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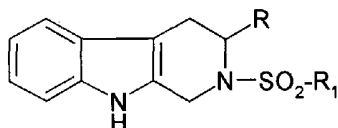
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(54) Title: 2-ALKYL/ARYL SULPHONYL-1,2,3,4-TETRAHYDRO-9H-PYRIDO (3,4-B) INDOLE-3-CARBOXYLIC ACID ESTERS/AMIDES USEFUL AS ANTITHROMBOTIC AGENTS



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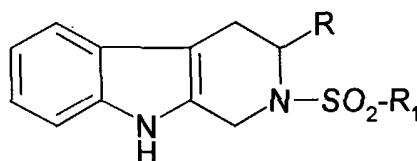
(57) Abstract: The present invention relates to antithrombotic compounds 2-alkyl aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido(3,4-b) indole -3- carboxylic acid esters /amides, pharmaceutically acceptable salts and compositions thereof to be used in the treatment of intravascular thrombosis such as myocardial ischemia and stroke. The compound has the following general structure (I) wherein R represents methyl ester or amide and R₁ represents alkyl, aryl and heteroaryl moiety.

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2-ALKYL/ARYL SULPHONYL-1,2,3,4-TETRAHYDRO-9H-PYRIDO (3,4-b) INDOLE-3-CARBOXYLIC ACID ESTERS/AMIDES USEFUL AS ANTITHROMBOTIC AGENTS

Field of the invention

The present invention relates to antithrombotic compounds 2-alkyl aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido(3,4-b) indole-3-carboxylic acid esters/amides, pharmaceutically acceptable salts and compositions thereof useful in treatment of intravascular thrombosis such as myocardial ischemia and stroke. The compound has the following general structure



Formula 1:

wherein R represents methyl ester or amide and R₁ represents alkyl, aryl and heteroaryl moiety. The present invention particularly relates to novel compounds 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides, which are potent antithrombotic agents and can be useful in treatment of intravascular thrombosis, such as myocardial ischemia and stroke. The present invention also relates to processes for preparing the said novel compounds. More particularly the present invention relates to 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides, processes for preparing the said compounds and to their use in medicine.

BACKGROUND OF THE INVENTION AND PRIOR ART

Cardiovascular diseases associated with intravascular thrombosis are the most common cause of death in both developed and developing countries. Arterial and venous thromboses are the principal causes for the evolution of myocardial infarction, thromboembolic stroke and deep vein thrombosis. Approximately three million individuals die each year in the United States only from venous (deep vein thrombosis and pulmonary embolism) or arterial thrombosis (acute myocardial infarction and unstable angina).

Initiation of thrombosis is a complex process. The final event i.e. the thrombus formation, however, is primarily due to the activation of platelets and coagulation cascade. Clinical and experimental studies indicate that abnormalities in the normal blood flow, activation of platelets, coagulation cascade or fibrinolysis contribute to the pathogenesis of intravascular thrombosis/thromboembolism. Though the treatment strategy for thrombosis has improved with newer diagnostic and surgical tools but effective antithrombotic therapy with minimal side effects still poses a challenge to scientists around the globe.

Antithrombotic agents have been researched and developed for use in treating cardiovascular and other diseases. Presently established antithrombotic agents include heparin, coumarin, and aspirin. There are, however, limitations with these agents. For example, both heparin¹ and coumarin² have a highly-variable dose-related response, and their anticoagulant effects must be closely monitored to avoid a risk of serious bleeding. The erratic anticoagulant response of heparin is likely due to its propensity to bind non-specifically to plasma proteins. Aspirin has a limited efficacy and at high doses presents a risk of gastrointestinal bleeding.

Tissue plasminogen activators^{3,4}, platelet GPIIb/IIIa antagonists⁵, ADP receptor antagonists⁶, are also being currently used to treat thrombosis, however, these drugs have some inherent problems and limitations. Therefore, new search is taken up to develop next generation anti-thrombotic agents such as direct thrombin inhibitors⁷, tissue factor pathway inhibitors⁸, Factor Xa inhibitors⁹, collagen antagonists¹⁰ and gene therapy. The search of a potent orally active and specific anti-thrombotic agent with minimal danger of bleeding or unrelated side effects is thus an area of interest. Moreover, the high cost of anticoagulant and antithrombotic therapy necessitates the search for efficacious new chemical entities.

