.03.2009 und der Zustimmungsbeschlüsse vom selben Tage ist die BerliServe Professional Services GmbH mit Sitz in Berlin	a) 31.03.2009 Schmidt

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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					(AG Charlottenburg, HRB 74678) durch Übertragung ihres Vermögens unter Auflösung ohne Abwicklung als Ganzes auf die Gesellschaft verschmolzen.	
51				176. Blume, Helmut, *11.09.1959, Lindlar Einzelprokura Nicht mehr Prokurist: 161. Krokowski, Reinhard		a) 20.04.2009 Waligorski
52			b) Änderung zu Nr. 15: infolge Berichtigung des Wohnortes Vorstand: Dr. Metzner, Bernd, *13.10.1970, Hemau	177. Marschmann, Bernd, *19.09.1968, Düsseldorf Einzelprokura 178. Moritz, Matthias, *03.10.1959, Köln Einzelprokura		a) 30.04.2009 Waligorski

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				179. Dr. Zimmermann, Jürgen, *13.12.1954, Odenthal Einzelprokura		
53				Nicht mehr Prokurist: 5. Krüger, Horst		a) 13.08.2009 Rudolph
54			b) Nicht mehr Vorstand: 11. Dr. Riemann, Gunnar	Nicht mehr Prokurist: 86. Dr. Kreuzburg, Christa 180. Dr. Mrotzek, Werner, *20.07.1952, Berlin Einzelprokura		a) 17.08.2009 Kremer
55				181. Dr. Schauer, Gerhard, *10.10.1961, Berlin Einzelprokura		a) 28.08.2009 Boos

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				182. Dr. Wienhold, Christian, *18.06.1953, Berlin Einzelprokura		
56					a) Durch Beschluss der Hauptversammlung vom 26.08.2009 ist die Satzung insgesamt neu gefasst. b) Das am 26.04.2001 beschlossene bedingte Kapital besteht nicht mehr. Das am 16.04.2004 beschlossene bedingte Kapital besteht nicht mehr. Das genehmigte Kapital vom 16.04.2004 ist durch Zeitablauf erloschen. (Genehmigtes Kapital 2004/I)	a) 03.09.2009 Wengert
57			b) Nicht mehr Vorstand:	183. Baldus, Berthold, *12.03.1954, Ber-		a) 26.10.2009

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
			10. Baumann, Werner	Iin Einzelprokura 184. Brüning, Lars, *29.03.1963, Berlin Einzelprokura 185. Dr. Hein, Thomas, *29.09.1963, Neuruppin Einzelprokura 186. Lauterbach, Christian, *13.03.1966, Essen Einzelprokura 187. Dr. Steindl, Ludwig, *28.02.1956, Berg Einzelprokura		Köpke

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				188. Dr. Trube, Claus Moritz, *13.08.1967, Erkrath Einzelprokura		
58				Nicht mehr Prokurist: 116. Schmidt, Jens 189. Dr. Fischer-Carius, Andreas, *29.01.1967, Berlin Einzelprokura 190. Dr. Wegner, Peter, *30.04.1955, Berlin Einzelprokura		a) 26.01.2010 Köpke
59				191. Schildmeyer, Gerrit, *14.12.1971, Köln		a) 31.05.2010 Köpke

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Einzelprokura 192. Dr. Wood, Clive, *23.12.1960, Heiligenhaus Einzelprokura		
60				193. Dr. Dussan Molinos, Alejandro, *10.01.1964, Berlin Einzelprokura 194. Dr. Waibel, Franz, *09.05.1959, Berlin Einzelprokura		a) 10.06.2010 Köpke
61				Änderung zu Nr. 13: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen.		a) 10.06.2010 Köpke

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Dr. Benz, Wolfgang Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 16: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Klose, Walter Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 21: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Haumesser, Winfried		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 24: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Alburg, Frank Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 36: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Hartmann, Uwe Prokura gemeinsam mit einem Vor-		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				stand oder einem weiteren Prokuristen Änderung zu Nr. 38: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Hübl, Dieter Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 39: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Steinbeck, Matthias Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Änderung zu Nr. 42: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Hakert, Hubertus Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 44: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Schmeier, Dieter Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 47:		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Renneke, Franz-Josef Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 48: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Muráti-Laebe, Ilona Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 49: Korrektur der Ausgabe der Vertre-		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				tungsbefugnis im aktuellen Ausdruck von Amts wegen. Krieger, Andreas Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 53: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Schmid, Eva Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 55: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen.		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Topf-Schleuning, Maren Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 56: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Schröder, Steffen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 57: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Baron von Behr, Nicolas		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 60: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Scheuermann, Hans-Jörg Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 63: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Baltzer, Markus Prokura gemeinsam mit einem Vor-		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
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				stand oder einem weiteren Prokuristen Änderung zu Nr. 64: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Noeske-Jungblut, Christiane, geb. Noeske Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen Änderung zu Nr. 65: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Dr. Eisenhauer, Martin Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuris-		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				ten Änderung zu Nr. 67: Korrektur der Ausgabe der Vertretungsbefugnis im aktuellen Ausdruck von Amts wegen. Krüger, Gerd Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen		
62				Nicht mehr Prokurist: 117. Dr. Schneider, Stephan		a) 23.06.2010 Köpke
63			b) Änderung zu Nr. 3: Ergänzung des Geburtsdatums: Vorstandsmitglied: Dr. Köstlin, Ulrich, *31.12.1952, Berlin	195. De Prins, Werner, *13.07.1959, Berlin Einzelprokura 196. Dr. Oernskov, Flemming,		a) 07.07.2010 Köpke

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				*21.01.1958, Berlin Einzelprokura Nicht mehr Prokurist: 141. Yeomans, Michael Nicht mehr Prokurist: 188. Dr. Trube, Claus Moritz Änderung zu Nr. 107: Ergänzung der Personendaten. Dr. Klusik, Hartmut, *30.07.1956, Leverkusen Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen		
64				197. Dr. Mangold, Matthias, *10.02.1961, Berlin		a) 08.09.2010 Köpke

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Einzelprokura		
65				Nicht mehr Prokurist: 21. Dr. Haumesser, Winfried Nicht mehr Prokurist: 63. Baltzer, Markus Nicht mehr Prokurist: 88. Behrens, Jens Nicht mehr Prokurist: 92. Dr. de Jonge, Maarten Nicht mehr Prokurist: 131. Dr. Pintsch, Tanja Nicht mehr Prokurist: 150. Dr. Brehm, Oliver		a) 22.10.2010 Köpke

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Nicht mehr Prokurist: 154. Dr. Harenberg, Horst-Eberhard		
66				198. Dr. Ashman, Philip, *25.02.1965, Berlin Einzelprokura 199. Dr. Immler, Dorian, *03.06.1972, Leverkusen Einzelprokura		a) 08.11.2010 Kremer
67				Nicht mehr Prokurist: 13. Dr. Benz, Wolfgang		a) 22.11.2010 Lampe
68				200. Dr. Leifker, Gregor, *10.03.1954, Leverkusen Einzelprokura		a) 29.11.2010 Köpke

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
69	b) Die Zweigniederlassung Nr. 1 in 59192 Bergkamen ist aufgehoben.			201. Schneider, Ralf, *14.04.1964, Leverkusen Einzelprokura		a) 27.12.2010 Köpke
70				Nicht mehr Prokurist: 110. Milon, Jean-Philippe Nicht mehr Prokurist: 126. Dr. Brill, Gisela		a) 14.02.2011 Kremer
71				Änderung zu Nr. 172: nunmehr Franzen, Reinhard, *01.04.1958, Berlin Einzelprokura		a) 25.02.2011 Kremer
72					b) Die Gesellschaft hat auf Grund des	a) 29.03.2011

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
					Spaltungs- und Übernahmevertrages vom 23.12.2010 und der Zustimmungsbeschlüsse vom selben Tage Teile ihres Vermögens (Alters- und und Hinterbliebenenversorgung für ehemalige Beschäftigte) im Wege der Ausgliederung auf die Bayer Altersversorgungs GmbH (vormals: 2. BHCV GmbH) mit Sitz in Leverkusen (Amtsgericht Köln, HRB 53571) übertragen.	Schmidt
73			b) Nicht mehr Vorstandsmitglied: 3. Dr. Köstlin, Ulrich Nicht mehr Vorstand: 12. Dr. Malik, Kemal Nicht mehr Vorstand: 13. Prof. Dr. Busch, Andreas Nicht mehr Vorstand: 15. Dr. Metzner, Bernd Vorstand:	Nicht mehr Prokurist: 85. Schmidt, Sven Nicht mehr Prokurist: 107. Dr. Klusik, Hartmut		a) 12.04.2011 Morgenstern

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
			16. Dr. Klusik, Hartmut, *30.07.1956, Leverkusen Vorstand: 17. Vehreschild, Manfred, *09.08.1957, Leverkusen			
74				202. Prof. Dr. Busch, Andreas, *26.08.1963, Wuppertal Einzelprokura 203. Dr. Malik, Kemal, *29.09.1962, Berlin Einzelprokura Nicht mehr Prokurist: 118. Dr. Schöneseiffen, Josef Nicht mehr Prokurist:		a) 14.04.2011 Morgenstern

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				139. Dr. Hausner, Thomas Peter		
75				Nicht mehr Prokurist: 142. Bier, Bernd-Peter		a) 19.04.2011 Beyer
76				204. Triana, Julio, *21.09.1965, Berlin Einzelprokura		a) 03.05.2011 Hagen
77				Nicht mehr Prokurist: 96. Font, Jean-Christophe Nicht mehr Prokurist: 44. Dr. Schmeier, Dieter Nicht mehr Prokurist: 48. Dr. Muráti-Laebe, Ilona Nicht mehr Prokurist:		a) 24.05.2011 Beyer

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				81. Dr. Maier, Hans Nicht mehr Prokurist: 98. Dr. Frie, Monika Nicht mehr Prokurist: 127. Dr. Große-Bley, Michael Nicht mehr Prokurist: 159. Dr. Köhler, Ferdinand Nicht mehr Prokurist: 183. Baldus, Berthold 205. Grote, Manfred, *25.02.1964, Borgsdorf Einzelprokura 206. Dr. Reisinger, Claus-Peter,		

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				*30.09.1967, Berlin Einzelprokura Änderung zu Nr. 95: Nachname berichtigt. Dr. Fleßner, Timo, *26.11.1970, Wuppertal Prokura gemeinsam mit einem Vorstand oder einem weiteren Prokuristen		
78	a) Bayer Pharma Aktiengesellschaft				a) Durch Beschluss der Hauptversammlung vom 14.02.2011 ist die Satzung geändert in § 1 Abs. 1 (Firma).	a) 01.07.2011 Schmidt
79				207. Dr. Bertram, Christoph, *22.05.1966, Berlin Einzelprokura		a) 11.07.2011 Morgenstern

Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, inländische Geschäftsanschrift, empfangsberechtigte Person, Zweigniederlassungen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsregelung b) Vorstand, Leitungsorgan, geschäftsführende Direktoren, persönlich haftende Gesellschafter, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnis	Prokura	a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				208. Dr. Haning, Helmut, *02.10.1965, Wuppertal Einzelprokura 209. Rosenberg, Dirk, *04.05.1967, Wuppertal Einzelprokura Nicht mehr Prokurist: 113. Dr. Pickel, Markus Nicht mehr Prokurist: 164. Mohr, Thomas	

Notarielle Bescheinigung gemäß § 21 Bundesnotarordnung

Notarial Certificate according to § 21 of the German National Rules and Regulations for Notaries

Aufgrund meiner heutigen Einsichtsnahme in

- das elektronische Handelsregister beim Amtsgericht Charlottenburg, Berlin zu HR B 283 B (Bayer Schering Pharma Aktiengesellschaft)

According to my inspection of today of the

- electronical version of the abstract from the register for companies of the district court at Charlottenburg, Berlin, concerning HR B 283 B (Bayer Schering Pharma Aktiengesellschaft)

bescheinige ich,

der unterzeichnende Notar Klaus Striewski im Bezirk des Oberlandesgerichts Köln mit dem Amtssitz in Leverkusen

I, the undersigning notary public Klaus Striewski for the district of the regional court of appeals at Cologne, with offical residence at Leverkusen,

hiermit Folgendes:

hereby certify

Die Bayer Schering Pharma Aktiengesellschaft hat ihre Firma in Bayer Pharma Aktiengesellschaft geändert. Die Umfirmierung ist mit Eintragung in das Handelsregister des Amtsgerichts Charlottenburg, Berlin, (HR B 283 B) am 01.07.2011 wirksam geworden.

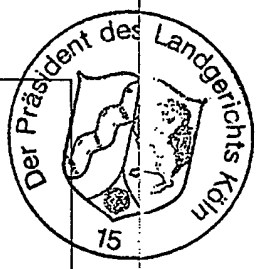
that:

The name of Bayer Schering Pharma Aktiengesellschaft has been amended to Bayer Pharma Aktiengesellschaft. The change of the name has become effective upon it's registration in the register for companies of the district court at Charlottenburg, Berlin, (HR B 283 B) on July 1, 2011.

Leverkusen, 06.07.2011 / July 06, 2011

KLAUS STRIEWSKI NOTAR IN LEVERKUSEN

Klaus Striewski
(Notar in Leverkusen)



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

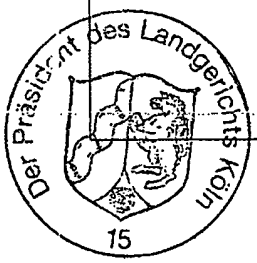
1. Land: Bundesrepublik Deutschland

   Diese öffentliche Urkunde
2. ist unterschrieben von Klaus Striewski
3. in seiner Eigenschaft als Notar
4. sie ist versehen mit dem Stempel des Notars Klaus Striewski in Leverkusen

Bestätigt

5. in Köln 6. am 8.7.2011
7. durch den Vizepräsidenten des Landgerichts
8. unter Nr.: 3085/11
9. Stempel: 10. Unterschrift:

Dr. Dumke



Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
1	a) Schering Aktiengesellschaft b) Berlin c) To research, develop, manufacture, purchase and sell all types of chemical and biotechnological products, including, but not limited to, pharmaceuticals, basic pharmaceutical substances, diagnostic products and vaccines for human and veterinary medicine, as well as fine chemicals, radioactive substances and intermediate products; to research, develop, manufacture, purchase and sell drugs and equipment for medical and laboratory requirements; and to develop, acquire and exploit chemical, biological and technical processes and facilities.	EUR 194,000,000	a) The Board of Management shall be made up of at least two persons. The Company shall be legally represented by two members of the Board of Management or by a member of the Board of Management together with one authorized signatory with full power of representation [Prokurist]. b) Member of the Board of Management.: 1. Dr. Ing. Erlen, Hubertus, *Dipl.-Ingenieur* (graduate in civil engineering), of Berlin Member of the Board of Management.: 2. Prof. Dr. Stock, Günter, medical doctor, of Berlin Member of the Board of Management: 3. Dr. Köstlin, Ulrich, *Wirtschaftsjurist* (business jurist), of Berlin Member of the Board of Management.: 4. Lingnau, Lutz, *Mar. 9, 1943, of New York, USA Member of the Board of Management.: 5. Dr. Spiekerkötter, Jörg, *May 15, 1958, of Klein-Machnow Member of the Board of Management.: 6. Rubin, Marc, *Jan. 10, 1955, of Chapel Hill, North Carolina, USA	1. Rademacher, Gilbert, *Oct. 19, 1956, of Bergkamen *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 2. Mette, Klaus-Jürgen, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 3. Nowak, Christian, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 4. Weber, Mechthild, née Schulte-Pelkum, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 5. Krüger, Horst, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 6. Valentien, Dietz-Cornelius, of Berlin	a) Stock corporation Articles of incorporation: December 15, 1890 Last amended: April 16, 2004 b) By resolution of the stockholders' meeting of April 26, 2001, the capital stock was increased conditionally by up to EUR 5,000,000. (conditional capital 2001/I) By revocation of the conditional capital of EUR 11,538,462 created by the stockholders' meeting on April 27, 1999, the capital stock has been increased conditionally by up to EUR 10,000,000 by resolution of the stockholders' meeting dated April 16, 2004. (conditional capital 2004/I) By resolution of the stockholders' meeting of April 16, 2004, the board of mgmt. is authorized to increase the capital stock until April 15, 2009 with the consent of the supervisory board by issuing new shares against cash or non-cash contributions on one or more occasions, But by a total amount not to exceed EUR 97,000,000. (authorized capital 2004/I) To date, the following companies have been merged into the Company: CHEBAG Beteiligungs-Aktiengesellschaft, of Bergkamen (Local Court of Kamen, HRB 0058) Germapharm Gesellschaft mit beschränkter Haftung Import-Export Spedition, of Hamburg (Local Court of Hamburg, HRB 7142)	a) June 22, 2004 Müller b) Date of first entry March 9, 1965

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1	2	3	4	5	6	7
				Prokura held jointly with a member of the Board of Management or another *Prokurist* with the authority to sell and encumber real properties 7. Hendrix, Gerwin, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 8. Dr. Raack, Rainer, of Kleinmachnow *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 9. Dr. Wagenknecht, Jobst, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 10. Wulf, Klaus, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 11. Schwitters, Jürgen, of Berlin		

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1	2	3	4	5	6	7
				Prokura held jointly with a member of the Board of Management or another *Prokurist* 12. Dr. Schwarz, Rainer, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 13. Dr. Benz, Wolfgang, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 14. Dr. Dohse, Knuth, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 15. Körner, Ulrich, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 16. Dr. Klose, Walter, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 17. Mack, Helmuth, of Berlin		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Prokura held jointly with a member of the Board of Management or another *Prokurist* 18. Dr. Berkemeier, Astrid, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 19. Bernhardt, Wilfried, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 20. Amsink, Gerold, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 21. Dr. Haumesser, Winfried, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 22. Dr. Papendieck, Hatto, of Unna *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 23. Ünal, Kemalettin, of Berlin		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Prokura held jointly with a member of the Board of Management or another *Prokurist* 24. Alburg, Frank, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 25. Draeger, Karl-Helmuth, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 26. Grigoleit, Gerrit, of Dortmund *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 27. Dr. McBride, Garth, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 28. Dr. Ernst, Dirk, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 29. Buchwald, Hartmut, of Berlin		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Prokura held jointly with a member of the Board of Management or another *Prokurist* 30. Hoffmeister, Uwe, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 31. Rook, Hans-Michael, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 32. Unglaube, Jürgen, of Glienicke *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 33. Dr. Müller, Bernd, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 34. Dr. Koch, Ulrich, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 35. Eiderdanz, Angelika, of Berlin		

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1	2	3	4	5	6	7
				Prokura held jointly with a member of the Board of Management or another *Prokurist* 36. Dr. Hartmann, Uwe, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 37. Wündisch, Karl, of Berlin *Prokura* held jointly with a member of the Board Management or another *Prokurist* 38. Dr. Hübl, Dieter, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 39. Steinbeck, Matthias, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 40. Dr. Narr-Linder, Gudrun, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 41.		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Schröder, Jürgen, of Nuremberg *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 42. Dr. Hakert, Hubertus, *Oct. 3, 1955, of Glienicke *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 43. Fragner, Reinhard, *Oct. 21, 1947, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 44. Dr. Schmeier, Dieter, *Dec. 28, 1948, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 45. Prof. Wallmark, Björn, *Mar. 20, 1952, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 46. Dr. Crisp-Jungklaus, Susan, *Oct. 24, 1948, of Berlin *Prokura* held jointly with a		

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1	2	3	4	5	6	7
				member of the Board of Management or another *Prokurist* 47. Dr. Renneke, Franz-Josef, *Aug. 30, 1952, of Nordkirchen *Prokura* held jointly with a member of the Board of Management or another *Prokurist* Rademacher, Gilbert, *Oct. 19, 1956, Bergkamen *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 48. Dr. Muráti-Laebe, Ilona, *Aug. 28, 1965, of Potsdam *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 49. Krieger, Andreas, *Aug. 30, 1964, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 50. Dr. Schwarz, Norbert, *Nov. 8, 1943, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist*		

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1	2	3	4	5	6	7
				51. Dr. Seuß, Thomas, *Sep. 17, 1963, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 52. Dr. Förster, Jutta, *Sep. 13, 1957, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 53. Dr. Schmid, Eva, *Nov. 25, 1968, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 54. Winkler von Mohrenfels, Yvonne, *Apr. 19, 1966, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 55. Topf-Schleuning, Maren, *Sep. 15, 1956, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 56. Schröder, Steffen, *Oct. 7, 1965,		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 57. Baron von Behr, Nicolas, *Mar. 26, 1965, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 58. Bergmann, Ulrich, *Jan. 7, 1966, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 59. Schlosser, Harald, *Jun. 18, 1961, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 60. Dr. Scheuermann, Hans-Jörg, *May 15, 1954, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 61. Göckel, Thomas, *Mar. 21, 1958, of Berlin *Prokura* held jointly with a		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				member of the Board of Management or another *Prokurist* 62. Schmidt, Sven, *Jul. 27, 1968, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 63. Baltzer, Marcus, *Dec. 26, 1963, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 64. Dr. Noeske-Jungblut, Christiane, née Noeske, *Jun. 26, 1957, of Potsdam *Prokura* held jointly with a member of Board of management or another *Prokurist* 65. Dr. Eisenhauer, Martin, *Aug. 20, 1967, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist* 66. Dr. Azmatullah, Syed, *Oct. 9, 1957, of Berlin *Prokura* held jointly with a member of Board of		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				management or another *Prokurist* 67. Krüger, Gerd, *Aug. 3, 1963, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* 68. Seeger, Stefan, *Jul. 21, 1946, of Berlin *Prokura* held jointly with a member of the Board of Management or another *Prokurist*		
2				Signatory authorization revoked: 2. Mette, Klaus-Jürgen Signatory authorization revoked: 34. Dr. Koch, Ulrich Signatory authorization revoked: 4. Weber, Mechthild, née Schulte-Pelkum Signatory authorization revoked: 45. Prof. Wallmark, Björn Signatory authorization revoked: 12. Dr. Schwarz, Rainer Signatory authorization revoked: 69. Gaulke, Christian, of Berlin *Prokura* held jointly with a member of the Board of		a) July 19, 2004 Hrymon b) Folio 68

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Management or another *Prokurist*		
3	b) The entry serial No. 1 was supplemented *ex officio* as follows: Branch(es) established: under the name of: Schering Aktiengesellschaft Zweigniederlassung Bergkamen (Bergkamen Branch), with registered office in Bergkamen (Local Court of Kamen, HRB 665)			Signatory authorization revoked: 18. Dr. Berkemeier, Astrid 70. Schmitt, Thomas, *Feb. 22, 1965, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* 71. Dr. Herold, Jens, *May 11, 1956, of Münster *Prokura* held jointly with a member of Board of management or another *Prokurist*		a) August 24, 2004 Schonk b) Folios 73 ff.
4			b) Board of Management 7. Dr. Dorrepaal, Karin, *Mar. 6, 1961, of Berlin	Signatory authorization revoked: 3. Nowak, Christian Signatory authorization revoked: 15. Körner, Ulrich Signatory authorization revoked: 62. Schmidt, Sven 72. Warmbier, Peter, *Feb., 16, 1950, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* 73. Dr. Geisler, Viktor,		a) September 30, 2004 Beyer b) Folio 89

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				*Nov. 13, 1961, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist*		
5				Part of the entry serial No. 1, concerning the *Prokurist* Rademacher, Gilbert (no. 1) has been deleted *ex officio* because of a duplicate entry.		a) October 8, 2004 Hübscher b) The entry serial No. 1 (amending entry) has been supplemented *ex officio* as follows: This folio has been amended to allow for computer processing and thus supersedes the prior register folio.
6				74. Ranze, Heike, *Oct. 30, 1970, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* Signatory authorization revoked: 10. Wulf, Klaus		a) November 25, 2004 Hrymon b) Folios 104/106
7					a) By resolution of the stockholders' meeting of April 14, 2005, § 13 of the	a) April 20, 2005 Wiechert

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
					articles of incorporation (Compensation of the Supervisory Board) was amended.	b) Resolution folio 8 f
8				75. Dr. Menken, Klaus, *Jan. 10, 1959, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* 76. Dr. Wozniewski, Thomas, *Jul. 26, 1962, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* 77. Dr. Berlage, Hans, *Jan. 30, 1956, of Greven *Prokura held jointly with a member of the Board of Management or another Prokurist* Signatory authorization revoked: 66. Dr. Azmatullah, Syed Signatory authorization revoked: 46. Dr. Crisp-Jungklaus, Susan Signatory authorization revoked: 40. Dr. Narr-Lindner, Gudrun Signatory authorization revoked: 30. Hoffmeister, Uwe Signatory authorizatio nrevoked:		a) June 14, 2005 Duzinksi b) Folios 55 ff., Special Vol. XIX

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				26. Grigoleit, Gerrit Signatory authorization revoked: 7. Hendrix, Gerwin Signatory authorization revoked: 54. Winkler von Mohrenfels, Yvonne		
9	b) Amendment regarding the branch located in: Bergkamen (Local Court of Kamen, HRB 665) concerning: Registry court, Register No. henceforth: Branch(es) established: under the name of: Schering Aktiengesellschaft Zweigniederlassung Bergkamen (Bergkamen Branch), with registered office in Bergkamen (Local Court of Hamm, HRB 4681)					a) August 8, 2008 Reiner
10				78. Gorski, Cornelia, *Sep. 26, 1969, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* Signatory authorization revoked: 58. Bergmann, Ulrich Signatory authorization revoked: 25. Draeger, Karl-Helmuth		a) August 17, 2005 Reiner b) Folio 71

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Signatory authorization revoked: 11. Schwitters, Jürgen		
11					a) By resolution of the stockholders' meeting of April 14, 2005, § 14 (Notice of Meeting) and § 15 (Participation in the Stockholders' Meeting) of the articles of incorporation were amended.	a) September 29, 2005 Ehrensberger b) Resolution folio 9f., Vol. XIX
12					a) The entry serial No. 11, concerning the entry of the amendments to the articles of incorporation, has been corrected *ex officio* and is entered correctly as follows: By resolution of the stockholders' meeting of April 14, 2005, § 14 (Notice of Meeting) and § 15 (Participation in the Stockholders' Meeting) of the articles of incorporation were amended effective November 1, 2005.	a) October 17, 2005 Ehrensberger
13				79. Grohé, Ulrich, *Oct. 29, 1958, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist*		a) October 31, 2005 Pacholke
14				Signatory authorization revoked: 29. Buchwald, Hartmut Signatory authorization revoked: 74. Ranze, Heike 80. Schumann, Arnd, *Jul. 10, 1974, of Berlin		a) December 7, 2005 Richter b) Folio 90

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Prokura held jointly with a member of Board of management or another *Prokurist*		
15			b) No longer a managing director: 2. Prof. Dr. Stock, Günter No longer a managing director: 4. Lingnau, Lutz Board of Management: 8. Prof. Dr. Metternich, Rainer, *Apr. 17, 1955, of Berlin	81. Dr. Maier, Hans, *Jul. 13, 1955, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* Signatory authorization revoked: 31. Rook, Hans-Michael Signatory authorization revoked: 37. Wündisch, Karl Signatory authorization revoked: 51. Dr. Seuss, Thomas Signatory authorization revoked: 50. Dr. Schwarz, Norbert Signatory authorization revoked: 28. Dr. Ernst, Dirk		a) January 2, 2006 Boos b) Folios 92-107 Special Vol.
16			b) The entry serial No. 15 concerning the deletion of Messrs. Prof. Dr. Günter Stock and Lutz Lingnau is corrected *ex officio* so that the entry must read as follows: No longer a member of the board of management.			a) January 2, 2006 Boos b) Entered as a correction
17				82. Dr. Kilger, Ute, *Feb. 10, 1966, of Berlin		a) April 3, 2006 Richter b)

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Prokura held jointly with a member of Board of management or another *Prokurist* Signatory authorization revoked: 6. Valentien, Dietz-Cornelius Signatory authorization revoked: 17. Mack, Helmuth		Folio 1, Special Vol. XX
18					a) By resolution of the stockholders' meeting of April 19, 2006, § 16 (2) of the articles of incorporation (Chair of the Stockholders' Meeting) was amended.	a) April 26, 2006 Dr. Lehmann b) Articles of incorporation Vol. XX, folios 15 ff. Resolution Vol. XX. Folios 11 ff.
19				83. Gardyan-Eisenlohr, Eva *May 22, 1964, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* Signatory authorization revoked: 9. Dr. Wagenknecht, Jobst		a) June 9, 2006 Hagen b) Folios 23-25, Special Vol. XX
20					a) By resolution of the stockholders' meeting of September 13, 2006, § 10 (Constitutive Meeting) and § 11 (Rules of Procedure, Voting) were amended. b) A control and profit-transfer agreement exists with Dritte BV GmbH, with registered office in Leverkusen (Local Court of Cologne, HRB 52162), as controlling company,	a) October 27, 2006 Dr. Schulte b) Resolution folios 26 ff., Special Vol. XX Company-transfer agreement folios 27 ff., Special Vol. XX Consenting resolutions, folios 26 ff., 28 Special Vol. XX

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
					whose part concerning the profit transfer will take effect on January 1, 2007, to which the stockholders' meeting consented by resolution of September 13, 2006.	
21				84. Prof. Dr. Busch, Andreas *Aug. 26, 1963, of Kelkheim *Prokura* held jointly with a member of Board of management or another *Prokurist*		a) November 9, 2006 Richter
22	a) Bayer Schering Pharma Aktiengesellschaft		b) No longer a member of the Board of Management: 7. Dr. Dorrepaal, Karin No longer a member of the Board of Management: 1. Dr. Ing. Erlen, Hubertus No longer a member of the Board of Management: 8. Prof. Dr. Metternich, Rainer No longer a member of the Board of Management: 5. Dr. Spiekerkötter, Jörg Member of the Board of Management: 9. Higgins, Arthur J., *Mar. 6, 1956, of Düsseldorf Member of the Board of Management: 10. Baumann, Werner, *Oct. 6, 1962, of Krefeld Member of the Board of Management: 11. Dr. Riemann, Gunnar, *Oct. 26, 1958, of Leverkusen	85. Schmidt, Sven, *Jul. 27, 1968, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* Signatory authorization revoked: 20. Amsink, Gerold Signatory authorization revoked: 41. Schröder, Jürgen Signatory authorization revoked: 27. Dr. McBride, Garth Signatory authorization revoked: 32. Unglaube, Jürgen	a) By resolution of the stockholders' meeting of September 13, 2006, § 1 (1) (Name of Company) of the articles of incorporation was amended. The amendment will take effect on December 29, 2006. Section 13 (Compensation of the Supervisory Board) was also amended. This amendment will take effect on January 2, 2007.	a) December 20, 2006 Wohlfeil b) Resolution folios 86 ff
23	b) The annotation concerning the branch office is reworded as follows per § 13 of the German Commercial Code (HGB):					a) January 10, 2007 Schulze

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1	2	3	4	5	6	7
	henceforth: Schering Aktiengesellschaft Zweigniederlassung Bergkamen 59192 Bergkamen					
24	b) Amendment to No. 1: Schering Aktiengesellschaft Zweigniederlassung Bergkamen 59192 Bergkamen henceforth: Bayer Schering Pharma Aktiengesellschaft Zweigniederlassung Bergkamen 59192 Bergkamen			86. Dr. Kreuzburg, Christa, *Dec. 28, 1959, of Duisburg *Prokura* held jointly with a member of Board of management or another *Prokurist*		a) January 17, 2007 Waligorski
25				Signatory authorization revoked: 1. Rademacher, Gilbert Signatory authorization revoked: 33. Dr. Müller, Bernd Signatory authorization revoked: 68. Seeger, Stefan Signatory authorization revoked: 73. Dr. Geisler, Viktor Signatory authorization revoked: 75. Dr. Menken, Klaus Signatory authorization revoked: 82. Dr. Kilger, Ute 87. Dr. Angerbauer, Rolf, *Jun. 20, 1951, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist*		a) March 5, 2007 Waligorski

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1	2	3	4	5	6	7
				88. Behrens, Jens, *Mar. 22, 1964, of Niederkassel *Prokura* held jointly with a member of Board of management or another *Prokurist* 89. Bergmann, Ulrich, *Jan. 7, 1966, of Berlin *Prokura* held jointly with a member of Board of management or another *Prokurist* 90. Dr. Brocks, Dietrich, *Jun. 4, 1950, of Bergisch Gladbach *Prokura* held jointly with a member of Board of management or another *Prokurist* 91. Dr. Bühner, Klaus, *Apr. 3, 1954, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 92. Dr. de Jonge, Maarten, *Jul. 1, 1977, of Weeze *Prokura* held jointly with a member of Board of management or another *Prokurist* 93.		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Decker-Conradi, Jörg, *Jan. 17, 1965, of Hennef *Prokura* held jointly with a member of Board of management or another *Prokurist* 94. Dr. Fischer, Horst, *Jul. 17, 1954, of Cologne *Prokura* held jointly with a member of Board of management or another *Prokurist* 95. Dr. Flessner, Timo, *Nov. 11, 1970, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 96. Font, Jean-Christophe, *May 11, 1964, of Colmar, France *Prokura* held jointly with a member of Board of management or another *Prokurist* 97. Dr. Freund, Wolf-Dietrich, *Dec. 19, 1960, of Leichlingen *Prokura* held jointly with a member of Board of management or another *Prokurist* 98. Dr. Frie, Monika, *Mar. 6, 1956, of Odenthal		

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1	2	3	4	5	6	7
				Prokura held jointly with a member of Board of management or another *Prokurist* 99. Guenther, Andreas, *Feb. 3, 1961, of Sankt Augustin *Prokura* held jointly with a member of Board of management or another *Prokurist* 100. Günter, Monika, *Jul. 25, 1947, of Wolfen *Prokura* held jointly with a member of Board of management or another *Prokurist* 101. Dr. Hagen, Gustav, *Jan. 5, 1963, of Leverkusen *Prokura* held jointly with a member of Board of management or another *Prokurist* 102. Härtel, Frank, *Sep. 1, 1964, of Leverkusen *Prokura* held jointly with a member of Board of management or another *Prokurist* 103. Heckler, Robert, *Nov. 22, 1967, of Bonn *Prokura* held jointly with a member of Board of		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				management or another *Prokurist* 104. Dr. Heiden, Paul-Gerhard, *Mar. 24, 1958, of Leichlingen *Prokura* held jointly with a member of Board of management or another *Prokurist* 105. Dr. Höhl, Hans-Walter, *Aug. 19, 1954, of Burscheid *Prokura* held jointly with a member of Board of management or another *Prokurist* 106. Dr. Kanhai, Wolfgang, *Apr. 30, 1962, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 107. Klusik, Hartmut, *Jul. 30, 1956, of Leverkusen *Prokura* held jointly with a member of Board of management or another *Prokurist* 108. Lohkamp-Heikaus, Gudrun, *Nov. 9, 1957, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist*		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				109. Dr. Michaelis, Johannes, *Oct. 13, 1959, of Leverkusen *Prokura* held jointly with a member of Board of management or another *Prokurist* 110. Milon, Jean-Philippe, *Sep. 15, 1960, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 111. Dr. Möller, Jörg, *Nov. 11, 1964, of Meltmann *Prokura* held jointly with a member of Board of management or another *Prokurist* 112. Dr. Neipp, Joachim, *Jul. 9, 1949, of Langenfeld *Prokura* held jointly with a member of Board of management or another *Prokurist* 113. Dr. Pickel, Markus, *Apr. 28, 1962, of Leichlingen *Prokura* held jointly with a member of Board of management or another *Prokurist* 114. Dr. Rall, Klaus, *Jun. 24, 1960, of Leverkusen		

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1	2	3	4	5	6	7
				Prokura held jointly with a member of Board of management or another *Prokurist* 115. Salge, Andreas, *Jul. 17, 1958, of Leverkusen *Prokura* held jointly with a member of Board of management or another *Prokurist* 116. Schmidt, Jens, *Mar. 24, 1969, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 117. Dr. Schneider, Stephan, *Mar. 26, 1959, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 118. Dr. Schöneseiffen, Josef, *Sep. 24, 1953, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 119. Dr. Streicher-Saled, Ursula, *May 22, 1957, of Düsseldorf *Prokura* held jointly with a member of Board of		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				management or another *Prokurist* 120. Dr. von Keutz, Eckardt, *Jan. 7, 1956, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 121. Dr. Wild, Hanno, *Jun. 23, 1957, of Wuppertal *Prokura* held jointly with a member of Board of management or another *Prokurist* 122. Dr. Zimmermann, Jürgen, *Dec. 13, 1954, of Odenthal *Prokura* held jointly with a member of Board of management or another *Prokurist*		
26				Amendment to No. 94: *ex officio* (correction of clerical error): Dr. Fischer, Horst, *Jul. 10, 1954, of Cologne *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 119: *ex officio* (correction of clerical error):		a) March 13, 2007 Waligorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Dr. Streicher-Saied, Ursula, *May 22, 1957, of Düsseldorf *Prokura* held jointly with a member of Board of management or another *Prokurist*		
27			b) Member of the Board of Management: 12. Dr. Malik, Kemal, *Sep. 29, 1962, of Berlin No longer a member of the Board of Management: 6. Rubin, Marc			a) March 19, 2007 Waligorski
28			b) Member of the Board of Management: 13. Prof. Dr. Busch, Andreas, *Aug. 26, 1963, of Wuppertal			a) April 27, 2007 Waligorski
29				123. Dr. Atzor, Michael, *May 31, 1956, of Leverkusen *Prokura* held jointly with a member of Board of Management or another *Prokurist* 124. Berrang, Thomas, *Apr. 29, 1950, of Leichlingen *Prokura* held jointly with a member of Board of Management or another *Prokurist* 125. Dr. Bey, Alexander, *Apr. 2, 1962, of Cologne *Prokura* held jointly with a member of Board of		a) June 8, 2007 Waligorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Management or another *Prokurist* 126. Dr. Brill, Gisela, *Nov. 18, 1951, of Düsseldorf *Prokura* held jointly with a member of Board of Management or another *Prokurist* 127. Dr. Grosse-Bley, Michael, *May 4, 1958, of Leverkusen *Prokura* held jointly with a member of Board of Management or another *Prokurist* 128. Dr. Klotz, Rainer, *Sep. 30, 1953, of Niederkassel *Prokura* held jointly with a member of Board of Management or another *Prokurist* 129. Dr. Königer, Ursula, *Apr. 5, 1969, of Berlin *Prokura* held jointly with a member of Board of Management or another *Prokurist* 130. Meixner, Frank, *Feb. 18, 1966, of Düsseldorf *Prokura* held jointly with a member of Board of Management or another *Prokurist*		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				131. Dr. Pintsch, Tanja, *Jun. 3, 1973, of Berlin *Prokura* held jointly with a member of Board of Management or another *Prokurist* 132. Reinkober, Ingrid, *Mar. 15, 1960, of Leverkusen *Prokura* held jointly with a member of Board of Management or another *Prokurist* 133. Dr. Thomaier, Jörg, *Nov. 23, 1966, of Bergisch Gladbach *Prokura* held jointly with a member of Board of Management or another *Prokurist* Signatory authorization revoked: 23. Ünal, Kemalettin Signatory authorization revoked: 52. Dr. Förster, Jutta Signatory authorization revoked: 59. Schlosser, Harald Signatory authorization revoked: 80. Schumann, Arnd		
30					b) Based on the merger agreement of August 20, 2007 and the consenting resolution of the same date of the company being acquired, IDF Institut	a) August 30, 2007 Schmidt

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
					für Diagnostikforschung GmbH, with registered office in Berlin (Local Court of Charlottenburg, HRB 24843), was merged into the Company after being wound up without going into liquidation and having all of its assets and liabilities transferred to the Company.	
31				Signatory authorization revoked: 84. Prof. Dr. Busch, Andreas		a) October 10, 2007 Waligorski
32				Signatory authorization revoked: 114. Dr. Rall, Klaus Signatory authorization revoked: 122. Dr. Zimmermann, Jürgen		a) November 14, 2007 Waligorski
33				134. Drescher, Günter, *Aug. 22, 1961, of Nordwalde Individual authorized signatory with full power of representation (Prokurist).		a) December 4, 2007 Waligorski
34				135. Schalk, Christian, *May 23, 1966, of Leverkusen *Prokura* held jointly with a member of Board of Management or another *Prokurist* Signatory authorization revoked: 8. Dr. Raack, Rainer Signatory authorization revoked: 35. Eierdanz, Angelika		a) January 30, 2008 Waligorski
35					b)	a)

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
					Based on the merger agreement of June 4, 2008 and the consenting resolution of the same date of the company being acquired, Schering-Forschungsgesellschaft, with registered office in Berlin (Local Court of Charlottenburg, HRB 39650), was merged into the Company after being wound up without going into liquidation and having all of its assets and liabilities transferred to the Company.	June 10, 2008 Schmidt
36				136. Dr. Bayreuther, Stefan, *Jun. 4, 1969, of Düsseldorf Individual authorized signatory with full power of representation (Prokurist). 137. Brill, Klaus, *Feb. 14, 1953, of Berlin Individual authorized signatory with full power of representation (Prokurist). 138. Devoy, Michael, *Sep. 28, 1962, of Berlin Individual authorized signatory with full power of representation (Prokurist). 139. Dr. Hausner, Thomas-Peter, *Apr. 13, 1959, of Berlin Individual authorized signatory with full power of representation (Prokurist). 140. Linder, Claudia, *Apr. 5, 1966, of Solingen		a) June 20, 2008 Wallgorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Individual authorized signatory with full power of representation (Prokurist). 141. Yeomans, Michael, *Jun. 8, 1949, of Berlin Individual authorized signatory with full power of representation (Prokurist). Signatory authorization revoked: 19. Bernhardt, Wilfried		
37				142. Bier, Bernd-Peter, *Jul. 15, 1966, of Cologne Individual authorized signatory with full power of representation (Prokurist). 143. von Schmeling, Ulrike, *Feb. 28, 1954, of Bergisch Gladbach Individual authorized signatory with full power of representation (Prokurist). Amendment to no. 108: due to change of name Lohkamp, Gudrun, *Nov. 9, 1957, of Wuppertal *Prokura held jointly with a member of the Board of Management or another Prokurist* Signatory authorization revoked:		a) July 28, 2008 Waligorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				14. Dr. Dohse, Knuth Signatory authorization revoked: 22. Dr. Papendieck, Hatto Signatory authorization revoked: 43. Fragner, Reinhard Signatory authorization revoked: 61. Göckel, Thomas		
38				Signatory authorization revoked: 70. Schmitt, Thomas		a) July 31, 2008 Waligorski
39				144. Mechelhoff, Ralf, *Sep. 27, 1953, of Münster Individual authorized signatory with full power of representation (Prokurist). 145. Prof. Dr. Schneider, Martin, *Nov. 23, 1951, of Berlin Individual authorized signatory with full power of representation (Prokurist).		a) August 8, 2008 Waligorski
40					b) The stockholders' meeting of January 17, 2007, resolved that the shares held by the remaining stockholders (minority stockholders) be transferred to the principal stockholder, Bayer Schering GmbH, headquartered in Cologne (Local Court of Cologne, HRB 52162), against cash compensation.	a) September 25, 2008 Schmidt
41			b) Member of the Board of Management: 14. Fibig, Andreas, *Feb. 23, 1962,			a) October 6, 2008 Waligorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
			of Berlin No longer a member of the Board of Management: 9. Higgins, Arthur J.			
42			b) Member of the Board of Management: 15. Dr. Bernd, Metzner, *Oct. 13, 1970, of Hernau			a) November 3, 2008 Waligorski
43				146. Dr. Petry, Wolfgang, *Aug. 1, 1958, of Berlin Individual authorized signatory with full power of representation (Prokurist). 147. Schmitt, Thomas, *May 18, 1970, of Berlin Individual authorized signatory with full power of representation (Prokurist). Signatory authorization revoked: 78. Gorski, Cornelia		a) November 10, 2008 Waligorski
44		EUR 194,001,000			a) By resolution of the stockholders' meeting of December 4, 2008, the capital stock was increased by EUR 1,000 to EUR 194,001,000 for the purposes of the merger with Bayer HealthCare Aktiengesellschaft, headquartered in Leverkusen (Local Court of Cologne, HRB 49694), and § 4 (Capital stock, shares) of the articles of incorporation was amended. The capital stock increase has been effected. b) As a result of the merger, the control and profit-transfer agreement with	a) December 9, 2008 Schmidt

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
					Dritte BV GmbH (now Bayer Schering GmbH), headquartered in Leverkusen, now exists with Bayer AG, headquartered in Leverkusen (Local Court of Cologne, HRB 48248).	
45					a) By resolution of the stockholders' meeting of December 11, 2008, § 13 of the articles of incorporation (Compensation of the Supervisory Board) was amended. b) On the basis of the merger agreement of December 4, 2008 and the consenting resolutions made on the same day, Bayer HealthCare Aktiengesellschaft, headquartered in Leverkusen (Local Court of Cologne, HRB 49894), was merged into the Company, having the effect of being wound up without going into liquidation, and having all of its assets and liabilities transferred to the Company.	a) December 30, 2008 Schmidt
46	b) Business address: Müllerstraße 178, 13353 Berlin			148. Dr. Bechem, Martin, * Aug. 7, 1954, of Wuppertal Individual authorized signatory with full power of representation (Prokurist). 149. Dr. Brinda, Maria Luisa, * May 28, 1956, of Leverkusen Individual authorized signatory with full power of representation (Prokurist). 150. Dr. Brehm, Oliver, * Jan. 18, 1965, of Langenfeld Individual authorized signatory		a) January 22, 2009 Wallgorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				with full power of representation (Prokurist). 151. Dr. Burkert, Frank, * Jan. 31, 1950, of Odenthal Individual authorized signatory with full power of representation (Prokurist). 152. Dr. Groß, Dietmar, * Aug. 31, 1962, of Teltow Individual authorized signatory with full power of representation (Prokurist). 153. Dr. Gunkel, Frank-Andreas, * Mar. 31, 1959, of Bergisch Gladbach Individual authorized signatory with full power of representation (Prokurist). 154. Dr. Harenberg, Horst-Eberhard, * Jan. 8, 1950, of Berlin Individual authorized signatory with full power of representation (Prokurist). 155. Dr. Hörlein, Hans-Dietrich, * May 25, 1949, of Wuppertal Individual authorized signatory with full power of representation (Prokurist). 156. Dr. Jacke, Jürgen, * Nov. 11, 1960, of Unna		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Individual authorized signatory with full power of representation (Prokurist). 157. Dr. Jelich, Klaus, * Mar. 2, 1953, of Wuppertal Individual authorized signatory with full power of representation (Prokurist). 158. Klotzki, Volker, * Jun. 23, 1959, of Langenfeld Individual authorized signatory with full power of representation (Prokurist). 159. Dr. Köhler, Ferdinand, * Nov. 15, 1954, of Düsseldorf Individual authorized signatory with full power of representation (Prokurist). 160. Dr. Kraemer, Hans-Peter, * Mar. 3, 1949, of Mettmann Individual authorized signatory with full power of representation (Prokurist). 161. Krokowski, Reinhard, * Mar. 21, 1967, of Cologne Individual authorized signatory with full power of representation (Prokurist). 162. Dr. Kubin, Maria, * Jul. 25, 1962, of Langenfeld		

