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(71) Applicants *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). KYLE, Jeffrey, Alan [US/US]; 10434 Collingswood Lane, Fishers, IN 46038 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BEIGHT, Douglas, Wade [US/US]; 3468 South County Road 600 West, Frankfort, IN 46041 (US). CRAFT, Trelia, Joyce [US/US]; 10404 East 46th Street, Indianapolis, IN 46236 (US). FRANCISKOVICH, Jeffry, Bernard [US/US]; 5036 Quail Ridge Lane, Indianapolis, IN 46254 (US). GOODSON, Theodore, Junior [US/US]; 4045 Devon Drive, Indianapolis, IN 46226 (US). HALL, Steven, Edward [US/US]; 102 Nuttal Place, Chapel Hill, NC 27514 (US). HERRON, David, Kent [US/US]; 5945 Andover Road, Indianapolis, IN 46220 (US). JOSEPH, Sajan [US/US]; 625 Canal View Drive, Apartment I, Indianapolis, IN 46202 (US). KLIMKOWSKI, Valentine, Joseph [US/US]; 4504 Camelot Lane, Carmel, IN 46033 (US). MASTERS, John, Joseph [US/US]; 12047 Flint Stone Court, Fishers, IN 46038 (US). MENDEL, David [US/US]; 11348 Woods Bay Lane, Indianapolis, IN 46236 (US). MILOT, Guy [CA/US]; 2 Farrington Street, Foxborough, MA 02035 (US). PINEIRO–NUNEZ, Marta, Maria [ES/US]; 364 Thornburg Parkway, Brownsburg, IN 46112 (US). SAWYER, Jason, Scott [US/US]; 5718 North Winthrop Avenue, Indianapolis, IN 46220 (US). SHUMAN, Robert, Theodore [US/US]; 180 Barcelona Road, Sedona, AZ 86336 (US). SMITH, Gerald, Floyd [US/US]; 1848 Lanarkshire Drive, Greenwood, IN 46143 (US). TEBBE, Anne, Louise [US/US]; 6202 North Sherman Drive, Indianapolis, IN 46220 (US). TINSLEY, Jennifer, Marie [US/US]; 4542 State Road 39 North, Martinsville, IN 46151 (US). WEIR, Leonard, Crayton [US/US]; 6520 Englehardt Drive, Raleigh, NC 27613 (US). WIKEL, James, Howard [US/US]; 4068 Sunshine Way, Greenwood, IN 46142 (US). WILEY, Michael, Robert [US/US]; 7725 Langwood Drive, Indianapolis, IN 46268 (US). YEE, Ying, Kwong [US/US]; 5127 Briarstone Trace, Carmel, IN 46033 (US).

(74) Agents: JACKSON, Thomas, E. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

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(54) Title: ANTITHROMBOTIC AMIDES

(57) Abstract

This application relates to a compound of formula (I) (or a pharmaceutically acceptable salt thereof) as defined herein, pharmaceutical compositions thereof, and its use as an inhibitor of factor Xa, as well as a process for its preparation and intermediates therefor.

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ANTITHROMBOTIC AMIDES

This application claims the benefit of U.S. Provisional Application No. 60/113,778, filed 23 December 1998.

This invention relates to antithrombotic aromatic amides which demonstrate activity as inhibitors of factor Xa and, accordingly, which are useful anticoagulants in mammals. In particular it relates to aromatic amides having high anticoagulant activity, and antithrombotic activity. Thus, this invention relates to new amides which are inhibitors of factor Xa, pharmaceutical compositions containing the amides as active ingredients, and the use of the amides as anticoagulants for prophylaxis and treatment of thromboembolic disorders such as venous thrombosis, pulmonary embolism, arterial thrombosis, in particular myocardial ischemia, myocardial infarction and cerebral thrombosis, general hypercoagulable states and local hypercoagulable states, such as following angioplasty and coronary bypass operations, and generalized tissue injury as it relates to the inflammatory process. In addition, the antithrombotic agents are useful as anticoagulants in *in vitro* applications.

The process of blood coagulation, thrombosis, is triggered by a complex proteolytic cascade leading to the formation of thrombin. Thrombin proteolytically removes activation peptides from the Aα-chains and the Bβ-chains of fibrinogen, which is soluble in blood plasma, initiating insoluble fibrin formation. The formation of thrombin from prothrombin is catalyzed by factor Xa.

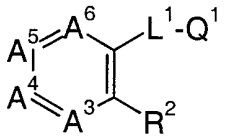
Anticoagulation currently is achieved by the administration of heparins and coumarins. Parenteral pharmacological control of coagulation and thrombosis is based on inhibition of thrombin through the use of heparins. Heparins act indirectly on thrombin by accelerating the inhibitory effect of endogenous antithrombin III (the main physiological inhibitor of thrombin). Because antithrombin III levels vary in plasma and because clot-bound thrombin seems resistant to this indirect mechanism, heparins can be an ineffective treatment. Because coagulation assays are believed to be associated with efficacy and with safety, heparin levels must be monitored with coagulation assays (particularly the activated partial thromboplastin time (APTT) assay). Coumarins impede the generation of thrombin by blocking the posttranslational gamma-carboxylation in the synthesis of prothrombin and other proteins of this type. Because of their mechanism of action, the effect of coumarins can only develop slowly, 6-24 hours after administration. Further, they are not selective anticoagulants. Coumarins also require monitoring with coagulation assays (particularly the prothrombin time (PT) assay).

Recently, interest has grown in small synthetic molecules which demonstrate potent direct inhibition of thrombin and factor Xa. See, Joseph P. Vacca (Annette M. Doherty Section Editor), Annual Reports in Medicinal Chemistry, (1998), 33, 81-90.

Although the heparins and coumarins are effective anticoagulants, there still exists a need for anticoagulants which act selectively on factor Xa or thrombin, and which, independent of antithrombin III, exert inhibitory action shortly after administration, preferably by an oral route, and do not interfere with lysis of blood clots, as required to maintain hemostasis.

The present invention is directed to the discovery that the amides of the present invention, as defined below, are potent inhibitors of factor Xa which may have high bioavailability following oral administration.

According to the invention there is provided a compound of formula I



I

(or a pharmaceutically acceptable salt thereof) wherein:

A^3, A^4, A^5 and A^6, together with the two carbons to which they are attached, complete a substituted benzene in which A^3 is CR^3, A^4 is CR^4, A^5 is CR^5, and A^6 is CR^6; wherein

R^3 is hydrogen;

one of R^4 and R^5 is hydrogen, methyl, fluoro, chloro, R^fO_2C-, or R^gNH-;

the other of R^4 and R^5 is hydrogen; and

R^6 is hydrogen;

in which R^f is hydrogen, (1-4C)alkyl or benzyl; R^g is hydrogen, or R^hSO_2-; and R^h is (1-4C)alkyl or dimethylamino; or

A^3, A^4, A^5 and A^6, together with the two carbons to which they are attached, complete a substituted heteroaromatic ring in which

(a) one of A^3, A^4, A^5 and A^6 is N, and each of the others is CR^3, CR^4, CR^5 or CR^6, respectively; or

(b) two non-adjacent residues of A^3, A^4, A^5 and A^6 are each N, and each of the others is CR^3, CR^4, CR^5 or CR^6, respectively; wherein

each of R^3, R^4, R^5 and R^6 is independently hydrogen or methyl, or one of R^3, R^4, R^5 and R^6 attached to a carbon

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