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OBJECTS OF THE INVENTION

The main object of the invention is to provide novel molecules 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides that exhibit better therapeutic efficacy to treat intravascular thrombosis, myocardial ischemia and stroke over the existing antithrombotic agents.

It is another object of the invention to provide novel 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid esters/amides exhibiting activity against intravascular thrombosis for which there is/are no/few agent/agents available till date.

It is another object of the invention to provide 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides as therapeutic agents for diseases arising out of alterations/impairment in intravascular thrombosis leading to myocardial ischemia and stroke.

It is another object of the invention to provide a process for preparing novel 2-alkyl/ aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides.

It is another object of the invention to provide a pharmaceutical composition comprising 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides and pharmaceutically acceptable additive(s) and a process for preparing such composition.

It is another object of the invention to provide for the use of compounds of the present invention in the treatment or prevention of primary arterial thrombotic complications of atherosclerosis such as thrombotic stroke, peripheral vascular disease, and myocardial infarction without thrombolysis.

It is another object of the invention to provide for the use of compounds of the invention for the treatment or prevention of arterial thrombotic complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery.

It is another object of the invention to provide for the use of the compounds of the invention for the treatment or prevention of thrombotic complications of surgical or mechanical damage such as tissue salvage following surgical or accidental trauma, reconstructive surgery including skin flaps, and "reductive" surgery such as breast reduction.

It is another object of the invention to provide for the use of compounds of the present invention for the prevention of mechanically-induced platelet activation in vivo such as cardiopulmonary bypass (prevention of microthromboembolism), prevention of mechanically-induced platelet activation in vitro such as the use of the compounds in the preservation of blood products, e.g. platelet concentrates, prevention of shunt occlusion such as renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis and organ graft rejection.

It is another object of the invention to provide for the use of compounds of the present invention for the indicating with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombocytopenia and pre-eclampsia/eclampsia.

It is another object of the invention to provide for the use of compounds of the present invention for the treatment or prevention of venous thrombosis such as deep vein thrombosis, veno-occlusive disease, hematological conditions such as thrombocythemia and polycythemia, and migraine.

It is another object of the invention to provide for the use of compounds of the present invention in treatment of unstable angina, coronary angioplasty and myocardial infarction.

It is another object of the invention to provide for the use of compounds of the present invention for adjunctive therapy in the prevention of coronary arterial thrombosis during the management of unstable angina, coronary angioplasty and acute myocardial infarction, i.e. perithrombolysis.

It is another object of the invention to provide for a method of treating mammals to alleviate the pathological effects of atherosclerosis and arteriosclerosis, acute MI, chronic stable angina, unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts.

It is another object of the invention to provide for the use of compounds of the present invention *in vitro* to inhibit the aggregation of platelets in blood and blood products, e.g. for storage, or for *ex vivo* manipulations such as in diagnostic or research use.

It is another object of the invention to provide for the use of compounds of the present invention for the to inhibit platelet aggregation and clot formation in a mammal, especially a human, which comprises the internal administration.

It is another object of the invention to provide for the use of compounds of the present invention for the treatment of chronic or acute states of hyperaggregability, such as disseminated intravascular coagulation (DIC), septicemia, surgical or infectious shock, post-operative and post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta, thrombotic thrombocytopenic purpura (TTP), snake venom and immune diseases, which are likely to be responsive to these compounds.

It is another object of the invention to provide for the use of compounds of the present invention in a method for inhibiting the reocclusion of an artery or vein following fibrinolytic therapy, which comprises internal administration of compound and a fibrinolytic agent.

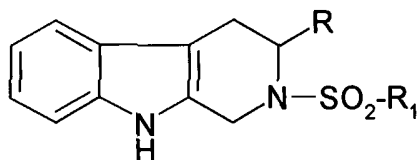
It is another object of the invention to provide for the use of compounds of the present invention for extracorporeal circulation, which is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit.

It is another object of the invention to provide for the use of compounds of the present invention for prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures.

To achieve the above and other objects the present invention provides novel pharmacologically active compounds, specifically new 2-alkyl aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido(3,4-b) indole -3- carboxylic acid esters /amides which are used as potential therapeutic agents for intravascular thrombosis, myocardial ischemia and stroke and other disorders as mentioned above.