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1	2	3	4	5	6	7
				Individual authorized signatory with full power of representation (Prokurist). 163. Dr. Linkenheil, Dieter, * Aug. 30, 1955, of Mönchengladbach Individual authorized signatory with full power of representation (Prokurist). 164. Mohr, Thomas, * Jul. 30, 1956, of Berlin Individual authorized signatory with full power of representation (Prokurist). 165. Dr. Mohrs, Klaus-Helmut, * Dec. 16, 1952, of Wuppertal Individual authorized signatory with full power of representation (Prokurist). 166. Richartz, André, * Mar. 30, 1962, of Haan Individual authorized signatory with full power of representation (Prokurist). 167. Dr. Schultz, Michael, * Mar. 27, 1957, of Berlin Individual authorized signatory with full power of representation (Prokurist). 168. Dr. Smits, Philip,		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				* Jun. 2, 1959, of Berlin Individual authorized signatory with full power of representation (Prokurist). 169. Staunton, Angela, * Jun. 27, 1959, of Berlin Individual authorized signatory with full power of representation (Prokurist). 170. Talmage, Ian, * Feb. 11, 1950, of Düsseldorf Individual authorized signatory with full power of representation (Prokurist). 171. Wernecke, Knut, * Dec. 13, 1958, of Leichlingen Individual authorized signatory with full power of representation (Prokurist). Signatory authorization revoked: 76. Dr. Wozniewski, Thomas		
47			b) Amendment to No. 15: As a result of correction Member of the Board of Management: Dr. Metzner, Bernd, *Oct. 13, 1970, of Hernau	Amendment to No. 92: As a result of correction Dr. de Jonge, Maarten, *Feb. 13, 1958, of Hohen Neuendorf *Prokura held jointly with a member of the Board of Management or another Prokurist* Signatory authorization revoked:		a) February 12, 2009 Waligorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				79. Grohé, Ulrich		
48				172. Franzen, Reinhard, * Mar. 30, 1962, of Haan Individual authorized signatory with full power of representation (Prokurist). 173. Dr. Raubach, Hans-Joachim, * Oct. 31, 1969, of Bonn Individual authorized signatory with full power of representation (Prokurist). 174. Renner, Oliver, * Dec. 6, 1965, of Leverkusen Individual authorized signatory with full power of representation (Prokurist). 175. Schmidt, Joachim, * Apr. 15, 1967, of Leverkusen Individual authorized signatory with full power of representation (Prokurist).		a) March 6, 2009 Waligorski
49					b) On the basis of the merger agreement of March 17, 2009 and the consenting resolutions made on the same day, DIREVO Biotech Aktiengesellschaft, headquartered in Cologne (Local Court of Cologne, HRB 35249), was merged into the Company, having the effect of being wound up without going into liquidation, and having all of its assets and liabilities transferred to the Company.	a) March 31, 2009 Schmidt
50					b)	a)

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1	2	3	4	5	6	7
					On the basis of the merger agreement of March 17 2009 and the consenting resolutions made on the same day, BerliServe Professional Services GmbH, headquartered in Berlin (Local Court of Charlottenburg, HRB 74678), was merged into the Company, having the effect of being wound up without going into liquidation, and having all of its assets and liabilities transferred to the Company.	March 31, 2009 Schmidt
51				176. Blume, Helmut,* Sep. 11, 1959, of Lindlar Individual authorized signatory with full power of representation (Prokurist). Signatory authorization revoked: 161. Krokowski, Reinhard		a) April 20, 2009 Waligorski
52			b) Amendment to No. 15: As a result of correction of the place of residence Member of the Board of Management: Dr. Metzner, Bernd, *Oct. 13, 1970, of Hemau	177. Marschmann, Bernd, * Sep. 19, 1968, of Düsseldorf Individual authorized signatory with full power of representation (Prokurist). 178. Moritz, Matthias, * Oct. 3, 1959, of Cologne Individual authorized signatory with full power of representation (Prokurist). 179. Dr. Zimmermann, Jürgen, * Dec. 13, 1954, of Odenthal Individual authorized signatory with full power of representation (Prokurist).		a) April 30, 2009 Waligorski

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
53				Signatory authorization revoked: 5. Krüger, Horst		a) August 13, 2009 Rudolph
54			b) No longer a member of the Board of Management: 11. Dr. Riemann, Gunnar	Signatory authorization revoked: 86. Dr. Kreuzburg, Christa 180. Dr. Mrotzek, Werner, * Jul. 20, 1952, of Berlin Individual authorized signatory with full power of representation (Prokurist).		a) August 17, 2009 Kremer
55				181. Dr. Schauer, Gerhard, * Oct. 10, 1961, of Berlin Individual authorized signatory with full power of representation (Prokurist). 182. Dr. Wienhold, Christian, * Jun. 18, 1953, of Berlin Individual authorized signatory with full power of representation (Prokurist).		a) August 28, 2009 Boos
56					a) By resolution of the stockholders' meeting of August 26, 2009, the articles of incorporation as a whole were amended. b) The conditional capital created on April 26, 2001, no longer exists. The conditional capital created on April 16, 2004, no longer exists.	a) September 3, 2009 Wengert

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1	2	3	4	5	6	7
					The authorized capital of April 16, 2004, has expired. (Authorized Capital 2004/I)	
57			b) No longer a member of the Board of Management: 10. Baumann, Werner	183. Baldus, Berthold, * Mar. 12, 1954, of Berlin Individual authorized signatory with full power of representation (Prokurist). 184. Brüning, Lars, * Mar. 29, 1963, of Berlin Individual authorized signatory with full power of representation (Prokurist). 185. Dr. Hein, Thomas, * Sep. 29, 1963, of Neuruppin Individual authorized signatory with full power of representation (Prokurist). 186. Lauterbach, Christian, * Mar. 13, 1966, of Essen Individual authorized signatory with full power of representation (Prokurist). 187. Dr. Steindl, Ludwig, * Feb. 28, 1956, of Berg Individual authorized signatory with full power of representation (Prokurist). 188.		a) October 26, 2009 Köpke

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Dr. Trube, Claus Moritz, * Aug. 13, 1967, of Erkrath Individual authorized signatory with full power of representation (Prokurist).		
58				Signatory authorization revoked: 116. Schmidt, Jens 189. Dr. Fischer-Carius, Andreas, * Jan. 29, 1967, of Berlin Individual authorized signatory with full power of representation (Prokurist). 190. Dr. Wegner, Peter, * Apr. 30, 1955, of Berlin Individual authorized signatory with full power of representation (Prokurist).		a) January 26, 2010 Köpke
59				191. Schildmeyer, Gerrit, * Dec. 14, 1971, of Cologne Individual authorized signatory with full power of representation (Prokurist). 192. Dr. Wood, Clive, * Dec. 23, 1960, of Heiligenhaus Individual authorized signatory with full power of representation (Prokurist).		a) May 31, 2010 Köpke
60				193. Dr. Dussan Molinos, Alejandro, *Jan. 10, 1964, of Berlin		a) June 10, 2010 Köpke

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Individual authorized signatory with full power of representation (Prokurist). 194. Dr. Waibel, Franz, *May 9, 1959, of Berlin Individual authorized signatory with full power of representation (Prokurist).		
61				Amendment to No. 13: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Benz, Wolfgang *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 16: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Klose, Walter *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 21: Correction *ex officio* in the current printout of the presentation of the authorization.		a) June 10, 2010 Köpke

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Dr. Haumesser, Winfried *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 24: Correction *ex officio* in the current printout of the presentation of the authorization. Alburg, Frank *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 36: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Hartmann, Uwe *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 38: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Hübl, Dieter *Prokura held jointly with a member of the Board of Management or another Prokurist*		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Amendment to No. 39: Correction *ex officio* in the current printout of the presentation of the authorization. Steinbeck, Matthias *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 42: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Hakert, Hubertus *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 44: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Schmeier Dieter *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 47: Correction *ex officio* in the current printout of the presentation of the		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				authorization. Dr. Renneke, Franz-Josef *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 48: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Muráti-Laebe, Ilona *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 49: Correction *ex officio* in the current printout of the presentation of the authorization. Krieger, Andreas *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 53: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Schmid, Eva *Prokura held jointly with a member of the Board of*		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Management or another Prokurist Amendment to No. 55: Correction *ex officio* in the current printout of the presentation of the authorization. Topf-Schleuning, Maren *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 56: Correction *ex officio* in the current printout of the presentation of the authorization. Schröder, Steffen *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 57: Correction *ex officio* in the current printout of the presentation of the authorization. Baron von Behr, Nicolas *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 60: Correction *ex officio* in the		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				current printout of the presentation of the authorization. Dr. Scheuermann, Hans-Jörg *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 63: Correction *ex officio* in the current printout of the presentation of the authorization. Baltzer, Markus *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 64: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Noeske-Jungblut, Christiane, née Noeske *Prokura held jointly with a member of the Board of Management or another Prokurist* Amendment to No. 65: Correction *ex officio* in the current printout of the presentation of the authorization. Dr. Eisenhauer, Martin		

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Prokura held jointly with a member of the Board of Management or another Prokurist Amendment to No. 67: Correction *ex officio* in the current printout of the presentation of the authorization. Krüger, Gerd *Prokura held jointly with a member of the Board of Management or another Prokurist*		
62				Signatory authorization revoked: 117. Dr. Schneider, Stephan		a) June 23, 2010 Köpke
63			b) Amendment to No. 3: Date of birth added: Member of the Board of Management: Dr. Köstlin, Ulrich, *Dec. 31, 1952, of Berlin	195. De Prins, Werner, *Jul. 13, 1959, of Berlin Individual authorized signatory with full power of representation (Prokurist). 196. Dr. Oernskov, Flemming, *Jan. 21, 1958, of Berlin Individual authorized signatory with full power of representation (Prokurist). Signatory authorization revoked: 141. Yeomans, Michael Signatory authorization revoked: 188. Dr. Trube, Claus Moritz		a) July 7, 2010 Köpke

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Amendment to No. 107: Personal information supplemented. Dr. Klusik, Hartmut, *Jul. 30, 1956, of Leverkusen *Prokura held jointly with a member of the Board of Management or another Prokurist*		
64				197. Dr. Mangold, Matthias, *Feb. 10, 1961, of Berlin Individual authorized signatory with full power of representation (Prokurist).		a) September 8, 2010 Köpke
65				Signatory authorization revoked: 21. Dr. Haumesser, Winfried Signatory authorization revoked: 63. Baltzer, Markus Signatory authorization revoked: 88. Behrens, Jens Signatory authorization revoked: 92. Dr. de Jonge, Maarten Signatory authorization revoked: 131. Dr. Pintsch, Tanja Signatory authorization revoked: 150. Dr. Brehm, Oliver Signatory authorization revoked:		a) October 22, 2010 Köpke

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				154. Dr. Harenberg, Horst-Eberhard		
66				198. Dr. Ashman, Philip, *Feb. 25, 1965, of Berlin Individual authorized signatory with full power of representation (Prokurist). 199. Dr. Immler, Dorian, *Jun. 3,1972, of Leverkusen Individual authorized signatory with full power of representation (Prokurist).		a) November 8, 2010 Kremer
67				Signatory authorization revoked: 13. Dr. Benz, Wolfgang		a) November 22, 2010 Lampe
68				200. Dr. Leifker, Gregor, *Mar. 10, 1954, of Leverkusen Individual authorized signatory with full power of representation (Prokurist).		a) November 29, 2010 Köpke
69	b) The Zweigniederlassung (branch office) No. 1 in 59192 Bergkamen is cancelled.			201. Schneider, Ralf, *Apr. 14, 1964, of Leverkusen Individual authorized signatory with full power of representation (Prokurist).		a) December 27, 2010 Köpke
70				Signatory authorization revoked: 110. Milon, Jean-Philippe Signatory authorization revoked: 126. Dr. Brill, Gisela		a) February 14, 2011 Kremer

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
71				Change to No. 172: now Franzen, Reinhard, *Apr. 4, 1958, of Berlin Individual authorized signatory with full power of representation (Prokurist).		a) February 25, 2011 Kremer
72					b) Under the Spin-Off and Acquisition Agreement of December 23, 2010, and the approval resolutions of the same date,, the company transferred part of its assets (pension and surviving dependents' benefits for former emplyees) to Bayer Altersversorgung GmbH (formerly 2. BHCV GmbH), registered office in Leverkusen (Local Court of Cologne, HRB 53571), by way of an spin-off.	a) March 29, 2011 Schmidt
73			b) No longer a member of the Board of Management: 3. Dr. Köstlin, Ulrich No longer a member of the Board of Management: 12. Dr. Malik, Kemal No longer a member of the Board of Management: 13. Prof. Dr. Busch, Andreas No longer a member of the Board of Management: 15. Dr. Metzner, Bernd Member of the Board of Management: 16. Dr. Klusik, Hartmut, *Jul. 30, 1956, of Leverkusen Member of the Board of Management: 17. Vehreschild, Manfred, *Aug. 9, 1957, of Leverkusen	Signatory authorization revoked: 85. Schmidt, Sven Signatory authorization revoked: 107. Dr. Klusik, Hartmut		a) April 12, 2011 Morgenstern
74				202. Prof. Dr. Busch, Andreas, *Aug. 26, 1963, of Wuppertal		a) April 14, 2011 Morgenstern

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				Individual authorized signatory with full power of representation (Prokurist). 203. Dr. Malik, Kemal, *Sep. 9, 1962, of Berlin Individual authorized signatory with full power of representation (Prokurist). Signatory authorization revoked: 118. Dr. Schöneseiffen, Josef Signatory authorization revoked: 139. Dr. Hausner, Thomas-Peter		
75				Signatory authorization revoked: 142. Bier, Bernd-Peter		a) April 19, 2011 Beyer
76				204. Triana, Julio, *Sep. 21, 1965, of Berlin Individual authorized signatory with full power of representation (Prokurist).		a) May 3, 2011 Hagen
77				Signatory authorization revoked: 96. Font, Jean-Christophe Signatory authorization revoked: 44. Dr. Schmeler, Dieter Signatory authorization revoked: 48. Dr. Muráti-Laebe, Ilona Signatory authorization revoked: 81. Dr. Maier, Hans Signatory authorization revoked:		a) May 24, 2011 Beyer

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
				98. Dr. Frie, Monika Signatory authorization revoked: 127. Dr. Groß-Bley, Michael Signatory authorization revoked: 159. Dr. Köhler, Ferdinand Signatory authorization revoked: 183. Baldu, Berthold 205. Grothe, Manfred, *Feb. 25, 1964, of Borgsdorf Individual authorized signatory with full power of representation (Prokurist). 206. Dr. Relsinger, Claus-Peter, *Sep. 30, 1967, of Berlin Individual authorized signatory with full power of representation (Prokurist). Change to No. 95: Corretion of family name. Dr. Fleßner, Timo, *Nov. 26, 1970, of Wuppertal *Prokura* held jointly with a member of the Board of Management or another *Prokurist*		
78	Bayer Pharma Aktiengesellschaft				a) By resolution of the stockholders' meeting of February 14, 2011, §1 (1) (Name of Company) of the articles of incorporation was amended.	a) July 1, 2011 Schmidt

Entry no.	a) Company name b) Registered office, office, business address, authorized recipient, branches c) Object of the Company	Capital stock or nominal capital	a) General provisions on representation b) Board of Management, executive body, executive directors, general partners, managing directors, authorized representatives and special powers of representation	*Prokura* (Signatory Authorization)	a) Legal form, inception, articles of association / articles of incorporation or partnership agreement b) other legal relations	a) Date of entry b) Comments
1	2	3	4	5	6	7
79				207. Dr. Bertram, Christoph, *Mar. 22, 1966, of Berlin Individual authorized signatory with full power of representation (Prokurist). 208. Dr. Haning, Helmut, *Oct. 2, 1965, of Wuppertal Individual authorized signatory with full power of representation (Prokurist). 209. Rosenberg, Dirk, *May 4, 1967, of Wuppertal Individual authorized signatory with full power of representation (Prokurist). Signatory authorization revoked: 113. Dr. Pickel, Markus Signatory authorization revoked: 164. Mohr, Thomas	a) July 11, 2011 Morgenstern

The translated version of the Commercial Register is a convenience translation.
Only its German version is legally binding.

I hereby certify that the foregoing (60 pages) is a truthful and complete translation of the 95-page original German document.
Cologne, July 22, 2011

Dipl.-Übers. Günter Merboth
vom LG Köln ermächtigter Übersetzer für die englische und die italienische Sprache
Kuenstr. 10 · D-50733 Köln

Authorized English and Italian translator for the district of the Higher Regional Court of Cologne, Germany

0396

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.

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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	[signature]	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

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 , a Corporation
(Name of Assignee) (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.

F

Janssen Pharmaceuticals, Inc.
1000 US Highway 202
Raritan, NJ 08869
908.927.5757 tel
908.927.2823 fax
www.janssenpharmaceuticalsinc.com

janssen
PHARMACEUTICAL COMPANIES
OF Johnson & Johnson

August 23, 2011

Bayer Pharma Aktiengesellschaft
Mullerstrasse 178
Berlin
Germany 13535

Dear Sir or Madam:

Janssen Pharmaceuticals, Inc. (hereinafter "JPI"), the exclusive licensee in the US and marketing applicant for Xarelto® (rivaroxaban), hereby authorizes Bayer Pharma Aktiengesellschaft (hereinafter "BPA") to rely upon the information generated and activities undertaken either by JPI or on its behalf, for the IND and NDA phases of regulatory review of Xarelto® (collectively "Information") for the limited purpose of BPA submitting and prosecuting an application for patent term extension under 35 U.S.C. §156 for U.S. Patent No. 7,157,456. For avoidance of doubt, Information shall include that information generated and activities undertaken by Johnson & Johnson Pharmaceutical Research and Development, LLC in support of the regulatory review and FDA approval of Xarelto®.

Very truly yours,
Janssen Pharmaceuticals, Inc.

Patricia C. Lukens

Patricia C. Lukens
Vice President, Law

XARELTO®

(rivaroxaban) film-coated oral tablets

02X11070A
(07/11)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARELTO® (rivaroxaban) safely and effectively. See full prescribing information for XARELTO

XARELTO (rivaroxaban) film-coated oral tablets

Initial U.S. Approval: 2011

WARNING: SURGICAL SETTINGS--SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.1) and Drug Interactions (7)].*

----------INDICATIONS AND USAGE----------

XARELTO is a factor Xa inhibitor indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. (1)

----------DOSAGE AND ADMINISTRATION----------

- 10 mg orally, once daily with or without food (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablet: 10 mg (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to XARELTO (4)
- Active major bleeding (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Pregnancy related hemorrhage: Use XARELTO with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reaction (>5%) was bleeding. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Combined P-gp and strong CYP3A4 inhibitors: Avoid concomitant use unless the lack of a significant interaction is proven (7.1)
- Combined P-gp and weak or moderate CYP3A4 inhibitors: Avoid concomitant use unless the benefit outweighs the bleeding risk in patients with renal impairment (7.2)
- Combined P-gp and strong CYP3A4 inducers: Avoid concomitant use or consider an increased dose (2.1, 7.3)
- Anticoagulants: Avoid concomitant use (7.4)
- Clopidogrel: Avoid concomitant use unless the benefit outweighs the bleeding risk (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: discontinue drug or discontinue nursing (8.3)
- Renal impairment: Avoid use in patients with severe impairment (CrCl <30 mL/min). Use with caution in moderate impairment (CrCl 30 to <50 mL/min) (8.7)
- Hepatic impairment: Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or in patients with any degree of hepatic disease associated with coagulopathy (8.8)

See 17 for PATIENT COUNSELING INFORMATION.

Issued: July 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SURGICAL SETTINGS--SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.1) and Drug Interactions (7)].*

1 INDICATIONS AND USAGE

XARELTO (rivaroxaban) Tablets are indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

2 DOSAGE AND ADMINISTRATION

The recommended dose of XARELTO is 10 mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

If a dose of XARELTO is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and continued on the following day with the once daily intake as recommended.

Administration via GI feeding tube:
Rivaroxaban absorption is dependent on the site of drug release in the gastrointestinal (GI) tract (gastric versus small intestine). When administering XARELTO as a crushed tablet via a feeding tube, confirm gastric placement of the tube *[see Clinical Pharmacology (12.3)]*.

2.1 Use with P-gp and Strong CYP3A4 Inducers

Concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) should be avoided. A XARELTO dose increase to 20 mg (i.e., two 10 mg tablets) should be considered if these drugs must be coadministered. The 20 mg dose should be taken with food *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

XARELTO 10 mg tablets are round, light red, biconvex and film-coated with a triangle pointing down above a "10" marked on one side and "Xa" on the other side.

4 CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- hypersensitivity to XARELTO
- active major bleeding *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

5.2 Risk of Bleeding

XARELTO increases the risk of bleeding and can cause serious and fatal bleeding. Major hemorrhages including intracranial, epidural hematoma, gastrointestinal, retinal, and adrenal bleeding have been reported. Use XARELTO with caution in conditions with increased risk of hemorrhage.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include platelet aggregation inhibitors, other antithrombotic agents, fibrinolytic therapy, thienopyridines and chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.4), (7.5), (7.6)]*.

Bleeding can occur at any site during therapy with XARELTO. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site. Promptly evaluate any signs or symptoms of blood loss.

5.3 Risk of Pregnancy Related Hemorrhage

XARELTO should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

5.4 Renal Impairment

Avoid the use of XARELTO in patients with severe renal impairment (creatinine clearance <30 mL/min) due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.

Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations (8.7)]*.

XARELTO® (rivaroxaban) film-coated oral tablets

5.5 Hepatic Impairment

Clinical data in patients with moderate hepatic impairment indicate a significant increase in rivaroxaban exposure and pharmacodynamic effects. No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Use in Specific Populations (8.8)]*.

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Trials

In three randomized, controlled clinical trials (RECORD 1-3) in elective joint replacement surgery, 4487 patients received XARELTO 10 mg orally once daily. The mean duration of XARELTO treatment was 11.9 days in the total knee replacement study and 33.4 days in the total hip replacement studies. Overall, the mean age of the patients studied in the XARELTO group was 64 years, 59% were female and 82% were Caucasian. Twenty-seven percent (1206) of patients underwent knee replacement surgery and 73% (3281) underwent hip replacement surgery.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

6.2 Hemorrhage

The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions (5.2)]*. The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 1.

Table 1: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N = 4487 n (%)**	**N = 4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N = 3281 n (%)**	**N = 3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N = 1206 n (%)**	**N = 1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

6.3 Other Adverse Reactions

Table 2 shows other adverse drug reactions (ADRs) reported in ≥1% of XARELTO-treated patients in the RECORD clinical studies.

Table 2: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

System/Organ Class Adverse Reaction	XARELTO 10 mg (N = 4487) n (%)	Enoxaparin† (N = 4524) n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* ADR occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication.

† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

The following ADR occurred in <1% of XARELTO-treated patients in the clinical studies:

Renal and urinary disorders: dysuria

The laboratory abnormalities in Table 3 were observed in clinical studies:

Table 3: Laboratory Abnormalities in RECORD 1-3 Clinical Studies

Laboratory Abnormality	XARELTO 10 mg	Enoxaparin*
Alanine aminotransferase >3 x ULN	114/4441 (2.6%)	167/4456 (3.8%)
Aspartate aminotransferase >3 x ULN	122/4441 (2.8%)	152/4456 (3.4%)
Total bilirubin >1.5 x ULN	140/4442 (3.2%)	128/4456 (2.9%)
Gamma-glutamyltransferase >3 x ULN	292/4442 (6.6%)	391/4457 (8.8%)
Platelet counts <100,000/mm³ or <50% of baseline value	116/4425 (2.6%)	131/4447 (3.0%)

*Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

6.4 Postmarketing Experience

The following additional adverse reactions have been reported in countries where XARELTO has been marketed. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis

Immune system disorder: hypersensitivity, anaphylactic reaction, anaphylactic shock

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

7 DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters may result in changes in rivaroxaban exposure.

7.1 Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- *Ketoconazole (combined P-gp and strong CYP3A4 inhibitor):* Steady-state rivaroxaban AUC and C_{max} increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Ritonavir (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Clarithromycin (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.

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- *Erythromycin (combined P-gp and moderate CYP3A4 inhibitor):* Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

When clinical data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

7.2 Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Based on simulated pharmacokinetic data, patients with renal impairment receiving XARELTO with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected. Since these increases may increase bleeding risk, use XARELTO in this situation only if the potential benefit justifies the potential risk *[see Use in Specific Populations (8.7)]*.

7.3 Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems

In a drug interaction study, co-administration of XARELTO (20 mg single dose with food) with a drug that is a combined P-gp and strong CYP3A4 inducer (rifampicin titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in AUC and C_{max}, respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Consider increasing the XARELTO dose if these drugs must be coadministered *[see Dosage and Administration (2.1)]*.

7.4 Anticoagulants

In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and XARELTO (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. Enoxaparin did not affect the pharmacokinetics of rivaroxaban. In another study, single doses of warfarin (15 mg) and XARELTO (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Warfarin did not affect the pharmacokinetics of rivaroxaban. The safety of long-term concomitant use of these drugs has not been studied.

Avoid concurrent use of XARELTO with other anticoagulants due to the increased bleeding risk other than during therapeutic transition periods where patients should be observed closely. Promptly evaluate any signs or symptoms of blood loss *[see Warnings and Precautions (5.2)]*.

7.5 NSAIDs/Aspirin

In a single-dose drug interaction study there were no pharmacokinetic or pharmacodynamic interactions observed after concomitant administration of naproxen or aspirin (acetylsalicylic acid) with XARELTO. The safety of long-term concomitant use of these drugs has not been studied.

NSAIDs/aspirin are known to increase bleeding, and bleeding risk may be increased when these drugs are used concomitantly with XARELTO.

Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with NSAIDs and/or platelet aggregation inhibitors *[see Warnings and Precautions (5.2)]*.

7.6 Clopidogrel

In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and XARELTO (15 mg single dose) were co-administered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Avoid concurrent administration of clopidogrel with XARELTO unless the benefit outweighs the risk of increased bleeding *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no

increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 11 times the human exposure of unbound drug, based on AUC comparisons at the maximum recommended human dose of 10 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 40 times the human exposure of unbound drug.

8.2 Labor and Delivery

Safety and effectiveness of rivaroxaban during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 17 times maximum human exposure of the unbound drug at the human dose of 10 mg/day).

8.3 Nursing Mothers

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 53% were 65 years and over, while about 15% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years.

Elderly subjects exhibited an increase in exposure that may be caused by age related changes in renal function. For patients 65 years of age and older, consideration should be given to assessment of renal function prior to starting therapy with XARELTO. Promptly evaluate any signs or symptoms of blood loss *[see Clinical Pharmacology (12.3)]*.

8.6 Females of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

8.7 Renal Impairment

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Table 4). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed.

Table 4: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Renal Insufficiency from a Dedicated Renal Impairment Study

Parameter		Renal Impairment Class [CrCl (mL/min)]		
		Mild [50 to 79] N=8	Moderate [30 to 49] N=8	Severe [15 to 29] N=8
Exposure	AUC	44	52	64
(% increase relative to normal)	C_{max}	28	12	26
FXa Inhibition	AUC	50	86	100
(% increase relative to normal)	E_{max}	9	10	12
PT Prolongation	AUC	33	116	144
(% increase relative to normal)	E_{max}	4	17	20

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect; and CrCl = creatinine clearance

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Patients with any degree of renal impairment with concurrent use of P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure which may increase bleeding risk *[see Drug Interactions (7.2)]*.

The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with moderate renal impairment and reported a possible increase in total VTE in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Avoid the use of XARELTO in patients with severe renal impairment (CrCl <30 mL/min) *[see Warnings and Precautions (5.2, 5.4)]*.

8.8 Hepatic Impairment

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Table 5). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B). Increases in pharmacodynamic effects were also observed.

Table 5: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Hepatic Insufficiency from a Dedicated Hepatic Impairment Study

Parameter		Hepatic Impairment Class (Child-Pugh Class)	
		Mild (Child-Pugh A) N=8	Moderate (Child-Pugh B) N=8
Exposure	AUC	15	127
(% increase relative to normal)	C_{max}	0	27
FXa Inhibition	AUC	8	159
(% increase relative to normal)	E_{max}	0	24
PT Prolongation	AUC	6	114
(% increase relative to normal)	E_{max}	2	41

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect

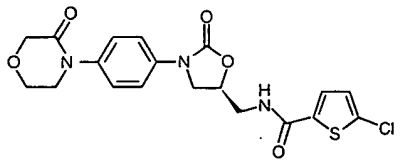
Avoid the use of XARELTO in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Warnings and Precautions (5.2, 5.5)]*.

10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. A specific antidote of rivaroxaban is not available. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Rivaroxaban, a factor Xa inhibitor, is the active ingredient in XARELTO Tablets with the chemical name 5-Chloro-N-{{(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl}-2-thiophenecarboxamide. The molecular formula of rivaroxaban is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. The structural formula is:



Rivaroxaban is a pure (*S*)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder. Rivaroxaban is only slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media.

Each XARELTO tablet contains 10 mg of rivaroxaban. The inactive ingredients of XARELTO are: Microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and Opadry® Pink, a proprietary filmcoating mixture containing polyethylene glycol 3350, hypromellose, titanium dioxide, and ferric oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XARELTO is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

12.2 Pharmacodynamics

Dose-dependent inhibition of factor Xa activity was observed in humans and the Neoplastin® prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban. There are no data on the use of the International Normalized Ratio (INR). The predictive value of these coagulation parameters for bleeding risk or efficacy has not been established.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is high (estimated to be 80% to 100%) for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

Rivaroxaban pharmacokinetics are linear with no relevant accumulation beyond steady-state after multiple doses. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.

The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Coadministration of XARELTO (30 mg single dose) with the H_2-receptor antagonist ranitidine (150 mg twice daily) or the antacid aluminum hydroxide/magnesium hydroxide (10 mL) did not show an effect on the bioavailability and exposure of rivaroxaban.

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) which can result in reduced absorption and related drug exposure *(see Dosage and Administration (2)).*

Distribution

Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism

Approximately 51% of an orally administered [^{14}C]-rivaroxaban dose was recovered as metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion

Following oral administration of a [^{14}C]-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug). Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated Bcrp). Rivaroxaban's affinity for influx transporter proteins is unknown.

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Special Populations

Gender

Gender did not influence the pharmacokinetics or pharmacodynamics of XARELTO.

Race

Healthy Japanese subjects were found to have 50% higher exposures compared to other ethnicities including Chinese.

Elderly

In clinical studies, elderly subjects exhibited higher rivaroxaban plasma concentrations than younger subjects with mean AUC values being approximately 50% higher, mainly due to reduced (apparent) total body and renal clearance. Age related changes in renal function may play a role in this age effect. The terminal elimination half-life is 11 to 13 hours in the elderly *(see Use in Specific Populations (8.5)).*

Body Weight

Extremes in body weight (<50 kg or >120 kg) did not influence rivaroxaban exposure.

Drug Interactions

In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A4 nor induces CYP1A2, 2B6, 2C19, or 3A4.

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In vitro data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.

In addition, there were no significant pharmacokinetic interactions observed in studies comparing concomitant rivaroxaban 20 mg and 7.5 mg single dose of midazolam (substrate of CYP3A4), 0.375 mg once-daily dose of digoxin (substrate of P-gp), or 20 mg once daily dose of atorvastatin (substrate of CYP3A4 and P-gp) in healthy volunteers.

12.4 QT/QTc Prolongation

In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for XARELTO (15 mg and 45 mg, single-dose).

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 3- and 5-times, respectively, the human exposure of unbound drug at the human dose of 10 mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 4- and 10-times, respectively, the human exposure.

Rivaroxaban was not mutagenic in bacteria (Ames-Test) or clastogenic in V79 Chinese hamster lung cells *in vitro* or in the mouse micronucleus test *in vivo.*

No impairment of fertility was observed in male or female rats when given up to 200 mg/kg/day of rivaroxaban orally. This dose resulted in exposure levels, based on the unbound AUC, at least 33 times the exposure in humans given 10 mg rivaroxaban daily.

14 CLINICAL STUDIES

XARELTO was studied in 9011 patients (4487 XARELTO-treated, 4524 enoxaparin-treated patients) in the RECORD 1, 2, and 3 studies.

The two randomized, double-blind, clinical studies (RECORD 1 and 2) in patients undergoing elective total hip replacement surgery compared XARELTO 10 mg once daily starting at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin 40 mg once daily started 12 hours preoperatively. In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age [± standard deviation (SD)] was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥65 years and 55% of patients were female. More than 82% of patients were White, 7% were Asian, and less than 2% were Black. The studies excluded patients undergoing staged bilateral total hip replacement, patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min, or patients with significant liver disease (hepatitis or cirrhosis). In RECORD 1, the mean exposure duration (± SD) to active XARELTO and enoxaparin was 33.3 ± 7.0 and 33.6 ± 8.3 days, respectively. In RECORD 2, the mean exposure duration to active XARELTO and enoxaparin was 33.5 ± 6.9 and 12.4 ± 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration. The efficacy data for RECORD 1 and 2 are provided in Table 6.

Table 6: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 1			RECORD 2		
Treatment Dosage and Duration	XARELTO 10 mg once daily	Enoxaparin 40 mg once daily	RRR*, p-value	XARELTO 10 mg once daily	Enoxaparin† 40 mg once daily	RRR*, p-value
Number of Patients	N = 1513	N = 1473		N = 834	N = 835	
Total VTE	17 (1.1%)	57 (3.9%)	71% (95% CI: 50, 83), p<0.001	17 (2.0%)	70 (8.4%)	76% (95% CI: 59, 86), p<0.001
Components of Total VTE						
Proximal DVT	1 (0.1%)	31 (2.1%)		5 (0.6%)	40 (4.8%)	
Distal DVT	12 (0.8%)	26 (1.8%)		11 (1.3%)	43 (5.2%)	
Non-fatal PE	3 (0.2%)	1 (0.1%)		1 (0.1%)	4 (0.5%)	
Death (any cause)	4 (0.3%)	4 (0.3%)		2 (0.2%)	4 (0.5%)	
Number of Patients	N= 1600	N = 1587		N= 928	N = 929	
Major VTE‡	3 (0.2%)	33 (2.1%)	91% (95% CI: 71, 97), p<0.001	6 (0.7%)	45 (4.8%)	87% (95% CI: 69, 94), p<0.001
Number of Patients	N = 2103	N = 2119		N = 1178	N = 1179	
Symptomatic VTE	5 (0.2%)	11 (0.5%)		3 (0.3%)	15 (1.3%)	

* Relative Risk Reduction; CI=confidence interval

† Includes the placebo-controlled period of RECORD 2

‡ Proximal DVT, nonfatal PE or VTE-related death

One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared XARELTO 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after

wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients in the study was 68 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (± SD) to active XARELTO and enoxaparin was 11.9 ± 2.3 and 12.5 ± 3.0 days, respectively. The efficacy data are provided in Table 7.

Table 7: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery- Modified Intent-to-Treat Population

	RECORD 3		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N = 813**	**N = 871**	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non-fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	**N = 895**	**N = 917**	
Major VTE†	9 (1.0%)	23 (2.5%)	60% (95% CI: 14, 81), p=0.024
Number of Patients	**N = 1206**	**N = 1226**	
Symptomatic VTE	8 (0.7%)	24 (2.0%)	

* Relative Risk Reduction; CI=confidence interval

† Proximal DVT, nonfatal PE or VTE-related death

16 HOW SUPPLIED/STORAGE AND HANDLING

XARELTO (rivaroxaban) 10 mg Tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side. The tablets are supplied in the packages listed:

NDC 50458-580-30 Bottle containing 30 tablets

NDC 50458-580-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

Store at 25° C (77° F) or room temperature; excursions permitted to 15°-30° C (59°-86° F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

17.1 Instructions for Patient Use

- Advise patients to take XARELTO only as directed.
- Remind patients not to discontinue XARELTO prematurely without first talking to their healthcare professional.
- If a dose is missed, advise the patient to take XARELTO as soon as possible and continue on the following day with their once daily dose regimen.

17.2 Bleeding Risks

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as tingling, numbness (especially in the lower limbs) and muscular weakness. If any of these symptoms occur, advise the patient to contact his or her physician immediately.

Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with XARELTO *[see Warnings and Precautions (5.2)]*.

17.3 Concomitant Medication and Herbals

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions *[see Drug Interactions (7)]*.

17.4 Pregnancy and Pregnancy-Related Hemorrhage

Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with XARELTO *[see Use in Specific Populations (8.1)]*.

XARELTO® (rivaroxaban) film-coated oral tablets

Advise pregnant women receiving XARELTO to immediately report to their physician any bleeding or symptoms of blood loss *[see Warnings and Precautions (5.3)]*.

17.5 Nursing

Advise patients to discuss with their physician if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.3)]*.

17.6 Females of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with their physician *[see Use in Specific Populations (8.6)]*.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

janssen

10185200

02X11070A
(07/11)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022406

NDA APPROVAL

Johnson and Johnson Pharmaceutical Research and Development, LLC
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) dated July 28, 2008, received July 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xarelto® (rivaroxaban) 10 mg immediate release Tablets.

We acknowledge receipt of your amendments dated January 4, February 2, 18, 25, March 25, April 18, 25, 26, 28, May 2, 4, 6, 10, 11, 25 and June 8, 20 and 30, 2011.

The December 30, 2010, submission constituted a complete response to our May 27, 2009, action letter.

This new drug application provides for the use of Xarelto® (rivaroxaban) 10 mg immediate release Tablets, for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing: hip replacement surgery or knee replacement surgery.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 22406."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable and because there are too few children with disease/condition to study.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the serious risks of major bleeding events and renal impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1797-1 A postmarketing pharmacovigilance study of the risk factors, clinical management, and outcome of cases of major bleeding in association with Xarelto® (rivaroxaban) use.

You agree to conduct an "Enhanced Pharmacovigilance Plan" that will consist of the collection, analysis, and reporting of events termed "major bleeding," to consist of active solicitation of the events and associated risk factors, subsequent therapy, and outcomes. Major bleeding is defined as in the clinical protocols and current drug labeling.

You agree to provide reports quarterly for the first three years following drug approval, then annually. The final plan will be submitted by October 30, 2011.

Submit summary information (total cases and summary of key facts in those cases, with pertinent expert analysis of clinically relevant information from the case series and any potential regulatory implications such as label changes) quarterly for 3 years, then annually.

The timetable you submitted on June 30, 2011 states that you will conduct this study according to the following schedule.

Final Protocol Submission:	November 30, 2011
Interim report submission:	Quarterly thereafter for 3 years, then annually
Study Completion:	June 30, 2016
Final Report Submission:	December 30, 2018

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the serious risks of renal impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1797-2 Perform a clinical trial to evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations.

The timetable you submitted on June 30, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Submitted February 4, 2011
Trial Completion:	February 29, 2012
Final Report Submission:	June 30, 2012

Submit protocols to your IND 64892, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify each submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required**

Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENT NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 1797-3 Develop and propose a 5 mg strength tablet or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. For a scored 10 mg tablet, show that half-tablets follow the same dissolution profile and specifications (based on percent) as the whole and show that the half-tablets are otherwise proportionately equivalent. A 5 mg strength tablet should be sufficiently distinguishable from the 10 mg tablet in physical characteristics. If feasible, we recommend that you consider a proportional formulation for a 5 mg strength tablet. Full chemistry, manufacturing and controls (CMC) information for a 5 mg tablet including the batch data and stability data, labels, updated labeling, a request for a biowaiver for the lower 5 mg strength based on [proportional] formulation and the F2 metric, and an updated environmental assessment section will be submitted in a prior approval supplement.

The timetable you submitted on June 30, 2011, states that you will conduct this study according to the following schedule:

Final CMC Supplement Submission: April 2012

Submit chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report,"** or **"Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Tyree Newman, Regulatory Project Manager, at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARELTO® (rivaroxaban) safely and effectively. See full prescribing information for XARELTO

XARELTO (rivaroxaban) film-coated oral tablets

Initial U.S. Approval: 2011

WARNING: SURGICAL SETTINGS–SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.1) and Drug Interactions (7)]*.

INDICATIONS AND USAGE

XARELTO is a factor Xa inhibitor indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. (1)

DOSAGE AND ADMINISTRATION

- 10 mg orally, once daily with or without food (2)

DOSAGE FORMS AND STRENGTHS

Tablet: 10 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to XARELTO (4)
- Active major bleeding (4)

WARNINGS AND PRECAUTIONS

- Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Pregnancy related hemorrhage: Use XARELTO with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. (5.3)

ADVERSE REACTIONS

The most common adverse reaction (>5%) was bleeding. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A4 inhibitors: Avoid concomitant use unless the lack of a significant interaction is proven (7.1)
- Combined P-gp and weak or moderate CYP3A4 inhibitors: Avoid concomitant use unless the benefit outweighs the bleeding risk in patients with renal impairment (7.2)
- Combined P-gp and strong CYP3A4 inducers: Avoid concomitant use or consider an increased dose (2.1, 7.3)
- Anticoagulants: Avoid concomitant use (7.4)
- Clopidogrel: Avoid concomitant use unless the benefit outweighs the bleeding risk (7.6)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: discontinue drug or discontinue nursing (8.3)
- Renal impairment: Avoid use in patients with severe impairment (CrCl <30 mL/min). Use with caution in moderate impairment (CrCl 30 to <50 mL/min) (8.7)
- Hepatic impairment: Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or in patients with any degree of hepatic disease associated with coagulopathy (8.8)

See 17 for PATIENT COUNSELING INFORMATION.

Issued: July 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SURGICAL SETTINGS--SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.1) and Drug Interactions (7)]*.

1 INDICATIONS AND USAGE

XARELTO (rivaroxaban) Tablets are indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

2 DOSAGE AND ADMINISTRATION

The recommended dose of XARELTO is 10 mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

If a dose of XARELTO is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and continued on the following day with the once daily intake as recommended.

Administration via GI feeding tube:

Rivaroxaban absorption is dependent on the site of drug release in the gastrointestinal (GI) tract (gastric versus small intestine). When administering XARELTO as a crushed tablet via a feeding tube, confirm gastric placement of the tube *[see Clinical Pharmacology (12.3)]*.

2.1 Use with P-gp and Strong CYP3A4 Inducers

Concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) should be avoided. A XARELTO dose increase to 20 mg (i.e., two 10 mg tablets) should be considered if these drugs must be coadministered. The 20 mg dose should be taken with food *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

XARELTO 10 mg tablets are round, light red, biconvex and film-coated with a triangle pointing down above a "10" marked on one side and "Xa" on the other side.

4 CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- hypersensitivity to XARELTO
- active major bleeding *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

5.2 Risk of Bleeding

XARELTO increases the risk of bleeding and can cause serious and fatal bleeding. Major hemorrhages including intracranial, epidural hematoma, gastrointestinal, retinal, and adrenal bleeding have been reported. Use XARELTO with caution in conditions with increased risk of hemorrhage.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include platelet aggregation inhibitors, other antithrombotic agents, fibrinolytic therapy, thienopyridines and chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.4), (7.5), (7.6)]*.

Bleeding can occur at any site during therapy with XARELTO. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site. Promptly evaluate any signs or symptoms of blood loss.

5.3 Risk of Pregnancy Related Hemorrhage

XARELTO should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

5.4 Renal Impairment

Avoid the use of XARELTO in patients with severe renal impairment (creatinine clearance <30 mL/min) due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.

Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations (8.7)]*.

5.5 Hepatic Impairment

Clinical data in patients with moderate hepatic impairment indicate a significant increase in rivaroxaban exposure and pharmacodynamic effects. No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Use in Specific Populations (8.8)]*.

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Trials

In three randomized, controlled clinical trials (RECORD 1-3) in elective joint replacement surgery, 4487 patients received XARELTO 10 mg orally once daily. The mean duration of XARELTO treatment was 11.9 days in the total knee replacement study and 33.4 days in the total hip replacement studies. Overall, the mean age of the patients studied in the XARELTO group was 64 years, 59% were female and 82% were Caucasian. Twenty-seven percent (1206) of

patients underwent knee replacement surgery and 73% (3281) underwent hip replacement surgery.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

6.2 Hemorrhage

The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions (5.2)]*. The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 1.

Table 1: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	N = 4487 n (%)	N = 4524 n (%)
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	N = 3281 n (%)	N = 3298 n (%)
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	N = 1206 n (%)	N = 1226 n (%)
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.

† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

6.3 Other Adverse Reactions

Table 2 shows other adverse drug reactions (ADRs) reported in ≥1% of XARELTO-treated patients in the RECORD clinical studies.

Table 2: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

System/Organ Class Adverse Reaction	XARELTO 10 mg (N = 4487) n (%)	Enoxaparin† (N = 4524) n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* ADR occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication.
† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

The following ADR occurred in <1% of XARELTO-treated patients in the clinical studies:

Renal and urinary disorders: dysuria

The laboratory abnormalities in Table 3 were observed in clinical studies:

Table 3: Laboratory Abnormalities in RECORD 1-3 Clinical Studies

Laboratory Abnormality	XARELTO 10 mg	Enoxaparin*
Alanine aminotransferase >3 x ULN	114/4441 (2.6%)	167/4456 (3.8%)
Aspartate aminotransferase >3 x ULN	122/4441 (2.8%)	152/4456 (3.4%)
Total bilirubin >1.5 x ULN	140/4442 (3.2%)	128/4456 (2.9%)
Gamma-glutamyltransferase >3 x ULN	292/4442 (6.6%)	391/4457 (8.8%)
Platelet counts <100,000/mm^3 or <50% of baseline value	116/4425 (2.6%)	131/4447 (3.0%)

* Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

6.4 Postmarketing Experience

The following additional adverse reactions have been reported in countries where XARELTO has been marketed. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis

Immune system disorder: hypersensitivity, anaphylactic reaction, anaphylactic shock

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

7 DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters may result in changes in rivaroxaban exposure.

7.1 Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- *Ketoconazole (combined P-gp and strong CYP3A4 inhibitor):* Steady-state rivaroxaban AUC and C_{max} increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Ritonavir (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Clarithromycin (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
- *Erythromycin (combined P-gp and moderate CYP3A4 inhibitor):* Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

When clinical data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

7.2 Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Based on simulated pharmacokinetic data, patients with renal impairment receiving XARELTO with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected. Since these increases may increase bleeding risk, use XARELTO in this situation only if the potential benefit justifies the potential risk *[see Use in Specific Populations (8.7)]*.

7.3 Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems

In a drug interaction study, co-administration of XARELTO (20 mg single dose with food) with a drug that is a combined P-gp and strong CYP3A4 inducer (rifampicin titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in AUC and C_{max}, respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Consider increasing the XARELTO dose if these drugs must be coadministered *[see Dosage and Administration (2.1)]*.

7.4 Anticoagulants

In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and XARELTO (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. Enoxaparin did not affect the pharmacokinetics of rivaroxaban. In another study, single doses of warfarin (15 mg) and XARELTO (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Warfarin did not affect the pharmacokinetics of rivaroxaban. The safety of long-term concomitant use of these drugs has not been studied.

Avoid concurrent use of XARELTO with other anticoagulants due to the increased bleeding risk other than during therapeutic transition periods where patients should be observed closely. Promptly evaluate any signs or symptoms of blood loss *[see Warnings and Precautions (5.2)]*.

7.5 NSAIDs/Aspirin

In a single-dose drug interaction study there were no pharmacokinetic or pharmacodynamic interactions observed after concomitant administration of naproxen or aspirin (acetylsalicylic acid) with XARELTO. The safety of long-term concomitant use of these drugs has not been studied.

NSAIDs/aspirin are known to increase bleeding, and bleeding risk may be increased when these drugs are used concomitantly with XARELTO.

Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with NSAIDs and/or platelet aggregation inhibitors *[see Warnings and Precautions (5.2)]*.

7.6 Clopidogrel

In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and XARELTO (15 mg single dose) were co-administered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Avoid concurrent administration of clopidogrel with XARELTO unless the benefit outweighs the risk of increased bleeding *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant

rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 11 times the human exposure of unbound drug, based on AUC comparisons at the maximum recommended human dose of 10 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 40 times the human exposure of unbound drug.

8.2 Labor and Delivery

Safety and effectiveness of rivaroxaban during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 17 times maximum human exposure of the unbound drug at the human dose of 10 mg/day).

8.3 Nursing Mothers

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 53% were 65 years and over, while about 15% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years.

Elderly subjects exhibited an increase in exposure that may be caused by age related changes in renal function. For patients 65 years of age and older, consideration should be given to assessment of renal function prior to starting therapy with XARELTO. Promptly evaluate any signs or symptoms of blood loss *[see Clinical Pharmacology (12.3)]*.

8.6 Females of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

8.7 Renal Impairment

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Table 4). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed.

Table 4: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Renal Insufficiency from a Dedicated Renal Impairment Study

Parameter		Renal Impairment Class [CrCl (mL/min)] Mild [50 to 79] N=8	Moderate [30 to 49] N=8	Severe [15 to 29] N=8
Exposure	AUC	44	52	64
(% increase relative to normal)	C_{max}	28	12	26
FXa Inhibition	AUC	50	86	100
(% increase relative to normal)	E_{max}	9	10	12
PT Prolongation	AUC	33	116	144
(% increase relative to normal)	E_{max}	4	17	20

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect; and CrCl = creatinine clearance

Patients with any degree of renal impairment with concurrent use of P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure which may increase bleeding risk *[see Drug Interactions (7.2)]*.

The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with moderate renal impairment and reported a possible increase in total VTE in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Avoid the use of XARELTO in patients with severe renal impairment (CrCl <30 mL/min) *[see Warnings and Precautions (5.2, 5.4)]*.

8.8 Hepatic Impairment

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Table 5). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B). Increases in pharmacodynamic effects were also observed.

Table 5: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Hepatic Insufficiency from a Dedicated Hepatic Impairment Study

Parameter		Hepatic Impairment Class (Child-Pugh Class)	
		Mild (Child-Pugh A) N=8	Moderate (Child-Pugh B) N=8
Exposure (% increase relative to normal)	AUC	15	127
	C_{max}	0	27
FXa Inhibition (% increase relative to normal)	AUC	8	159
	E_{max}	0	24
PT Prolongation (% increase relative to normal)	AUC	6	114
	E_{max}	2	41

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect

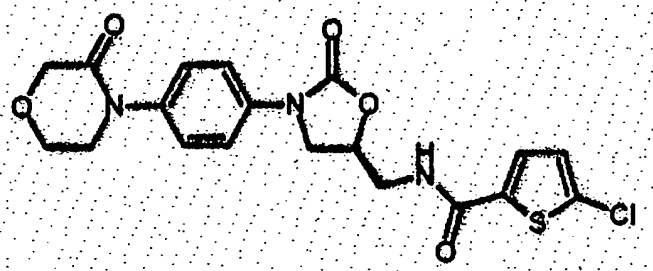
Avoid the use of XARELTO in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Warnings and Precautions (5.2, 5.5)]*.

10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. A specific antidote of rivaroxaban is not available. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Rivaroxaban, a factor Xa inhibitor, is the active ingredient in XARELTO Tablets with the chemical name 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. The structural formula is:



Rivaroxaban is a pure (*S*)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder. Rivaroxaban is only slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media.

Each XARELTO tablet contains 10 mg of rivaroxaban. The inactive ingredients of XARELTO are: Microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and Opadry® Pink, a proprietary filmcoating mixture containing polyethylene glycol 3350, hypromellose, titanium dioxide, and ferric oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XARELTO is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

12.2 Pharmacodynamics

Dose-dependent inhibition of factor Xa activity was observed in humans and the Neoplastin® prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban. There are no data on the use of the International Normalized Ratio (INR). The predictive value of these coagulation parameters for bleeding risk or efficacy has not been established.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is high (estimated to be 80% to 100%) for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

Rivaroxaban pharmacokinetics are linear with no relevant accumulation beyond steady-state after multiple doses. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.

The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Coadministration of XARELTO (30 mg single dose) with the H_2-receptor antagonist ranitidine (150 mg twice daily) or the antacid aluminum hydroxide/magnesium hydroxide (10 mL) did not show an effect on the bioavailability and exposure of rivaroxaban.

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is

released in proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) which can result in reduced absorption and related drug exposure *[see Dosage and Administration (2)]*.

Distribution

Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism

Approximately 51% of an orally administered [^{14}C]-rivaroxaban dose was recovered as metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion

Following oral administration of a [^{14}C]-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug). Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated Bcrp). Rivaroxaban's affinity for influx transporter proteins is unknown.

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Special Populations

Gender

Gender did not influence the pharmacokinetics or pharmacodynamics of XARELTO.

Race

Healthy Japanese subjects were found to have 50% higher exposures compared to other ethnicities including Chinese.

Elderly

In clinical studies, elderly subjects exhibited higher rivaroxaban plasma concentrations than younger subjects with mean AUC values being approximately 50% higher, mainly due to reduced (apparent) total body and renal clearance. Age related changes in renal function may

play a role in this age effect. The terminal elimination half-life is 11 to 13 hours in the elderly *[see Use in Specific Populations (8.5)]*.

Body Weight

Extremes in body weight (<50 kg or >120 kg) did not influence rivaroxaban exposure.

Drug Interactions

In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A4 nor induces CYP1A2, 2B6, 2C19, or 3A4.

In vitro data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.

In addition, there were no significant pharmacokinetic interactions observed in studies comparing concomitant rivaroxaban 20 mg and 7.5 mg single dose of midazolam (substrate of CYP3A4), 0.375 mg once-daily dose of digoxin (substrate of P-gp), or 20 mg once daily dose of atorvastatin (substrate of CYP3A4 and P-gp) in healthy volunteers.

12.4 QT/QTc Prolongation

In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for XARELTO (15 mg and 45 mg, single-dose).

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 3- and 5-times, respectively, the human exposure of unbound drug at the human dose of 10 mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 4- and 10-times, respectively, the human exposure.

Rivaroxaban was not mutagenic in bacteria (Ames-Test) or clastogenic in V79 Chinese hamster lung cells *in vitro* or in the mouse micronucleus test *in vivo*.

No impairment of fertility was observed in male or female rats when given up to 200 mg/kg/day of rivaroxaban orally. This dose resulted in exposure levels, based on the unbound AUC, at least 33 times the exposure in humans given 10 mg rivaroxaban daily.

14 CLINICAL STUDIES

XARELTO was studied in 9011 patients (4487 XARELTO-treated, 4524 enoxaparin-treated patients) in the RECORD 1, 2, and 3 studies.

The two randomized, double-blind, clinical studies (RECORD 1 and 2) in patients undergoing elective total hip replacement surgery compared XARELTO 10 mg once daily starting at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin 40 mg once daily started 12 hours preoperatively. In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age [± standard deviation (SD)] was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥65 years and 55% of patients were female. More than 82% of patients were White, 7% were Asian, and less than 2% were Black. The studies excluded patients undergoing staged bilateral total hip replacement, patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min, or patients with significant liver disease (hepatitis or cirrhosis). In RECORD 1, the mean exposure duration (± SD) to active XARELTO and enoxaparin was 33.3 ± 7.0 and 33.6 ± 8.3 days, respectively. In RECORD 2, the mean exposure duration to active XARELTO and enoxaparin was 33.5 ± 6.9 and 12.4 ± 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration. The efficacy data for RECORD 1 and 2 are provided in Table 6.

Table 6: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 1			RECORD 2		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**	**XARELTO 10 mg once daily**	**Enoxaparin† 40 mg once daily**	**RRR*, p-value**
Number of Patients	N=1513	N=1473		N=834	N=835	
Total VTE	17 (1.1%)	57 (3.9%)	71% (95% CI: 50, 83), p<0.001	17 (2.0%)	70 (8.4%)	76% (95% CI: 59, 86), p<0.001
Components of Total VTE						
Proximal DVT	1 (0.1%)	31 (2.1%)		5 (0.6%)	40 (4.8%)	
Distal DVT	12 (0.8%)	26 (1.8%)		11 (1.3%)	43 (5.2%)	
Non-fatal PE	3 (0.2%)	1 (0.1%)		1 (0.1%)	4 (0.5%)	
Death (any cause)	4 (0.3%)	4 (0.3%)		2 (0.2%)	4 (0.5%)	
Number of Patients	N=1600	N=1587		N=928	N=929	
Major VTE‡	3 (0.2%)	33 (2.1%)	91% (95% CI: 71, 97), p<0.001	6 (0.7%)	45 (4.8%)	87% (95% CI: 69, 94), p<0.001
Number of Patients	N=2103	N=2109		N=1078	N=1079	
Symptomatic VTE	5 (0.2%)	11 (0.5%)		3 (0.3%)	15 (1.3%)	

*Relative Risk Reduction; CI=confidence interval
†Includes the placebo-controlled period of RECORD 2
‡Proximal DVT, nonfatal PE or VTE-related death

One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared XARELTO 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD

3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients in the study was 68 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (± SD) to active XARELTO and enoxaparin was 11.9 ± 2.3 and 12.5 ± 3.0 days, respectively. The efficacy data are provided in Table 7.

Table 7: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery-Modified Intent-to-Treat Population

	RECORD 3		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**
Number of Patients	N=813	N=871	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non-fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	N=895	N=917	
Major VTE†	9 (1.0%)	23 (2.5%)	60% (95% CI: 14, 81), p=0.024
Number of Patients	N=1206	N=1226	
Symptomatic VTE	8 (0.7%)	24 (2.0%)	

* Relative Risk Reduction; CI=confidence interval
† Proximal DVT, nonfatal PE or VTE-related death

16 HOW SUPPLIED/STORAGE AND HANDLING

XARELTO (rivaroxaban) Tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side. The tablets are supplied in the packages listed:

NDC 50458-580-30 Bottle containing 30 tablets

NDC 50458-580-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

Store at 25° C (77° F) or room temperature; excursions permitted to 15°-30° C (59°-86° F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

17.1 Instructions for Patient Use

- Advise patients to take XARELTO only as directed.
- Remind patients not to discontinue XARELTO prematurely without first talking to their healthcare professional.
- If a dose is missed, advise the patient to take XARELTO as soon as possible and continue on the following day with their once daily dose regimen.

17.2 Bleeding Risks

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as tingling, numbness (especially in the lower limbs) and muscular weakness. If any of these symptoms occur, advise the patient to contact his or her physician immediately.

Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with XARELTO *[see Warnings and Precautions (5.2)]*.

17.3 Concomitant Medication and Herbals

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions *[see Drug Interactions (7)]*.

17.4 Pregnancy and Pregnancy-Related Hemorrhage

Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with XARELTO *[see Use in Specific Populations (8.1)]*.

Advise pregnant women receiving XARELTO to immediately report to their physician any bleeding or symptoms of blood loss *[see Warnings and Precautions (5.3)]*.

17.5 Nursing

Advise patients to discuss with their physician if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.3)]*.

17.6 Females of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with their physician *[see Use in Specific Populations (8.6)]*.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

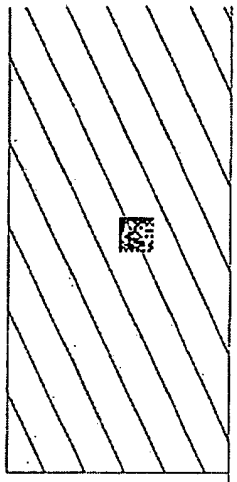
Xarelto®
(rivaroxaban)
Tablets 10mg

Each tablet contains: rivaroxaban 10 mg

Package Not Child Resistant

For Hospital Use Only.

Rx only



Xarelto®
(rivaroxaban)
Tablets 10mg

10 Blister Strips. 10 Tablets each.

Rx only

janssen

NDC 50458-580-10

Dosage: See package insert for full prescribing information.

Store at 25°C (77°F) or room temperature; excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

Keep out of reach of children.

For Hospital Use Only.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

janssen

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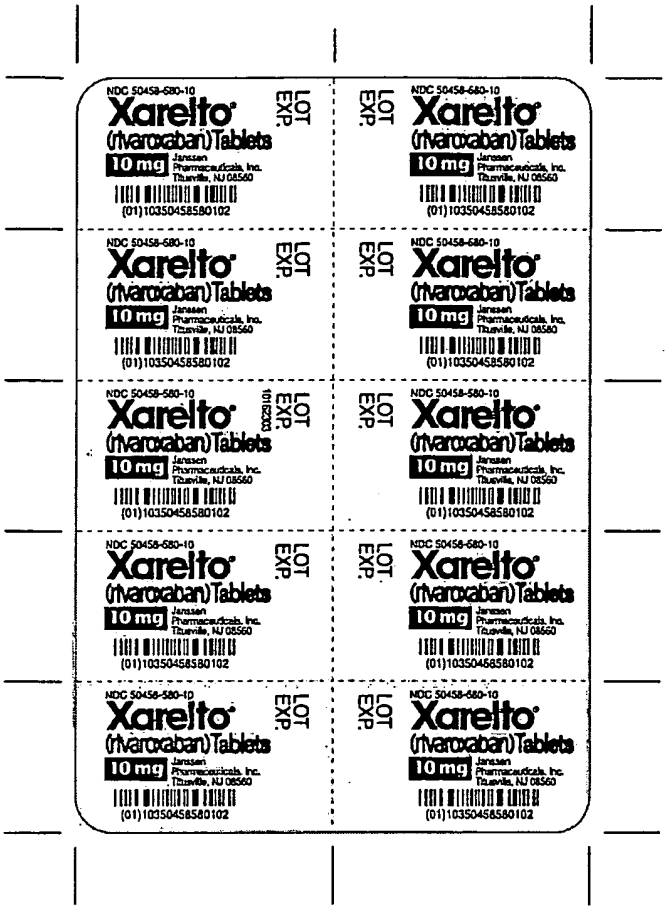
NDC 50458-580-10

10 Blister Strips
10 Tablets Each

Xarelto®
(rivaroxaban)
Tablets 10mg

Package Not Child Resistant



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Tel.: François Vermeylen: +32 14606865 - E-mail: fvermeyl@gpsbe.jnj.com
FOIL XARELTO
Article Number: 10162303
Format Name: G/F/57312/V1
Technical Info/Spec:
File Name: 10162303.ai (CS4-mac)

Market: USA
Mat. ID Code:
Operator: RSE

Black
Diecut (not to be printed)

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LABEL XARELTO
Article Number: 10185502
Format Name: G/L/14134/V2
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Market: USA
Mat. ID Code: 10185502
Operator: RSE

- **Black**
- **PMS Cool Grey 10**
- **PMS 268**
- **PMS 226**
- **Microprint (XARELTO)**
- **Security ink LPI-1013 or FL-1024**
- **Varnish free**
- **Diecut (not to be printed)**

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RICHARD PAZDUR
07/01/2011

US007157456B2

(12) **United States Patent**
Straub et al.

(10) **Patent No.: US 7,157,456 B2**
(45) **Date of Patent: Jan. 2, 2007**

(54) **SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION**

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(73) Assignee: **Bayer HealthCare AG**, Leverkusen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 59 days.

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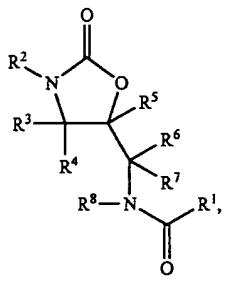
(57) **ABSTRACT**

The invention relates to the field of blood coagulation. Novel oxazolidinone derivatives of the general formula (I)

(I)



processes for their preparation and their use as medicinally active compounds for the prophylaxis and/or treatment of disorders are described.

30 Claims, No Drawings

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SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

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

The present invention relates to the field of blood coagulation. In particular, the present invention relates to novel oxazolidinone derivatives, to processes for their preparation and to their use as active compounds in medicaments.

Blood coagulation is a protective mechanism of the organism which helps to "seal" defects in the wall of the blood vessels quickly and reliably. Thus, loss of blood can be avoided or kept to a minimum. Haemostasis after injury of the blood vessels is effected mainly by the coagulation system in which an enzymatic cascade of complex reactions of plasma proteins is triggered. Numerous blood coagulation factors are involved in this process, each of which factors converts, on activation, the respectively next inactive precursor into its active form. At the end of the cascade comes the conversion of soluble fibrinogen into insoluble fibrin, resulting in the formation of a blood clot. In blood coagulation, traditionally the intrinsic find the extrinsic system, which end in a joint reaction path, are distinguished. Here factor Xa, which is formed from the proenzyme factor X, plays a key role, since it connects the two coagulation paths. The activated serine protease Xa cleaves prothrombin to thrombin. The resulting thrombin, in turn, cleaves fibrinogen to fibrin, a fibrous/gelatinous coagulant. In addition, thrombin is a potent effector of platelet aggregation which likewise contributes significantly to haemostasis.

Maintenance of normal haemostasis—between bleeding and thrombosis—is subject to a complex regulatory mechanism. Uncontrolled activation of the coagulant system or defective inhibition of the activation processes may cause formation of local thrombi or embolisms in vessels (arteries, veins, lymph vessels) or in heart cavities. This may lead to serious disorders, such as myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses; hereinbelow, these disorders are collectively also referred to as thromboembolic disorders. In addition, in the case of consumption coagulopathy, hypercoagulability may—systemically—result in disseminated intravascular coagulation.

These thromboembolic disorders are the most frequent cause of morbidity and mortality in most industrialized countries (Pschyrembel, Klinisches Wörterbuch [clinical dictionary], 257th edition, 1994, Walter de Gruyter Verlag, page 199 ff., entry "Blutgerinnung" [blood coagulation]; Römpp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Blutgerinnung"; Lubert Stryer, Biochemie [biochemistry], Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, page 259 ff.).

The anticoagulants, i.e. substances for inhibiting or preventing blood coagulation, which are known from the prior art have various, often grave disadvantages. Accordingly, in practice, an efficient treatment method or prophylaxis of thromboembolic disorders is very difficult and unsatisfactory.

In the therapy and prophylaxis of thromboembolic disorders, use is firstly made of heparin, which is administered parenterally or subcutaneously. Owing to more favourable pharmacokinetic properties, preference is nowadays more and more given to low-molecular-weight heparin; however, even with low-molecular-weight heparin, it is not possible to

avoid the known disadvantages described below, which are involved in heparin therapy. Thus, heparin is ineffective when administered orally and has a relatively short half-life. Since heparin inhibits a plurality of factors of the blood coagulation cascade at the same time, the action is nonselective. Moreover, there is a high risk of bleeding; in particular, brain haemorrhages and gastrointestinal bleeding may occur, which may result in thrombopenia, drug-induced alopecia or osteoporosis (Pschyrembel, Klinisches Wörterbuch, 257th edition, 1994, Walter de Gruyter Verlag, page 610, entry "Heparin"; Römpp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Heparin").

A second class of anticoagulants are the vitamin K antagonists. These include, for example, 1,3-indanediones, and especially compounds such as warfarin, phenprocoumon, dicumarol and other coumarin derivatives which inhibit the synthesis of various products of certain vitamin K-dependent coagulation factors in the liver in a nonselective manner. Owing to the mechanism of action, however, the onset of the action is very slow (latency to the onset of action 36 to 48 hours). It is possible to administer the compounds orally; however, owing to the high risk of bleeding and the narrow therapeutic index, a time-consuming individual adjustment and monitoring of the patient are required. Moreover, other adverse effects, such as gastrointestinal disturbances, hair loss and skin necroses, have been described (Pschyrembel, Klinisches Wörterbuch, 257th edition, 1994, Walter de Gruyter Verlag, page 292 ff., entry "coumarin derivatives"; Ullmann's Encyclopedia of Industrial Chemistry, 5th edition, VCH Verlagsgesellschaft, Weinheim, 1985–1996, entry "vitamin K").

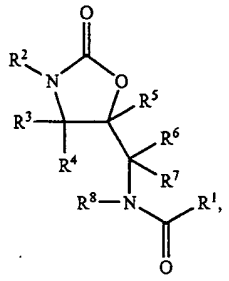
Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa (cf. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research 1999, 93, 203; F. Al-Obeidi, J. A. Ostrem, Factor Xa inhibitors by classical and combinatorial chemistry, DDT 1998, 3, 223; F. Al-Obeidi, J. A. Ostrem, Factor Xa inhibitors, Exp. Opin. Ther. Patents 1999, 9, 931; B. Kaiser, Thrombin and factor Xa inhibitors, Drugs of the Future 1998, 23, 423; A. Uzan, Antithrombotic agents, Emerging Drugs 1998, 3, 189; B.-Y. Zhu, R. M. Scarborough, Curr. Opin. Card. Pulm. Ren. Inv. Drugs 1999, 1 (1), 63). It has been shown that, in animal models, various both peptidic and nonpeptidic compounds are effective as factor Xa inhibitors.

Accordingly, it is an object of the present invention to provide novel substances for controlling disorders, which substances have a wide therapeutic spectrum.

In particular, they should be suitable for a more efficient prophylaxis and/or treatment of thromboembolic disorders, avoiding—at least to some extent—the disadvantages of the prior art described above, where the term "thromboembolic disorders" in the context of the present invention is to be understood as meaning, in particular, serious disorders, such as myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses.

It is another object of the present invention to provide novel anticoagulants which inhibit the blood coagulation factor Xa with increased selectivity, avoiding—at least to some extent—the problems of the therapeutic methods for thromboembolic disorders known from the prior art.

Accordingly, the present invention provides substituted oxazolidinones of the general formula (I)



(I)

in which:

R^1 represents optionally benzo-fused thiophene (thienyl) which may optionally be mono- or polysubstituted;

R^2 represents any organic radical;

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

Preference is given here to compounds of the general formula (I),

in which

R^1 represents optionally benzo-fused thiophene (thienyl) which may optionally be mono- or polysubstituted by a radical 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 one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" represents $(C_6–C_{14})$-aryl, preferably $(C_6–C_{10})$-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl;

the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the group consisting of S, N, NO (N-oxide) and O;

the radical "D" represents a saturated or partially unsaturated, mono- or bicyclic, optionally benzo-fused 4- to 9-membered heterocycle which contains up to three heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

the radical "M" represents —NH—, $—CH_2—$, $—CH_2CH_2—$, —O—, $—NH—CH_2—$, $—CH_2—NH—$, $—OCH_2—$, $—CH_2O—$, —CONH—, —NHCO—, —COO—, —OOC—, —S—, $—SO_2—$ or represents a covalent bond;

where

the groups "A", "B" and "D" defined above may each optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; nitro; carbamoyl; pyridyl; $(C_1–C_6)$-alkanoyl; $(C_3–C_7)$-cycloalkanoyl; $(C_6–C_{14})$-arylcarbonyl; $(C_5–C_{10})$-heteroarylcarbonyl; $(C_1–C_6)$-alkanoyloxymethyloxy; $(C_1–C_4)$-hydroxy-alkylcarbonyl; $—COOR^{27}$; $—SO_2R^{27}$; $C(NR^{27}R^{28})=NR^{29}$; $—CONR^{28}R^{29}$; $—SO_2NR^{28}R^{29}$; $—OR^{30}$; $—NR^{30}OR^{31}$, $(C_1–C_6)$-alkyl and $(C_3–C_7)$-cycloalkyl,

where $(C_1–C_6)$-alkyl and $(C_3–C_7)$-cycloalkyl for their part may optionally be substituted by a radical from the group consisting of cyano; $—OR^{27}$; $—NR^{28}R^{29}$; $—CO(NH)_v(NR^{27}R^{28})$ and $—C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1 and

R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl, $(C_3–C_7)$-cycloalkyl, $(C_1–C_4)$-alkanoyl, carbamoyl, trifluoromethyl, phenyl or pyridyl, and/or

R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group consisting of N, O and S, and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl, $(C_3–C_7)$-cycloalkyl, $(C_1–C_4)$-alkylsulphonyl, $(C_1–C_4)$-hydroxyalkyl, $(C_1–C_4)$-aminoalkyl, di-$(C_1–C_4)$-alkylamino-$(C_1–C_4)$-alkyl, $—CH^2C(NR^{27}R^{28})=NR^{29}$ or $—COR^{33}$,

where

R^{33} represents $(C_1–C_6)$-alkoxy, $(C_1–C_4)$-alkoxy-$(C_1–C_4)$-alkyl, $(C_1–C_4)$-alkoxycarbonyl-$(C_1–C_4)$-alkyl, $(C_1–C_4)$-aminoalkyl, $(C_1–C_4)$-alkoxycarbonyl, $(C_1–C_4)$-alkanoyl-$(C_1–C_4)$-alkyl, $(C_3–C_7)$-cycloalkyl, $(C_1–C_6)$-alkenyl, $(C_1–C_8)$-alkyl, which may optionally be substituted by phenyl or acetyl, $(C_6–C_{14})$-aryl, $(C_5–C_{10})$-heteroaryl, trifluoromethyl, tetrahydrofuranyl or butyrolactone,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

Preference is also given here to compounds of the general formula (I),

in which

R^1 represents thiophene (thienyl), in particular 2-thiophene, which may optionally be mono- or polysubstituted by halogen, preferably chlorine or bromine, by amino, aminomethyl or $(C_1–C_8)$-alkyl, preferably methyl, where the

(C_1–C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen, preferably fluorine,

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" represents (C_6–C_{14})-aryl, preferably (C_6–C_{10})-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl;

the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the group consisting of S, N, NO (N-oxide) and O;

the radical "D" represents a saturated or partially unsaturated 4 to 7-membered heterocycle which contains up to three heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

the radical "M" represents —NH—, —CH_2—, —CH_2CH_2—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO—, —COO—, —OOC—, —S— or represents a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; nitro; carbamoyl; pyridyl; (C_1–C_6)-alkanoyl; (C_3–C_7)-cycloalkanoyl; (C_6–C_{14})-arylcarbonyl; (C_5–C_{10})-heteroarylcarbonyl; (C_1–C_6)-alkanoyloxymethyloxy; —$COOR^{27}$; —SO_2R^{27}; —$C(NR^{27}R^{28})$=NR^{29}; —$CONR^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OR^{30}; —$NR^{30}R^{31}$, (C_1–C_6)-alkyl and (C_3–C_7)-cycloalkyl,

where (C_1–C_6)-alkyl and (C_3–C_7)-cycloalkyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OR^{27}; —$NR^{28}R^{29}$; —$CO(NH)_v(NR^{27}R^{28})$ and —$C(NR^{27}R^{28})$=NR^{29},

where:

v is either 0 or 1 and

R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1–C_4)-alkyl or (C_3–C_7)-cycloalkyl, and/or

R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group consisting of N, O and S, and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1–C_4)-alkyl, (C_3–C_7)-cycloalkyl, (C_1–C_4)-alkylsulphonyl, (C_1–C_4)-hydroxyalkyl, (C_1–C_4)-aminoalkyl, di-(C_1–C_4)-alkylamino-(C_1–C_4)-alkyl, (C_1–C_4)-alkanoyl, (C_6–C_{14})-arylcarbonyl, (C_5–C_{10})-heteroarylcarbonyl, (C_1–C_4)-alkylaminocarbonyl or —$CH_2C(NR^{27}R^{28})$=NR^{29},

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

Particular preference is given here to compounds of the general formula (I),

in which

R^1 represents thiophene (thienyl), in particular 2-thiophene, which may optionally be mono- or polysubstituted by halogen, preferably chlorine or bromine, or by (C_1–C_8)-alkyl, preferably methyl, where the (C_1–C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen, preferably fluorine,

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" represents phenyl or naphthyl, in particular phenyl; the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 2 heteroatoms from the group consisting of S, N, NO (N-oxide) and O;

the radical "D" represents a saturated or partially unsaturated 5- or 6-membered heterocycle which contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

the radical "M" represents —NH—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO— or represents a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; pyridyl; (C_1–C_3)-alkanoyl; (C_6–C_{10})-arylcarbonyl; (C_5–C_6)-heteroarylcarbonyl; (C_1–C_3)-alkanoyloxymethyloxy; —$C(NR^{27}R^{28})$=NR^{29}; —$CONR^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OH; —$NR^{30}R^{31}$; (C_1–C_4)-alkyl; and cyclopropyl, cyclopentyl or cyclohexyl,

where (C_1–C_4)-alkyl and cyclopropyl, cyclopentyl or cyclohexyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OH; —OCH_3; —$NR^{28}R^{29}$; —$CO(NH)_v(NR^{27}R^{28})$ and —$C(NR^{27}R^{28})$=NR^{29},

where:

v is either 0 or 1, preferably 0, and

R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1–C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl

and/or

R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached may form a saturated or partially unsaturated 5- to 7-membered heterocycle

having up to two identical or different heteroatoms from the group consisting of N, O and S, and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, $(C_1–C_4)$-alkylsulphonyl, $(C_1–C_4)$-hydroxyalkyl, $(C_1–C_4)$-aminoalkyl, di-$(C_1–C_4)$-alkylamino-$(C_1–C_4)$-alkyl, $(C_1–C_3)$-alkanoyl or phenylcarbonyl,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

Particular preference is given here to compounds of the general formula (I),

in which

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

R^2 represents one of the groups below:

A-,

A-M-,

D-M-A-,

B-M-A-,

B-,

B-M-,

B-M-B-,

D-M-B-,

where:

the radical "A" represents phenyl or naphthyl, in particular phenyl;

the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 2 heteroatoms from the group consisting of S, N, NO (N-oxide) and O;

the radical "D" represents a saturated or partially unsaturated 5- or 6-membered heterocycle which contains a nitrogen atom and optionally a further heteroatom and/or hetero chain member from the group consisting of S, SO, SO_2 and O; or contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2 and O;

the radical "M" represents —NH—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO— or represents a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; pyridyl; $(C_1–C_3)$-alkanoyl; $(C_6–C_{10})$-arylcarbonyl; $(C_5–C_6)$-heteroarylcarbonyl; $(C_1–C_3)$-alkanoyloxymethyloxy; —$CONR^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OH; —$NR^{30}R^{31}$; $(C_1–C_4)$-alkyl; and cyclopropyl, cyclopentyl or cyclohexyl, where $(C_1–C_4)$-alkyl and cyclopropyl, cyclopentyl or cyclohexyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OH; —OCH_3; —$NR^{28}R^{29}$; —$CO(NH)_v$ $(NR^{27}R^{28})$ and —$C(NR^{27}R^{28})$=NR^{29},

where:

v is either 0 or 1, preferably 0, and

R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl

and/or

R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached may form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to two identical or different heteroatoms from the group consisting of N, O and S, and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, $(C_1–C_4)$-alkylsulphonyl, $(C_1–C_4)$-hydroxyalkyl, $(C_1–C_4)$-aminoalkyl, di-$(C_1–C_4)$-alkylamino-$(C_1–C_4)$-alkyl, $(C_1–C_3)$-alkanoyl or phenylcarbonyl,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

Very particular preference is given here to compounds of the general formula (I),

in which

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

R^2 represents D-A-:

where:

the radical "A" represents phenylene;

the radical "D" represents a saturated 5- or 6-membered heterocycle,

which is attached to "A" via a nitrogen atom,

which has a carbonyl group directly adjacent to the linking nitrogen atom and

in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;

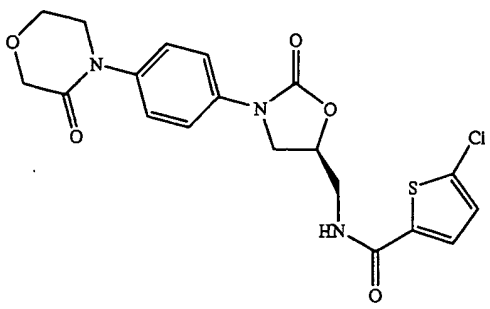
where

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 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

and their pharmaceutically acceptable salts, hydrates and prodrugs.

Very particular preference is also given here to the compound having the following formula



and to its pharmaceutically acceptable salts, hydrates and prodrugs.

In the compounds of the general formula (I) above, the radical

R^1 may in particular represent optionally benzo-fused thiophene (thienyl) which may optionally be mono- or polysubstituted by a radical from the group consisting of halogen; cyano; nitro; $(C_1–C_8)$-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-$(C_1–C_4)$-alkylaminocarbonyl.

In the compounds of the general formula (I), the radical R^1 may preferably represent thiophene (thienyl), in particular 2-thiophene, which may optionally be mono- or polysubstituted by halogen, preferably chlorine or bromine, or by $(C_1–C_8)$-alkyl, preferably methyl, where the $(C_1–C_8)$-alkyl radical, preferably the methyl radical, may for its part optionally be mono- or polysubstituted by halogen, preferably fluorine.

In the compounds of the general formula (I), the radicals R^3, R^4, R^5, R^6, R^7 and R^8 may be identical or different and may represent, in particular, hydrogen or $(C_1–C_6)$-alkyl, preferably hydrogen or $(C_1–C_4)$-alkyl, very particularly preferably hydrogen.

The radical R^2, i.e. the organic radical, can in particular be selected from the substituent groups listed below:

In the compounds of the general formula (I), the radical R^2 may, in particular, represent a group of the following formula:

$$Y—X'—(CH_2)_p—X—(CO)_n—(CH_2)_{o_1}—(CR^9R^{10})_m—(CH_2)_{o_2}—$$

where:

m is an integer from 0 to 6, preferably from 1 to 3,

n is either 0 or 1,

p is an integer from 0 to 3, preferably either 0 or 1,

o_1 is an integer 0 or 1,

o_2 is an integer 0 or 1,

R^9 and R^{10} are identical or different and each represents hydrogen; $(C_1–C_4)$-alkyl, preferably methyl; $(C_1–C_4)$-alkoxy, preferably methoxy; $(C_3–C_7)$-cycloalkyl; hydroxyl or fluorine,

X and X' are identical or different and each represents O; $N—R^{11}$ or a covalent bond,

where R^{11} represents H; $(C_1–C_4)$-alkyl, preferably methyl, or $(C_3–C_7)$-cycloalkyl,

Y represents a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical which optionally contains 1 to 3 identical or different heteroatoms and/or hetero chain members from the group consisting of N, O, S, SO and SO_2,

where:

this radical Y may optionally be substituted by a 5- or 6-membered aromatic or a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical which optionally contains up to 3 identical or different heteroatoms from the group consisting of N, O and S and

where this radical may for its part optionally be substituted by a radical from the group consisting of cyano; hydroxyl; halogen; $(C_1–C_4)$-alkyl; $—C(=NR^{12})NR^{13}R^{13'}$; and $—NR^{14}R^{15}$,

where:

R^{12} represents hydrogen, $(C_1–C_4)$-alkyl or $(C_3–C_7)$-cycloalkyl;

R^{13} and $R^{13'}$ are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl or $(C_3–C_7)$-cycloalkyl

and/or

R^{13} and $R^{13'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S;

R^{14} and R^{15} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl, $(C_3–C_7)$-cycloalkyl or $(C_1–C_5)$-alkanoyl;

and/or

this radical Y may furthermore optionally be substituted by a radical from the group consisting of oxo; cyano; thiono; halogen; $—OR^{16}$; $=NR^{16}$; $—NR^{16}R^{17}$; $—C(=NR^{18})NR^{19}R^{19'}$ and $(C_1–C_4)$-alkyl,

in which $(C_1–C_4)$-alkyl for its part may optionally be substituted by a radical from the group consisting of hydroxyl; cyano; $—NR^{16}R^{17}$ and $—C(=NR^{18})NR^{19}R^{19'}$,

where:

R^{16} and R^{17} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl, $(C_3–C_7)$-cycloalkyl or $(C_1–C_3)$-alkanoyl;

R^{18} represents hydrogen, $(C_1–C_4)$-alkyl or $(C_3–C_7)$-cycloalkyl;

R^{19} and $R^{19'}$ are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl or $(C_3–C_7)$-cycloalkyl and/or

R^{19} and $R^{19'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S.

Particular preference is given to compounds of the general formula (I) in which the radical

R^2 represents a group of the following formula:

$$Y—X'—(CH_2)_p—X—(CO)_n—(CH_2)_{o_1}—(CR^9R^{10})_m—(CH_2)_{o_2}—$$

where

m is an integer from 0 to 3,

n is an integer 0 or 1,

p is an integer 0 or 1,

o_1 is an integer 0 or 1,

o_2 is an integer 0 or 1,

R^9 and R^{10} are identical or different and each represents hydrogen; methyl; methoxy; hydroxyl or fluorine,

X and X' are identical or different and each represents O; N—R^{11} or a covalent bond,

where R^{11} represents H or methyl,

Y represents a 5- to 7-membered saturated cyclic hydrocarbon radical which optionally contains 1 or 2 identical or different heteroatoms and/or hetero chain members from the group consisting of N, O, S, SO and SO_2, in particular cyclohexyl, piperazinyl, morpholinyl, thiomorpholinyl, diazepinyl, pyrrolidinyl and piperidinyl,

where:

this radical Y may optionally be substituted by a 5- or 6-membered aromatic or a 5- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical which optionally contains up to 2 identical or different heteroatoms from the group consisting of N, O and S and

where this radical for its part may be substituted by a radical from the group consisting of cyano; hydroxyl; fluorine; chlorine; $(C_1–C_4)$-alkyl; —C(=NR^{12})$NR^{13}R^{13'}$; and —$NR^{14}R^{15}$,

where:

R^{12} represents hydrogen, methyl, ethyl, cyclopropyl, cyclopentyl or cyclohexyl;

R^{13} and $R^{13'}$ are identical or different and independently of one another each represents hydrogen, methyl, ethyl, cyclopropyl, cyclopentyl or cyclohexyl and/or

R^{13} and $R^{13'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S, in particular piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl;

R^{14} and R^{15} are identical or different and independently of one another each represents hydrogen, methyl, ethyl, cyclopropyl, cyclopentyl or cyclohexyl or else acetyl;

and/or

this radical Y may furthermore optionally be substituted by a radical from the group consisting of oxo; cyano; thiono; fluorine; chlorine; —OH; —OCH_3; =NR^{16}; —NH_2; —$N(CH_3)_2$; —C(=NR^{18})$NR^{19}R^{19'}$ and methyl,

in which methyl for its part may optionally be substituted by a radical from the group consisting of hydroxyl; cyano; —$NR^{16}R^{17}$ and —C(=NR^{18})$NR^{19}R^{19'}$,

where:

R^{16} and R^{17} are identical or different and independently of one another each represents hydrogen, methyl, $(C_3–C_7)$-cycloalkyl or acetyl;

R^{18} represents hydrogen, methyl or $(C_3–C_7)$-cycloalkyl;

R^{9} and $R^{19'}$ are identical or different and independently of one another each represents hydrogen, methyl or $(C_3–C_7)$-cycloalkyl

and/or

R^{19} and $R^{19'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S, in particular piperidinyl, piperazinyl, morpholinyl and thio-morpholinyl.

Likewise, in the compounds of the general formula (I), the radical

R^2 may represent a group of the formula below:

$$Z—(CO)_t—(CR^{20}R^{21})_s—$$

where:

s is an integer from 1 to 6,

t is either 0 or 1,

R^{20} and R^{21} are identical or different and each represents hydrogen, $(C_1–C_4)$-alkyl, $(C_1–C_4)$-alkoxy, $(C_3–C_7)$-cycloalkyl, hydroxyl or fluorine,

Z represents a radical which is selected from the group consisting of cyano; —C($NR^{22}R^{23}$)=NR^{24}; —CO$(NH)_u NR^{22}R^{23}$; and —$NR^{25}R^{26}$,

where:

u is either 0 or 1, preferably 0, and

R^{22}, R^{23} and R^{24} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl or $(C_3–C_7)$-cycloalkyl, preferably hydrogen or methyl, and/or

R^{22} and R^{23} together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms and/or hetero chain members from the group consisting of N, O, S, SO and SO_2;

R^{25} and R^{26} are identical or different and independently of one another each represents hydrogen, $(C_1–C_4)$-alkyl or $(C_3–C_7)$-cycloalkyl, preferably hydrogen, methyl or ethyl, where $(C_1–C_4)$-alkyl and $(C_3–C_7)$-cycloalkyl for their part may optionally be substituted by hydroxyl or $(C_1–C_6)$-alkoxy.

Furthermore, in the compounds of the general formula (I), the radical

R^2 may represent one of the following groups:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" represents $(C_6–Cl_4)$-aryl, preferably $(C_6–C_{10})$-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl;

the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the group consisting of S, N, NO (N-oxide) and O;

the radical "D" represents a saturated or partially unsaturated 4- to 7-membered heterocycle which contains up to three heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

the radical "M" represents —NH—, —CH_2—, —CH_2CH_2—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO—, —COO—, —OOC—, —S— or represents a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; nitro; carbamoyl; pyridyl; $(C_1–C_6)$-alkanoyl; $(C_3–C_7)$-Cycloalkanoyl; $(C_6–C_{14})$-

arylcarbonyl; (C_5–C_{10})-heteroarylcarbonyl; (C_1–C_6)-alkanoyloxymethyloxy; —$COOR^{27}$; —SO_2R^{27}; —$C(NR^{27}R^{28})$=NR^{29}; —$CONR^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OR^{30}; —$NR^{30}R^{31}$, (C_1–C_6)-alkyl and (C_3–C_7)-cycloalkyl,

where (C_1–C_6)-alkyl and (C_3–C_7)-cycloalkyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OR^{27}; —$NR^{28}R^{29}$; —$CO(NH)_v(NR^{27}R^{28})$ and —$C(NR^{27}R^{28})$=NR^{29},

where:

v is either 0 or 1 and

R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1–C_4)-alkyl or (C_3–C_7)-cycloalkyl and/or

R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group consisting of N, O and S, and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1–C_4)-alkyl, (C_3–C_7)-cycloalkyl, (C_1–C_4)-alkyl-sulphonyl, (C_1–C_4)-hydroxyalkyl, (C_1–C_4)-aminoalkyl, di-(C_1–C_4)-alkylamino-(C_1–C_4)-alkyl, (C_1–C_4)-alkanoyl, (C_6–C_{14})-arylcarbonyl, (C_5–C_{10})-heteroarylcarbonyl, (C_1–C_4)-alkylaminocarbonyl or —$CH_2C(NR^{27}R^{28})$=NR^{29}.

Preference is also given to compounds of the general formula (I) in which the radical

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" represents phenyl or naphthyl, in particular phenyl;

the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 2 heteroatoms from the group consisting of S, N, NO (N-oxide) and O;

the radical "D" represents a saturated or partially unsaturated 5- or 6-membered heterocycle which contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

the radical "M" represents —NH—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO— or represents a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; pyridyl; (C_1–C_3)-alkanoyl; (C_6–C_{10})-arylcarbonyl; (C_5–C_6)-heteroarylcarbonyl; (C_1–C_3)-alkanoyloxymethyloxy; —$C(NR^{27}R^{28})$=NR^{29}; —$CONR^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OH; —$NR^{30}R^{31}$; (C_1–C_4)—, alkyl; and cyclopropyl, cyclopentyl or cyclohexyl,

where (C_1–C_4)-alkyl and cyclopropyl, cyclopentyl or cyclohexyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OH; —OCH_3; —$NR^{28}R^{29}$; —$CO(NH)_v(NR^{27}R^{28})$ and —$C(NR^{27}R^{29})$=NR^{29},

where:

v is either 0 or 1, preferably 0, and

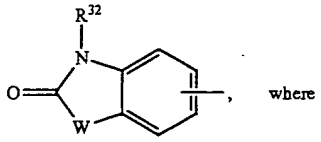
R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1–C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl and/or

R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached may form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to two identical or different heteroatoms from the group consisting of N, O and S, and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1–C_4)-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, (C_1–C_4)-alkylsulphonyl, (C_1–C_4)-hydroxyalkyl, (C_1–C_4)-aminoalkyl, di-(C_1–C_4)-alkylamino-(C_1–C_4)-alkyl, (C_1–C_3)-alkanoyl or phenylcarbonyl.