SUMMARY OF THE INVENTION

Accordingly the present invention relates to 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid esters/ amides having formula 1:



Formula 1

wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety.

In one embodiment of the invention, the compound comprises at least one of:

- a. 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- b. 2[2,4,6, trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- c. 2[2,nitrobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- d. 2[1-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- e. 2-4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- f. 2[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester

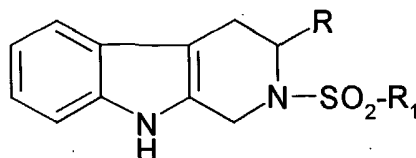
- g. 2-[dansyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- h. 2[2,4,6 tri isopropyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- i. 2[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- j. 2[2-tri floro methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- k. 2[methyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- l. 2-[2-napthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- m. 2[benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- n. 2[4-methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester

In other embodiment the compound includes at least one of:

- o. 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- p. 2[-4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- q. 2[-1-naphtylsulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- r. 2[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- s. 2[-4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- t. 2[methane sulphonyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- u. 2[3-nitro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- v. 2[2,4,6 trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide

w. 2-[2-napthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide

The present invention also provides a process for synthesis of 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid esters/amides of formula 1:



Formula 1

wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety, the process comprising condensing an alkyl or aryl sulphonyl chloride wherein aryl includes substituted phenyl substituted by group selected from the group consisting of hydrogen, halogens, alkyl and alkoxy, substituted naphthyl substituted by group selected from the group consisting of hydrogen and dimethyl amino; and heteroaryl like quinoline with dimethyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate Formula 2 in the presence of a base and an organic solvent at temperature ranging from 30°C to 120°C for 8 to 24 hours to produce the corresponding 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters.

In another embodiment, the invention relates to a process for the synthesis of the above compounds by condensing an alkyl or aryl sulphonyl chloride where in aryl includes, substituted phenyl by groups like hydrogens, halogens, alkyl, alkoxy etc., substituted naphthyl by hydrogen, di methyl amino, and heteroaryl like quinoline with dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide formula 3 in the presence of a base and an organic solvent at temperature ranging from 30°C to 120°C for 8 to 24 hours to produce the corresponding 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amides.

In another embodiment, the invention relates to a process for the synthesis of the above compounds wherein 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters is treated with methanolic ammonia for 24 to 48 hours hrs to obtain the corresponding 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amides.

In another preferred embodiment, the synthesis of 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/amide of formula 1 includes the presence of one of the organic solvent selected from a group of acetone, DMF, THF,

dioxane, a base including at least one of TEA, K_2CO_3 , Na_2CO_3 , pyridine and a temperature of about 30°C to 120°C for 8 to 24 hours.

In another embodiment, the molar ratios of the substituted sulphonyl chloride to dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate/ dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole-3-amide is about 1:2. In yet another preferred embodiment the organic solvents include acetone, DMF, THF, dioxane and the organic solvent is present about 0.8-2.2 ml per mmol.

In another embodiment, the molar ratio of the base to the dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate / dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide is about 1:4.

The invention also relates to pharmaceutical compositions having the compound of formula 1 described above in a mixture with a pharmaceutically acceptable carrier. The invention further relates to a process for preparing the pharmaceutical composition by bringing the compound into association with a pharmaceutically acceptable additive.

The invention also relates to method of treating various diseases with the pharmaceutical compositions of the present invention. In one embodiment, the method involves treating intravascular thrombosis in mammals by administering to a patient in need thereof a therapeutically effective amount of the pharmaceutical composition. In one embodiment, the method involves treating myocardial ischemia in mammals, by administering to a patient in need thereof a therapeutically effective amount of the pharmaceutical composition. In one embodiment, the method involves treating stroke in mammals, by administering to a patient in need thereof a therapeutically effective amount of the pharmaceutical composition.

In a preferred embodiment, the diseases treated are selected to be intravascular thrombosis, myocardial ischemia and stroke or a combination thereof. In another preferred embodiment the intravascular diseases are selected to include as mentioned above. In another preferred embodiment halogen of the compound is selected from the group of chlorine, bromine fluorine and iodine, and mixtures thereof, the alkoxy is selected to be a C_1 - C_{10} oxy, the alkyl is selected to be C_1 - C_{10} alkyl, and the heteroaryl is selected to be a C_4 - C_{10} heteroaryl.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphical representation of the effect of compound (i) on human platelet aggregation.