Likewise, in the compounds of the general formula (I), the radical

R^2 may represent a group of the following formula:



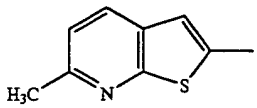
where

R^{32} represents hydrogen or (C_1–C_4)-alkyl, preferably hydrogen or methyl, and

W represents S, NH or O, preferably S.

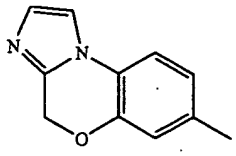
Moreover, in the compounds of the general formula (I), the radical

R^2 may be a group of the formula below



Finally, in the compounds of the general formula (I), the radical

R^2 may be a group of the formula below



To date, oxazolidinones have essentially only been described as antibiotics, and in individual cases also as MAO inhibitors and fibrinogen antagonists (review: Riedl, B., Endermann, R., Exp. Opin. Ther. Patents 1999, 9 (5), 625), where a small 5-[acyl-aminomethyl] group (preferably 5-[acetylaminomethyl]) appears to be essential for the antibacterial activity.

Substituted aryl- and heteroarylphenyloxazolidinones in which a mono- or polysubstituted phenyl radical may be attached to the N atom of the oxazolidinone ring and which may have an unsubstituted N-methyl-2-thiophenecarboxamide radical in the 5-position of the oxazolidinone ring, and their use as antibacterial substances, are known from U.S. Pat. Nos. 5,929,248, 5,801,246, 5,756,732, 5,654,435, 5,654,428 and 5,565,571.

In addition, benzamidine-containing oxazolidinones are known as synthetic intermediates in the synthesis of factor Xa inhibitors and/or fibrinogen antagonists (WO-A-99/31092, EP-A-623615).

Depending on the substitution pattern, the compounds of the general formula (I) according to the invention may exist in stereoisomeric forms which are either like image and mirror image (enantiomers) or not like image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and to their respective mixtures. The racemic forms, like the diastereomers, can be separated in a known manner into the stereoisomerically uniform components.

Furthermore, certain compounds of the general formula (I) can be present in tautomeric forms. This is known to the person skilled in the art, and such compounds are likewise within the scope of the invention.

Physiologically acceptable, i.e. pharmaceutically compatible, salts can be salts of the compounds according to the invention with inorganic or organic acids. Preference is given to salts with inorganic acids, such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or to salts with organic carboxylic or sulphonic acids, such as, for example, acetic acid, trifluoroacetic acid, propionic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid, or methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

Other pharmaceutically compatible salts which may be mentioned are salts with customary bases, such as, for example, alkali metal salts (for example sodium or potassium salts), alkaline earth metal salts (for example calcium or magnesium salts) or ammonium salts, derived from ammonia or organic amines, such as, for example, diethylamine, triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine or methylpiperidine.

According to the invention, "hydrates" are forms of the compounds of the general formula (I) above which form a molecule compound (solvate) in the solid or liquid state by hydration with water. In the hydrates, the water molecules are attached through secondary valencies by intermolecular forces, in particular hydrogen bridges. Solid hydrates contain water as so-called crystal water in stoichiometric ratios, where the water molecules do not have to be equivalent with respect to their binding state. Examples of hydrates are sesquihydrates, monohydrates, dihydrates or trihydrates. Equally suitable are the hydrates of salts of the compounds according to the invention.

According to the invention, "prodrugs" are forms of the compounds of the general formula (I) above which for their part can be biologically active or inactive, but which can be converted into the corresponding biologically active form (for example metabolically, solvolytically or in another way).

Halogen represents fluorine, chlorine, bromine and iodine. Preference is given to chlorine or fluorine.

$(C_1–C_8)$-Alkyl represents a straight-chain or branched alkyl radical having 1 to 8 carbon atoms. Examples which may be mentioned are: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl and n-hexyl. The corresponding alkyl groups with fewer carbon atoms, such as, for example, $(C_1–C_6)$-alkyl and $(C_1–C_4)$-alkyl, are derived analogously from this definition. In general, preference is given to $(C_1–C_4)$-alkyl.

The meaning of the corresponding component of other more complex substituents, such as, for example, alkylsulphonyl, hydroxyalkyl, hydroxyalkylcarbonyl, alkoxyalkyl, alkoxycarbonyl-alkyl, alkanoylalkyl, aminoalkyl or alkylaminoalkyl is likewise derived from this definition.

$(C_3–C_7)$-Cycloalkyl represents a cyclic alkyl radical having 3 to 7 carbon atoms. Examples which may be mentioned are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. The corresponding cycloalkyl groups having fewer carbon atoms, such as, for example, $(C_3–C_5)$-cycloalkyl, are derived analogously from this definition. Preference is given to cyclopropyl, cyclopentyl and cyclohexyl.

The meaning of the corresponding component of other more complex substituents, such as, for example, cycloalkanoyl, is likewise derived from this definition.

In the context of the invention, $(C_2–C_6)$-alkenyl represents a straight-chain or branched alkenyl radical having 2 to 6 carbon atoms. Preference is given to a straight-chain or branched alkenyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are: vinyl, allyl, isopropenyl and n-but-2-en-1-yl.

$(C_1–C_8)$-Alkoxy represents a straight-chain or branched alkoxy radical having 1 to 8 carbon atoms. Examples which may be mentioned are: methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy, n-hexoxy, n-heptoxy and n-octoxy. The corresponding alkoxy groups having fewer carbon atoms, such as, for example, $(C_1–C_6)$-alkoxy and $(C_1–C_4)$-Alkoxy, are derived analogously from this definition. In general, preference is given to $(C_1–C_4)$-alkoxy.

The meaning of the corresponding component of other more complex substituents, such as, for example alkoxyalkyl, alkoxycarbonyl-alkyl and alkoxycarbonyl, is likewise derived from this definition.

Mono- or di-$(C_1–C_4)$-alkylaminocarbonyl represents an amino group which is attached via a carbonyl group and which has a straight-chain or branched or two identical or different straight-chain or branched alkyl substitutents having in each case 1 to 4 carbon atoms. Examples which may be mentioned are: methylamino, ethylamino, n-propylamino, isopropylamino, t-butylamino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino and N-t-butyl-N-methylamino.

$(C_1–C_6)$-Alkanoyl represents a straight-chain or branched alkyl radical having 1 to 6 carbon atoms which carries a doubly attached oxygen atom in the 1-position and is attached via the 1-position. Examples which may be mentioned are: formyl, acetyl, propionyl, n-butyryl, i-butyryl, pivaloyl, n-hexanoyl. The corresponding alkanoyl groups with fewer carbon atoms, such as, for example, $(C_1–C_5)$-alkanoyl, $(C_1–C_4)$-alkanoyl and $(C_1–C_3)$-alkanoyl, are derived analogously from this definition. In general, preference is given to $(C_1–C_3)$-alkanoyl.

The meaning of the corresponding component of other more complex substituents, such as, for example, cycloalkanoyl and alkanoylalkyl, is likewise derived from this definition.

(C_3–C_7)-Cycloalkanoyl represents a cycloalkyl radical having 3 to 7 carbon atoms as, defined above which is attached via a carbonyl group.

(C_1–C_6)-Alkanoyloxymethyloxy represents a straight-chain or branched alkanoyloxymethyloxy radical having 1 to 6 carbon atoms. Examples which may be mentioned are: acetoxymethyloxy, propionoxymethyloxy, n-butyroxymethyloxy, i-butyroxymethyloxy, pivaloyloxymethyloxy, n-hexanoyloxymethyloxy. The corresponding alkanoyloxymethyloxy groups having fewer carbon atoms, such as, for example, (C_1–C_3)-alkanoyloxymethyloxy, are derived analogously from this definition. In general, preference is given to (C_1–C_3)-alkanoyloxymethyloxy.

(C_6–C_{14})-Aryl represents an aromatic radical having 6 to 14 carbon atoms. Examples which may be mentioned are: phenyl, naphthyl, phenanthrenyl and anthracenyl. The corresponding aryl groups with fewer carbon atoms, such as, for example, (C_6–C_{10})-aryl are derived analogously from this definition. In general, preference is given to (C_6–C_{10})-aryl.

The meaning of the corresponding component of other more complex substituents, such as, for example, arylcarbonyl, is likewise derived from this definition.

(C_5–C_{10})-Heteroaryl or a 5- to 10-membered aromatic heterocycle having up to 3 heteroatoms and/or hetero chain members from the group consisting of S, O, N and NO (N-oxide) represents a mono- or bicyclic heteroaromatic which is attached via a carbon ring atom of the heteroaromatic or, if appropriate, via a nitrogen ring atom of the heteroaromatic. Examples which may be mentioned are: pyridyl, pyridyl N-oxide, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl or isoxazolyl, indolizinyl, indolyl, benzo[b]thienyl, benzo[b]furyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl, quinazolinyl. The corresponding heterocycles having a smaller ring size, such as, for example, 5- or 6-membered aromatic heterocycles, are derived analogously from this definition. In general, preference is given to 5- or 6-membered aromatic heterocycles, such as, for example, pyridyl, pyridyl N-oxide, pyrimidyl, pyridazinyl, furyl and thienyl.

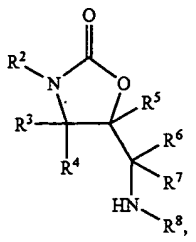
The meaning of the corresponding component of other more complex substituents, such as, for example, (C_5–C_{10})-heteroarylcarbonyl, is likewise derived from this definition.

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. Preference is given to piperidinyl, morpholinyl and pyrrolidinyl.

The corresponding cycles having a smaller ring size, such as, for example, 5- to 7-membered cycles, are derived analogously from this definition.

The present invention also provides a process for preparing the compounds of the general formula (I) according to the invention where either, according to one process alternative

[A] compounds of the general formula (II)

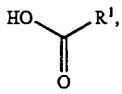


(II)

in which

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

are reacted with carboxylic acids of the general formula (III)



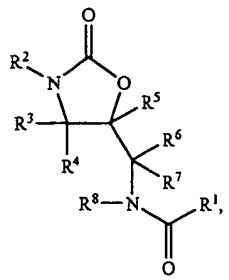
(III)

in which

the radical R^1 is as defined above,

or else with the corresponding carbonyl halides, preferably carbonyl chlorides, or else with the corresponding symmetric or mixed carboxylic anhydrides of the carboxylic acids of the general formula (III) defined above

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



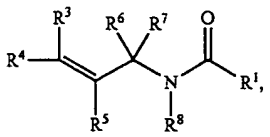
(I)

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 above,

or else according to a process alternative

[B] compounds of the general formula (IV)

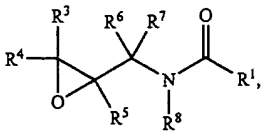


(IV)

in which

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

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

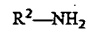


(V)

in which

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

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

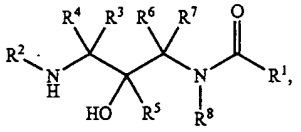


(VI),

in which

the radical R^2 is as defined above,

the compounds of the general formula (VII)



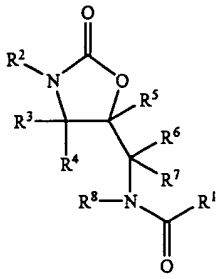
(VII)

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 above,

are initially prepared and

subsequently, in an inert solvent in the presence of phosgene or phosgene equivalents, such as, for example, carbonyldiimidazole (CDI), cyclized to give the compounds 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 above,

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

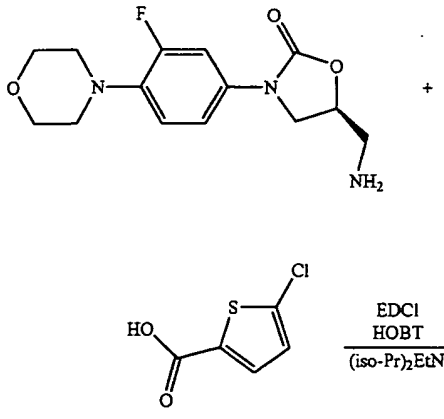
where—both for process alternative [A] and for process alternative [B]—in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with various reagents such as carboxylic acids, carboxylic anhydrides, carbonyl chlorides, isocyanates, sulphonyl chlorides or alkyl halides to give the corresponding derivatives 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 amines to give the corresponding sulphonamides may follow.

The processes according to the invention can be illustrated in an exemplary manner by the equations below:

[A]



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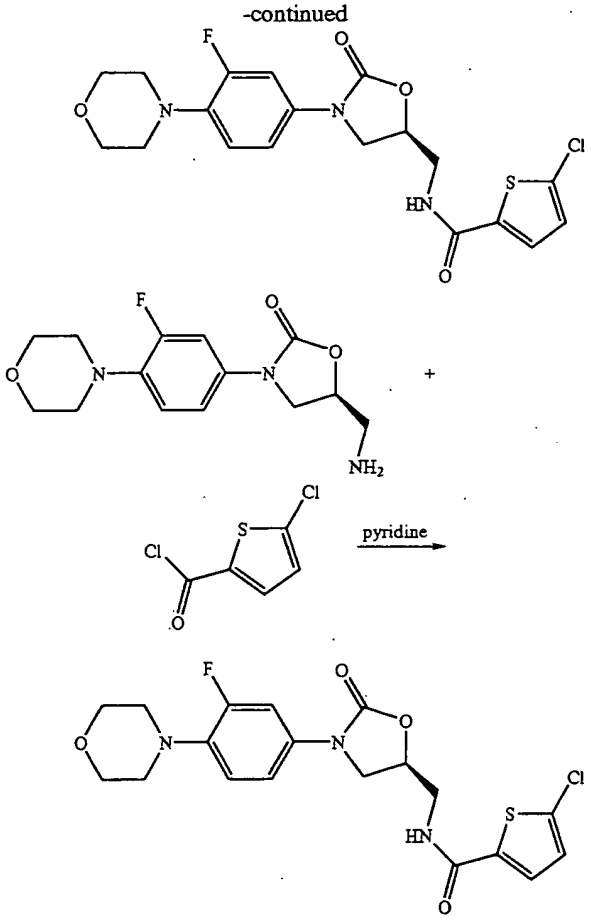

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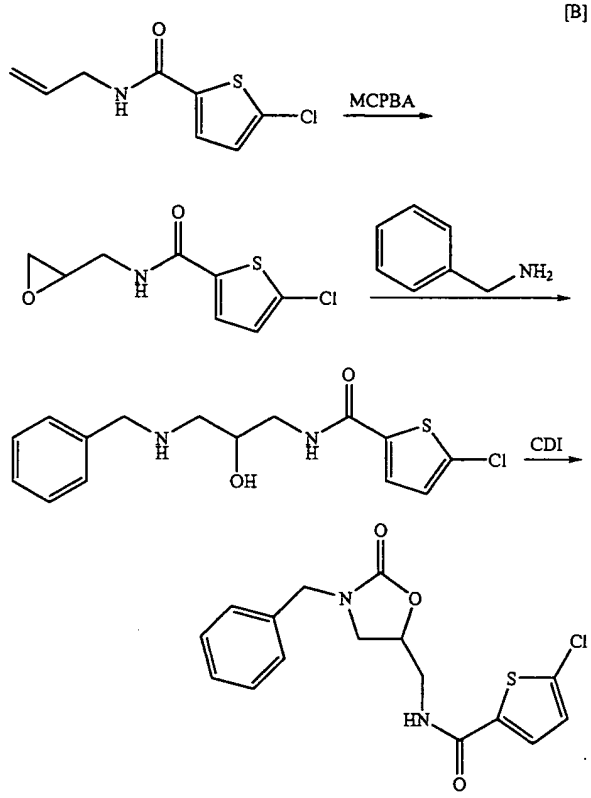
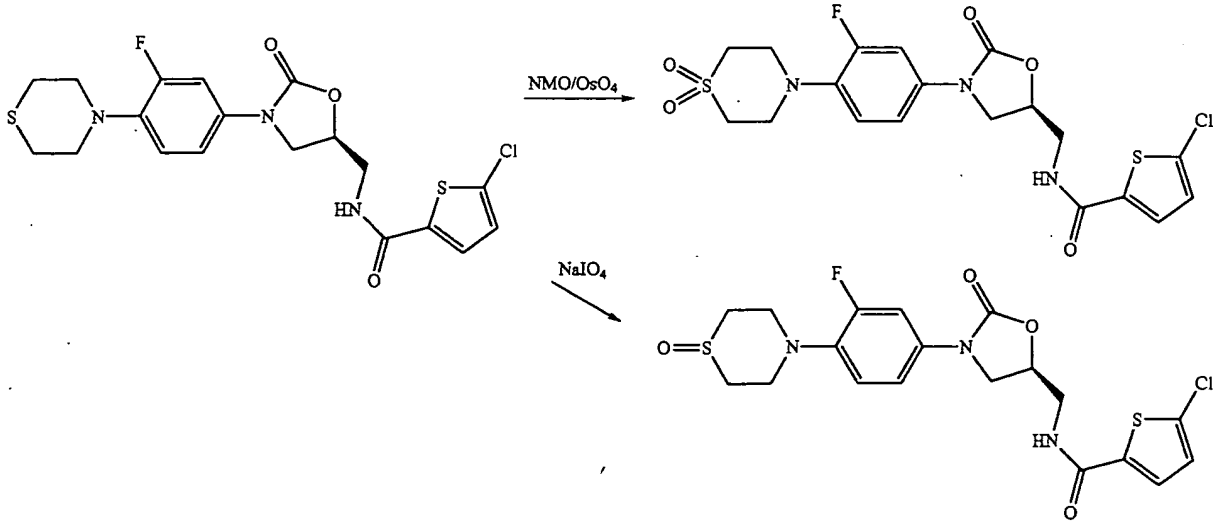
[B]



The oxidation step described above, which is optional, can be illustrated in an exemplary manner by the equation below:



Suitable solvents for the processes described above are organic solvents which are inert under the reaction conditions. These include halogenated hydrocarbons, such as dichloromethane, trichloromethane, carbon tetrachloride, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, ethers, such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols, such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons, such as benzene, xylene, toluene, hexane or cyclohexane, dimethylformamide, dimethyl sulphoxide, acetonitrile, pyridine, hexamethylphosphoric triamide or water.

It is also possible to use solvent mixtures of the solvents mentioned above.

Suitable activating or coupling agents for the processes described above are the reagents which are customarily used for this purpose, for example N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide·HCl, N,N'-dicyclohexylcarbodiimide, 1-hydroxy-1H-benzotriazole·H_2O and the like.

Suitable bases are the customary inorganic or organic bases. These preferably include alkali metal hydroxides, such as, for example, sodium hydroxide or potassium hydroxide, or alkali metal carbonates, such as sodium carbonate or potassium carbonate, or sodium methoxide or potassium methoxide or sodium ethoxide or potassium ethoxide or potassium-tert-butoxide, or amides, such as sodium amide, lithium bis-(trimethylsilyl)amide or lithium diisopropylamide, or amines, such as triethylamine, diisopropylethylamine, diisopropylamine, 4-N,N-dimethylaminopyridine or pyridine.

The base can be employed here in an amount of from 1 to 5 mol, preferably from 1 to 2 mol, based on 1 mol of the compounds of the general formula (II).

The reactions are generally carried out in a temperature range of from −78° C. to reflux temperature, preferably in the range from 0° C. to reflux temperature.

The reactions can be carried out at atmospheric, elevated or reduced pressure (for example in the range from 0.5 to 5 bar). In general, the reactions are carried out at atmospheric pressure.

Suitable selective oxidizing agents, both for the preparation of the epoxides and for the optional oxidation to give the sulphone, sulphoxide or N-oxide, are m-chloroperbenzoic acid (MCPBA), sodium metaperiodate, N-methylmorpholine N-oxide (NMO), monoperoxyphthalic acid or osmium tetroxide.

With respect to the preparation of the epoxides, the preparation conditions which are customary for this purpose are employed.

With respect to more detailed process conditions for the optional oxidation to give the sulphone, sulphoxide or N-oxide, reference is made to the following literature: M. R. Barbachyn et al., J. Med. Chem. 1996, 39, 680 and WO-A-97/10223.

Furthermore, reference is made to Examples 14 to 16 given in the experimental part.

The optional amidation is carried out under customary conditions. For more details, reference is made to Examples 31 to 35 and 140 to 147.

The compounds of the general formulae (II), (III), (IV) and (VI) are known per se to the person skilled in the art or can be prepared by customary methods. For oxazolidinones, in particular the 5-(aminomethyl)-2-oxooxazolidines required, cf. WO-A-98/01446; WO-A-93/23384; WO-A-97/03072; J. A. Tucker et al., J. Med. Chem. 1998, 41, 3727; S. J. Brickner et al., J. Med. Chem. 1996, 39, 673; W. A. Gregory et al., J. Med. Chem. 1989, 32, 1673.

The compounds of the general formula (a) according to the invention have an unforeseeable useful pharmacological activity spectrum and are therefore particularly suitable for the prophylaxis and/or treatment of disorders.

The compounds of the general formula (I) according to the invention—including the compounds which are excluded by disclaimer from the chemical product protection—act in particular as anticoagulants and can therefore preferably be employed in medicaments for the prophylaxis and/or therapy of thromboembolic disorders. For the purpose of the present invention, "thromboembolic disorders" include, in particular, serious disorders such as myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusion disorders, pulmonary embolisms or deep venous thromboses.

Furthermore, the compounds of the general formula (I) according to the invention—including the compounds which are excluded by disclaimer from the, chemical product protection—are also suitable for treating disseminated intravascular coagulation (DIC).

Finally, the compounds of the general formula (I) according to the invention—including the compounds which are excluded by disclaimer from the chemical product protection—are also suitable for the prophylaxis and/or treatment of atherosclerosis and arthritis, and additionally also for the prophylaxis and/or treatment of Alzheimer's disease and cancer.

The compounds of the general formula (I) according to the invention—including the compounds excluded by disclaimer from the chemical product protection—act in particular 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, such as thrombin, plasmin or trypsin.

In the context of the present invention, inhibitors of the blood coagulation factor Xa in which the IC_{50} values for the factor Xa inhibition are lower by a factor of 100, preferably by a factor of 500, in particular by a factor of 1000, than the IC_{50} values for the inhibition of other serine proteases, in particular thrombin, plasmin and trypsin, are referred to as being "selective", where with a view to the test methods for selectivity, reference is made to the test methods of Examples A-1) a.1) and a.2) described below.

The compounds of the general formula (I) according to the invention—including the compounds which are excluded by disclaimer from the chemical product protection—can furthermore be used for preventing coagulation ex vivo, for example for banked blood or biological samples which contain factor Xa.

The present invention thus provides oxazolidinones of the formula (I) effecting in particular an unexpected, strong and selective inhibition of factor Xa, and this also applies to the compounds excluded by disclaimer from the chemical product protection.

The present invention further provides medicaments and pharmaceutical compositions comprising at least one compound of the general formula (I) according to the invention together with one or more pharmacologically acceptable auxiliaries or excipients, which medicaments and pharmaceutical compositions can be used for the indications mentioned above.

Furthermore, the present invention relates to a method for the prophylaxis and/or treatment of disorders of the human

or animal body, in particular of the abovementioned disorders, using the compounds of the general formula (I) according to the invention—including the compounds excluded by disclaimer from the chemical product protection.

Furthermore, the present invention also includes a method for preventing blood coagulation in vitro, in particular in banked blood or biological samples which contain factor Xa, which method is characterized in that compounds of the general formula (I)—including the compounds excluded by disclaimer from the chemical product protection—are added.

All customary administration forms are suitable for administration of the compounds according to the invention. Administration is preferably carried out orally, lingually, sublingually, buccally, rectally or parenterally (i.e. bypassing the intestinal tract, that is intravenously, intraarterially, intracardially, intracutaneously, subcutaneously, transdermally, intraperitoneally or intramuscularly). Particularly suitable are oral and intravenous administration. Very particular preference is given to oral administration, this being a further advantage with respect to the prior-art therapy of thromboembolic disorders.

The novel active compounds of the general formula (I) can be converted in a known manner into the customary formulations, such as tablets, sugar-coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert non-toxic pharmaceutically suitable excipients or solvents. Here, the therapeutically active compound should in each case be present in a concentration of from about 0.1 to 95% by weight, preferably from 0.5 to 90% by weight, in particular from 1 to 85% by weight, of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

In spite of this, if appropriate, it may be necessary to depart from the amounts mentioned, namely depending on the body weight or on the type of administration route, on the individual response to the medicament, on the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be adequate to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into several individual administrations over the course of the day.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, it being possible, for example if the diluent used is water, optionally to use organic solvents as auxiliary solvents.

In general it has proved advantageous in the case of intravenous administration to administer amounts from approximately 0.001 to 10 mg/kg, preferably approximately 0.01 to 10 mg/kg, in particular approximately 0.1 to 8 mg/kg, of body weight to achieve effective results.

In general, it has proved advantageous in the case of oral administration to administer amounts from approximately 0.01 to 50 mg/kg, preferably approximately 0.1 to 10 mg/kg, in particular approximately 0.5 to 8 mg/kg, of body weight to achieve effective results.

In spite of this, if appropriate, it may be necessary in the case of intravenous or oral administration to depart from the amounts mentioned, namely depending on the body weight or on the type of administration route, on the individual response to the medicament, on the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be adequate to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these over the course of the day, namely into several individual doses or as a continuous infusion.

Compared to the conventional preparations for treating thromboembolic disorders, the compounds of the general formula (I) according to the invention—including the compounds excluded by disclaimer from the chemical product protection—are distinguished in particular by the fact that a greater therapeutic range is achieved by the selective inhibition of factor Xa. For the patient, this means a lower risk of, bleeding, and for the treating physician, this means that the patient is easier to adjust. Moreover—owing to the mechanism—the onset of action is more rapid. Above all, however, the compounds according to the invention permit an oral administration form, which is a further advantage of the therapy with the compounds according to the invention.

The present invention is illustrated by the examples below; however, these examples are not meant to restrict the invention in any way.

EXAMPLES

A Evaluation of the Physiological Activity

1. General Test Methods

The particularly advantageous biological properties of the compounds according to the invention can be determined by the following methods.

a) Test Description (In Vitro)

a.1) Determination of the Factor Xa Inhibition

The enzymatic activity of human factor Xa (FXa) was measured using the conversion of a chromogenic substrate specific for FXa. Factor Xa cleaves p-nitroaniline from the chromogenic substrate. The determinations were carried out in microtitre plates as follows.

The test substances, in various concentrations, were dissolved in DMSO and incubated at 25° C. with human FXa (0.5 nmol/l dissolved in 50 mmol/l of tris buffer [C,C,C-tris (hydroxymethyl)-aminomethane], 150 mmol/l of NaCl, 0.1% BSA (bovine serum albumin), pH=8.3) for 10 minutes. Pure DMSO was used as control. The chromogenic substrate (150 μmol/l of Pefachrome® FXa from Pentapharm) was then added. After an incubation time of 20 minutes at 25° C., the extinction at 405 nm was determined. The extinctions of the test mixtures containing test substance were compared with the control mixtures without test substance, and the IC_{50} values were calculated from these data.

a.2) Determination of the Selectivity

To assess selective FXa inhibition, the test substances were examined for their inhibition of other human serine proteases such as thrombin, trypsin and plasmin. To determine the enzymatic activity of thrombin (75 mU/ml), trypsin (500 mU/ml) and plasmin (3.2 mmol/l), these enzymes were dissolved in tris buffer (100 mmol/l, 20 mmol/l $CaCl_2$, pH=8.0) and incubated with test substance or solvent for 10 minutes. The enzymatic reaction was then started by adding the corresponding specific chromogenic substrates (Chromozym Thrombin® from Boehringer Mannheim, Chromozym Trypsin® from Boehringer Mannheim, Chromozym Plasmin® from Boehringer Mannheim) and the extinction at

405 nm was determined after 20 minutes. All determinations were carried out at 37° C. The extinctions of the test mixtures containing test substance were compared with the control samples without test substance, and the IC_{50} values were calculated from these data.

a.3) Determination of the Anticoagulant Action

The anticoagulant action of the test substances was determined in vitro in human plasma. To this end, human blood was drawn off in a mixing ratio of sodium citrate/blood of 1/9 using a 0.11 molar sodium citrate solution as receiver. Immediately after the blood had been drawn off, it was mixed thoroughly and centrifuged at about 2000 g for 10 minutes. The supernatant was pipetted off. The prothrombin time (PT, synonyms: thromboplastin time, quick test) was determined in the presence of varying concentrations of test substance or the corresponding solvent using a commercial test kit (Neoplastin® from Boehringer Mannheim). The test compounds were incubated with the plasma at 37° C. for 10 minutes. Coagulation was then started by addition of thromboplastin, and the time when coagulation occurred was determined. The concentration of test substance which effected a doubling of the prothrombin time was determined.

b) Determination of the Antithrombotic Activity (In Vivo)

b.1) Arteriovenous Shunt Model (Rat)

Fasting male rats (strain: HSD CPB:WU) having a weight of 200–250 g were anaesthetized using a Rompun/Ketavet solution (12 mg/kg/ 50 mg/kg). Thrombus formation was initiated in an arteriovenous shunt in accordance with the method described by Christopher N. Berry et al., Br. J. Pharmacol. (1994), 113, 1209–1214. To this end, the left jugular vein and the right carotid artery were exposed. The two vessels were connected by an extracorporeal shunt using a polyethylene tube (PE 60) of a length of 10 cm. In the middle, this polyethylene tube was attached to a further polyethylene tube (PE 160) of a length of 3 cm which contained a roughened nylon thread which had been arranged to form a loop, to form a thrombogenic surface. The extracorporeal circulation was maintained for 15 minutes. The shunt was then removed and the nylon thread with the thrombus was weighed immediately. The weight of the nylon thread on its own had been determined before the experiment was started. Before the extracorporeal circulation was set up, the test substances were administered to the animals while awake either intravenously via the tail vein or orally using a pharyngeal tube.

The results are shown in Table 1:

TABLE 1

Antithrombotic activity in the arteriovenous shunt model (rat) after oral or intravenous administration

Example	ED_{50} [mg/kg]p.o.	ED_{50} [mg/kg]i.v.
1		10
17		6
44	3	
95		3
114		3
115		3
123	3	
162		3

b.2) Arteriel Thrombosis Model (Rat)

Male fasting rats (strain: HSD CPB: WU) were anaesthetized as described above. On average, the rats had a weight of about 200 g. The left carotid artery was exposed (about 2 cm). The formation of an arterial thrombus was induced by mechanical injury to the blood vessel in accordance with the method described by K. Meng et al., Naunyn-Schmiedeberg's Arch. Pharmacol. (1977), 301, 115–119. To this end, the exposed carotid artery was clamped from the blood flow, cooled to −12° C. in a metal trough for 2 minutes and, to standardize the size of the thrombi, simultaneously compressed using a weight of 200 g. The blood flow was then additionally reduced by a clip which was placed around the carotid artery distally from the injured section of the vessel. The proximal clamp was removed, and the wound was closed and re-opened after 4 hours to remove the injured section of the vessel. The section of the vessel was opened longitudinally and the thrombus was removed from the injured section of the vessel. The moist weight of the thrombi was determined immediately. The test substances were administered to the animals while awake at the beginning of the experiment, either intravenously via the tail vein or orally using a pharyngeal tube.

b.3) Venous Thrombosis Model (Rat)

Male fasting rats (strain: HSD CPB: WU) were anaesthetized as described above. On average, the rats had a weight of about 200 g. The left jugular vein was exposed (about 2 cm). The formation of a venous thrombus was induced by mechanical injury to the blood vessel in accordance with the method described by K. Meng, et al., Naunyn-Schmiedeberg's Arch. Pharmacol. (1977), 301, 115–119. To this end, the jugular vein was clamped from the blood flow, cooled to −12° C. in a metal trough for 2 minutes and, to standardize the size of the thrombi, simultaneously compressed using a weight of 200 g. The blood flow was re-opened and the wound was closed. After 4 hours, the wound was re-opened to remove the thrombi from the injured sections of the vessel. The moist weight of the thrombi was determined immediately. The test substances were administered to the animals while awake at the beginning of the experiment, either intravenously via the tail vein or orally using a pharyngeal tube.

B Preparation Examples

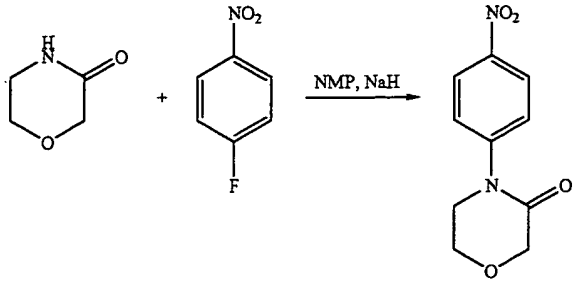
Starting Materials

The preparation of 3-morpholinone is described in U.S. Pat. No. 5,349,045.

The preparation of N-(2,3-epoxypropyl)phthalimide is described in J.-W. Chern et al. Tetrahedron Lett. 1998,39, 8483.

The substituted anilines can be obtained by reacting, for example, 4-fluoronitrobenzene, 2,4-difluoronitrobenzene or 4-chloronitrobenzene with the appropriate amines or amides in the presence of a base. This can also be carried out using Pd catalysts, such as $Pd(OAc)_2$/DPPF/NaOt-Bu (Tetrahedron Lett. 1999,40,2035) or copper (Renger, Synthesis 1985, 856; Aebischer et al., Heterocycles 1998,48,2225). Likewise, it is possible to initially convert halogenated aromatics without nitro group into the corresponding amides, followed by nitration in the 4-position (U.S. Pat. No. 3,279,880).

I. 4-(4-Morpholin-3-onyl)nitrobenzene



2 mol (202 g) of morpholin-3-one (E. Pfeil, U. Harder, Angew. Chem. 79, 1967, 188) are dissolved in 2 l of N-methylpyrrolidone (NNP). Over a period of 2 h, 88 g (2.2 mol) of sodium hydride (60% in paraffin) are then added a little at a time. After the evolution of hydrogen has ceased, 282 g (2 mol) of 4-fluoronitrobenzene are added dropwise with cooling at room temperature, over a period of 1 h, and the reaction mixture is then stirred overnight. At 12 mbar and 76° C., 1.71 l of the liquid volume are then distilled off, the residue is poured into 2 l of water and this mixture is extracted twice with in each case 1 l of ethyl acetate. After washing of the combined organic phases with water, the mixture is dried over sodium sulphate and the solvent is distilled off under reduced pressure. Purification is carried out by silica gel chromatography using hexane/ethyl acetate (1:1) and subsequent crystallization from ethyl acetate. This gives 78 g of product as a colourless to brownish solid, in a yield of 17.6% of theory.

^{1}H-NMR (300 MHz, $CDCl_3$): 3.86 (m, 2 H, CH_2CH_2), 4.08 (m, 2 H, CH_2CH_2), 4.49 (s, 2H, CH_2CO), 7.61 (d, 2 H, ^{3}J=8.95 Hz, CHCH), 8.28 (d, 2H, ^{3}J=8.95 Hz, CHCH) MS (r.I. %)=222 (74, $M^{+\cdot}$), 193 (100), 164 (28), 150 (21), 136 (61), 117 (22), 106 (24), 90 (37), 76 (38), 63 (32), 50 (25)

The following compounds were synthesized analogously:

3-fluoro4-(4-morpholin-3-onyl)nitrobenzene

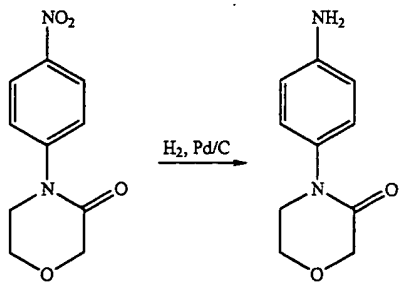
4-(N-piperidonyl)nitrobenzene

3-fluoro-4-(N-piperidonyl)nitrobenzene

4(N-pyrrolidonyl)nitrobenzene

3-fluoro4-(N-pyrrolidonyl)nitrobenzene

II. 4-(4-Morpholin-3-onyl)aniline



In an autoclave, 63 g (0.275 mol) of 4-(4-morpholin-3-onyl)nitrobenzene are dissolved in 200 ml of tetrahydrofuran, admixed with 3.1 g of Pd/C (5% ig) and hydrogenated at 70° C. and a hydrogen pressure of 50 bar for 8 h. The catalyst is filtered off, the solvent is then distilled off under reduced pressure and the product is purified by crystallization from ethyl acetate. 20 g of product are obtained as a colourless to bluish solid, in a yield of 37.6% of theory.

Purification can also be carried out by silica gel chromatography using hexane/ethyl acetate.

^{1}H-NMR (300 MHz, $CDCl_3$): 3.67 (m, 2 H, CH_2CH_2), 3.99 (m, 2 H, CH_2CH_2), 4.27 (s, 2 H, CH_2CO), 6.68 (d, 2 H, ^{3}J=8.71 Hz, CHCH), 7.03 (d, 2 H, ^{3}J=8.71 Hz, CHCH) MS (r.I. %)=192 (100, $M^{+\cdot}$), 163 (48), 133 (26), 119 (76), 106 (49), 92 (38), 67 (27), 65 (45), 52 (22), 28 (22)

The following compounds were synthesized analogously:

3-fluoro4-(4-morpholin-3-onyl)aniline

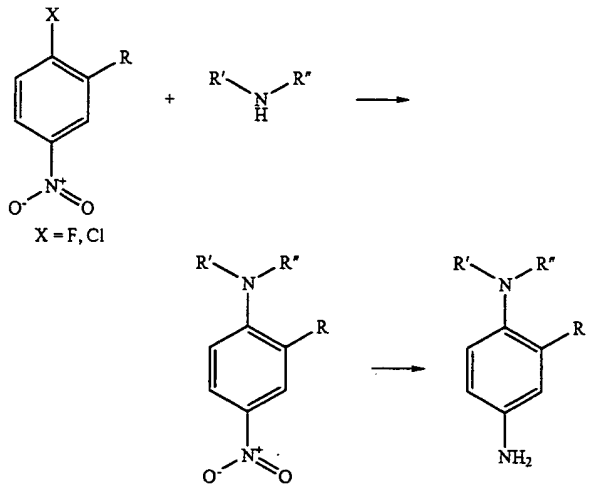
4-(N-piperidonyl)aniline

3-fluoro4-(N-piperidonyl)aniline

4-(N-pyrrolidonyl)aniline

3-fluoro4(N-pyrrolidonyl)aniline

General Method for Preparing 4-substituted Anilines by Reacting 1-fluoro-4-nitrobenzenes and 1-chloro-4-nitrobenzenes with Primary or Secondary Amines, Followed by Reduction



Equimolar amounts of the fluoronitrobenzene or chloronitrobenzene and the amine are dissolved in dimethyl sulphoxide or acetonitrile (0.1 M to 1 M solution), and the mixture is stirred at 100° C. overnight. After cooling to RT, the reaction mixture is diluted with ether and washed with water. The organic phase is dried over $MgSO_4$, filtered and concentrated. If a precipitate forms in the reaction mixture, the precipitate is filtered off and washed with ether or acetonitrile. If the mother liquor also contains product, it is worked up as described using ether and water. The crude products can be purified by silica gel chromatography (dichloromethane/cyclohexane and dichloromethane/ethanol mixtures).

For the subsequent reduction, the nitro compound is dissolved in methanol, ethanol or ethanol/dichloromethane mixtures (0.01 M to 0.5 M solution) admixed with palladium on carbon (10%) and stirred under an atmospheric hydrogen pressure overnight. The mixture is then filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase HPLC (acetonitrile/water mixtures).

Alternatively, the reducing agent used can also be iron powder. To this end, the nitro compound is dissolved in acetic acid (0.1 M to 0.5 M solution) and, at 90° C., six

equivalents of iron powder and water (0.3 to 0.5 times the volume of the acetic acid) are added a little at a time over a period of 10–15 min. After a further 30 min at 90° C., the mixture is filtered and the filtrate is concentrated. The residue is worked up by extraction with ethyl acetate and 2N aqueous sodium hydroxide solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase HPLC (acetonitrile/water mixtures).

The following starting materials were prepared in an analogous manner:

III-1. tert-butyl-1-(4-aminophenyl)-L-prolinate

MS (ESI): m/z (%)=304 (M+H+MeCN, 100), 263 (M+H, 20); HPLC (method 4): rt=2.79 min.

III-2. 1-(4-aminophenyl)-3-piperidinecarboxamide

MS (ESI): m/z (%)=220 (M+H, 100); HPLC (method 4): rt=0.59 min.

III-3. 1-(4-aminophenyl)-4-piperidincarboxamide

MS (ESI): m/z (%)=220 (M+H, 100); HPLC (method 4): rt=0.57 min.

III-4. 1-(4-aminophenyl)-4-piperidinone

MS (ESI): m/z (%)=191 (M+H, 100); HPLC (method 4): rt=0.64 min.

III-5. 1-(4-aminophenyl)-L-prolinamide

MS (ESI): m/z (%)=206 (M+H, 100); HPLC (method 4): rt=0.72 min.

III-6. [1-(4-aminophenyl)-3-piperidinyl]methanol

MS (ESI): m/z (%)=207 (M+H, 100); HPLC (method 4): rt=0.60 min.

III-7. [1-(4-aminophenyl)-2-piperidinyl]methanol

MS (ESI): m/z (%)=207 (M+H, 100); HPLC (method 4): rt=0.59 min.

III-8. ethyl 1-(4-aminophenyl)-2-piperidinecarboxylate

MS (ESI): m/z (%)=249 (M+H, 35), 175 (100); HPLC (method 4): rt=2.43 min.

III-9. [1-(4-aminophenyl)-2-pyrrolidinyl]methanol

MS (ESI): m/z (%)=193 (M+H, 45); HPLC (method 4): rt=0.79 min.

III-10. 4-(2-methylhexahydro-5H-pyrrolo[3,4-d] isoxazol-5-yl)phenylamine

starting from 2-methylhexahydro-2H-pyrrolo[3,4-d]isoxazole (Ziegler, Carl B., et al.; J. Heterocycl. Chem.; 25; 2; 1988; 719–723)

MS (ESI): m/z (%)=220 (M+H, 50), 171 (100); HPLC (method 4): rt=0.54 min.

III-11. 4-(1-pyrrolidinyl)-3-(trifluoromethyl)aniline

MS (ESI): m/z (%)=231 (M+H, 100); HPLC (method 7): rt=3.40 min.

III-12. 3-chloro-4-(1-Pyrrolidinyl)aniline

MS (ESI): m/z (%)=197 (M+H, 100); HPLC (method 4): rt=0.78 min.

III.-13. 5-amino-2-(4-morpholinyl)benzamide

MS (ESI): m/z (%)=222 (M+H, 100); HPLC (method 4): rt=0.77 min.

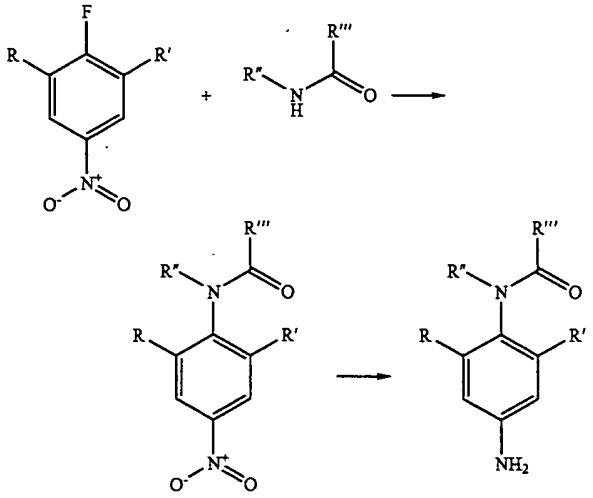
III-14. 3-methoxy-4-(4-morpholinyl)aniline

MS (ESI): m/z (%)=209 (M+H, 100); HPLC (method 4): rt=0.67 min.

III-15. 1-[5-amino-2-(4-morpholinyl)phenyl]ethanone

MS (ESI): m/z (%)=221 (M+H, 100); HPLC (method 4): rt=0.77 min.

General Method for Preparing 4-substituted Anilines by Reacting 1-fluoro4-nitrobenzenes with Amides, Followed by Reduction



The amide is dissolved in DMF and admixed with 1.5 equivalents of potassium tert-butoxide. The mixture is stirred at RT for 1 h, and 1.2 equivalents of the 1-fluoro4-nitrobenzene are then added a little at a time. The reaction mixture is stirred at RT overnight, diluted with ether or ethyl acetate and washed with sat. aqu. sodium bicarbonate solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures).

For the subsequent reduction, the nitro compound is dissolved in ethanol (0.01 M to 0.5 M solution), admixed with palladium on carbon (10%) and stirred under atmospheric hydrogen pressure overnight. The mixture is then filtered and concentrated. The crude product can be purified

by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase BPLC (acetonitrile/water mixtures).

Alternatively, the reducing agent used can also be iron powder. To this end, the nitro compound is dissolved in acetic acid (0.1 M to 0.5 M solution) and, at 90° C., six equivalents of iron powder and water (0.3 to 0.5 times the volume of the acetic acid) are added a little at a time over a period of 10–15 min. After a further 30 min at 90° C., the mixture is filtered and the filtrate is concentrated. The residue is worked up by extraction with ethyl acetate and 2N aqueous sodium hydroxide solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase HPLC (acetonitrile/water mixtures).

The following starting materials were prepared in an analogous manner:

IV-1. 1-[4-amino-2-(trifluoromethyl)phenyl]-2-pyrrolidinone

MS (ESI): m/z (%)=245 (M+H, 100); HPLC (method 4): rt=2.98 min

IV-2. 4-[4-amino-2-(trifluoromethyl)phenyl]-3-morpholinone

MS (ESI): m/z (%)=261 (M+H, 100); HPLC (method 4): rt=2.54 min.

IV-3. 4-(4-amino-2-chlorophenyl)-3-morpholinone

MS (ESI): m/z (%)=227 (M+H, 100); HPLC (method 4): rt=1.96 min.

IV-4. 4-(4-amino-2-methylphenyl)-3-morpholinone

MS (ESI): m/z (%)=207 (M+H, 100); HPLC (method 4): rt=0.71 min.

IV-5. 5-amino-2-(3-oxo-4-morpholinyl)benzonitrile

MS (ESI): m/z (%)=218 (M+H, 100); HPLC (method 4): rt=1.85 min.

IV-6. 1-(4-amino-2-chlorophenyl)-2-pyrrolidinone

MS (ESI): m/z (%)=211 (M+H, 100); HPLC (method 4): rt=2.27 min.

IV-7. 4-(4-amino-2,6-dimethylphenyl)-3-morpholinone

starting from 2-fluoro-1,3-dimethyl-5-nitrobenzene (Bartoli et al., J. Org. Chem. 1975, 40, 872):

MS (ESI): m/z (%)=221 (M+H, 100); HPLC (method 4): rt=0.77 min.

IV-8. 4-(2,4-diaminophenyl)-3-morpholinone

starting from 1-fluoro-2,4dinitrobenzene:

MS (ESI): m/z (%)=208 (M+H, 100); HPLC (method 4): rt=0.60 min.

IV-9. 4-(4-amino-2-chlorophenyl)-2-methyl-3-morpholinone

starting from 2-methyl-3-morpholinone (Pfeil, E.; Harder, U.; Angew. Chem. 1967, 79, 188):

MS (ESI): m/z (%)=241 (M+H, 100); HPLC (method 4): rt=2.27 min.

IV-10. 4-(4-amino-2-chlorophenyl)-6-methyl-3-morpholinone

starting from 6-methyl-3-morpholinone (EP 350 002):

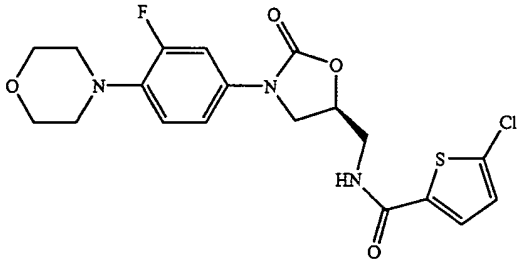
MS (ESI): m/z (%)=241 (M+H, 100); HPLC (method 4): rt=2.43 min.

Synthesis Examples

The Examples 1 to 13, 17 to 19 and 36 to 57 below refer to process variant [A].

Example 1

Preparation of 5-chloro-N-{[(5S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

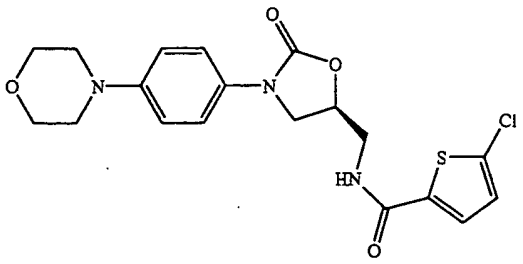


(5S)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)-1,3-oxazolidin-2-one (preparation see S. J. Brickner et al., J. Med. Chem. 1996, 39, 673) (0.45 g, 1.52 mmol), 5-chlorothiophene-2-carboxylic acid (0.25 g, 1.52 mmol) and 1-hydroxy-1H-benzotriazole hydrate (HOBT) (0.3 g, 1.3 equivalents) are dissolved in 9.9 ml of DMF. 0.31 g (1.98 mmol, 1.3 equivalents) of N-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI) are added, and 0.39 g (0.53 ml, 3.05 mmol, 2 equivalents) of diisopropylethylamine (DIEA) are added dropwise at room temperature. The mixture is stirred at room temperature overnight. 2 g of silica gel are added, and the mixture is evaporated to dryness under reduced pressure. The residue is chromatographed on silica gel using a toluene/ethyl acetate gradient. This gives 0.412 g (61.5% of theory) of the target compound of melting point (m.p.) 197° C.

R_f (SiO_2, toluene/ethyl acetate 1:1)=0.29 (starting material=0.0); MS (DCI) 440.2 (M+H), Cl pattern; ^{1}H-NMR (d_6-DMSO, 300 MHz) 2.95 (m, 4H), 3.6 (t, 2H), 3.72 (m, 4H), 3.8 (dd, 1H), 4.12 (t, 1H), 4.75–4.85 (m, 1H), 7.05 (t, 1H), 7.15–7.2 (m, 3H), 7.45 (dd, 1H), 7.68 (d, 1H), 8.95 (t, 1H).

Example 2

5-Chloro-N-{[(5S)-3-(4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

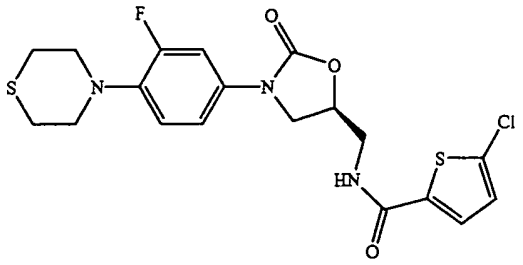


is obtained analogously from benzyl 4-morpholinophenylcarbamate via the (5S)-5-(aminomethyl)-3-(4-morpholinophenyl)-1,3-oxazolidin-2-one intermediate (see Example 1).

M.p.: 198° C.; IC_{50} value=43 nM; R_f(SiO_2, toluene/ethyl acetate 1:1)=0.24.

Example 3

5-Chloro-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

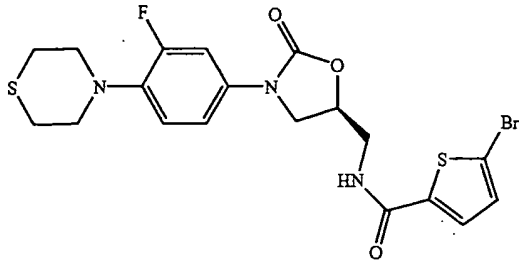


is obtained analogously from (5S)-5-(aminomethyl)-3-[3-fluoro4-(1,4-thiazinan4-yl)phenyl]-1,3-oxazolidin-2-one (preparation see M. R. Barbachyn et al., J. Med. Chem. 1996, 39, 680).

M.p.: 193° C.; Yield: 82%; R_f(SiO_2, toluene/ethyl acetate 1:1)=0.47 (starting material=0.0).

Example 4

5-Bromo-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

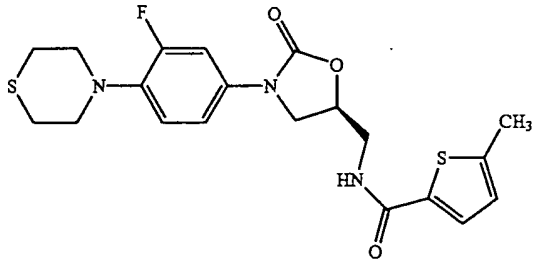


is obtained analogously from 5-bromothiophene-2-carboxylic acid.

M.p.: 200° C.

Example 5

N-({(5S)-3-[3-Fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-methyl-2-thiophenecarboxamide

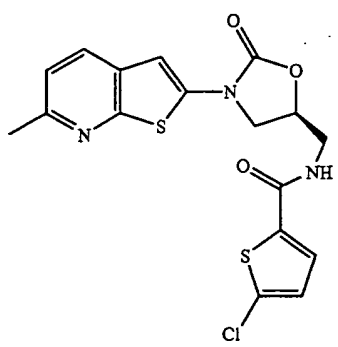


is obtained analogously from 5-methylthiophene-2-carboxylic acid.

M.p.: 167° C.

Example 6

5-Chloro-N-{[(5S)-3-(6-methylthieno[2,3-b]pyridin-2-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

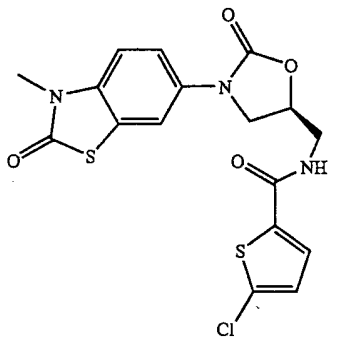


is obtained analogously from (5S)-5-(aminomethyl)-3-(6-methylthieno[2,3-b]pyridin-2-yl)-1,3-oxazolidin-2-one (preparation see EP-A-785 200).

M.p.: 247° C.

Example 7

5-Chloro-N-{[(5S)-3-(3-methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

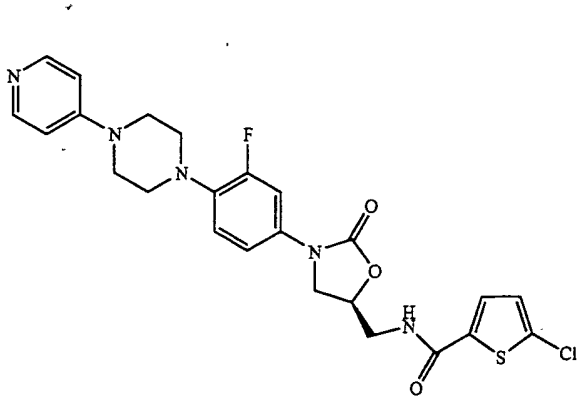


is obtained analogously from 6-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-3-methyl-1,3-benzothiazol-2(3H)-one (preparation see EP-A-738 726).

M.p.: 217° C.

Example 8

5-Chloro-N-[((5S)-3-{3-fluoro-4-[4-(4-pyridinyl)piperazino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

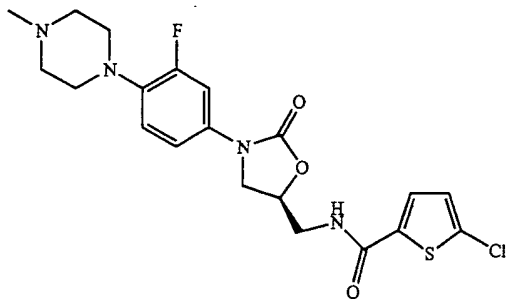


is obtained analogously from (5S)-5-(aminomethyl)-3-{3-fluoro-4-[4-(4-pyridinyl)piperazino]phenyl}-1,3-oxazolidin-2-one (preparation analogously to J. A. Tucker et al., J. Med. Chem. 1998, 41, 3727).

MS (ESI) 516 (M+H), Cl pattern.

Example 9

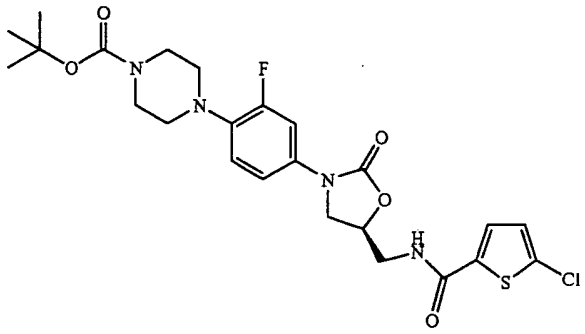
5-Chloro-N-({(5S)-3-[3-fluoro-4-(4-methylpiperazino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



is obtained analogously from (5S)-5-(aminomethyl)-3-[3-fluoro-4-(4-methylpiperazino)phenyl]-1,3-oxazolidin-2-one.

Example 10

5-Chloro-N-({(5S)-3-[3-fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

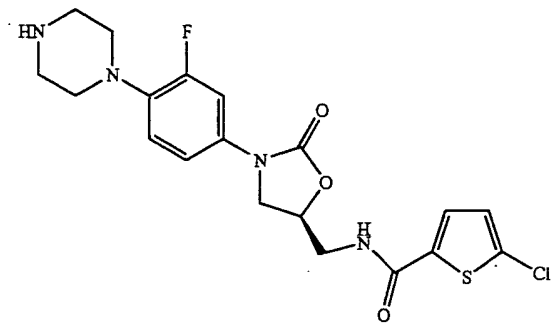


is obtained analogously from (5S)-5-(aminomethyl)-3-[3-fluoro-4-(4-tert-butoxy-carbonylpiperazin-1-yl)phenyl]-1,3-oxazolidin-2-one (preparation see WO-A-93/23384, which has already been cited).

M.p.: 184° C.; R_f (SiO_2, toluene/ethyl acetate 1:1)=0.42.

Example 11

5-Chloro-N-({(5S)-3-[3-fluoro-4-(piperazin-1-yl) phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



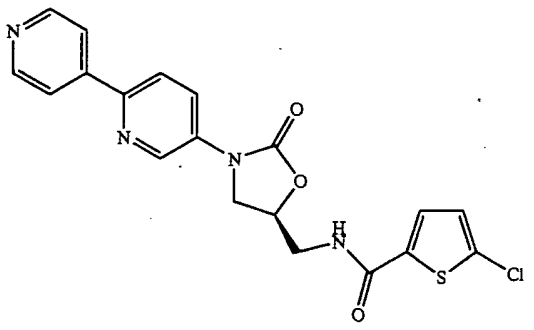
is obtained by reacting Example 10 with trifluoroacetic acid in methylene chloride.

IC_{50} value=140 nM;

^{1}H-NMR [d_6-DMSO]: 3.01–3.25 (m, 8H), 3.5–3.65 (m, 2H), 3.7–3.9 (m, 1H), 4.05–4.2 (m, 1H), 4.75–4.9 (m, 1H), 7.05–7.25 (m, 3H), 7.5 (dd, 1H), 7.7 (d, 1H), 8.4 (broad s, 1H), 9.0 (t, 1H).

Example 12

5-Chloro-N-[((5S)-3-(2,4'-bipyridinyl-5-yl)-2-oxo-1, 3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

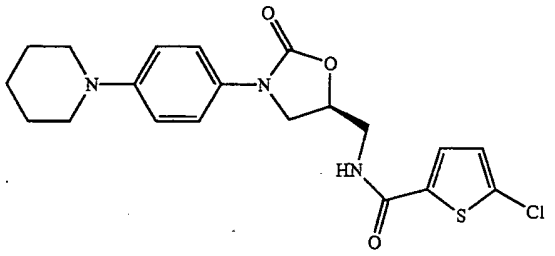


is obtained analogously from (5S)-5-aminomethyl-3-(2,4-bipyridinyl-5-yl)-2-oxo-1,3-oxazolidin-2-one (preparation see EP-A-789 026).

R_f (SiO_2, ethyl acetate/ethanol 1:2)=0.6; MS (ESI) 515 (M+H), Cl pattern.

Example 13

5-Chloro-N-{[(5S)-2-oxo-3-(4-piperidinophenyl)-1, 3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

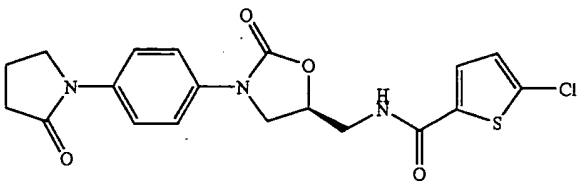


is obtained from 5-(hydroxymethyl)-3-(4-piperidinophenyl)-1,3-oxazolidin-2-one (preparation see DE 2708236) after mesylation, reaction with potassium phthalimide, hydrazinolysis and reaction with 5-chlorothiophene-2-carboxylic acid.

R_f (SiO_2, ethyl acetate/toluene 1:1)=0.31; m.p. 205° C.

Example 17

5-Chloro-N-({(5S)-2-oxo-3-[4-(2oxo-1-pyrrolidinyl) phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



Analogously to the known synthesis scheme (see S. J. Brickner et al., J. Med. Chem. 1996, 39, 673), 1-(4-aminophenyl)pyrrolidin-2-one (preparation see Reppe et al., Justus Liebigs Ann. Chem.; 596; 1955; 209) gives, after reaction with benzyloxycarbonyl chloride, followed by reaction with R-glycidyl butyrate, mesylation, reaction with potassium phthalimide, hydrazinolysis in methanol and reaction with 5-chlorothiophene-2-carboxylic acid, finally 5-chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl }methyl)-2-thio-phenecarboxamide. The 5-chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)-phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide obtained in this manner has an IC_{50} value of 4 nM (test method for the IC_{50} value according to Example A-1.a.1 described above) "determination of the inhibition of factor Xa").

M.p.: 229° C.; R_f value (SiO_2, toluene/ethyl acetate 1:1) =0.05 (starting material:=0.0); MS (ESI): 442.0 (21%, M+Na, Cl pattern), 420.0 (72%, M+H, Cl pattern), 302.3 (12%), 215(52%), 145 (100%); ^{1}H-NMR (d_6-DMSO, 300 MHz): 2.05 (m,2H), 2.45 (m,2H), 3.6 (t,2H), 3.77–3.85 (m,3H), 4.15(t,1H), 4.75–4.85 (m,1H), 7.2 (d,1H), 7.5 (d,2H), 7.65 (d,2H), 7.69 (d,1H), 8.96 (t,1H).

The individual steps of the synthesis of Example 17 described above with the respective precursors are as follows:

At −20° C., 4 g (22.7 mmol) of 1-(4-aminophenyl) pyrrolidin-2-one and 3.6 ml (28.4 mmol) of N,N-dimethylaniline in 107 ml of tetrahydrofuran are admixed slowly with 4.27 g (25.03 mmol) of benzyl chloroformate. The mixture is stirred at −20° C. for 30 minutes and then allowed to warm to room temperature. 0.5 l of ethyl acetate are added, and the organic phase is washed with 0.5 l of saturated NaCl solution. The organic phase is separated off and dried with $MgSO_4$, and the solvent is evaporated under reduced pressure. The residue is triturated with diethyl ether and filtered off with suction. This gives 5.2 g (73.8% of theory) of benzyl 4-(2-oxo-1-pyrrolidinyl)phenylcarbamate as light-beige crystals of melting point 174° C.

At −10° C. and under argon, 1.47 g (16.66 mmol) of isoamyl alcohol in 200 ml of tetrahydrofuran are admixed dropwise with 7.27 ml of a 2.5 M solution of n-butyllithium (BuLi) in hexane, a further 8 ml of BuLi solution being required for the added indicator N-benzylidenebenzylamine to change colour. The mixture is stirred at −10° C. for 10 minutes and cooled to −78° C., and a solution of 4.7 g (15.14 mmol) of benzyl 4-(2-oxo-1-pyrrolidinyl)phenylcarbamate is added slowly. Another 4 ml of n-BuLi solution are then added until the colour of the indicator changes to pink. The mixture is stirred at −78° C. for 10 minutes, 2.62 g (18.17 mmol) of R-glycidyl butyrate are added and the mixture is stirred at −78° C. for another 30 minutes.

Overnight, the mixture is allowed to warm to room temperature, 200 ml of water are added and the THF fraction is evaporated under reduced pressure. The aqueous residue is extracted with ethyl acetate and the organic phase is dried with $MgSO_4$ and evaporated under reduced pressure. The residue is triturated with 500 ml of diethyl ether and the precipitated crystals are filtered off with suction under reduced pressure.

This gives 3.76 g (90% of theory) of (5R)-5-(hydroxymethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one of melting point 148° C., with an R_f value (SiO_2, toluene/ethyl acetate 1:1) of 0.04 (starting material=0.3).

At 0° C., 3.6 g (13.03 mmol) of (5R)-5-(hydroxymethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one and 2.9 g (28.67 mmol) of triethylamine are initially charged with stirring in 160 ml of dichloromethane. 1.79 g (15.64 mmol) of methanesulphonyl chloride are added with stirring, and the mixture is stirred at 0° C. for 1.5 hours and then at room temperature for 3 h.

The reaction mixture is washed with water and the aqueous phase is reextracted with methylene chloride. The combined organic extracts are dried with $MgSO_4$ and concentrated. The residue (1.67 g) is then dissolved in 70 ml of acetonitrile, admixed with 2.62 g (14.16 mmol) of potassium phthalimide and stirred in a closed vessel at 180° C. in a microwave oven for 45 minutes.

The mixture is filtered off from insoluble residues, the filtrate is evaporated under reduced pressure and the residue (1.9 g) is dissolved in methanol and admixed with 0.47 g (9.37 mmol) of hydrazine hydrate. The mixture is boiled for 2 hours, cooled, admixed with saturated sodium bicarbonate solution and extracted six times with a total of 2 l of methylene chloride. The combined organic extracts of the crude (5S)-5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl) phenyl]-1,3-oxazolidin-2-one are dried with $MgSO_4$ and concentrated under reduced pressure.

The end product, 5-chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, is prepared by dissolving 0.32 g (1.16 mmol) of the (5S)-5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one prepared above, 5-chlorothiophene-2-carboxylic acid (0.19 g; 1.16 mmol) and 1-hydroxy-1H-benzotriazole hydrate (HOBT) (0.23 g, 1.51 mmol) in 7.6 ml of DMF. 0.29 g (1.51 mmol) of N-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI) are added, and 0.3 g (0.4 ml; 2.32 mmol, 2 equivalents) of diisopropylethylamine (DIEA) are added dropwise at room temperature. The mixture is stirred at room temperature overnight.

The mixture is evaporated to dryness under reduced pressure and the residue is dissolved in 3 ml of DMSO and chromatographed on an RP-MPLC using an acetonitrile/water/0.5% TFA gradient. From the appropriate fractions, the acetonitrile fraction is evaporated and the precipitated compound is filtered off with suction. This gives 0.19 g (39% of theory) of the target compound.

The following compounds were prepared in an analogous manner:

Example 18

5-Chloro-N-({(5S)-2-oxo-3-[4-(1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

Analogously to Example 17, 4-pyrrolidin-1-yl-aniline (Reppe et al., Justus Liebigs Ann. Chem.; 596; 1955; 151) gives the compound 5chloro-N-({(5S)-2-oxo-3-[4-(1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide.

IC_{50}=40 nM; m.p.: 216° C.; R_f value (SiO_2, toluene/ethyl acetate 1:1)=0.31 [starting material:=0.0].

Example 19

5-Chloro-N-({(5S)-2-oxo-3-[4-(diethylamino)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

Analogously, N,N-diethylphenyl-1,4-diamine (U.S. Pat. No. 2,811,555; 1955) gives the compound 5-chloro-N-({(5S)-2-oxo-3-[4-(diethylamino)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.

IC_{50}=270 nM; m.p.: 181° C.; R_f value (SiO_2, toluene/ethyl acetate 1:1)=0.25 [starting material:=0.0].

Example 36

5-Chloro-N-({(5S)-3-[2-methyl-4-(4-morpholinyl) phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

starting from 2-methyl4-(4-morpholinyl)aniline (J. E. LuValle et al. *J. Am. Chem. Soc.* 1948, 70, 2223):

MS (ESI): m/z (%)=436 ([M+H]$^+$, 100), Cl pattern; HPLC (method 1): rt (%)=3.77 (98). IC_{50}: 1.26 μM

Example 37

5-Chloro-N-{[(5S)-3-(3-chloro-4-morpholinophenyl)-2-oxo-1,3oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

starting from 3-chloro4(4-morpholinyl)aniline (H. R. Snyder et al. *J. Pharm. Sci.* 1977, 66, 1204):

MS (ESI): m/z (%)=456 ([M+H]$^+$, 100), Cl_2 pattern; HPLC (method 2): rt (%)=4.31 (100). IC_{50}: 33 nM

Example 38

5-Chloro-N-({(5S)-3-[4-(4-morpholinylsulphonyl) phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

starting from 4-(4-morpholinylsulphonyl)aniline (Adams et al. *J. Am. Chem. Soc.* 1939, 61, 2342):

MS (ESI): m/z (%)=486 ([M+H]$^+$, 100), Cl pattern; HPLC (method 3): rt (%)=4.07 (100). IC_{50}: 2 μM

Example 39

5-Chloro-N-({(5S)-3-[4-(1-azetidinylsulphonyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

starting from 4-(1-azetidinylsulphonyl)aniline:

MS (DCI, NH_3): m/z (%)=473 ([M+NH]$^+$, 100), Cl pattern; HPLC (method 3): rt (%)=4.10 (100). IC_{50}: 0.84 μM

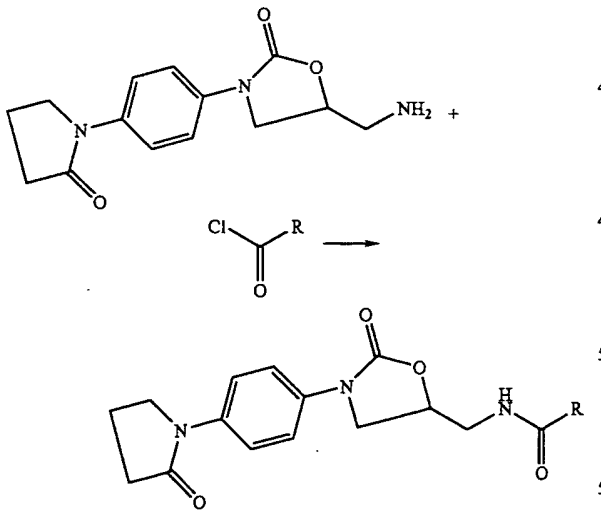
Example 40

5-Chloro-N-[((5S)-3-{4-[(dimethylamino)sulphonyl] phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

starting from 4-amino-N,N-dimethylbenzenesulphonamide (I. K. Khanna et al. *J. Med. Chem.* 1997,40, 1619):

MS (ESI): m/z (%)=444 ([M+H]$^+$, 100), Cl pattern; HPLC (method 3): rt (%)=4.22 (100). IC_{50}: 90 nM

General Method for the Acylation of 5-(aminomethyl)-3-[4-(2-oxo-1-pyrro-lidinyl)phenyl]-1,3-oxazolidin-2-one with Carbonyl Chlorides.



Under argon and at room temperature, an about 0.1 molar solution of 5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl) phenyl]-1,3-oxazolidin-2-one (from Example 45) (1.0 eq.) and absolute pyridine (about 6 eq.) in absolute dichloromethane is added dropwise to the appropriate acid chloride (2.5 eq.). The mixture is stirred at room temperature for about 4 h, and about 5.5 eq of PS-trisamine (Argonaut Technologies) are then added. The suspension is stirred gently for 2 h, diluted with dichloromethane/DMF (3:1) and then filtered (the resin is washed with dichloromethane/DMF) and the filtrate is concentrated. If appropriate, the product that is obtained is purified by preparative RP-HPLC.

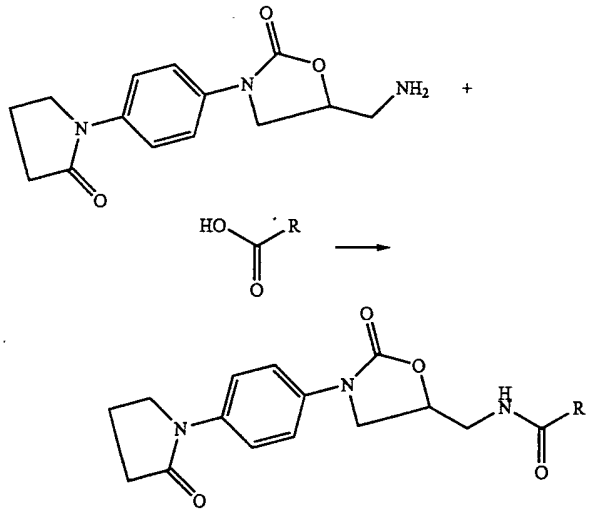
The following compounds were prepared in an analogous manner:

Example 41

N-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide

LC-MS (method 6): m/z (%)=386 (M+H, 100); LC-MS: rt (%)=3.04 (100). IC_{50}: 1.3 μM

General Method for Preparing Acyl Derivatives Starting from 5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one and Carboxylic Acids



The appropriate carboxylic acid (about 2 eq.) and a mixture of absolute dichloromethane/DMF (about 9:1) are added to 2.9 eq. of resin-bonded carbodiimide (PS-carbodiimide, Argonaut Technologies). The mixture is shaken gently at room temperature for about 15 min, 5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one (from Example 45) (1.0 eq.) is then added and the mixture is shaken overnight, after which the resin is filtered off (and washed with dichloromethane), and the filtrate is concentrated. If appropriate, the resulting product is purified by preparative RP-HPLC.

The following compounds were prepared in an analogous manner:

Example 42

5-Methyl-N-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl) phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

LC-MS: m/z (%)=400 (M+H, 100); LC-MS (method 6): rt (%)=3.23 (100). IC_{50}: 0.16 μM

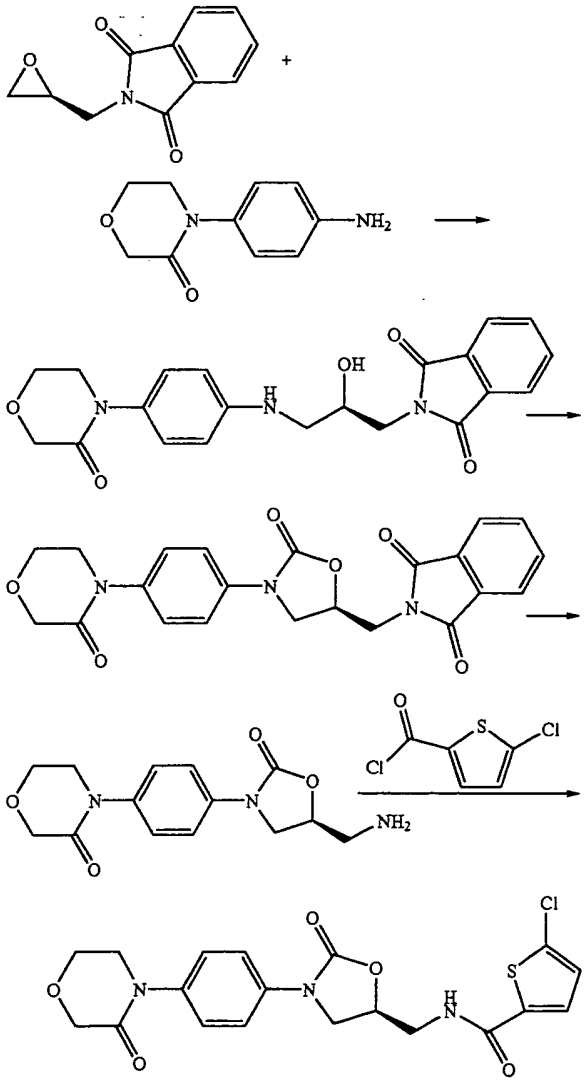
Example 43

5-Bromo-N-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl) phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

LC-MS: m/z (%)=466 (M+H, 100); LC-MS (method 5): rt (%)=3.48 (78). IC_{50}: 0.014 μM

Example 44

5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-13oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



a) 2-((2R)-2-Hydroxy-3-{[4-(3-oxo-4-morpholinyl)phenyl]amino}propyl)-1H-isoindole-1,3(2H)-dione:

A suspension of 2-[(2S)-2-oxiranylmethyl]-1H-isoindole-1,3(2H)-dione (A. Gutcait et al. *Tetrahedron Asym.* 1996, 7, 1641) (5.68 g, 27.9 mmol) and 4-(4-aminophenyl)-3-morpholinone (5.37 g, 27.9 mmol) in ethanol/water (9:1, 140 ml) is refluxed for 14 h (the precipitate dissolves, after some time again formation of a precipitate). The precipitate (desired product) is filtered off, washed three times with diethyl ether and dried. The combined mother liquors are concentrated under reduced pressure and, after addition of a second portion of 2-[(2S)-2-oxiranylmethyl]-1H-isoindole-1,3(2H)-dione (2.84 g, 14.0 mmol), suspended in ethanol/water (9:1, 70 ml) and refluxed for 13 h (the precipitate dissolves, after some time again formation of a precipitate). The precipitate (desired product) is filtered off, washed three times with diethyl ether and dried. Total yield: 10.14 g, 92% of theory.

MS (ESI): m/z (%)=418 ([M+Na]$^+$, 84), 396 ([M+H]$^+$, 93); HPLC (method 3): rt (%)=3.34 (100).

b) 2-({(5S)-2-Oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1H-isoindole-1,3(2H)-dione:

Under argon and at room temperature, N,N'-carbonyldiimidazole (2.94 g, 18.1 mmol) and dimethylaminopyridine (a catalytic amount) are added to a suspension of the amino alcohol (3.58 g, 9.05 mmol) in tetrahydrofuran (90 ml). The reaction suspension is stirred at 60° C. for 12 h (the precipitate dissolves, after some time again formation of a precipitate), admixed with a second portion of N,N'-carbonyldiimidazole (2.94 g, 18.1 mmol) and stirred at 60° C. for another 12 h. The precipitate (desired product) is filtered off, washed with tetrahydrofuran and dried. The filtrate is concentrated under reduced pressure and further product is purified by flash chromatography (dichloromethane/methanol mixtures). Total yield: 3.32 g, 87% of theory.

MS (ESI): m/z (%)=422 ([M+H]$^+$, 100); HPLC (method 4): rt (%)=3.37 (100).

c) 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide:

At room temperature, methylamine (40% strength in water, 10.2 ml, 0.142 mol) is added dropwise to a suspension of the oxazolidinone (4.45 g, 10.6 mmol) in ethanol (102 ml). The reaction mixture is refluxed for 1 h and concentrated under reduced pressure. The crude product is used without further purification for the next reaction.

Under argon and at 0° C., 5-chlorothiophene-2-carbonyl chloride (2.29 g, 12.7 mmol) is added dropwise to a solution of the amine in pyridine (90 ml). Ice-cooling is removed and the reaction mixture is stirred at room temperature for 1 h and admixed with water. Dichloromethane is added and the phases are separated, and the aqueous phase is then extracted with dichloromethane. The combined organic phases are dried (sodium sulphate), filtered and concentrated under reduced pressure. The desired product is purified by flash chromatography (dichloromethane/methanol mixtures).

Total yield: 3.92 g, 86% of theory. M.p: 232–233° C.; ^{1}H NMR (DMSO-d^6, 200 MHz): 9.05–8.90 (t, J=5.8 Hz, 1H), 7.70 (d, J=4.1 Hz, 1H), 7.56 (d, J=9.0 Hz, 2H), 7.41 (d, J=9.0 Hz, 2H), 7.20 (d, J=4.1 Hz, 1H), 4.93–4.75 (m, 1H), 4.27–4.12 (m, 3H), 4.02–3.91 (m, 2H), 3.91–3.79 (dd, J=6.1 Hz, 9.2 Hz, 1H), 3.76–3.66 (m, 2H), 3.66–3.54 (m, 2H); MS (ESI): m/z (%)=436 ([M+H]$^+$, 100, Cl pattern); HPLC (method 2): rt (%)=3.60 (100); $[\alpha]^{21}_D$=–38° (c 0.2985, DMSO); ee: 99%. IC_{50}: 0.7 nM

The following compounds were prepared in an analogous manner:

Example 45

5-Methyl-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=831 ([2M+H]$^+$, 100), 416 ([M+H]$^+$, 66); HPLC (method 3): rt (%)=3.65 (100). IC_{50}: 4.2 nM

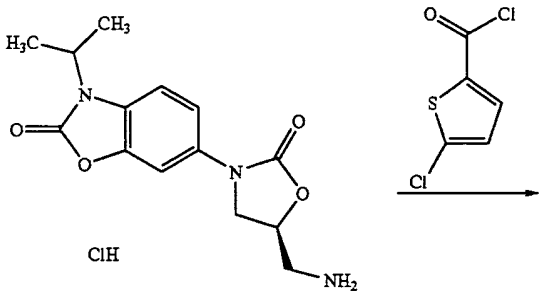
Example 46

5-Bromo-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=480 ([M+H]$^+$, 100, Br pattern); HPLC (method 3): rt (%)=3.87 (100). IC_{50}: 0.3 nM

Example 47

5-Chloro-N-{[(5S)-3-(3-isopropyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



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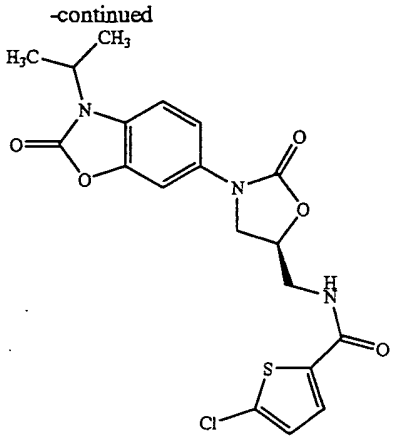
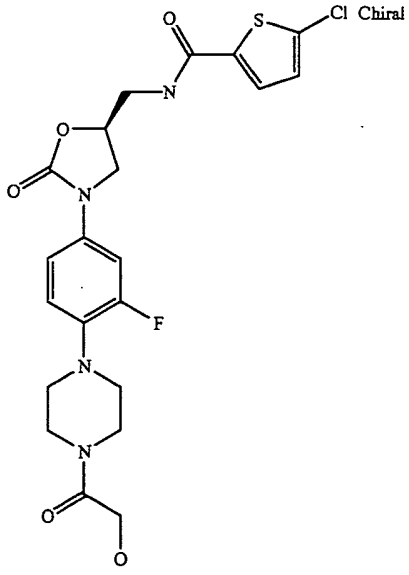


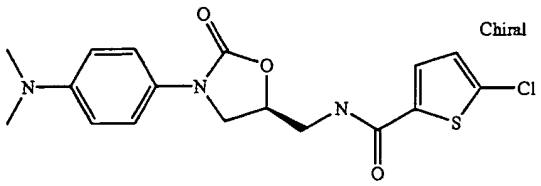
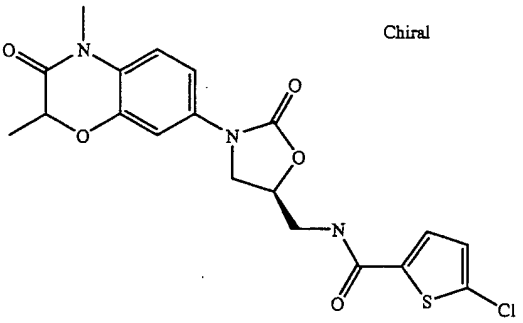
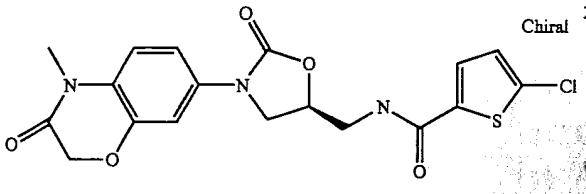
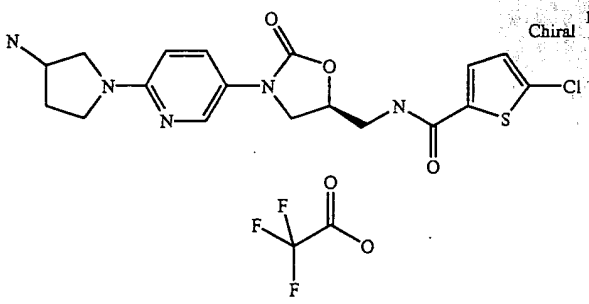
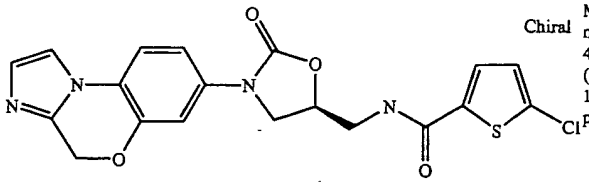
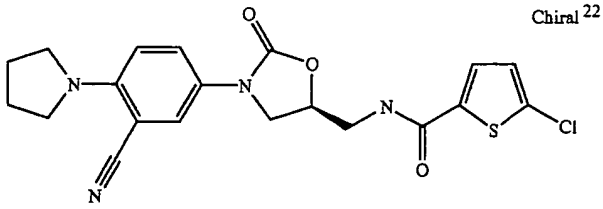
200 mg (0.61 mmol) of 6-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-3-isopropyl-1,3-benzoxazol-2(3H)-one hydrochloride (EP 738726) are suspended in 5 ml of tetrahydrofuran and admixed with 0.26 ml (1.83 mmol) of triethylamine and 132 mg (0.73 mmol) of 5-chlorothiophene-2-carbonyl chloride. The reaction mixture is stirred at room temperature overnight and then concentrated. The product is isolated by column chromatography (silica gel, methylene chloride/ethanol=50/1 to 20/1). This gives 115 mg (43% of theory) of the desired compound.

MS (ESI): m/z (%)=436 (M+H, 100); HPLC (method 4): rt=3.78 min.

The following compounds were prepared in an analogous manner;

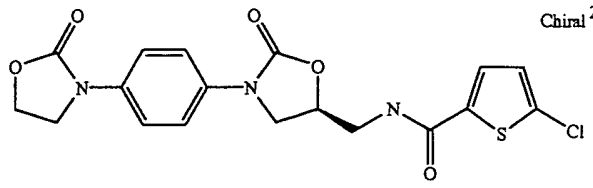
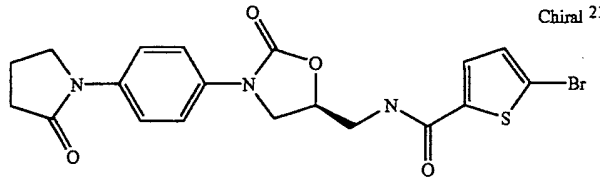
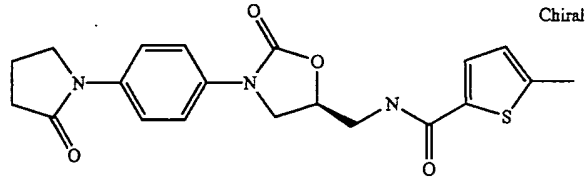
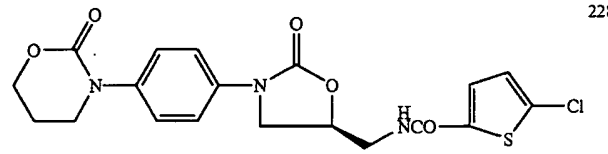
Example No.	Structure	M.p. [° C.]	IC_{50} [μM]
48	 Cl Chiral	210	0.12

-continued

Example No.	Structure	M.p. [° C.]	IC_{50} [μM]
49	 Chiral	234	0.074
50	 Chiral	195	1.15
51	 Chiral	212	1.19
52	 Chiral	160	0.19
53	 Chiral	MS (ESI): m/z (%) = 431 ([M + H]$^+$, 100), Cl pattern	0.74
54	 Chiral	221	0.13

from 5-amino-2-pyrrolidino-benzonitril (Grell, W., Hurnaus, R., Griss, G., Sauter, R.; Rupprecht, E. et al.; J. Med. Chem. 1998, 41; 5219)

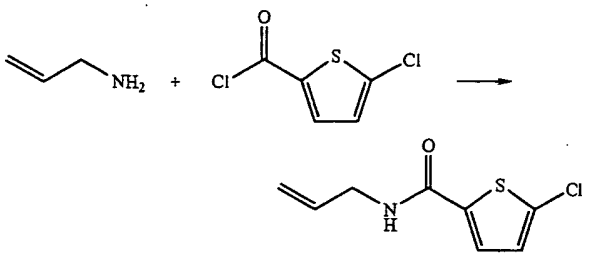
-continued

Example No.	Structure	M.p. [° C.]	IC_{50} [μM]
55		Chiral 256	0.04
	from 3-(4-amino-phenyl)-oxazolidin-2-one (Artico, M. et al.; Farmaco Ed. Sci. 1969, 24; 179)		
56		Chiral 218	0.004
57		Chiral 226	0.58
255		228–230	

Examples 20 to 30 and 58 to 139 below refer to process variant [B], and Examples 20 and 21 describe the preparation of precursors.

Example 20

Preparation of
N-allyl-5-chloro-2-thiophenecarboxamide

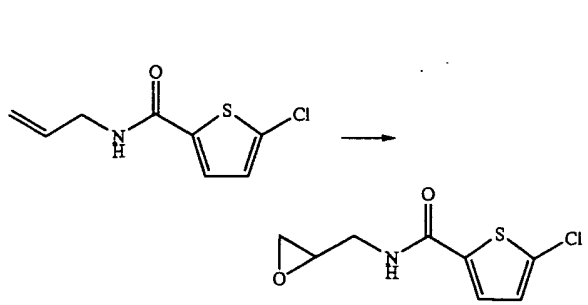


An ice-cooled solution of 2.63 ml (35 mmol) of allylamine in 14.2 ml of absolute pyridine and 14.2 ml of absolute THF is admixed dropwise with 5-chloro-thiophene-2-carbonyl chloride (7.61 g, 42 mmol). Ice-cooling is removed and the mixture is stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue is admixed with water and the solid is filtered off. The crude product is purified by flash chromatography over silica gel (dichloromethane).

Yield: 7.20 g (99% of theory); MS (DCI, NH_4): m/z (%)=219 ($M+NH_4$, 100), 202 (M+H, 32); HPLC (method 1): rt (%)=3.96 min (98.9).

Example 21

Preparation of 5-chloro-N-(2-oxiranylmethyl)-2-thiophenecarboxamide

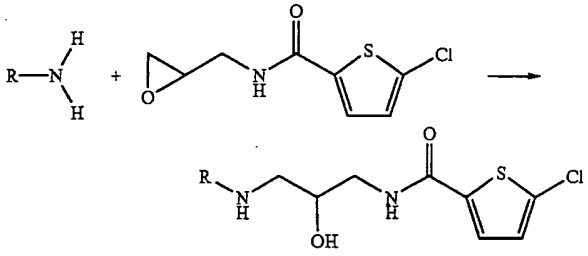


An ice-cooled solution of 2.0 g (9.92 mmol) of N-allyl-5-chloro-2-thiophenecarboxamide in 10 ml of dichloromethane is admixed with meta-chloroperbenzoic acid (3.83 g, about 60% strength). The mixture is stirred overnight, during which it is allowed to warm to room tempera-

ture, and is then washed with 10% sodium hydrogen sulphate solution (three times). The organic phase is washed with saturated sodium bicarbonate solution (twice) and with saturated sodium chloride solution, dried over magnesium sulphate and concentrated. The product is purified by silica gel chromatography (cyclohexane/ethyl acetate 1:1).

Yield: 837 mg (39% of theory); MS (DCI, NH_4): m/z (%)=253 ($M+NH_4$, 100), 218 (M+H, 80); HPLC (method 1): rt (%)=3.69 min (about 80).

General Method for Preparing Substituted N-(3-amino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide Derivatives Starting from 5-chloro-N-(2-oxiranylmethyl)-2-thiophenecarboxamide



At room temperature or at temperatures up to 80° C., 5-chloro-N-(2-oxiranylmethyl)-2-thiophenecarboxamide (1.0 eq.) is added a little at a time to a solution of the primary amine or aniline derivative (1.5 to 2.5 eq.) in 1,4-dioxane, 1,4-dioxane/water mixtures or ethanol, ethanol/water mixtures (about 0.3 to 1.0 mol/l). The mixture is stirred for 2 to 6 hours and then concentrated. From the reaction mixture, the product can be isolated by silica gel chromatography (cyclohexane/ethyl acetate mixtures, dichloromethane/methanol mixtures or dichloromethane/methanol/triethylamine mixtures).

The following compounds were prepared in an analogous manner:

Example 22

N-[3-(Benzylamino)-2-hydroxypropyl]-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=325 (M+H, 100); HPLC (method 1): rt (%)=3.87 min (97.9).