DETAILED DESCRIPTION OF THE INVENTION

The compound of the present invention achieves the following objects:

- i) providing novel molecules 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides that may exhibit better *therapeutic efficacy to treat intravascular thrombosis, myocardial ischemia and stroke over the existing antithrombotic agents.*
- ii) providing novel 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides exhibiting activity against intravascular thrombosis for which there is/are no/few agent/agents available till date to the best of the applicants knowledge.
- iii) providing 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides as therapeutic agents for the diseases arising out of alterations/impairment in intravascular thrombosis leading to myocardial ischemia and stroke.
- iv) providing processes for preparing novel 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides.
- v) providing a pharmaceutical composition comprising 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides. And pharmaceutically acceptable additive (s) and a process for preparing such composition.
- vi) providing for use of the compounds in the treatment or prevention of primary arterial thrombotic complications of atherosclerosis such as thrombotic stroke, peripheral vascular disease, and myocardial infarction without thrombolysis.
- vii) providing for the use of the compounds of the invention for the treatment or prevention of arterial thrombotic complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery.
- viii) providing for the use of the compounds of the invention for the treatment or prevention of thrombotic complications of surgical or mechanical damage such as tissue salvage following surgical or accidental trauma, reconstructive surgery including skin flaps, and "reductive" surgery such as breast reduction.
- ix) providing for the use of the compounds of the invention for the prevention of mechanically-induced platelet activation in vivo such as cardiopulmonary bypass (prevention of microthromboembolism), prevention of mechanically-induced

platelet activation *in vitro* such as the use of the compounds in the preservation of blood products, e.g. platelet concentrates, prevention of shunt occlusion such as renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis and organ graft rejection.

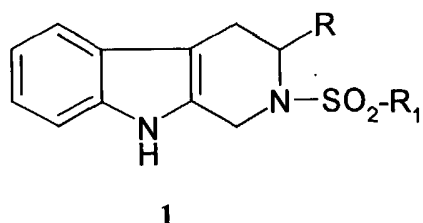
- x) providing for the use of the compounds of the invention as indicators with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombocytopenia and pre-eclampsia/eclampsia.
- xi) providing for the use of the compounds of the invention for the treatment or prevention of venous thrombosis such as deep vein thrombosis, veno-occlusive disease, hematological conditions such as thrombocythemia and polycythemia, and migraine.
- xii) providing for the use of the compounds of the invention for the treatment of unstable angina, coronary angioplasty and myocardial infarction.
- xiii) providing for the use of the compounds of the invention for the adjunctive therapy in the prevention of coronary arterial thrombosis during the management of unstable angina, coronary angioplasty and acute myocardial infarction, i.e. perithrombolysis. Agents commonly used for adjunctive therapy in the treatment of thrombotic disorders can be used, for example heparin and/or aspirin, just to mention a few.
- xiv) providing for the use of the compounds of the invention for a method of treating mammals to alleviate the pathological effects of atherosclerosis and arteriosclerosis, acute MI, chronic stable angina, unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts.
- xv) providing for the use of the compounds of the invention for the *in vitro* to inhibit the aggregation of platelets in blood and blood products, e.g. for storage, or for *ex vivo* manipulations such as in diagnostic or research use. This invention also provides a method of inhibiting platelet aggregation and clot formation in a mammal, especially a human, which comprises the internal administration.

- xvi) providing for the use of the compounds of the invention for treatment of chronic or acute states of hyperaggregability, such as disseminated intravascular coagulation (DIC), septicemia, surgical or infectious shock, post-operative and post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta, thrombotic thrombocytopenic purpura (TTP), snake venom and immune diseases, which are likely to be responsive to these compounds.
- xvii) providing for the use of the compounds of the invention in a method for inhibiting the reocclusion of an artery or vein following fibrinolytic therapy, which comprises internal administration of compound and a fibrinolytic agent. When used in the context of this invention, the term fibrinolytic agent is intended to mean any compound, whether a natural or synthetic product, which directly or indirectly causes the lysis of a fibrin clot. Plasminogen activators are a well known group of fibrinolytic agents. Useful plasminogen activators include, for example, anistreplase, urokinase (UK), pro-urokinase (pUK), streptokinase (SK), tissue plasminogen activator (tPA) and mutants, or variants thereof, which retain plasminogen activator activity, such as variants which have been chemically modified or in which one or more amino acids have been added, deleted or substituted or in which one or more functional domains have been added, deleted or altered such as by combining the active site of one plasminogen activator or fibrin binding domain of another plasminogen activator or fibrin binding molecule.
- xviii) providing for use of the compounds of the invention for extracorporeal circulation, which is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Platelets released from artificial surfaces show impaired hemostatic function. Compounds of the invention can be administered to prevent adhesion.
- xix) providing for the use of the compounds of the invention for other applications including prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures.