Example 23

5-Chloro-N-[3-(3-cyanoanilino)-2-hydroxypropyl]-2thiophenecarboxamide

MS (ESI): m/z (%)=336 (M+H, 100); HPLC (method 2): rt (%)=4.04 min (100).

Example 24

5-Chloro-N-[3-(4-cyanoanilino)-2-hydroxypropyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=336 (M+H, 100); HPLC (method 1): rt (%)=4.12 min (100).

Example 25

5-Chloro-N-{3-[4-(cyanomethyl)anilino]-2-hydroxypropyl}-2-thiophenecarboxamide

MS (ESI): m/z (%)=350 (M+H, 100); HPLC (method 4): rt (%)=3.60 min (95.4).

Example 26

5-Chloro-N-{3-[3-(cyanomethyl)anilino]-2-hydroxypropyl}-2-thiophenecarboxamide

MS (ESI): m/z (%)=350 (M+H, 100); HPLC (method 4): rt (%)=3.76 min (94.2).

Example 58

tert-Butyl 4-[(3-{[(5-chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]-benzylcarbamate

starting from tert-butyl 4-aminobenzylcarbamate (*Bioorg. Med. Chem. Lett.;* 1997; 1921–1926):

MS (ES-pos): m/z (%)=440 (M+H, 100), (ES-neg): m/z (%)=438 (M−H, 100); HPLC (method 1): rt (%)=4.08 (100).

Example 59

tert-Butyl 4-[(3-{[(5-chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]-phenyl-carbamate

starting from N-tert-butyloxycarbonyl-1,4-phenylenediamine:

MS (ESI): m/z (%)=426 (M+H, 45), 370 (100); HPLC (method 1): rt (%)=4.06 (100).

Example 60

tert-Butyl 2-hydroxy-3-{[4-(2-oxo-1-pyrrolidinyl)phenyl]amino}propyl-carbamate

starting from 1-(4-aminophenyl)-2-pyrrolidinone (*Justus Liebigs Ann. Chem.;* 1955; 596; 204):

MS (DCI, NH_3): m/z (%)=350 (M+H, 100); HPLC (method 1): rt (%)=3.57 (97).

Example 61

5-Chloro-N-(3-{[3-fluoro-4-(3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

800 mg (3.8 mmol) of 4-(4-amino-2-fluorophenyl)-3-morpholinone and 700 mg (3.22 mmol) of 5-chloro-N-(2-oxiranylmethyl)-2-thiophenecarboxamide in 15 ml of ethanol and 1 ml of water are heated under reflux for 6 hours. The mixture is concentrated under reduced pressure and treated with ethyl acetate, precipitated crystals are filtered off with suction and the mother liquor is chromatographed giving 276 mg (17% of theory) of the target compound.

R_f (ethyl acetate): 0.25.

Example 62

(N-(3-Anilino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide

starting from aniline:

MS (DCI, NH_3): m/z (%)=311 ($[M+H]^+$, 100), Cl pattern; HPLC (method 3): rt (%)=3.79 (100).

Example 63

5-Chloro-N-(2-hydroxy-3-{[4-(3-oxo-4morpholinyl) phenyl]amino}propyl)-2-thiophenecarboxamide

starting from 4-(4-aminophenyl)-3-morpholinone:

MS (ESI): m/z (%)=410 ([M+H]$^+$, 50), Cl pattern; HPLC (method 3): rt (%)=3.58 (100).

Example 64

N-[3-({4-[Acetyl(cyclopropyl)amino] phenyl}amino)-2-hydroxypropyl]-5-chloro-2-thiophenecarboxamide

starting from N-(4-aminophenyl)-N-cyclopropylacetamide:

MS (ESI): m/z (%)=408 ([M+H]$^+$, 100), Cl pattern; HPLC (method 3): rt (%)=3.77 (100).

Example 65

N-[3-({4-[Acetyl(methyl)amino]phenyl}amino)-2-hydroxypropyl]-5-chloro-2-thiophenecarboxamide

starting from N-(4-aminophenyl)-N-methylacetamide:

MS (ESI): m/z (%)=382 (M+H, 100); HPLC (method 4): rt=3.31 min.

Example 66

5-Chloro-N-(2-hydroxy-3-{[4-(1H-1,2,3-triazol-1-yl)phenyl]amino}propyl)-2-thiophenecarboxamide

starting from 4-(1H-1,2,3-triazol-1-yl)aniline (Bouchet et al.; J. Chem. Soc. Perkin Trans. 2; 1974; 449):

MS (ESI): m/z (%)=378 (M+H, 100); HPLC (method 4): rt=3.55 min.

Example 67

tert-butyl 1-{4-[(3-{[(5-chloro-2-thienyl)carbonyl] amino}-2-hydroxypropyl)-amino]phenyl}-L-prolinate

MS (ESI): m/z (%)=480 (M+H, 100); HPLC (method 4): rt=3.40 min.

Example 68

1-{4-[(3-{[(5-Chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]phenyl}-4-piperidinecarboxamide

MS (ESI): m/z (%)=437 (M+H, 100); HPLC (method 4): rt=2.39 min.

Example 69

1-{4-[(3-{[(5-Chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)-amino]phenyl}-3-piperidinecarboxamide

MS (ESI): m/z (%)=437 (M+H, 100); HPLC (method 4): rt=2.43 min.

Example 70

5-Chloro-N-(2-hydroxy-3-{[4-(4-oxo-1-piperidinyl) phenyl]amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=408 (M+H, 100); HPLC (method 4): rt=2.43 min.

Example 71

1-{4-[(3-{[(5-Chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]phenyl)-L-prolinamide

MS (ESI): m/z (%)=423 (M+H, 100); HPLC (method 4): rt=2.51 min.

Example 72

5-Chloro-N-[2-hydroxy-3-({4-[3-(hydroxymethyl)-1-piperidinyl]phenyl}-amino)propyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=424 (M+H, 100); HPLC (method 4): rt=2.43 min.

Example 73

5-Chloro-N-[2-hydroxy-3-({4-[2-(hydroxymethyl)-1-piperidinyl]phenyl}-amino)propyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=424 (M+H, 100); HPLC (method 4): rt=2.49 min.

Example 74

Ethyl 1-{4-[(3-{[(5-chloro-2-thienyl)carbonyl] amino}-2-hydroxypropyl)-amino]phenyl}-2-piperidinecarboxylate

MS (ESI): m/z (%)=466 (M+H, 100); HPLC (method 4): rt=3.02 min.

Example 75

5-Chloro-N-[2-hydroxy-3-({4-[2-(hydroxymethyl)-1-pyrrolidinyl]phenyl}amino)-propyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=410 (M+H, 100); HPLC (method 4): rt=2.48 min.

Example 76

5-Chloro-N-(2-hydroxy-3-{[4-(2-methylhexahydro-5H-pyrrolo[3,4-d]isoxazol-5-yl)phenyl] amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=437 (M+H, 100). HPLC (method 5): rt=1.74 min.

Example 77

5-Chloro-N-(2-hydroxy-3-{[4-(1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=448 (M+H, 100); HPLC (method 4): rt=3.30 min.

Example 78

5-Chloro-N-(2-hydroxy-3-{[4-(2-oxo-1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=462 (M+H, 100); HPLC (method 4): rt=3.50 min.

Example 79

5-Chloro-N-(3-{[3-chloro-4-(3-oxo-4-morpholinyl) phenyl]amino}-2-hydroxy-propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=444 (M+H, 100); HPLC (method 4): rt=3.26 min.

Example 80

5-Chloro-N-(2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-3-(trifluoromethyl)phenyl]-amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=478 (M+H, 100); HPLC (method 4): rt=3.37 min.

Example 81

5-Chloro-N-(2-hydroxy-3-{[3-methyl-4-(3-oxo-4-morpholinyl)phenyl]amino}-propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=424 (M+H, 100); HPLC (method 4): rt=2.86 min.

Example 82

5-Chloro-N-(3-{[3-cyano4-(3-oxo-4-morpholinyl) phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=435 (M+H, 100); HPLC (method 4): rt=3.10 min.

Example 83

5-Chloro-N-(3-{[3-chloro-4-(1-pyrrolidinyl)phenyl] amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=414 (M+H, 100); HPLC (method 4): rt=2.49 min.

Example 84

5-Chloro-N-(3-{[3-chloro-4-(2-oxo-1-pyrrolidinyl) phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=428 (M+H, 100); HPLC (method 4): rt=3.39 min.

Example 85

5-Chloro-N-(3-{[3,5-dimethyl-4-(3-oxo-4-morpholinyl)phenyl]amino)-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=438 (M+H, 100); HPLC (method 4): rt=2.84 min.

Example 86

N-(3-{[3-(Aminocarbonyl)-4-(4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=439 (M+H, 100); HPLC (method 4): rt=2.32 min.

Example 87

5-Chloro-N-(2-hydroxy-3-{[3-methoxy-4-(4-morpholinyl)phenyl]amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=426 (M+H, 100); HPLC (method 4): rt=2.32 min.

Example 88

N-(3-[3-Acetyl-4-(4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide

MS (EST): m/z (%)=438 (M+H, 100); HPLC (method 4): rt=2.46 min.

Example 89

N-(3-{[3-Amino-4-(3-oxo4-morpholinyl)phenyl] amino}-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=425 (M+H, 100); HPLC (method 4): rt=2.45 min.

Example 90

5-Chloro-N-(3-{[3-chloro-4-(2-methyl-3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=458 (M+H, 100); HPLC (method 4): rt=3.44 min.

Example 91

5-Chloro-N-(3-{[3-chloro-4-(2-methyl-5-oxo-4-morpholinyl)phenyl]amino)-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=458 (M+H, 100); HPLC (method 4): rt=3.48 min.

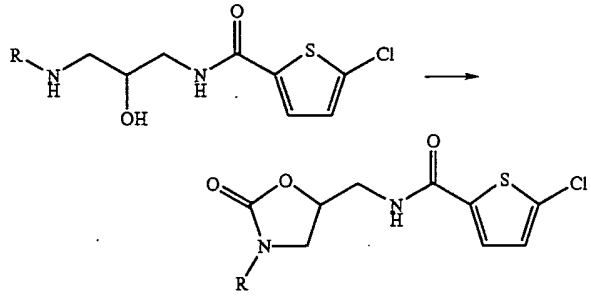
Example 91a

5-Chloro-N-[2-hydroxy-3-(14-[(3oxo4morpholinyl) methyl]phenyl}amino)-propyl]-2-thiophenecarboxamide

starting from 4-(4-amino-benzyl)-3-morpholinone (Surrey et al.; J. Amer. Chem. Soc.; 77; 1955; 633):

MS (ESI): m/z (%)=424 (M+H, 100); HPLC (method 4): rt=2.66 min.

General Method for Preparing 3-substituted 5-chloro-N-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide Derivatives Starting from Substituted N-(3-amino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide Derivatives



At room temperature, carbodiimidazole (1.2 to 1.8 eq.) or a similar phosgene equivalent are added to a solution of the substituted N-(3-amino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide derivative (1.0 eq.) in absolute THF (about 0.1 mol/l). At room temperature or, if appropriate, at elevated temperature (up to 70° C.), the mixture is stirred for 2 to 18 h and then concentrated under reduced pressure. The product can be purified by silica gel chromatography (dichloromethane/methanol mixtures or cyclohexane/ethyl acetate mixtures).

The following compounds were prepared in an analogous manner:

Example 27

N-[(3-Benzyl-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide

MS (DCI, NH_4): m/z (%)=372 (M+Na, 100), 351 (M+H, 45); HPLC (method 1): rt (%)=4.33 min (100).

Example 28

5-Chloro-N-{[3-(3-cyanophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

MS (DCI, NH_4): m/z (%)=362 (M+H, 42), 145 (100); HPLC (method 2): rt (%)=4.13 min (100).

Example 29

5-Chloro-N-({3-[4-(cyanomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=376 (M+H, 100); HPLC (method 4): rt=4.12 min

Example 30

5-Chloro-N-({3-[3-(cyanomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=376 (M+H, 100); HPLC (method 4): rt=4.17 min

Example 92

tert-Butyl 4-[5-({[(5-chloro-2-thienyl)carbonyl] amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]benzyl-carbamate

starting from Example 58:

MS (ESI): m/z (%)=488 (M+Na, 23), 349 (100); HPLC (method 1): rt (%)=4.51 (98.5).

Example 93

tert-Butyl 4-[5-({[(5-chloro-2-thienyl)carbonyl] amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl-carbamate

starting from Example 59:

MS (ESI): m/z (%)=493 (M+Na, 70), 452 (M+H, 10), 395 (100); HPLC (method 1): rt (%)=4.41 (100).

Example 94

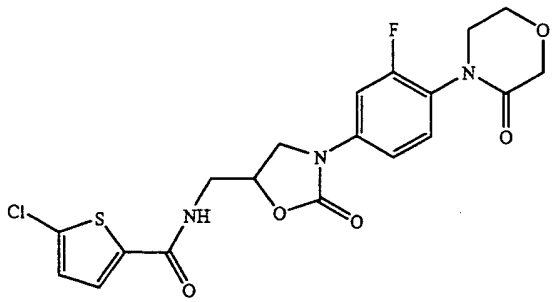
tert-Butyl 2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl-carbamate

starting from Example 60:

MS (DCI, NH_3): m/z (%)=393 (M+NH_4, 100); HPLC (method 3): rt (%)=3.97 (100).

Example 95

5-Chloro-N-({3-[3-fluoro-4-(3-oxo-4-morpholinyl) phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



260 mg (0.608 mmol) of 5-chloro-N-(3-{[3-fluoro4-(3-oxo4-morpholinyl)phenyl]-amino}-2-hydroxypropyl)-2-thiophenecarboxamide (from Example 61), 197 mg (1.22 mmol) of carbonylimidazole and 7 mg of dimethylaminopyridine in 20 ml of dioxane are boiled under reflux for 5 hours. 20 ml of acetonitrile are then added, and the mixture is stirred in a closed vessel in a microwave oven at 180° C. for 30 minutes. The solution is concentrated using a rotary

evaporator and chromatographed on an RP-HPLC column. This gives 53 mg (19% of theory) of the target compound.

NMR (300 MHz, d_6-DMSO): δ=3.6–3.7 (m,4H), 3.85 (dd,1H), 3.95 (m,2H), 4.2 (m,1H), 4.21 (s,2H), 4.85 (m,1H), 4.18 (s,2H), 7.19 (d,1H,thiophene), 7.35 (dd,1H), 7.45 (t,1H), 7.55 (dd,1H), 7.67 (d,1H,thiophene), 8.95 (t,1H, CONH).

Example 96

5-Chloro-N-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl) methyl]-2-thiophenecarboxamide

starting from Example 62:

MS (ESI): m/z (%)=359 ([M+Na]$^+$, 71), 337 ([M+H]$^+$, 100), Cl pattern; HPLC (method 3): rt (%)=4.39 (100). IC_{50}: 2 μM

Example 97

5-Chloro-N-({2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

starting from Example 63:

MS (ESI): m/z (%)=458 ([M+Na]$^+$, 66), 436 ([M+H]$^+$, 100), Cl pattern; HPLC (method 3): rt (%)=3.89 (100). IC_{50}: 1.4 nM

Example 98

N-[(3-{4-[Acetyl(cyclopropyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide

starting from Example 64:

MS (ESI): m/z (%)=456 ([M+Na]$^+$, 55), 434 ([M+H]+, 100), Cl pattern; HPLC (method 3): rt (%)=4.05 (100). IC_{50}: 50 nM

Example 99

N-[(3-{4-[Acetyl(methyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=408 (M+H, 30), 449 (M+H+MeCN, 100); HPLC (method 4): rt=3.66 min.

Example 100

5-Chloro-N-({2-oxo-3-[4-(1H-1,2,3-triazol-1-yl) phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=404 (M+H, 45), 445 (M+H+MeCN, 100); HPLC (method 4): rt=3.77 min.

Example 101

Tert-butyl 1-{4-[5-({[(5-chloro-2thienyl)carbonyl] amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-L-prolinate

MS (ESI): m/z (%)=450 (M+H−56, 25), 506 (M+H, 100); HPLC (method 4): rt=5.13 min.

Example 102

1-{4-[5-(([(5-Chloro-2-thienyl)carbonyl]aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-4-piperidinecarboxamide

MS (ESI): m/z (%)=463 (M+H, 100); HPLC (method 4): rt=2.51 min.

Example 103

1-{4-[5-({[(5-Chloro-2-thienyl)carbonyl] amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3-piperidinecarboxamide

MS (ESI): m/z (%)=463 (M+H, 100); HPLC (method 4): rt=2.67 min.

Example 104

5-Chloro-N-({2-oxo-3-[4-(4-oxo-1-piperidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=434 (M+H, 40), 452 (M+H+H_2O, 100), 475 (M+H+MeCN, 60); HPLC (method 4): rt=3.44 min.

Example 105

1-{4-[5-({[(5-Chloro-2-thienyl)carbonyl] amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-L-prolinamide

MS (ESI): m/z (%)=449 (M+H, 100); HPLC (method 4): rt=3.54 min.

Example 106

5-Chloro-N-[(3-{4-[3-(hydroxymethyl)-1-piperidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=450 (M+H, 100); HPLC (method 5): rt=2.53 min.

Example 107

5-Chloro-N-[(3-{4-[2-(hydroxymethyl)-1-piperidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=450 (M+H, 100); HPLC (method 5): rt=2.32 min.

Example 108

Ethyl 1-{4-[5-({[(5-chloro-2-thienyl)carbonyl] amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-piperidinecarboxylate

MS (ESI): m/z (%)=492 (M+H, 100); HPLC (method 5): rt=4.35 min.

Example 109

5-Chloro-N-[(3-{4-[2-(hydroxymethyl)-1-pyrrolidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=436 (M+H, 100); HPLC (method 4): rt=2.98 min.

Example 110

5-Chloro-N-({2-oxo-3-[4-(1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=474 (M+H, 100); HPLC (method 4): rt=4.63 min.

Example 111

5-Chloro-N-({3-[4-(2-methylhexahydro-5H-pyrrolo[3,4d]isoxazol-5-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=463 (M+H, 100); HPLC (method 4): rt=2.56 min.

Example 112

5-Chloro-N-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=488 (M+H, 100); HPLC (method 4): rt=3.64 min.

Example 113

5-Chloro-N-({3-[3-chloro4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=470 (M+H, 100); HPLC (method 4): rt=3.41 min.

Example 114

5-Chloro-N-({2-oxo-3-[4-(3-oxo-4-morpholinyl)-3-(trifluoromethyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=504 (M+H, 100); HPLC (method 4): rt=3.55 min.

Example 115

5-Chloro-N-({3-[3-methyl-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=450 (M+H, 100); HPLC (method 4): rt=3.23 min.

Example 116

5-Chloro-N-({3-[3-cyano-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=461 (M+H, 100); HPLC (method 4): rt=3.27 min.

Example 117

5-Chloro-N-({3-[3-chloro-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=440 (M+H, 100); HPLC (method 4): rt=3.72 min.

Example 118

5-Chloro-N-({3-[3-chloro-4-(2-oxo-1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=454 (M+H, 100); HPLC (method 4): rt=3.49 min.

Example 119

5-Chloro-N-({3-[3,5-dimethyl-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=464 (M+H, 100); HPLC (method 4): rt=3.39 min.

Example 120

N-({3-[3-(Aminocarbonyl)-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=465 (M+H, 100); HPLC (method 4): rt=3.07 min.

Example 121

5-Chloro-N-({3-[3-methoxy-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=452 (M+H, 100); HPLC (method 4): rt=2.86 min.

Example 122

N-({3-[3-Acetyl-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=464 (M+H, 100); HPLC (method 4): rt=3.52 min.

Example 123

N-({3-[3-Amino-4-(3-oxo4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=451 (M+H, 100); HPLC (method 6): rt=3.16 min.

Example 124

5-Chloro-N-({3-[3-chloro-4-(2-methyl-3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=484 (M+H, 100); HPLC (method 4): rt=3.59 min.

Example 125

5-Chloro-N-({3-[3-chloro-4-(2-methyl-5-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

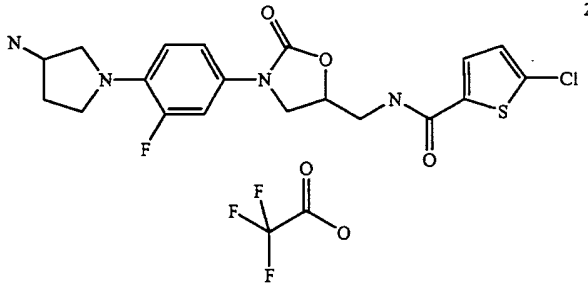
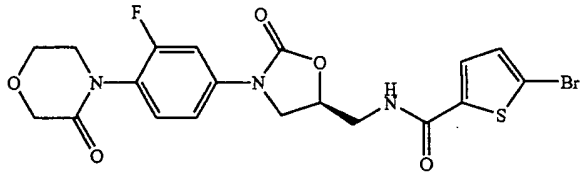
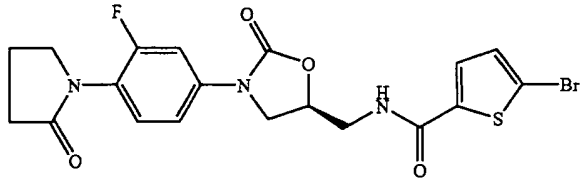
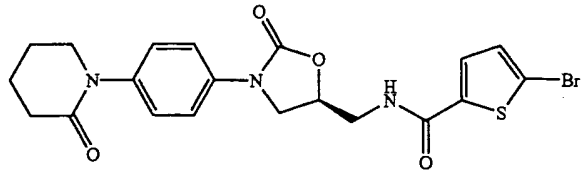
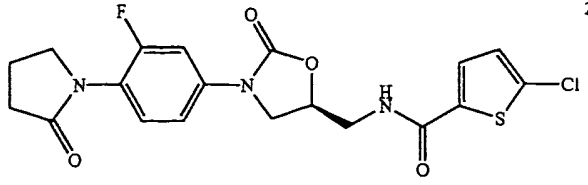
MS (ESI): m/z (%)=484 (M+H, 100); HPLC (method 4): rt=3.63 min.

Example 125a

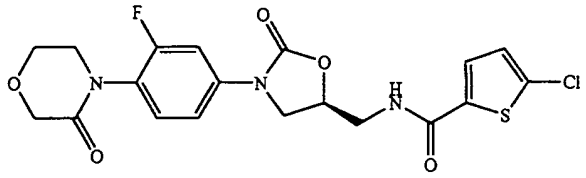
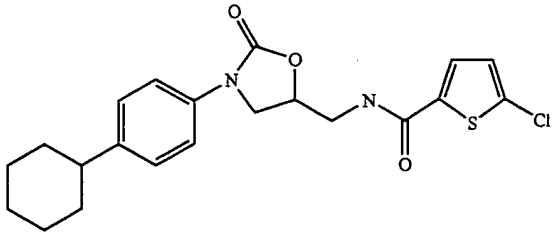
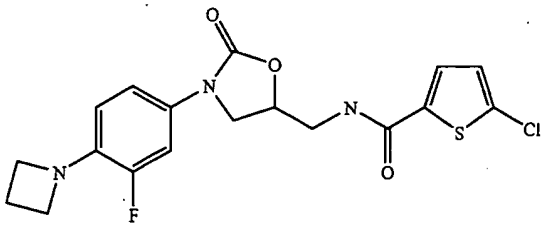
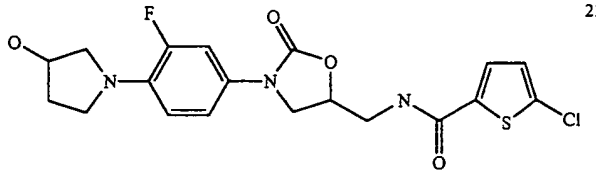
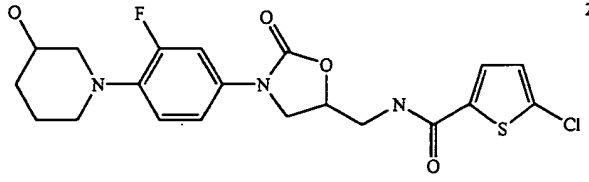
5-Chloro-N-[(2-oxo-3-{4-[(3-oxo-4-morpholinyl)methyl]phenyl}-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=450 (M+H, 100); HPLC (method 4): rt=3.25 min.

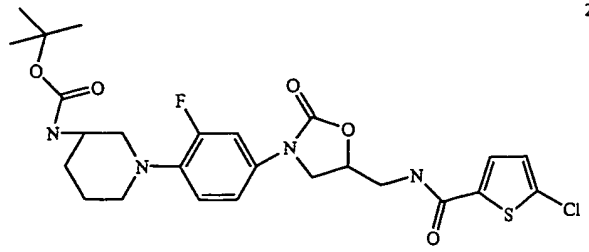
Via epoxide opening with an amine and subsequent cyclization to give the corresponding oxazolidinone, it was also possible to prepare the following compounds:

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

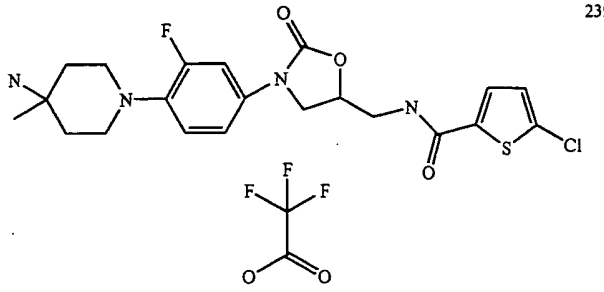
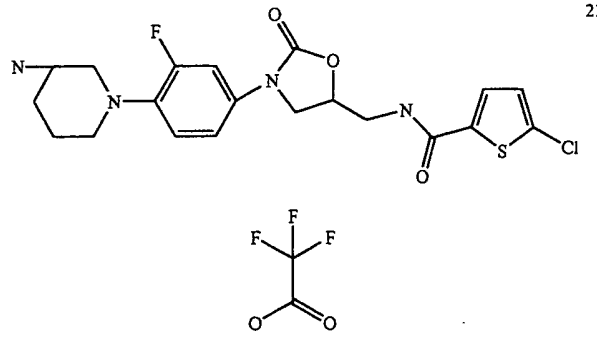
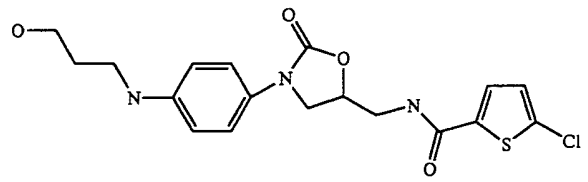
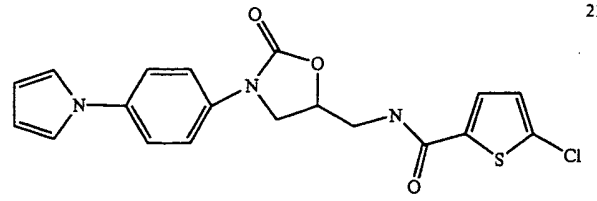
-continued

Example No.	Structure	M.p. [° C.]	IC_{50} [μM]
130a		194	
131		195	0.85
132		206	0.12
133		217	0.062
134		207	0.48

from 1-(4-amino-phenyl)-piperidin-3-ol (Tong, L. K. J. et al,; J. Amer. Chem. Soc. 1960; 82, 1988).

135		202	1.1

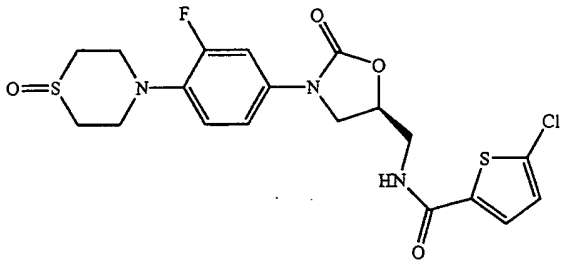
-continued

Example No.	Structure	M.p. [° C.]	IC_{50} [μM]
136		239	1.2
137		219	0.044
138		95	0.42
139		217	1.7

Examples 14 to 16 below are working examples for the optional oxidation step.

Example 14

5-Chloro-N-({(5S)-3-[3-fluoro-4-(1-oxo-1[lambda]^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

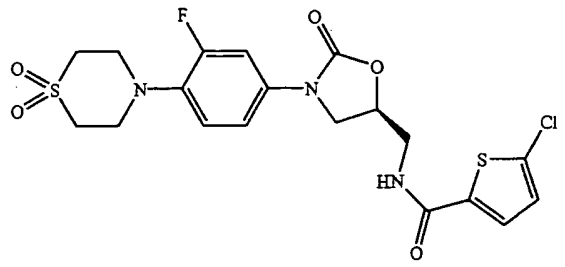


At 0° C., 5-chloro-N-({(5S)-3-[3-fluoro4-(1,4-thiazinan4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (0.1 g, 0.22 mmol) from Example 3 in methanol (0.77 ml) is added to a solution of sodium periodate (0.05 g, 0.23 mmol) in water (0.54 ml), and the mixture is stirred at 0° C. for 3 h. 1 ml of DMF is then added, and the mixture is stirred at RT for 8 h. After addition of a further 50 mg of sodium periodate, the mixture is once more stirred at RT overnight. The mixture is then admixed with 50 ml of water, and the insoluble product is filtered off with suction. Washing with water and drying gives 60 mg (58% of theory) of crystals.

M.p.: 257° C.; R_f (silica gel, toluene/ethyl acetate 1:1) =0.54 (starting material=0.46); IC_{50} value=1.1 μM; MS (DCI) 489 ($M+NH_4$), Cl pattern.

Example 15

Preparation of 5-chloro-N-({(5S)-3-[4-(1,1-dioxo-1 [lambda]^6,4-thiazinan-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



5-Chloro-N-({(5S)-3-[3-fluoro4-(1,4-thiazinan4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide from Example 3 (0.1 g, 0.22 mmol) in 3.32 ml of a mixture of 1 part of water and 3 parts of acetone is admixed with 80 mg (0.66 mmol) of N-methylmorpholine N-oxide (NMO) and 0.1 ml of a 2.5% strength solution of osmium tetroxide in 2-methyl-2-propanol. The mixture is stirred at room temperature overnight, and another 40 mg of NMO are added. The mixture is stirred for a further night and then poured into 50 ml of water and extracted three times with ethyl acetate. The organic phase gives, after drying and concentrating, 23 mg and the aqueous phase, after removal of the insoluble solid by filtration with suction, 19 mg (in total 39% of theory) of the target compound.

M.p.: 238° C.; R_f (toluene/ethyl acetate 1:1)=0.14 (starting material=0.46); IC_{50} value=210 nM; MS (DCI): 505 ($M+NH_4$), Cl pattern.

Example 16

5-Chloro-N-{[(5S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide N-oxide

is obtained by treating 5-chloro-N-{[(5S)-3-(3-fluoro4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide from Example 1 with the magnesium salt of monoperoxyphthalic acid. MS (ESI): 456 (M+H, 21%, Cl pattern), 439 (100%).

The Examples 31 to 35 and 140 to 147 below refer to the optional amidination step.

General Method for Preparing Amidines and Amidine Derivatives Starting from Cyanomethylphenyl-substituted 5-chloro-N-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide Derivatives

The cyanomethylphenyl-substituted 5-chloro-N-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide derivative in question (1.0 eq.) is, together with triethylamine (8.0 eq.), stirred at RT in a saturated solution of hydrogen sulphide in pyridine (about 0.05–0.1 mol/l) for one to two days. The reaction mixture is diluted with ethyl acetate (EtOAc) and washed with 2 N hydrochloric acid. The organic phase is dried with $MgSO_4$, filtered and concentrated under reduced pressure.

The crude product is dissolved in acetone (0.01–0.1 mol/l) and admixed with methyl iodide (40 eq.). The reaction mixture is stirred at room temperature (RT) for 2 to 5 h and then concentrated under reduced pressure.

The residue is dissolved in methanol (0.01–0.1 mol/l) and, to prepare the unsubstituted amidines, admixed with ammonium acetate (3 eq.) and ammonium chloride (2 eq.). To prepare the substituted amidine derivatives, primary or secondary amines (1.5 eq.) and acetic acid (2 eq.) are added to the methanolic solution. After 5–30 h, the solvent is removed under reduced pressure and the residue is purified by chromatography over an RP8 silica gel column (water/acetonitrile 9/1–1/1+0.1% trifluoroacetic acid).

The following compounds were prepared in an analogous manner:

Example 31

N-({3-[4-(2-Amino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=393 (M+H, 100); HPLC (method 4): rt=2.63 min

Example 32

5-Chloro-N-({3-[3-(4,5dihydro-1H-imidazol-2-ylmethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=419 (M+H, 100); HPLC (method 4): rt=2.61 min

Example 33

5-Chloro-N-[(3-{3-[2-imino-2-(4-morpholinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=463 (M+H, 100); HPLC (method 4): rt=2.70 min

Example 34

5-Chloro-N-[(3-{3-[2-imino-2-(1-pyrrolidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=447 (M+H, 100); HPLC (method 4): rt=2.82 min

Example 35

N-({3-[3-(2-Amino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=393 (M+H, 100); HPLC (method 4): rt=2.60 min

Example 140

5-Chloro-N-({3-[4-(4,5-dihydro-1H-imidazol-2-ylmethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=419 (M+H, 100); HPLC (method 4): rt=2.65 min

Example 141

5-Chloro-N-[(3-{4-[2-imino-2-(4-morpholinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=463 (M+H, 100); HPLC (method 4): rt=2.65 min

Example 142

5-Chloro-N-[(3-{4-[2-imino-2-(1-piperidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=461 (M+H, 100); HPLC (method 4): rt=2.83 min

Example 143

5-Chloro-N-[(3-{4-[2-imino-2-(1-pyrrolidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=447 (M+H, 100); HPLC (method 4): rt=2.76 min

Example 144

5-Chloro-N-[(3-{4-[2-(cyclopentylamino)-2-iminoethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=461 (M+H, 100); HPLC (method 4): rt=2.89 min

Example 145

5-Chloro-N-{[3-(4-{2-imino-2-[(2,2,2-trifluoroethyl)amino]ethyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

MS (ESI): m/z (%)=475 (M+H, 100); HPLC (method 4): rt=2.79 min

Example 146

N-({3-[4-(2-Anilino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%)=469 (M+H, 100); HPLC (method 4): rt=2.83 min

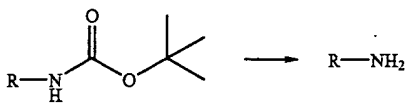
Example 147

5-Chloro-N-[(3-{4-[2-imino-2-(2-pyridinylamino)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=470 (M+H, 100); HPLC (method 4): rt=2.84 min

Examples 148 to 151 below refer to the removal of BOC amino protective groups:

General Method for Removing Boc Protective Groups (tert-butyloxycarbonyl)



Aqueous trifluoroacetic acid (TFA, about 90%) is added dropwise to an ice-cooled solution of a tert-butyloxycarbonyl-(Boc) protected compound in chloroform or dichloromethane (about 0.1 to 0.3 mol/l). After about 15 min, ice-cooling is removed and the mixture is stirred at room temperature for approximately 2–3 h, and the solution is then concentrated and dried under high vacuum. The residue is taken up in dichloromethane or dichloromethane/methanol and washed with saturated sodium bicarbonate or 1N sodium hydroxide solution. The organic phase is washed with saturated sodium chloride solution, dried over a little

magnesium sulphate and concentrated. If appropriate, purification is carried out by crystallization from ether or ether/dichloromethane mixtures.

The following compounds were prepared in an analogous manner from the corresponding Boc-protected precursors:

Example 148

N-({3-[4-(Aminomethyl)phenyl]-2-oxo1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide

starting from Example 92:

MS (ESI): m/z (%)=349 (M-NH_2, 25), 305 (100); HPLC (method 1): rt (%)=3.68 (98). IC_{50}: 2.2 μM

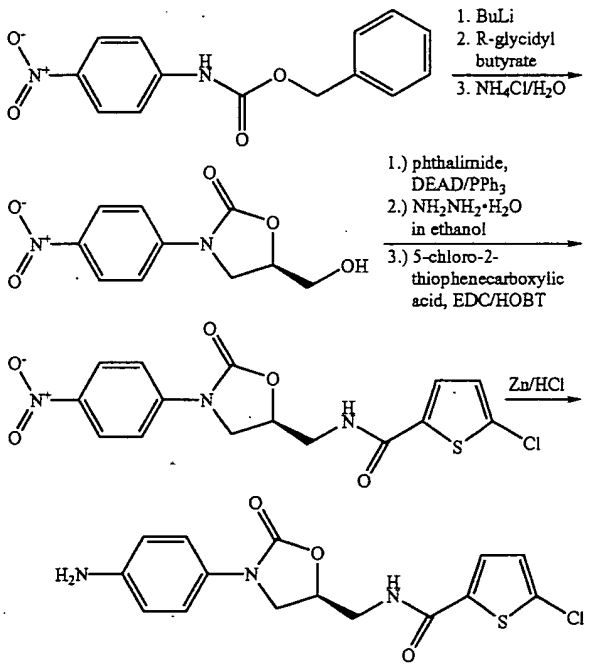
Example 149

N-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide

starting from Example 93:

MS (ESI): m/z (%)=352 (M+H, 25); HPLC (method 1): rt (%)=3.50 (100). IC_{50}: 2 μM

An alternative enantiomerically pure synthesis of this compound is shown in the scheme below (cf. also Delalande S. A., DE 2836305,1979; Chem. Abstr. 90, 186926):



Example 150

5-Chloro-N-({3-[4-(glycylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

starting from Example 152:

MS (ES-pos): m/z (%)=408 (100); HPLC (method 3): rt (%)=3.56 (97). IC_{50}: 2 μM

Example 151

5-(Aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl-1,3-oxazolidin-2-one

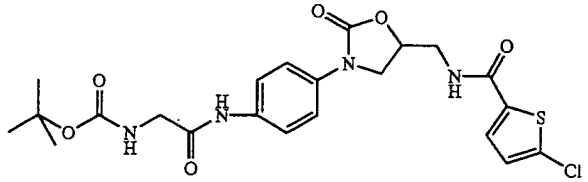
starting from Example 60:

MS (ESI): m/z (%)=276 (M+H, 100); HPLC (method 3): rt (%)=2.99 (100). IC_{50}: 2 μM

The Examples 152 to 166 below refer to the amino group derivatization of aniline- or benzylamine-substituted oxazolidinones using various reagents:

Example 152

5-Chloro-N-({3-[4-(N-tert-butyloxycarbonyl-glycylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

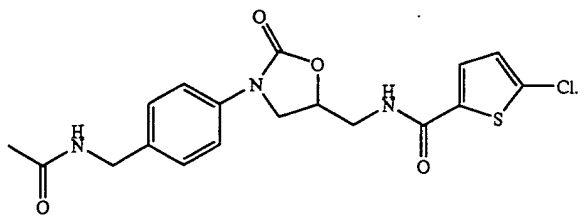


At 0° C., 754 mg (2.1 mmol) of N-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5chloro-2-thiophenecarboxamide (from Example 149) are added to a solution of 751 mg (4.3 mmol) of Boc-glycine, 870 mg (6.4 mmol) of HOBT (1-hydroxy-1H-benzotriazole×H_2O), 1790 mg (4.7 mmol) of HBTU [O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate] and 1.41 ml (12.9 mmol) of N-methylmorpholine in 15 ml of DM/CH_2Cl_2 (1:1). The mixture is stirred at room temperature overnight and then diluted with water. The precipitated solid is filtered off and dried. Yield: 894 mg (79.7% of theory);

MS (DCI, NH_3): m/z (%)=526 (M+NH_4, 100); HPLC (method 3): rt (%)=4.17 (97).

Example 153

N-[(3-{4-[(Acetylamino)methyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide



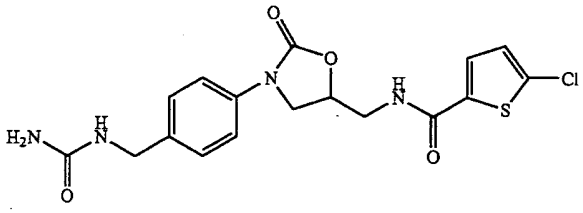
At 0° C., a mixture of 30 mg (0.082 mmol) of N-({3-[4-(aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide (from Example 148) in 1.5 ml of absolute THF and 1.0 ml of absolute dichloromethane, and 0.02 ml of absolute pyridine is mixed with acetic anhydride (0.015 ml, 0.164 mmol). The mixture is

stirred at room temperature overnight. Addition of ether and crystallization affords the product. Yield: 30 mg (87% of theory),

MS (ESI): m/z (%)=408 (M+H, 18), 305 (85); HPLC (method 1): rt (%)=3.78 (97). IC_{50}: 0.6 μM

Example 154

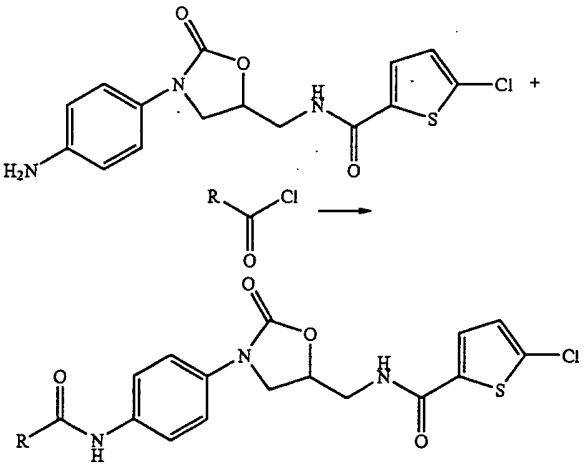
N-{[3-(4-{[(Aminocarbonyl)amino]methyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl}-5-chloro-2-thiophenecarboxamide



At room temperature, 0.19 ml (0.82 mmol) of trimethylsilylisocyanate are added dropwise to a mixture of 30 mg (0.082 mmol) of N-({3-[4-(aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl }methyl)-5-chloro-2-thiophene-carboxamide (from Example 148) in 1.0 ml of dichloromethane. The mixture is stirred overnight and, after addition of ether, the product is then obtained by filtration. Yield: 21.1 mg (52% of theory),

MS (ESI): m/z (%)=409 (M+H, 5), 305 (72); HPLC (method 1): rt (%)=3.67 (83). IC_{50}: 1.3 μM

General Method for Acylating N-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide with Carbonyl Chlorides:



Under argon, an approximately 0.1 molar solution of N-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide (from Example 149) (1.0 eq.) in absolute dichloromethane/pyridine (19:1) is added dropwise to the appropriate acid chloride (2.5 eq.). The mixture is stirred overnight and then admixed with about 5 eq. of PS trisamine (Argonaut Technologies) and 2 ml of absolute dichloromethane. The mixture is stirred gently for 1 h and then filtered off, and the filtrate is concentrated. If appropriate, the products are purified by preparative RP-HPLC.

The following compounds were prepared in an analogous manner:

Example 155

N-({3-[4-(Acetylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide

LC-MS: m/z (%)=394 (M+H, 100); LC-MS (method 6): rt (%)=3.25 (100) IC_{50}: 1.2 μM

Example 156

5-Chloro-N-[(2-oxo-3-{4-[(2-thienylcarbonyl)amino]phenyl}-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

LC-MS: m/z (%)=462 (M+H, 100); LC-MS (method 6): rt (%)=3.87 (100). IC_{50}: 1.3 μM

Example 157

5-Chloro-N-[(3-{4-[(methoxyacetyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)-methyl]-2-thiophenecarboxamide

LC-MS: m/z (%)=424 (M+H, 100); LC-MS (method 6): rt (%)=3.39 (100). IC_{50}: 0.73 μM

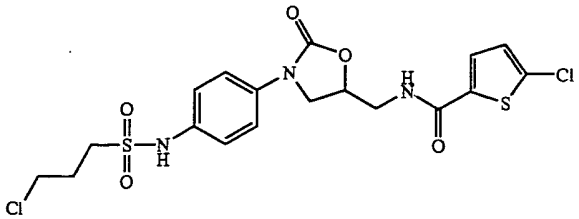
Example 158

N-{4-[5-({[(5-Chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3,5-dimethyl-4-isoxazolecarboxamide

LC-MS: m/z (%)=475 (M+H, 100). IC_{50}: 0.46 μM

Example 159

5-Chloro-N-{[3-(4-{[(3-chloropropyl)sulphonyl]amino}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



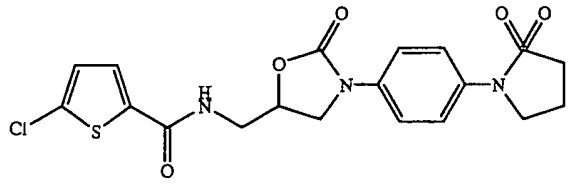
An ice-cooled solution of 26.4 mg (0.15 mmol) of 3-chloro-1-propanesulphonyl chloride and 0.03 ml (0.2 mmol) of triethylamine in 3.5 ml of absolute dichloromethane is admixed with 35 mg (0.1 mmol) of N-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl }-5-chloro-2-thiophene-carboxamide (from Example 149). After 30 min, ice-cooling is removed and the mixture is stirred at room temperature overnight, and 150 mg (about 5.5 eq.) of PS-trisamine (Argonaut Technologies) and 0.5 ml of dichlo-

romethane are then added. The suspension is stirred gently for 2 h and filtered (the resin is washed with dichloromethane/methanol), and the filtrate is concentrated. The product is purified by preparative RP-HPLC. Yield: 19.6 mg (40% of theory),

LC-MS: m/z (%)=492 (M+H, 100); LC-MS (method 5): rt (%)=3.82 (91). IC_{50}: 1.7 μM

Example 160

5-Chloro-N-({3-[4-(1,1-dioxido-2-isothiazolidinyl) phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

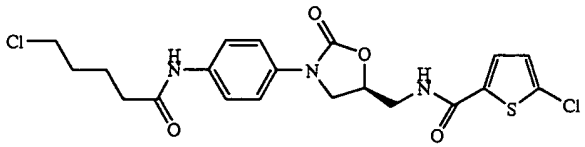


A mixture of 13.5 mg (0.027 mmol) of 5-chloro-N-{[3-(4-{[(3-chloropropyl)sulphonyl]amino }phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophene-carboxamide (from Example 159) and 7.6 mg (0.055 mmol) of potassium carbonate in 0.2 ml of DMF is heated at 100° C. for 2 h. After cooling, the mixture is diluted with dichloromethane and washed with water. The organic phase is dried and concentrated. The residue is purified by preparative thin-layer chromatography (silica gel, dichloromethane/methanol, 95:5). Yield: 1.8 mg (14.4% of theory),

MS (ESI): m/z (%)=456 (M+H, 15), 412 (100); LC-MS (method 4): rt (%)=3.81 (90). IC_{50}: 0.14 μM

Example 161

5-Chloro-N-[((5S)-3-{4(5-chloropentanoyl)amino] phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

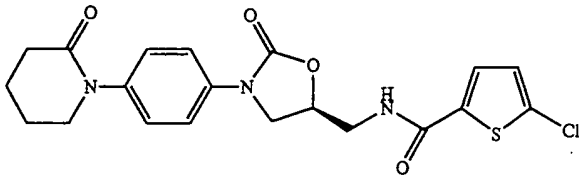


0.5 g (1.29 mmol) of N-{[(5S)-3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide (from Example 149) is dissolved in 27 ml of tetrahydrofuran and admixed with 0.2 g (1.29 mmol) of 5-chlorovaleryl chloride and 0.395 ml (2.83 mmol) of triethylamine. The mixture is concentrated under reduced pressure and chromatographed over silica gel using a toluene/ethyl acetate=1:1->ethyl acetate gradient. This gives 315 mg (52% of theory) of a solid.

M.p.: 211° C.

Example 162

5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-piperidinyl) phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

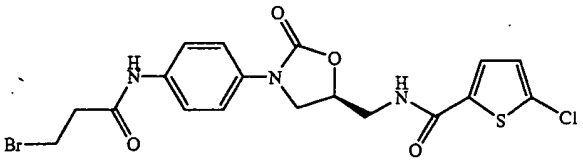


Under inert conditions, 5 ml of DMSO are admixed with 30 mg of NaH (60% in paraffin oil), and the mixture is heated at 75° C. for 30 min, until the evolution of gas has ceased. A solution of 290 mg (0.617 mmol) of 5-chloro-N-[((5S)-3-{4-[(5-chloropentanoyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophene-carboxamide (from Example 161) in 5 ml of methylene chloride is then added dropwise, and the mixture is stirred at room temperature overnight. The reaction is terminated and the mixture is poured into 100 ml of water and extracted with ethyl acetate. The evaporated organic phase is chromatographed on an RP-8 column and the product is eluted with acetonitrile/water. This gives 20 mg (7.5% of theory) of the target compound.

M.p.: 205° C.; NMR (300 MHz, d_6-DMSO): δ=1.85 (m,4H), 2.35 (m,2H), 3.58 (m,4H), 3.85 (m,1H), 4.2 (t,1H), 4.82 (m,1H), 7.18 (d,1H,thiophene), 7.26 (d,2H), 7.5 (d,2H), 2.68 (d,1H,thiophene), 9.0 (t,1H,CONH). IC_{50}: 2.8 nM

Example 163

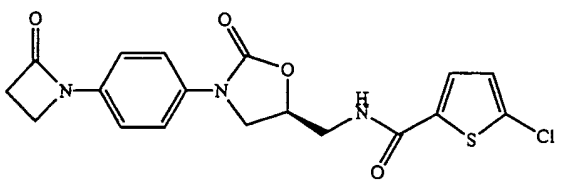
5-Chloro-N-[((5S)-3-{4-[(3-bromopropionyl)amino] phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



is obtained in an analogous manner from Example 149.

Example 164

5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-azetidinyl) phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

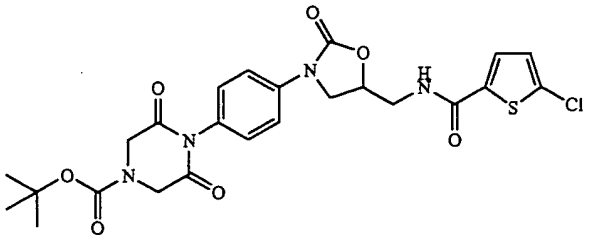


is obtained in an analogous manner by cyclization of the open-chain bromopropionyl compound from Example 163 using NaH/DMSO.

MS (ESI): m/z (%)=406 ([M+H]$^+$, 100), Cl pattern. IC_{50}: 380 nM

Example 165

tert-Butyl 4-{4-[5-({[(5-chloro-2-thienyl)carbonyl] amino}methyl)-2-oxo-1,3oxazolidin-3-yl]phenyl}-3, 5-dioxo-1-piperazinecarboxylate

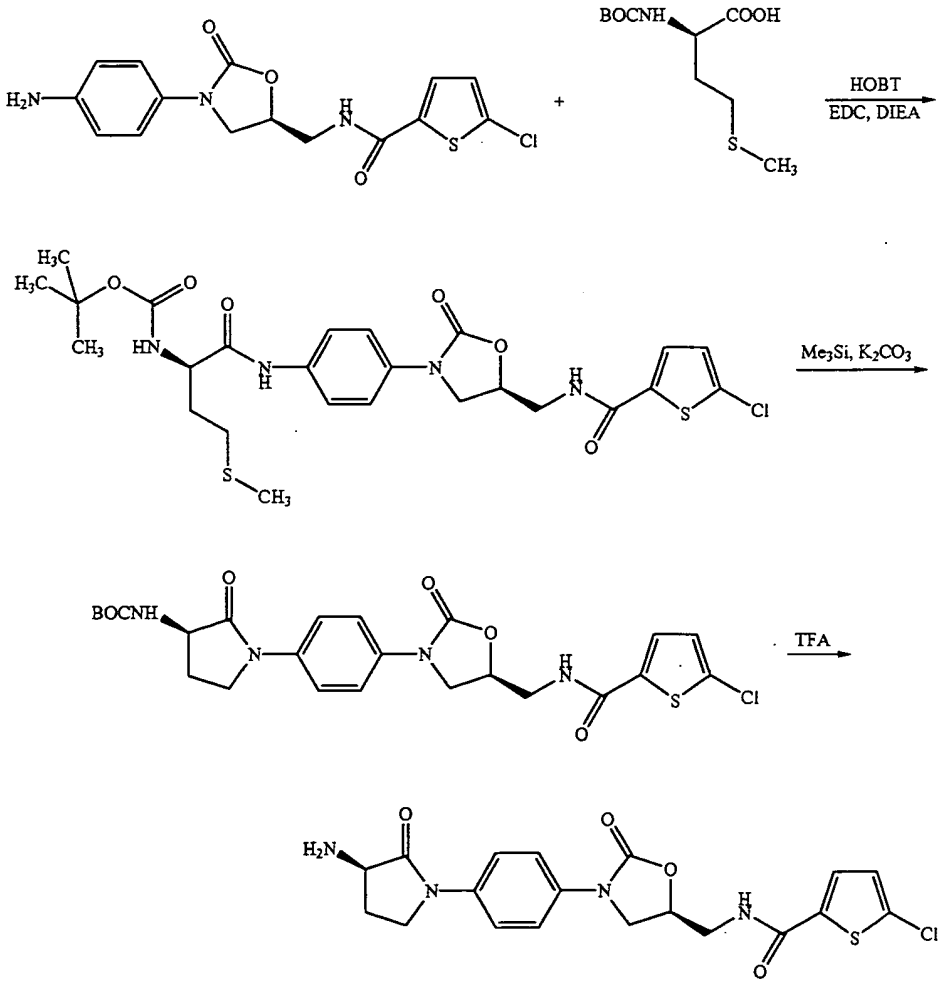


A solution of 199 mg (0.85 mmol) of Boc-iminodiacetic acid, 300 mg (2.2 mmol) of HOBT, 0.66 ml (6 mmol) of N-methylmorpholine and 647 mg (1.7 mmol) of HBTU is admixed with 300 mg (0.85 mmol) of N-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl }-5-chloro-2-thiophene-carboxamide in 6 ml of a mixture of DMF and dichloromethane (1:1). The mixture is stirred overnight, diluted with dichloromethane and then washed with water, saturated ammonium chloride solution, saturated sodium bicarbonate solution, water and saturated sodium chloride solution. The organic phase is dried over magnesium sulphate and concentrated. The crude product is purified by silica gel chromatography (dichloromethane/methanol 98:2). Yield: 134 mg (29% of theory);

MS (ESI): m/z (%)=571 (M+Na, 82), 493 (100); HPLC (method 3): rt (%)=4.39 (90). IC_{50}: 2 μM

Example 166

N-[((5S)-3-{4-[(3R)-3-Amino-2-oxo-1 pyrrolidinyl] phenyl }-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide trifluoroacetate



N2-(tert-Butoxycarbonyl)-N1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-D-methionineamide

429 mg (1.72 mmol) of N-BOC-D-methionine, 605 mg (1.72 mmol) of N-{[(5S)-3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl }-5-chloro-2-thiophenecarboxamide, and 527 mg (3.44 mmol) of HOBT hydrate are dissolved in 35 ml of DMF and admixed with 660 mg (3.441 mmol) of EDCI hydrochloride and then dropwise with 689 mg (5.334 mmol) of N-ethyl-diisopropylamine. The mixture is stirred at room temperature for two days. The resulting suspension is filtered off with suction and the residue is washed with DMF. The combined filtrates are admixed with a little silica gel, concentrated under reduced pressure and chromatographed over silica gel using a toluene->T10EA7 gradient. This gives 170 mg (17% of theory) of the target compound of melting point 183° C.

R_f (SiO_2, toluene/ethyl acetate=1:1):0.2. ^{1}H-NMR (300 MHz, d_6-DMSO): δ=1.4 (s,1H,BOC), 1.88–1.95 (m,2H), 2.08 (s,3H,SMe), 2.4–2.5 (m,2H, partially obscurbed by DMSO), 3.6 (m,2H), 3.8 (m,1H), 4.15 (m,2H), 4.8 (m,1H), 7.2 (1H, thiophene), 7.42 (d, part of an AB system, 2H), 7.6 (d, part of an AB system, 2H), 7.7 (d, 1H, thiophene), 8.95 (t,1H, CH_2NHCO), 9.93 (bs, 1H,NH).

tert-Butyl (3R)-1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-oxo-3-pyrrolidinylcarbamate

170 mg (0.292 mmol) of N2-(tert-butoxycarbonyl)-N1-(4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-D-methionine-amide are dissolved in 2 ml of DMSO and admixed with 178.5 mg (0.875 mmol) of trimethylsulphonium iodide and 60.4 mg (0.437 mmol) of potassium carbonate, and the mixture is stirred at 80° C. for 3.5 hours. The mixture is then concentrated under high vacuum and the residue is washed with ethanol. 99 mg of the target compound remain.

^{1}H-NMR (300 MHz, d_6-DMSO): δ=1.4 (s,1H,BOC), 1.88–2.05 (m,1; H), 2.3–2.4 (m,1H), 3.7–3.8 (m,3H), 3.8–3.9 (m,1H), 4.14.25 (m,1H), 4.25–4.45 (m,1H), 4.75–4.95 (m,1H), 7.15 (1H, thiophene), 7.25 (d,1H), 7.52 (d, part of an AB system, 2H), 7.65 (d, part of an AB system, 2H), 7.65 (d, 1H, thiophene), 9.0 (broad s,1H).

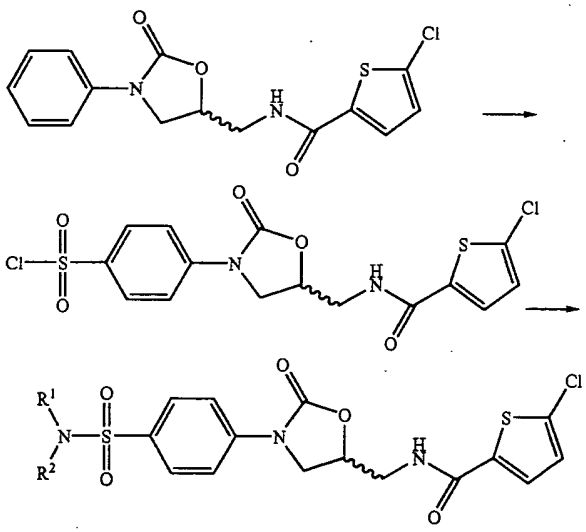
N[((5S)-3-{4-[(3R)-3-Amino-2-oxo-1-pyrrolidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide trifluoroacetate

97 mg (0.181 mmol) of tert-butyl (3R)-1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl }-2-oxo-3-pyrrolidinylcarbamate are suspended in 4 ml of methylene chloride, 1.5 ml of trifluoroacetic acid are added and the mixture is stirred at room temperature for 1 hour. The mixture is then concentrated under reduced pressure and the residue is purified on an RP-HPLC (acetonitrile/water/0.1% TFA gradient). Evaporation of the appropriate fraction gives 29 mg (37% of theory) of the target compound of melting point 241° C. (decomp.).

R_f (SiO_2,EtOH/TEA=17:1) 0.19. ^{1}H-NMR (300 MHz, d_6-DMSO): δ=1.92–2.2 (m,1H), 2.4–2.55 (m,1H, partially obscured by DMSO peak), 3.55–3.65 (m,2H), 3.75–3.95 (m,3H), 4.1–4.3 (m,2H), 4.75–4.9 (m,1H), 7.2 (1H, thiophene), 7.58 (d, part of an AB system, 2H), 7.7 (d, part of an AB system, 2H), 7.68 (d, 1H, thiophene), 8.4 (broad s,3H, NH3), 8.9 (t,1H,NHCO).

The Examples 167 to 170 below refer to the introduction of sulphonamide groups in phenyl-substituted oxazolidinones:

General Method for Preparing Substituted Sulphonamides Starting from 5-chloro-N-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



Under argon and at 5° C., 5-chloro-N-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide (from Example 96) is added to chlorosulphonic acid (12 eq.). The reaction mixture is stirred at room temperature for 2 h and then poured into ice-water. The resulting precipitate is filtered off, washed with water and dried.

Under argon and at room temperature, the precipitate is then dissolved in tetrahydrofuran (0.1 mol/l) and admixed with the appropriate amine (3 eq.), triethylamine (1.1 eq.) and dimethylaminopyridine (0.1 eq.). The reaction mixture is stirred for 1–2 h and then concentrated under reduced pressure. The desired product is purified by flash chromatography (dichloromethane/methanol mixtures).

The following compounds were prepared in an analogous manner:

Example 167

5-Chloro-N-({2-oxo-3-[4-(1-pyrrolidinylsulphonyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=492 ([M+Na]$^+$, 100), 470 ([M+H]$^+$, 68), Cl pattern; HPLC (method 3): rt (%)=4.34 (100). IC_{50}: 0.5 μM

Example 168

5-Chloro-N-[(3-{4-[(4-methyl-1-piperazinyl)sulphonyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=499 ([M+H]$^+$, 100), Cl pattern; HPLC (method 2): rt (%)=3.3 (100).

Example 169

5-Chloro-N-({2-oxo-3-[4-(1-piperidinylsulphonyl) phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%)=484 ([M+H]$^+$, 100), Cl pattern; HPLC (method 2): rt (%)=4.4 (100).

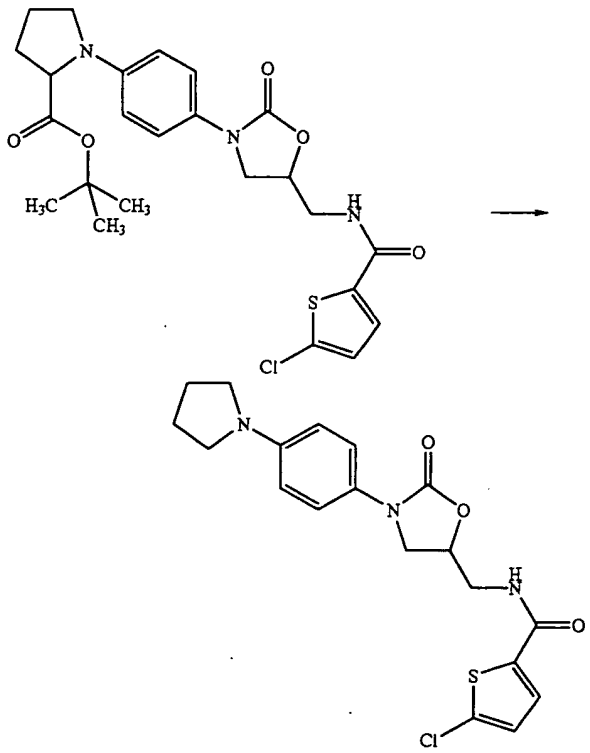
Example 170

5-Chloro-N-[(3-{4-[(4-hydroxy-1-piperidinyl)sulphonyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%)=500 ([M+H]$^+$, 100), Cl pattern; HPLC (method 3): rt (%)=3.9 (100).

Example 171

5-Chloro-N-({2-oxo-3-[4-(1-pyrrolidinyl)phenyl]-1, 3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



780 mg (1.54 mmol) of tert-butyl 1-{4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}-methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}prolinate are dissolved in 6 ml of dichloromethane and 9 ml of trifluoroacetic acid, and the mixture is stirred at 40° C. for two days. The reaction mixture is then concentrated and stirred with ether and 2N aqueous sodium hydroxide solution. The aqueous phase is concentrated and stirred with ether and 2N hydrochloric acid. The organic phase of this extraction is dried over $MgSO_4$, filtered and concentrated. The crude product is chromatographed over silica gel (CH_2Cl_2/EtOH/conc. aqu. NH_3 sol.=100/1/0.1 to 20/1/0.1). This gives 280 mg (40% of theory) of the product.

MS (ESI): m/z (%)=406 (M+H, 100); HPLC (method 4): rt=3.81 min.

HPLC Parameter and LC-MS Parameter for the HPLC and LC-MS Data Given in the Examples Above (the Unit of the Retention Time (rt) is Minutes):

[1] Column: Kromasil C18, L-R temperature: 30° C., flow rate=0.75 ml min^{-1}, eluent: A=0.01 M $HClO_4$, B=CH_3CN, gradient:->0.5 min 98% A->4.5 min 10% A->6.5 min 10% A

[2] Column: Kromasil C18 60*2, L-R temperature: 30° C., flow rate=0.75 ml min^{-1}, eluent: A=0.01 M H_3PO_4, B=CH_3CN, gradient:->0.5 min 90% A->4.5 min 10% A->6.5 min 10% A

[3] Column: Kromasil C18 60*2, L-R temperature: 30° C., flow rate=0.75 ml min^{-1}, eluent: A=0.005 M $HClO_4$, B=CH_3CN, gradient: ->0.5 min 98% A->4.5 min 10% A ->6.5 min 10% A

[4] Column: Symmetry C18 2.1x50 mm, column oven: 50° C., flow rate=0.6 ml min^{-1}, eluent: A=0.6 g 30% strength HCl/l of water, B=CH_3CN, gradient: 0.0 min 90% A ->4.0 min 10% A ->9 min 10% A

[5] MHZ-2Q, Instrument Micromass Quattro LCZ Column Symmetry C18, 50 mmx2.1 mm, 3.5 µm, temperature: 40° C., flow rate 0.5 ml min^{-1}, eluent A=CH_3CN+0.1% formic acid, eluent B=water+0.1% formic acid, gradient: 0.0 min 10% A->4 min 90% A->6 min 90% A

[6] MHZ-2P, Instrument Micromass Platform LCZ Column Symmetry C18, 50 mmx2.1 mm, 3.5 µm, temperature: 40° C., flow rate=0.5 ml min^{-1}, eluent A=CH_3CN+0.1% formic acid, eluent B=water+0.1% formic acid, gradient: 0.0 min 10% A->4 min 90% A->6 min 90% A

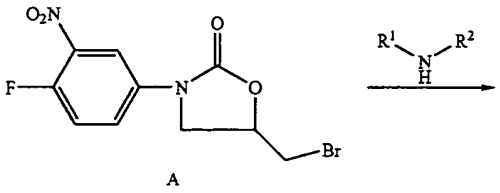
[7] MHZ-7Q, Instrument Micromass Quattro LCZ Column Symmetry C18, 50 mmx2.1 mm, 3.5 µm, temperature: 40° C., flow rate=0.5 ml min^{-1}, eluent A=CH_3CN+0.1% formic acid, eluent B=water+0.1% formic acid, gradient: 0.0 min 5% A->1 min 5% A->5 min 90% A->6 min 90% A

General Method for Preparing Oxazolidinones of the General Formula B by Solid-phase-supported Synthesis

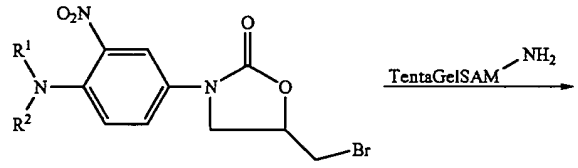
Reactions with different resin-bonded products were carried out in a set of separated reaction vessels.

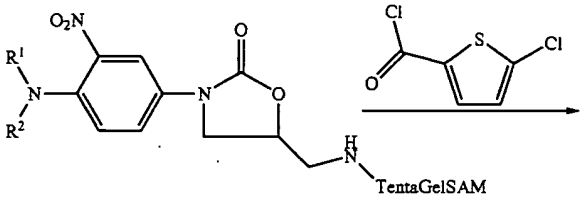
5-(Bromomethyl)-3-(4-fluoro-3-nitrophenyl)-1,3-oxazolidin-2-one A (prepared from epibromohydrin and 4-fluoro-3-nitrophenyl isocyanate using LiBr/Bu_3PO in xylene analogously to U.S. Pat. No. 4,128,654, Ex.2) (1.20 g, 3.75 mmol) and ethyldiisopropylamine (DIEA, 1.91 ml, 4.13 mmol) were dissolved in DMSO (70 ml), admixed with a secondary amine (1.1 eq., amine component 1) and reacted at 55° C. for 5 h. TentaGel SAM resin (5.00 g, 0.25 mmol/g) was added to this solution, and the mixture was reacted at 75° C. for 48 h. The resin was filtered, washed repeatedly with methanol (MeOH), dimethylformamide (DMF), MeOH, dichloromethane (DCM) and diethyl ether and dried. The resin (5.00 g) was suspended in dichloromethane (80 ml), admixed with DEEA (10 eq.) and 5-chlorothiophene-2-carbonyl chloride [prepared by reacting 5-chlorothiophene-2-carboxylic acid (5 eq.) and 1-chloro-1-dimethylamino-2-methylpropene (5 eq.) in DCM (20 ml) at room temperature for 15 minutes] and the mixture was reacted at room temperature for 5 h. The resulting resin was filtered, washed repeatedly with MeOH, DCM and diethyl ether and dried. The resin was then suspended in DMF/water (v/v 9:2, 80 ml), admixed with $SnCl_2$*$2H_2O$ (5 eq.) and reacted at room temperature for 18 h. The resin was washed repeatedly with MeOH, DMF, water, MeOH, DCM and diethyl ether and dried. This resin was suspended in DCM, admixed with

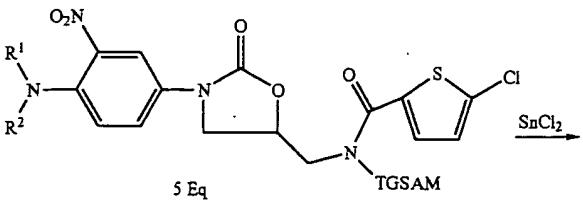
DIEA (10 eq.) and, at 0° C., with an acid chloride (5 eq. of acid derivative 1), and the mixture was reacted at room temperature overnight. Prior to the reaction, carboxylic acids were converted into the corresponding acid chlorides by reaction with 1-dimethylamino-1-chloro-2-methylpropene (1 eq., based on the carboxylic acid) in DCM at room temperature for 15 min. The resin was washed repeatedly with DMF, water, DMF, MeOH, DCM and diethyl ether and dried. If the acid derivative 1 used was an Fmoc-protected amino acid, the Fmoc protective group was removed in the last reaction step by reaction with piperidine/DMF (v/v, 1/4) at room temperature for 15 minutes, and the resin was washed with DMF, MeOH, DCM and diethyl ether and dried. The products were then removed from the solid phase using trifluoroacetic acid (TFA)/DCM (v/v, 1/1), the resin was filtered off and the reaction solutions were concentrated. The crude products were filtered over silica gel (DCM/MeOH, 9:1) and evaporated, giving a set of products B.



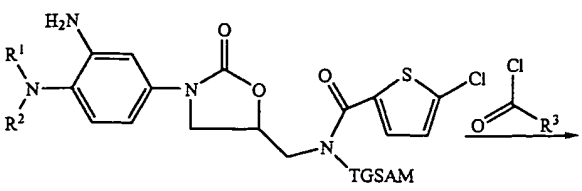
A







5 Eq



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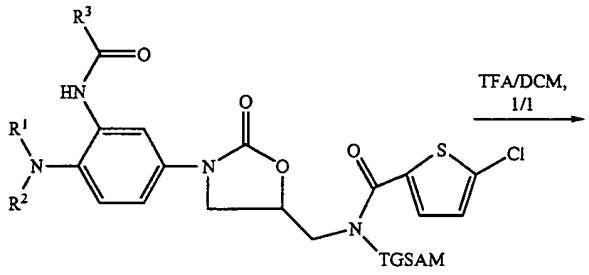
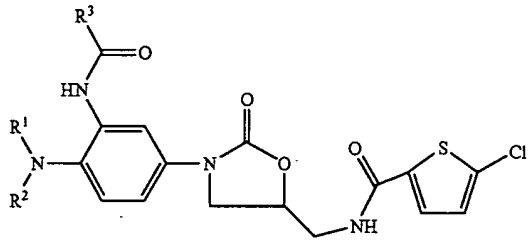


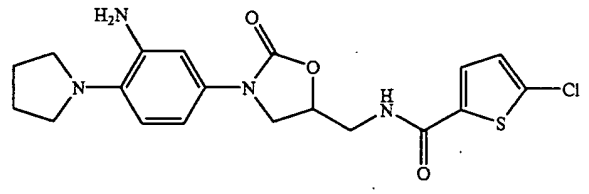


B

Compounds which were prepared by solid-phase-supported synthesis:

Example 172

N-({3-[3-Amino-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

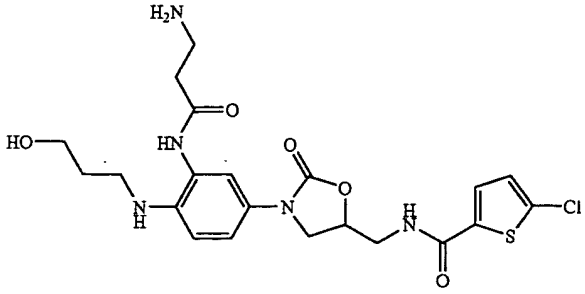


Analogously to the general procedure for preparing the derivatives B, 5 g (1.25 mmol) of TentaGel SAM resin were reacted with pyrrolidine as amine derivative 1. The aniline obtained after reduction with $SnCl_2*2H_2O$ was, without any further acylation step, removed from the solid phase and concentrated. The crude product was partitioned between ethyl acetate and $NaHCO_3$ solution and the organic phase was salted out using NaCl, decanted and evaporated to dryness. This crude product was purified by vacuum flash chromatography over silica gel (dichloromethane/ethyl acetate, 3:1–1:2).

^{1}H-NMR (300 MHz, $CDCl_3$): 1.95–2.08, br, 4 H; 3.15–3.30, br, 4 H; 3.65–3.81, m, 2 H; 3.89, ddd, 1H; 4.05, dd, 1 H; 4.81, dddd, 1 H; 6.46, dd, 1 H; 6.72, dd, 1 H; 6.90, dd, 1 H; 6.99, dd, 1 H; 7.03, dd, 1 H; 7.29, d, 1 H.

Example 173

N-[(3-{3-(B-Alanylamino)-4-[(3-hydroxypropyl) amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide

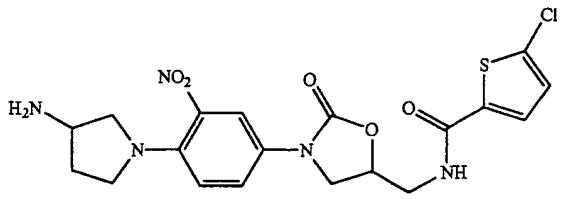


Analogously to the general procedure for preparing the derivatives B, 5 g (1.25 mmol) of TentaGel SAM resin were reacted with azetidine as amine derivative 1 and Fmoc-β-alanine as acid derivative 1. The crude product obtained after the removal was stirred in methanol at room temperature for 48 h and evaporated to dryness. This crude product was purified by reversed phase HPLC using a water/TFA/acetonitrile gradient.

^{1}H-NMR (400 MHz, CD_3OD): 2.31, tt, 2 H; 3.36, t, 2 H; 3.54, t, 2 H; 3.62, t, 2 H; 3.72, dd, 1 H; 3.79, dd, 1 H; 4.01, dd, 1 H; 4.29, dd, 2 H; 4.43, t, 2 H; 4.85–4.95, m, 1 H; 7.01, d, 1 H; 4.48–7.55, m, 2 H; 7.61, d, 1 H; 7.84, d, 1 H.

Example 174

N-({3-[4-(3-Amino-1-pyrrolidinyl)-3-nitrophenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chloro-2-thiophenecarboxamide

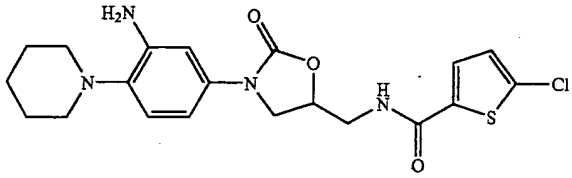


Analogously to the general procedure for preparing the derivatives B, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted with tert-butyl 3-pyrrolidinylcarbamate as amine derivative 1. The nitrobenzene derivative obtained after the acylation with 5-chlorothiophenecarboxylic acid was removed from the solid phase and concentrated. This crude product was purified by reversed phase HPLC using a water/TFA/acetonitrile gradient.

^{1}H-NMR (400 MHz, CD_3OH): 2.07–2.17, m, 1 H; 2.39–2.49, m, 1 H; 3.21–3.40, m, 2 H; 3.45, dd, 1 H; 3.50–3.60, m, 1 H; 3.67, dd, 1 H; 3.76, dd, 1 H; 3.88–4.00, m, 2 H; 4.14–4.21, t, 1 H; 4.85–4.95, m, 1 H; 7.01, d, 1 H; 7.11, d, 1 H; 7.52, d, 1 H; 7.66, dd, 1 H; 7.93, d, 1 H.

Example 175

N-({3-[3-Amino-4-(1-piperidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

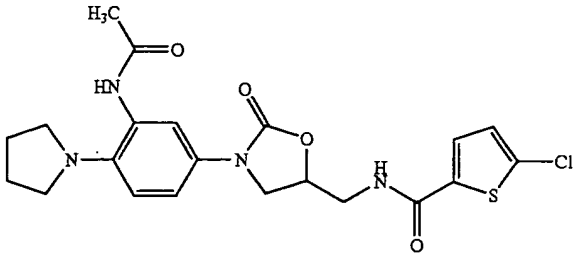


Analogously to the general procedure for preparing the derivatives B, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted with piperidine as amine derivative 1. The aniline obtained after the reduction was, without any further acylation step, removed from the solid phase and concentrated. This crude product was purified by reversed phase HPLC using a water/TFA/acetonitrile gradient.

^{1}H-NMR (400 MHz, CD_3OH): 1.65–1.75, m, 2 H; 1.84–1.95, m, 4 H; 3.20–3.28, m, 4 H; 3.68, dd, 1 H; 3.73, dd, 1H; 3.90, dd, 1 H; 4.17, dd, 1 H; 4.804.90, m, 1 H; 7.00, d, 1 H; 7.05, dd, 1 H; 7.30–7.38, m, 2H; 7.50, d, 1 H.

Example 176

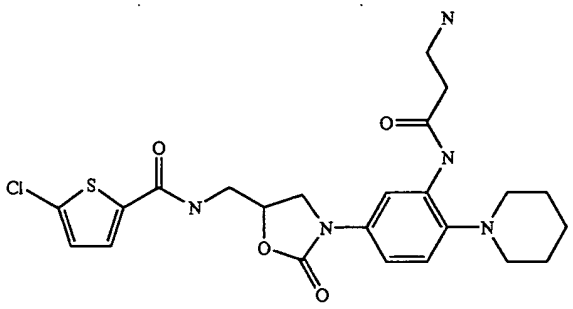
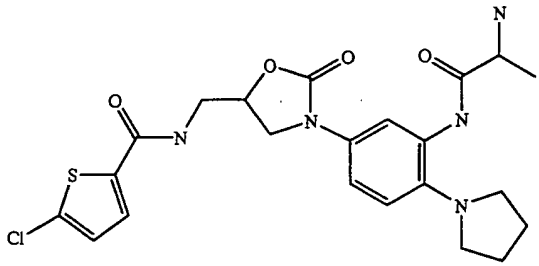
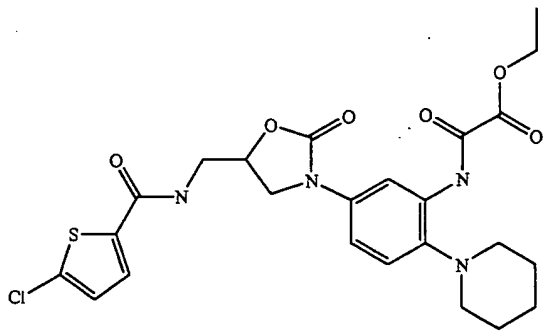
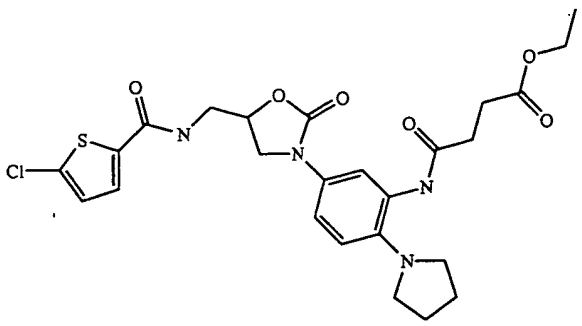
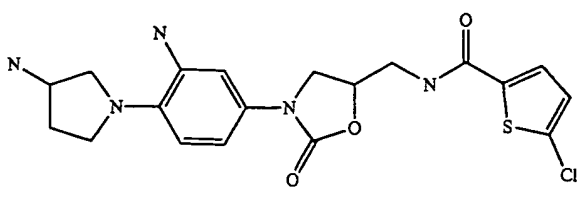
N-({3-[3-(Acetylamino)-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chloro-2-thiophenecarboxamide



Analogously to the general procedure for preparing the derivatives B, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted pyrrolidine as amine derivative 1 and acetyl chloride as acid derivative 1. The crude product was partitioned between ethyl acetate $NaHCO_3$ solution and the organic phase was salted out using NaCl, decanted and evaporated to dryness. This crude product was purified by vacuum flash chromatography over silica gel (dichloromethane/ethyl acetate, 1:1–0:1).

^{1}H-NMR (400 MHz, CD_3OH): 1.93–2.03, br, 4 H; 2.16, s, 3 H; 3.20–3.30, br, 4 H; 3.70, d, 2 H; 3.86, dd, 1H; 4.10, dd, 1 H; 4.14, dd, 1 H; 4.80–4.90, m, 1 H; 7.00, d, 1 H; 7.07, d, 1 H; 7.31, dd, 1 H; 7.51, d, 1 H; 7.60, d, 1 H.

The following compounds were prepared analogously to the general procedure.

Example	Structure	Ret. time	HPLC [%]
177		2.62	79.7
178		2.49	33.7
179		4.63	46.7
180		3.37	44.8
181		2.16	83

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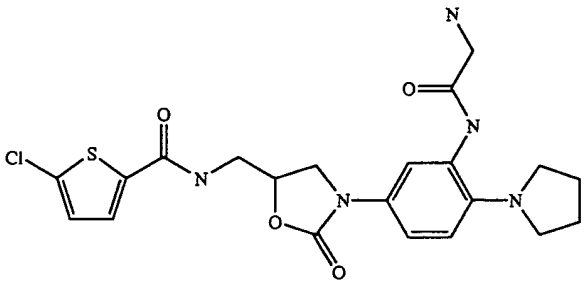
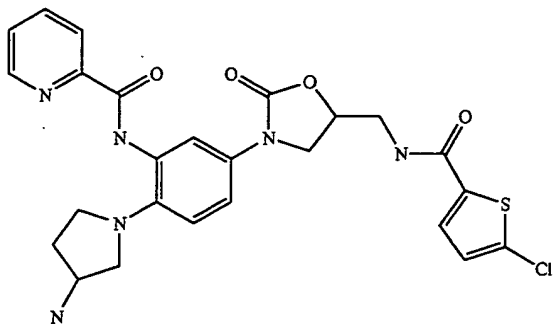
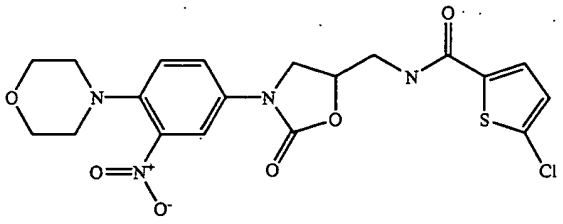
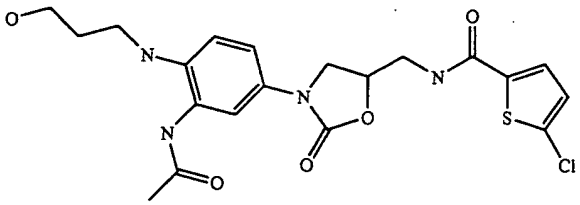
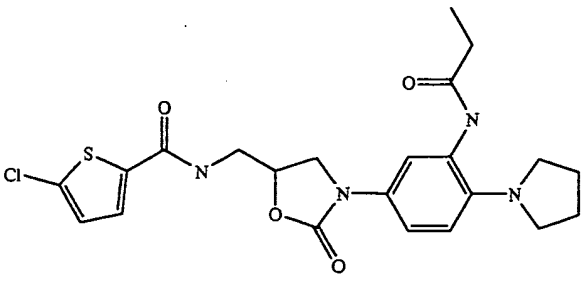
Example	Structure	Ret. time	HPLC [%]
182		2.31	93.3
183		2.7	100
184		3.91	51
185		2.72	75.2
186		3.17	46

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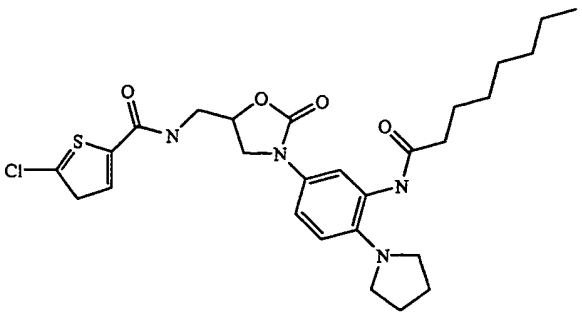
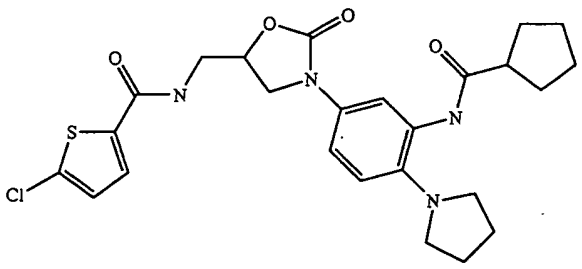
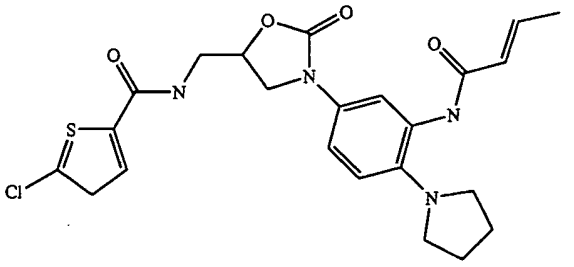
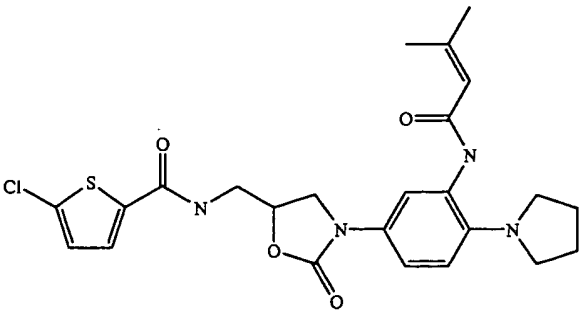
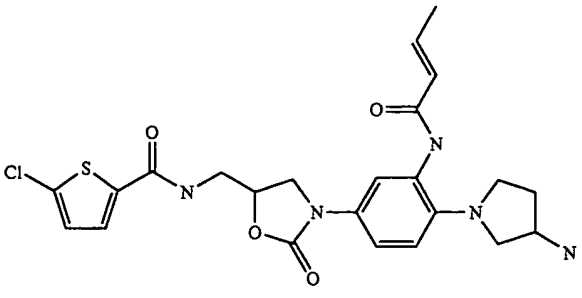
Example	Structure	Ret. time	HPLC [%]
187		4.61	50.2
188		3.89	56.6
189		3.37	52.9
190		3.6	63.9
191		2.52	70.1

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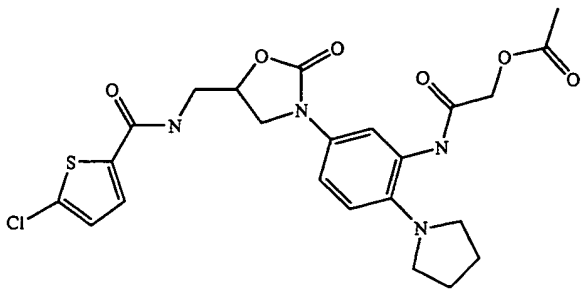
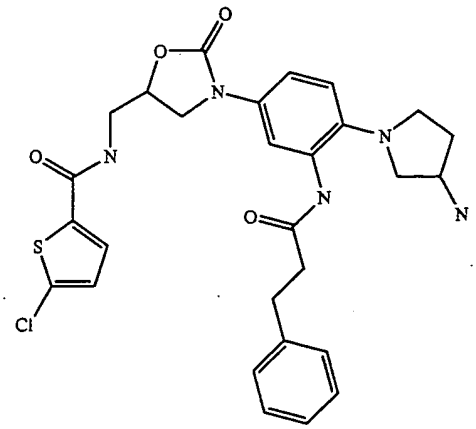
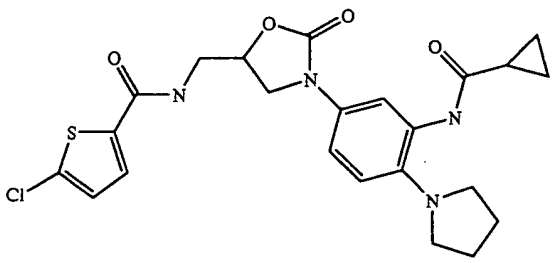
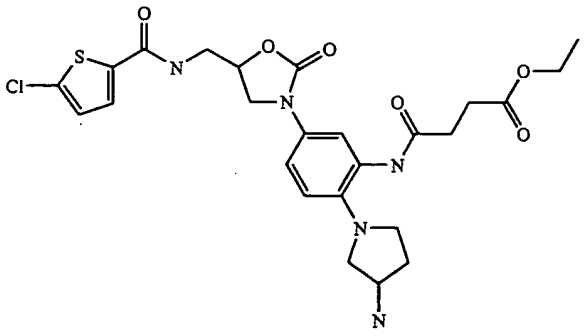
Example	Structure	Ret. time	HPLC [%]
192		3.52	46.6
193		2.87	50.1
194		3.25	71.1
195		2.66	67

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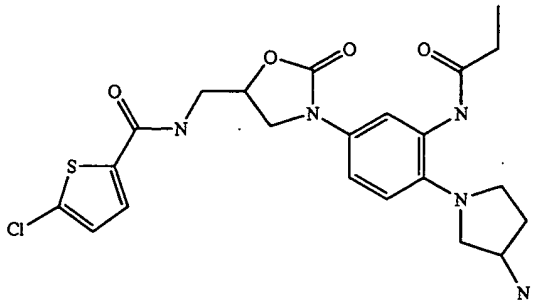
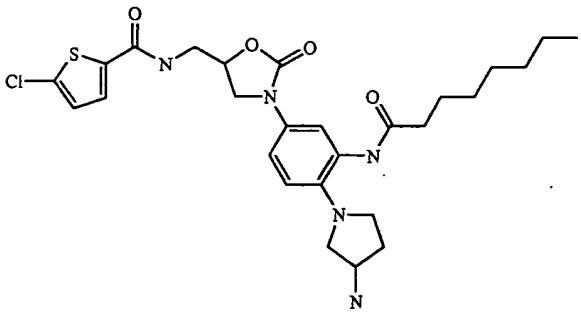
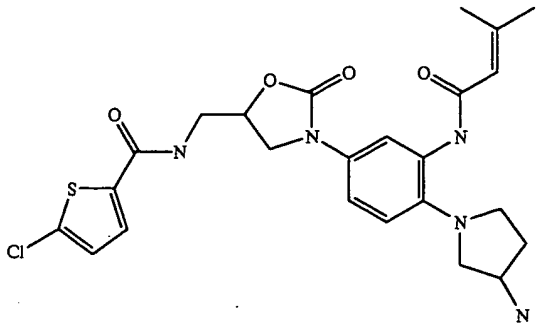
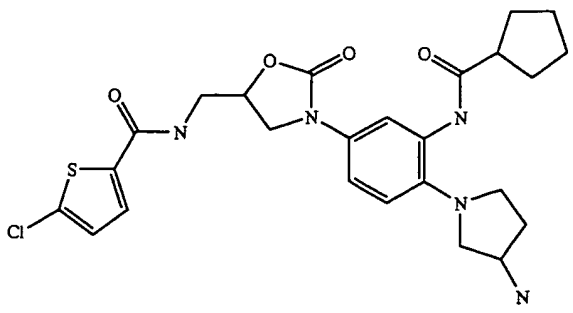
Example	Structure	Ret. time	HPLC [%]
196		2.4	52.1
197		3.13	48.9
198		2.67	75.5
199		2.72	65.7