To achieve the above and other objects the present invention provides novel pharmacologically active compounds, specifically new 2-alkyl aryl sulphonyl-1,2,3,4-

tetrahydro-9H-pyrido(3,4-b) indole -3- carboxylic acid esters /amides which are used as potential therapeutic agents for intravascular thrombosis, myocardial ischemia and stroke and other disorders as mentioned above.

The compound of the invention has the formula 1



wherein R represents methyl ester or amide and R₁ represents alkyl, aryl and heteroaryl moiety. Representative compounds include:

- a. 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- b. 2[2,4,6, trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- c. 2[2,nitrobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- d. 2[1-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- e. 2-4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- f. 2[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- g. 2-[dansyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- h. 2[2,4,6 tri isopropyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- i. 2[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- j. 2[2-tri floro methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- k. 2[methyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester

- l. 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- m. 2[benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- n. 2[4-methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester
- o. 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- p. 2[-4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- q. 2[-1-naphthylsulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- r. 2[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- s. 2[-4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- t. 2[methane sulphonyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- u. 2[3-nitro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- v. 2[2,4,6 trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide
- w. 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide

In the specification in formula 1, R designates methylester and amide R₁ designates alkyl group includes methyl, aryl group includes naphthyl and phenyl group substituted by alky, alkoxy, halogen groups and heteroaryl group includes quinoline.

A preferred group of compound comprises those in which R=methyl ester/ amide and R₁= methyl, benzene, 4-methyl benzene, 2-naphthalene, 2,5 dichlorobenzene, 2,4,6, trimethyl benzene, 2,nitrobenzene, 1-naphthyl, 4-metoxy benzene, 8-quinoline, dansyl, 2,4,6 tri isopropyl benzene, 4-floro benzene, tri floro methyl benzene.

The invention also provides a pharmaceutical composition comprising a compound of formula 1 in a mixture with a pharmaceutically acceptable conventional carriers and a process for the preparation of a pharmaceutical composition which comprises bringing a

compound of the formula 1 into association with a pharmaceutically acceptable conventional carrier.

In addition, the invention provides a method of treating intravascular thrombosis and myocardial ischemia and stroke in mammals, that comprises administering to a subject in need thereof an effective amount of a compound of formula 1.

The compounds of the invention are useful in therapy, particularly in the prevention of platelet aggregation. The compounds of the invention have shown to possess antithrombotic activity in different test models. The compounds of the present invention are thus useful as anti-thrombotic agents, and are thus useful in the treatment or prevention of unstable angina, coronary angioplasty and myocardial infarction. The compounds prevent intravascular thrombosis, its progression or recurrence. They may be useful as additive or synergistic therapy to reduce the incidence of myocardial ischemia, acute myocardial infarction, unstable angina, during and after angioplasty or stent replacement, prevent cerebrovascular events, secondary prevention of stroke and pulmonary thromboembolism. These agents may also be used in combination with antithrombotic drugs and anticoagulants in patients undergoing angioplasty or stenting for coronary artery disease and also in conjunction with fibrinolysis protocols.

Diseases or conditions associated with platelet aggregation are disorders or procedures characterized by thrombosis, primary arterial thrombotic complications of atherosclerotic disease, thrombotic complications of interventions of atherosclerotic disease, thrombotic complications of surgical or mechanical damage, mechanically-induced platelet activation, shunt occlusion, thrombosis secondary to vascular damage and inflammation, indications with a diffuse thrombotic/platelet consumption component, venous thrombosis, coronary arterial thrombosis, pathological effects of atherosclerosis and arteriosclerosis, platelet aggregation and clot formation in blood and blood products during storage, chronic or acute states of hyper-aggregability, reocclusion of an artery or vein following fibrinolytic therapy, platelet adhesion associated with extracorporeal circulation, thrombotic complications associated with thrombolytic therapy, thrombotic complications associated with coronary and other angioplasty, or thrombotic complications associated with coronary artery bypass procedures.