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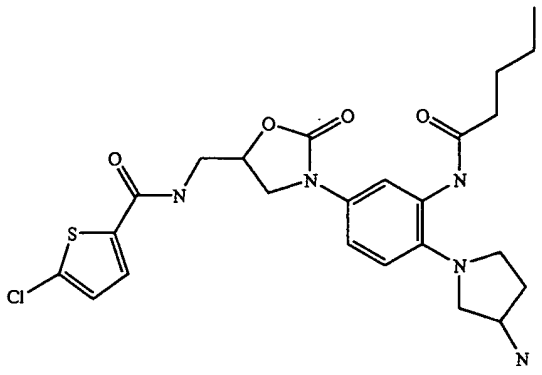
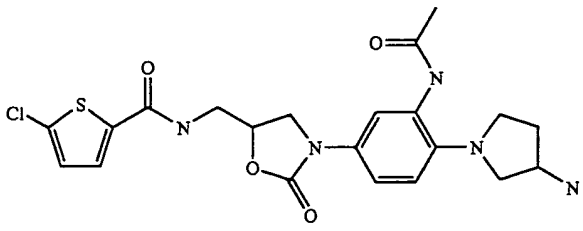
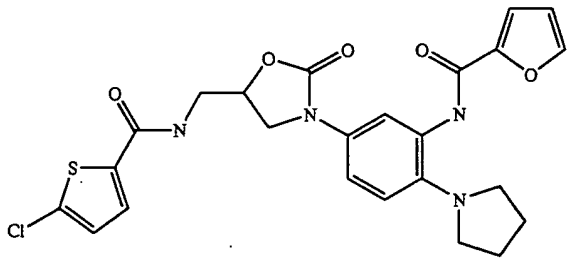
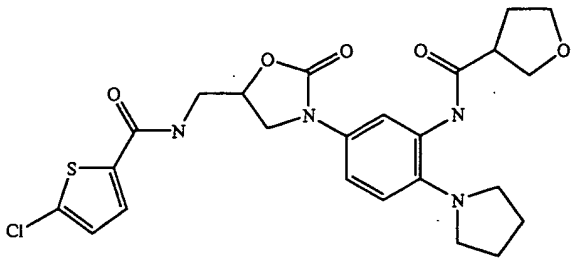
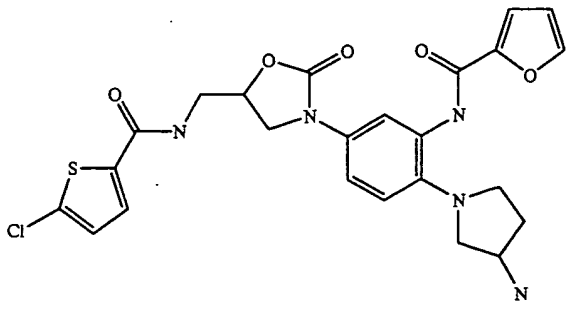
Example	Structure	Ret. time	HPLC [%]
200		2.71	57.3
201		2.22	100
202		3.89	75.7
203		3.19	49.6
204		2.55	88.2

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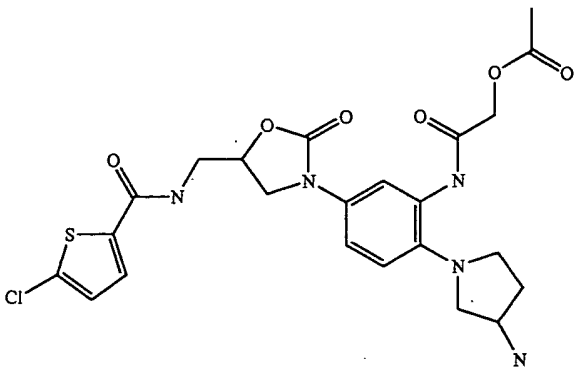
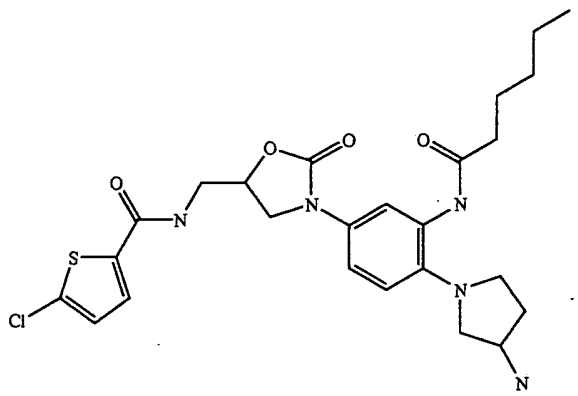
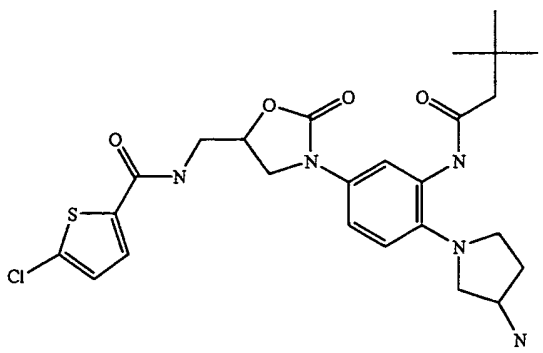
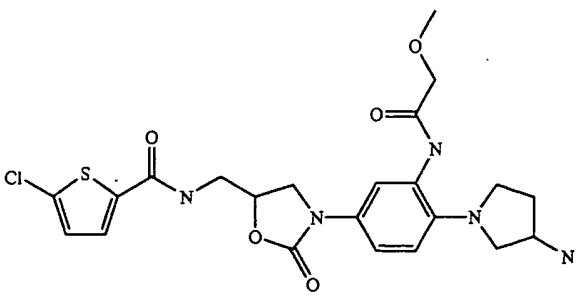
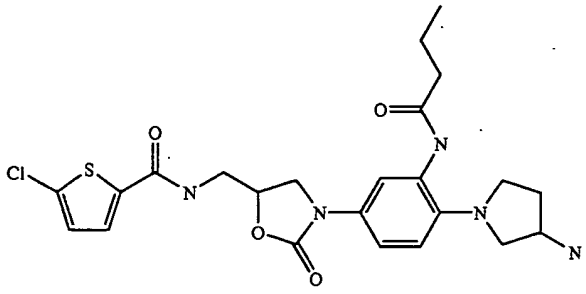
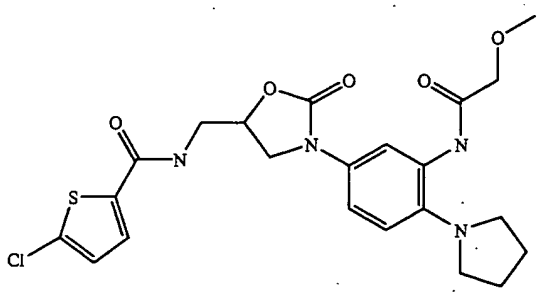
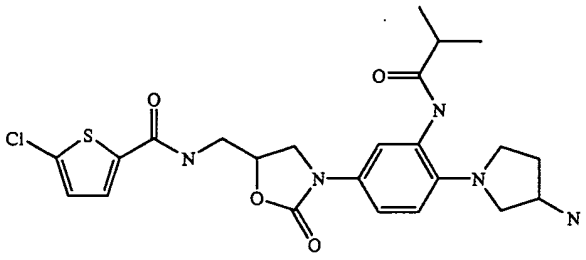
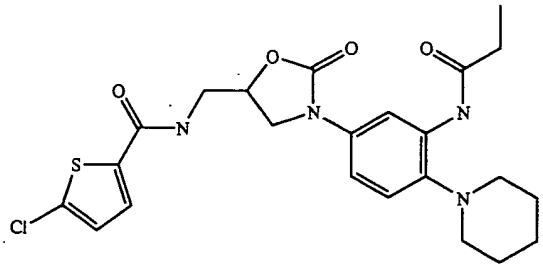
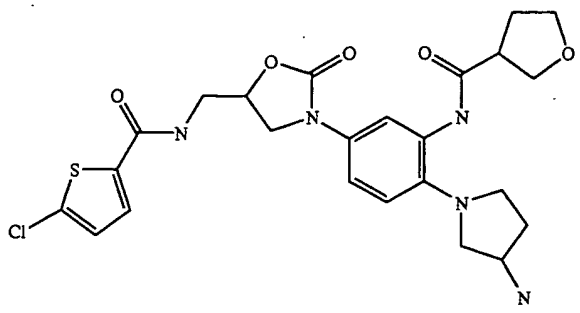
Example	Structure	Ret. time	HPLC [%]
205		2.44	68.6
206		2.86	71.8
207		2.8	63.6
208		2.41	77

-continued

Example	Structure	Ret. time	HPLC [%]
209		2.56	67.9
210		3.67	78.4
211		2.54	69.8
212		3.84	59.2
213		2.41	67.8

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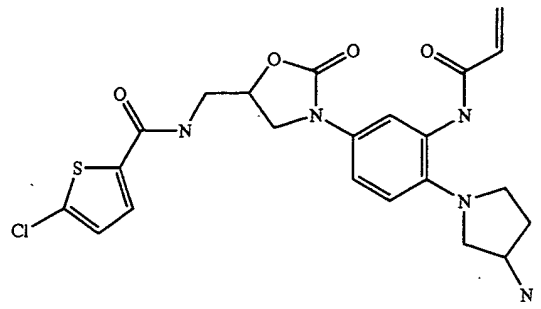
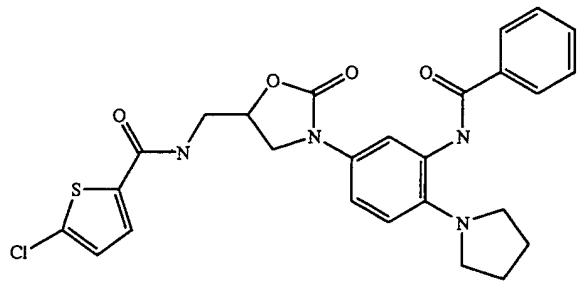
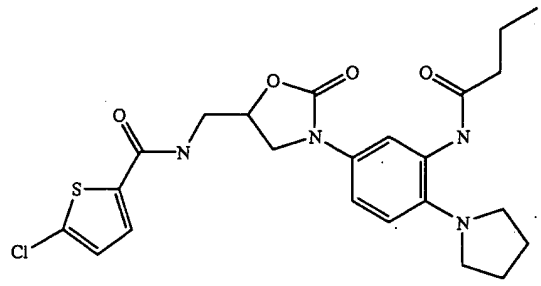
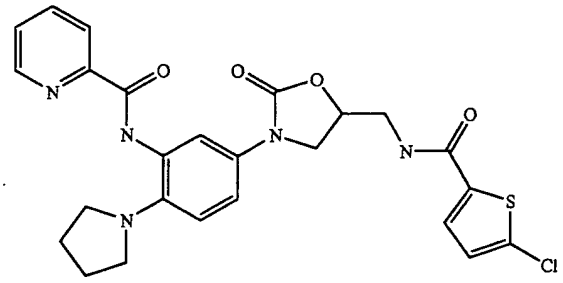
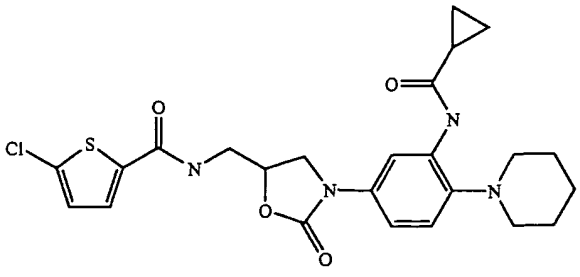
Example	Structure	Ret. time	HPLC [%]
214		2.41	75.4
215		4.01	81.3
216		3.46	49.5
217		4.4	60.2
218		3.79	70.9

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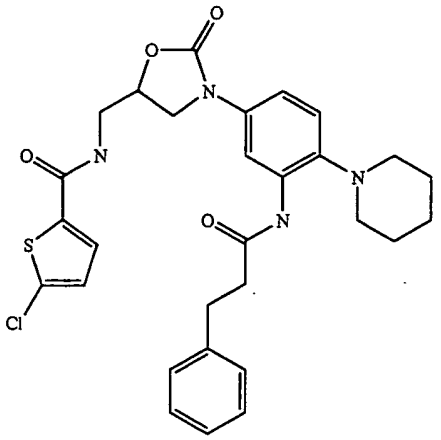
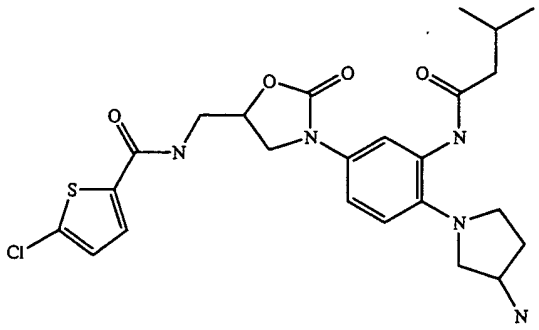
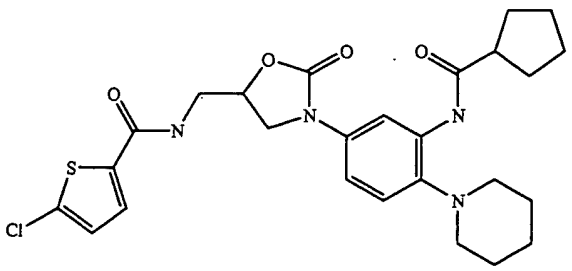
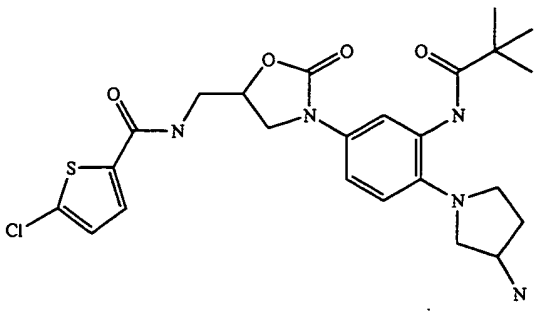
Example	Structure	Ret. time	HPLC [%]
219		4.57	51.5
220		2.68	100
221		4.53	63.5
222		2.66	89.2

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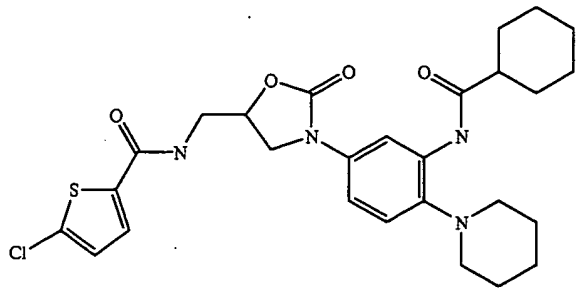
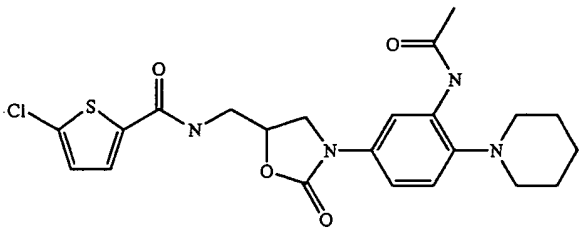
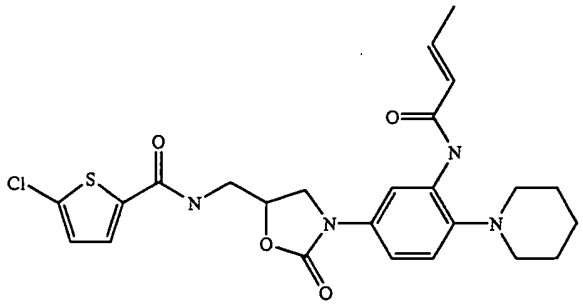
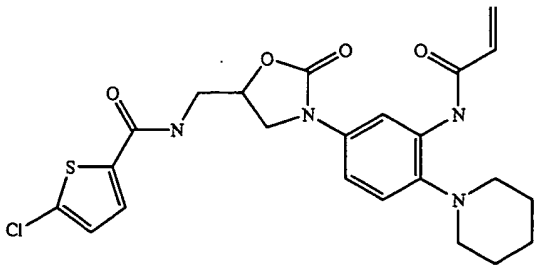
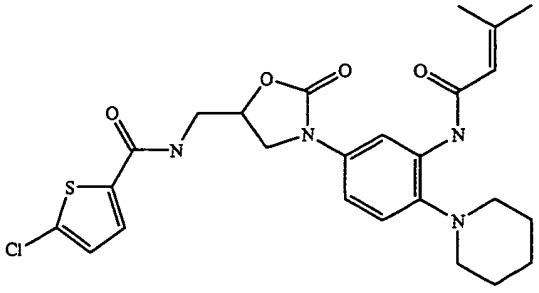
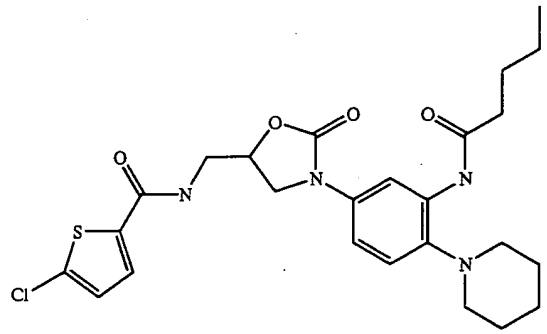
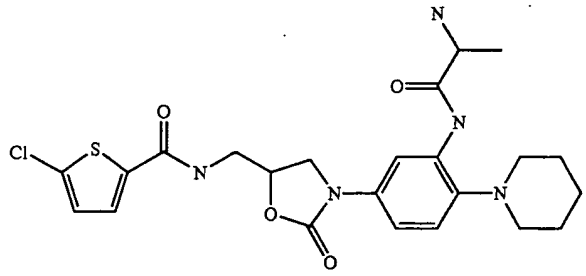
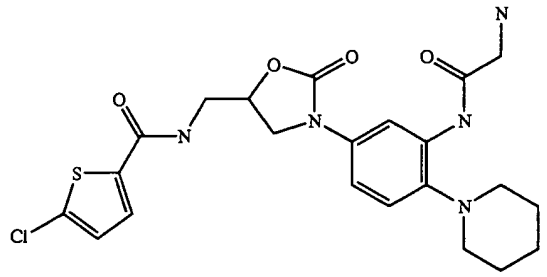
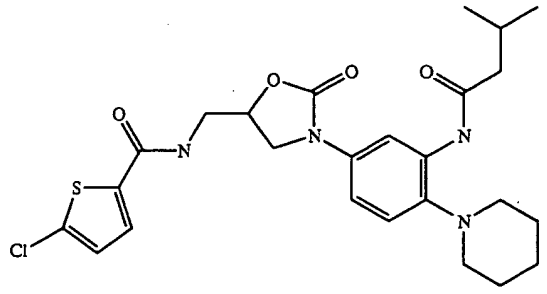
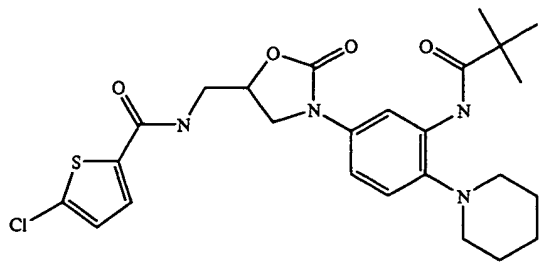
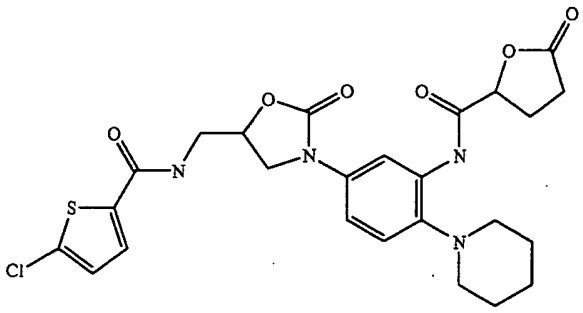
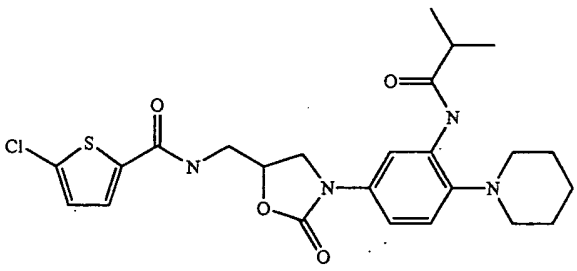
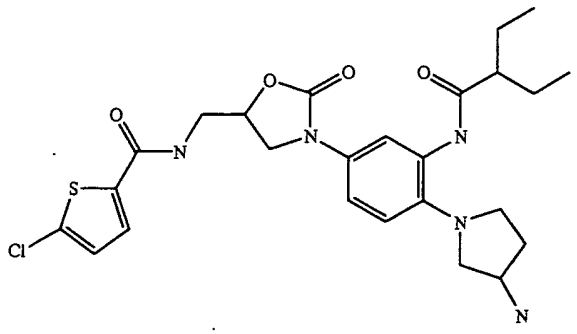
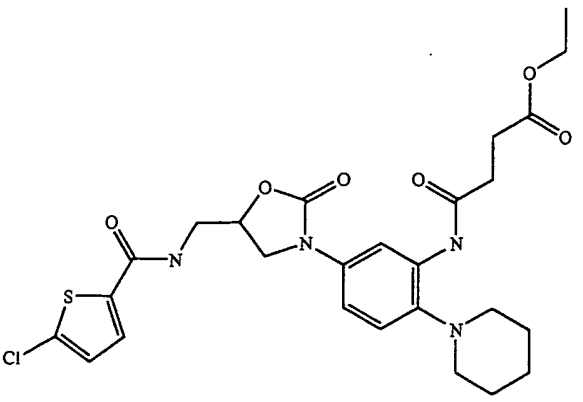
Example	Structure	Ret. time	HPLC [%]
223		4.76	69.3
224		3.45	77.4
225		3.97	63.2
226		3.94	61.4
227		4.15	66.3

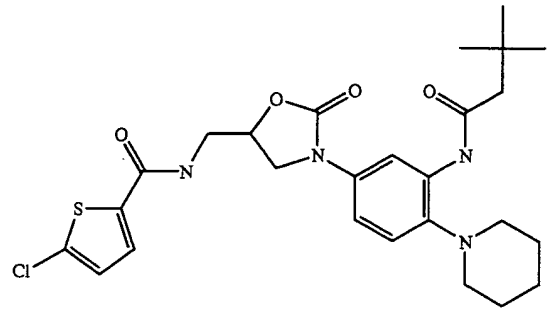
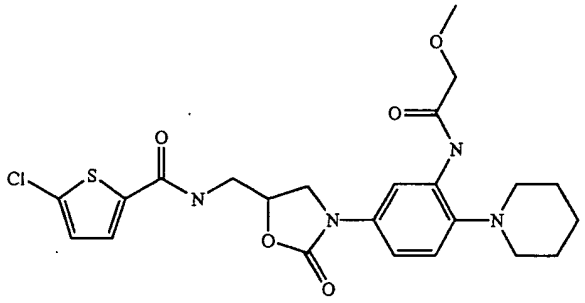
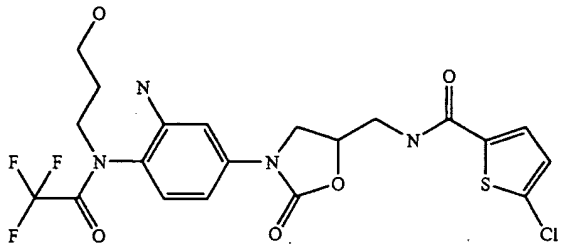
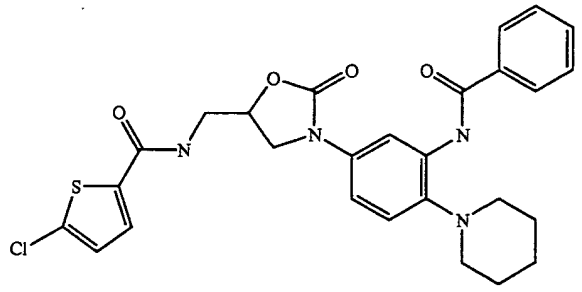
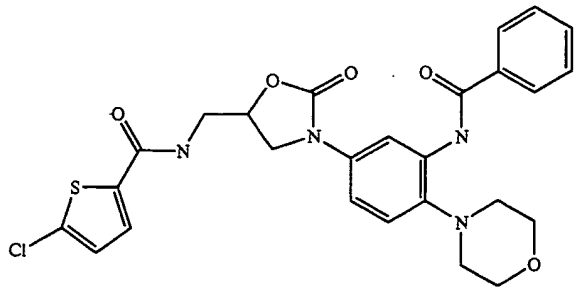
-continued

Example	Structure	Ret. time	HPLC [%]
228		4.41	55.1
229		2.83	41.1
230		2.7	83
231		4.39	64.2
232		4.85	74.9

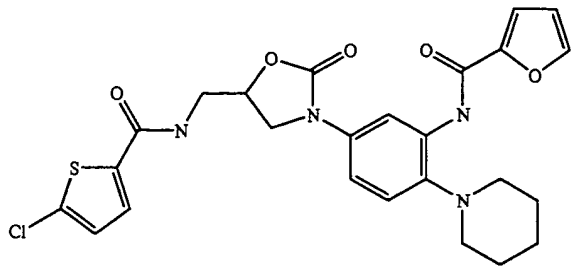
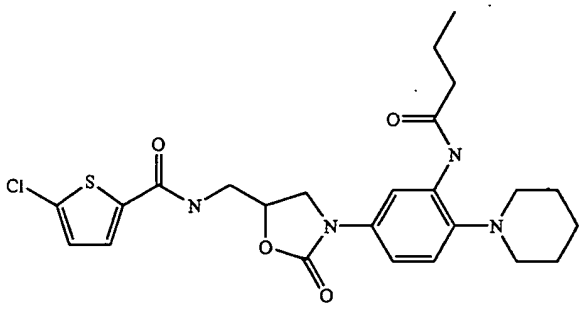
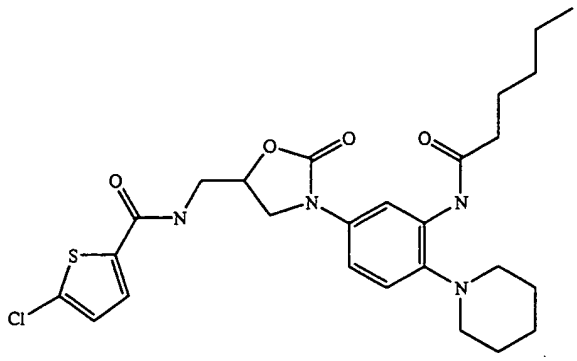
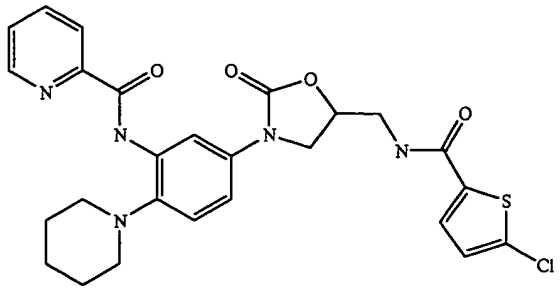
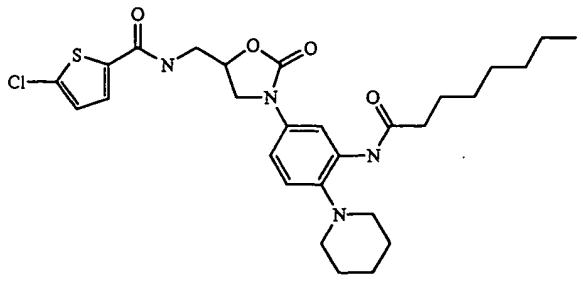
-continued

Example	Structure	Ret. time	HPLC [%]
233		4.17	41
234		4.21	61.8
235		2.75	100
236		3.94	50

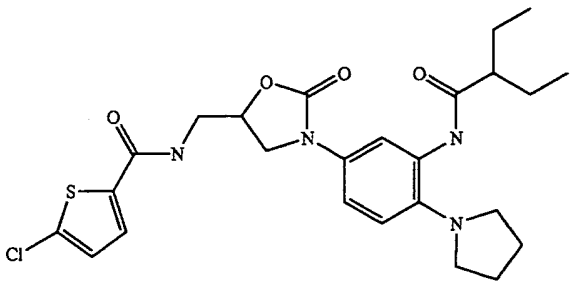
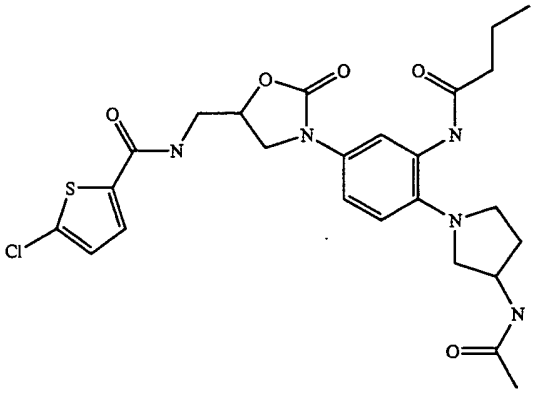
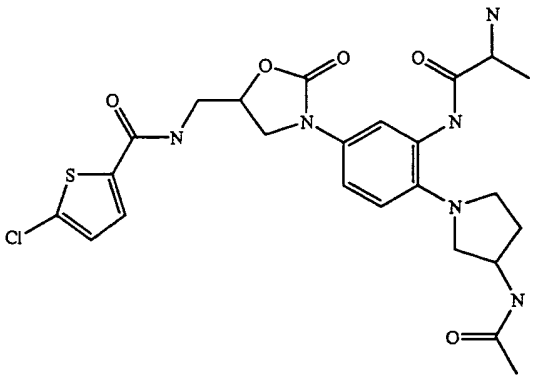
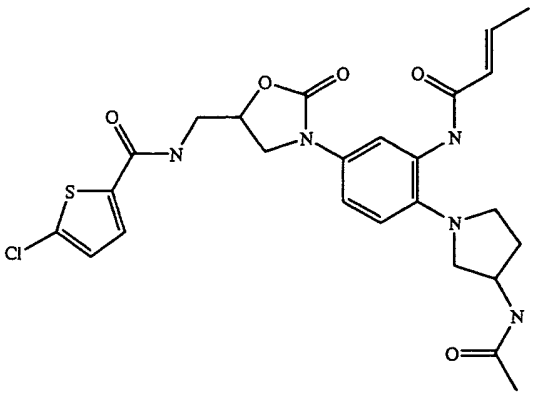
-continued

Example	Structure	Ret. time	HPLC [%]
237		4.65	75.8
238		4.4	75.3
239		4.24	62.2
240		4.76	75.1
241		4.17	72.5

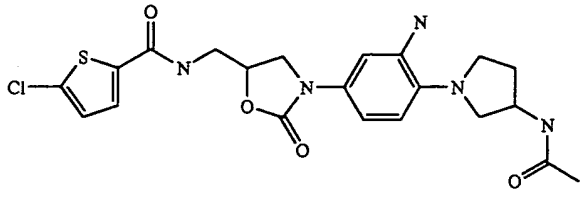
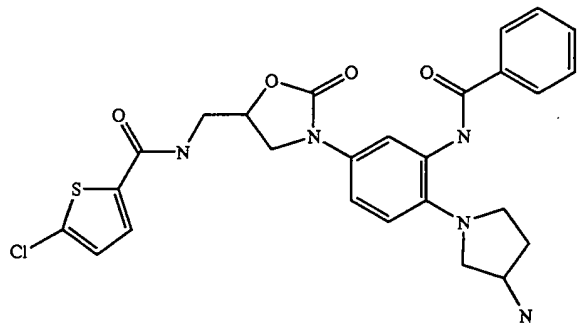
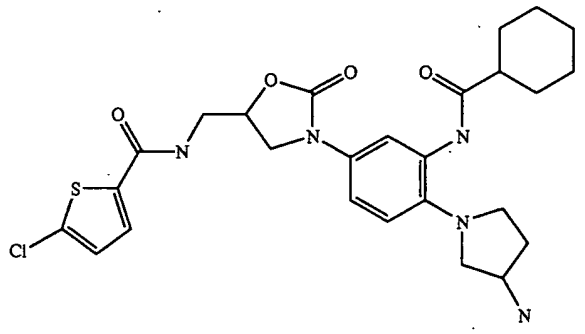
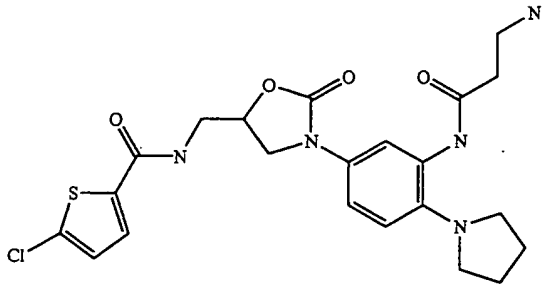
-continued

Example	Structure	Ret. time	HPLC [%]
242		4.6	74.8
243		4.12	51.6
244		4.71	66.2
245		4.86	62
246		5.23	58.3

-continued

Example	Structure	Ret. time	HPLC [%]
247		4.17	72.4
248		3.35	59.6
249		2.41	60.3
250		3.31	65.2

-continued

Example	Structure	Ret. time	HPLC [%]
251		2.86	36.5
252		2.69	89.8
253		2.81	67.4
254		2.19	75.4

All products of the solid-phase-supported synthesis were characterized by LC-MS. As standard, the following separation system was used: HP 1100 with UV detector (208–400 nm), oven temperature 40° C., Waters-Symmetry C18 column (50 mm×2.1 mm, 3.5 μm), mobile phase A: 99.9% acetonitrile/0.1% formic acid, mobile phase B: 99.9% water/0.1% formic acid; gradient:

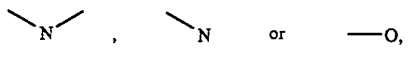
Time	A: %	B: %	flow rate
0.00	10.0	90.0	0.50

-continued

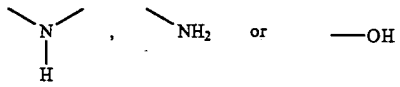
Time	A: %	B: %	flow rate
4.00	90.0	10.0	0.50
6.00	90.0	10.0	0.50
6.10	10.0	90.0	1.00
7.50	10.0	90.0	0.50

The substances were detected using a Micromass Quattro LCZ MS, ionization: ESI positive/negative.

In the structures listed above which comprise the radical(s)



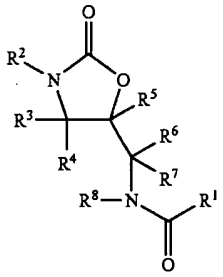
—O, what is meant is in each case a



or —OH function.

The invention claimed is:

1. A compound of the formula (I)



(I)

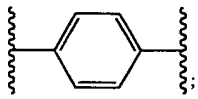
characterized in that

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

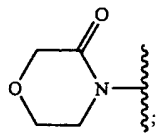
D-M-A-,

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.

2. The compound of the formula (I) according to claim 1, characterized in that

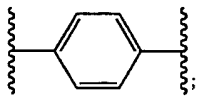
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen, amino, aminomethyl or $(C_1–C_8)$-alkyl, where the $(C_1–C_8)$-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

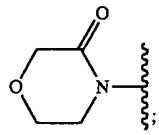
D-M-A-,

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.

3. The compound of the formula (I) according to claim 1, characterized in that

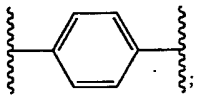
R^1 represents thiophene which may optionally be mono- or polysubstituted by halogen or by $(C_1–C_8)$-alkyl, where the $(C_1–C_8)$-alkyl radical for its part may optionally be mono- or polysubstituted by halogen,

R^2 represents

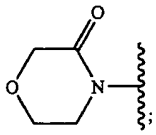
D-M-A-,

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.

4. The compound of the formula (I) according to claim 1, characterized in that

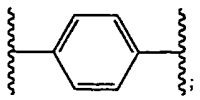
R^1 represents 2-thiophene which may optionally be substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents

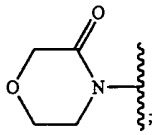
D-M-A-,

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.

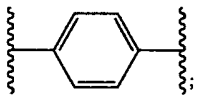
5. The compound of the formula (I) according to claim 1, characterized in that

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,

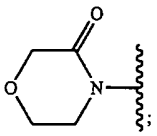
R^2 represents D-A-,

where:

the radical "A" represents



the radical "D" represents



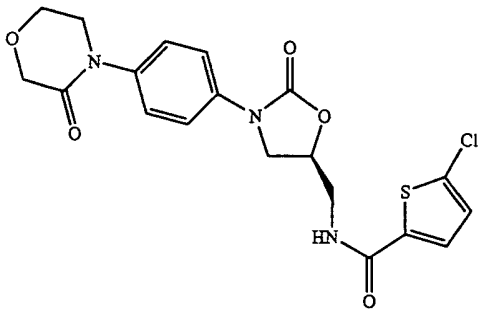
where

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.

6. The compound having the following formula

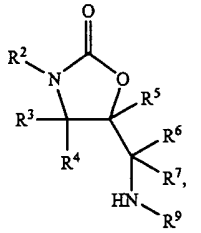


or a pharmaceutically acceptable salt or hydrate thereof.

7. Process for preparing the substituted oxazolidinone of claim 1, where

either according to a process alternative

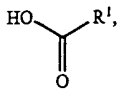
(A) a compound of the formula (II)



(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 1 is reacted with carboxylic acid of the formula (III)



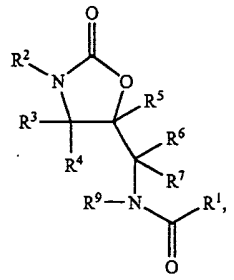
(III)

in which

the radical R^1 is as defined in claim 1,

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)

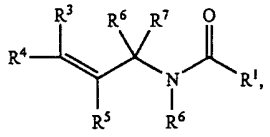


(I)

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 1, or else according to a process alternative

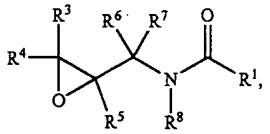
(B) a compound of the formula (IV)



(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 1, 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 1,

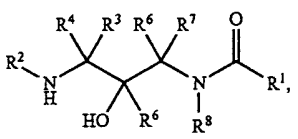
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the formula (VI)

R^2—NH_2 (VI),

in which

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

a compound of the formula (VII)

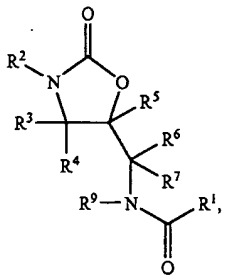


(VII)

in which

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

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.

8. A pharmaceutical composition comprising at least one compound of the formula (I) according to claim 1 and one or more pharmacologically acceptable auxiliaries or excipients.

9. A method for treatment of atherosclerosis comprising administering an effective amount of a compound of claim 1 to a patient in need thereof.

10. The compound of claim 2 or 3 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.

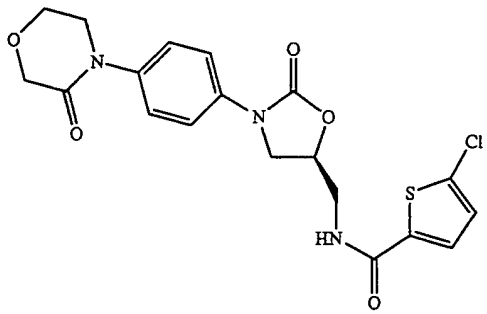
11. The process of claim 7 wherein in process alternative "A", the corresponding carbonyl halide of carboxylic acid (III) is a carbonyl chloride.

12. The process of claim 7 wherein in process alternative "B", the phosgene equivalent employed in the cyclization of compound (VII) is carbonyldimidazole (CDI).

13. A method for treatment of a thromboembolic disorder comprising administering to a patient in need thereof an effective amount of a compound of claim 1, wherein the thromboembolic disorder is myocardial infarct, pulmonary embolism or deep venous thrombosis.

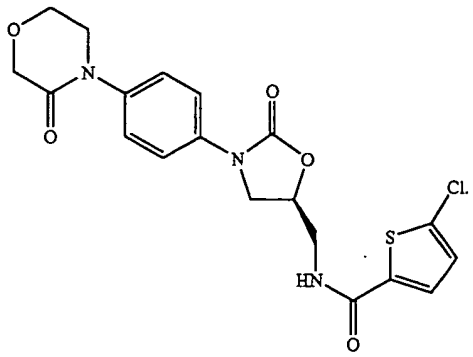
14. The compound of claim 6 that is purified and isolated.

15. A racemic mixture of a compound having the following formula



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

16. A compound having the following formula:

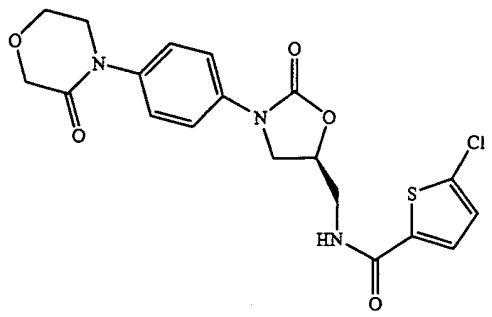


17. A pharmaceutical composition comprising the compound of claim 6 and one or more pharmacologically acceptable auxiliaries or excipients.

18. A pharmaceutical composition comprising the compound of claim 14 and one or more pharmacologically acceptable auxiliaries or excipients.

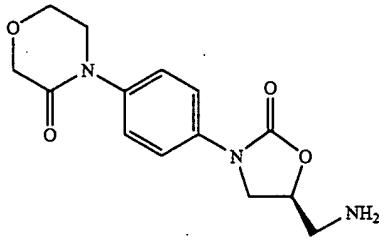
19. A pharmaceutical composition comprising the compound of claim 16 and one or more pharmacologically acceptable auxiliaries or excipients.

20. The process of claim 7 wherein the substituted oxazolidinone that is prepared is



or a pharmaceutically acceptable salt or hydrate thereof.

21. A process for the preparation of the compound of claim 6 comprising reacting a compound of the following formula



with 5-chlorothiophene-2-carbonyl chloride in an inert solvent to prepare the compound of claim 6.

22. The process of claim 21 wherein the inert solvent comprises pyridine.

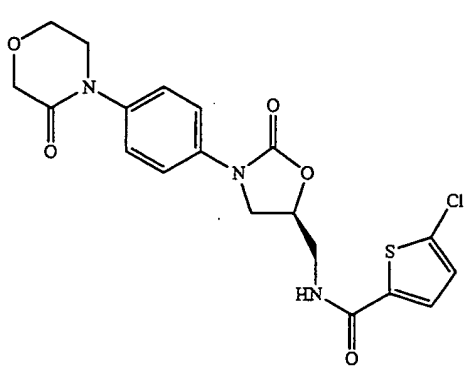
23. A method for the treatment of atherosclerosis comprising administering an effective amount of the composition of claim 17 to a patient in need thereof.

24. A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 17 to a patient in need thereof.

25. A method for the treatment of atherosclerosis comprising administering an effective amount of the composition of claim 18 to a patient in need thereof.

26. A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 18 to a patient in need thereof.

27. 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).

28. A pharmaceutical composition comprising the composition of claim 27 and one or more pharmacologically acceptable auxiliaries or excipients.

29. A method for the treatment of atherosclerosis comprising administering an effective amount of the composition of claim 28 to a patient in need thereof.

30. A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 28 to a patient in need thereof.

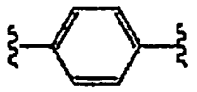
* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

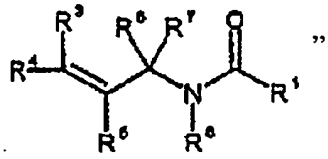
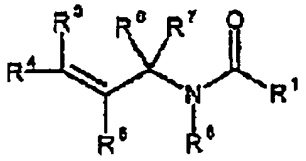
PATENT NO. : 7,157,456 B2
APPLICATION NO. : 10/181051
DATED : January 2, 2007
INVENTOR(S) : Alexander Straub et al.

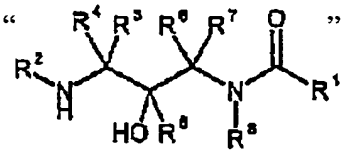
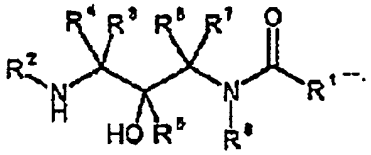
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

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

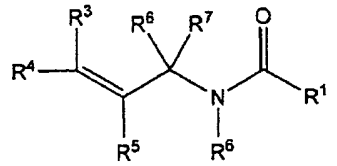
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

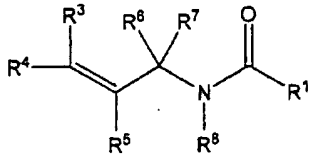
PATENT NO. : 7,157,456 B2
APPLICATION NO. : 10/181051
DATED : January 2, 2007
INVENTOR(S) : Alexander Straub et al.

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



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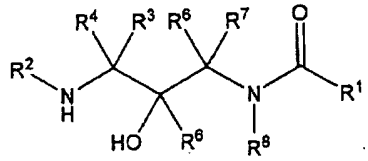
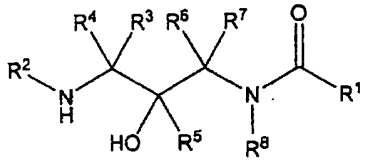
In Claim 7, at column 130, lines 60 - 66, Formula (VII),



" should read



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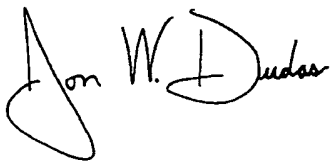
Signed and Sealed this

Nineteenth Day of February, 2008



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

K

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MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
7,157,456	**$980.00**	**$0.00**	**06/16/10**	**10/181,051**	**01/02/07**	**06/24/02**	**04**	**NO**	**LE A 34122**

PTOL-439 (Rev. 09/2006)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,892

Bayer Corporation Pharmaceutical Division
Attention: Gautam Shah, Ph.D.
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Shah:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 64,892

Sponsor: Bayer Corporation Pharmaceutical Division

Name of Drug: BAY 59-7939 Tablets

Date of Submission: May 29, 2002

Date of Receipt: May 31, 2002

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before June 30, 2002, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alice Kacuba
6/5/02 02:42:08 PM