Disorders or procedures associated with thrombosis are unstable angina, coronary angioplasty, or myocardial infarction; said primary arterial thrombotic complications of atherosclerosis are thrombotic stroke, peripheral vascular disease, or myocardial infarction without thrombolysis; said thrombotic complications of interventions of atherosclerotic

disease are angioplasty, endarterectomy, stent placement, coronary or other vascular graft surgery; said thrombotic complications of surgical or mechanical damage are associated with tissue salvage following surgical or accidental trauma, reconstructive surgery including skin flaps, or reductive surgery; said mechanically-induced platelet activation is caused by *cardiopulmonary bypass resulting in microthromboembolism and storage of blood products*; said shunt occlusion is renal dialysis and plasmapheresis; said thromboses secondary to vascular damage and inflammation are vasculitis, arteritis, glomerulonephritis or organ graft rejection; said indications with a diffuse thrombotic/platelet consumption component are disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, *heparin-induced thrombocytopenia, or pre-eclampsia/eclampsia*; said venous thrombosis are deep vein thrombosis, veno-occlusive disease, hematological conditions, or migraine; and said coronary arterial thrombosis is associated with unstable angina, coronary angioplasty or acute myocardial infarction.

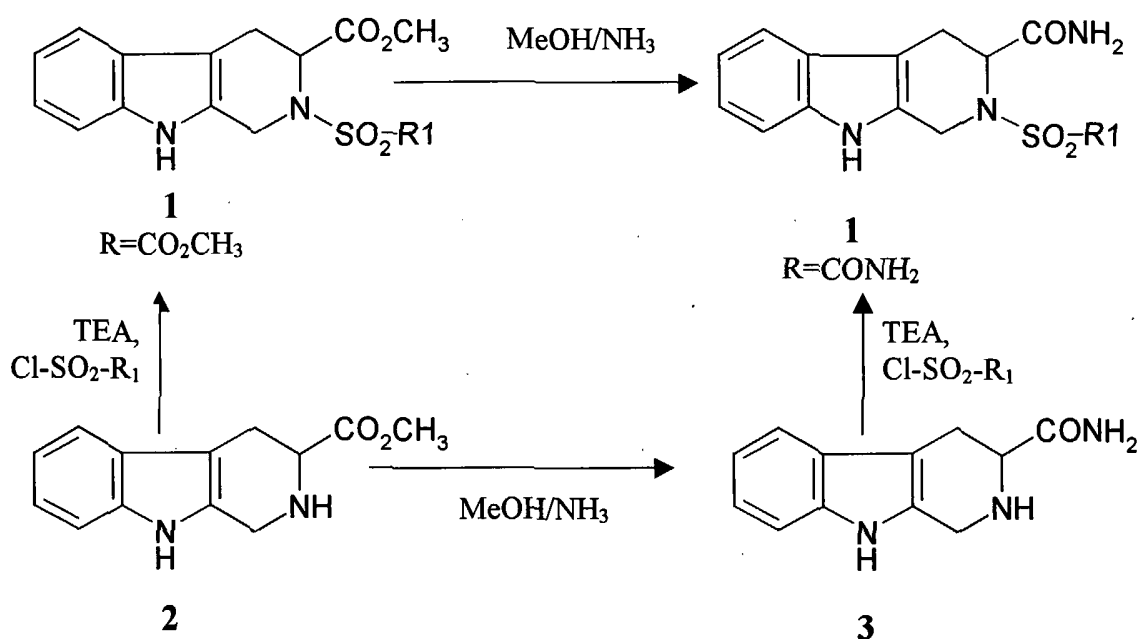
Pathological effects of atherosclerosis and arteriosclerosis are arteriosclerosis, acute myocardial infarction, *chronic stable angina, unstable angina, transient ischemic attacks*, strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, or anastomosis of vascular grafts; said chronic or acute states of hyper-aggregability is caused by DIC, septicemia, surgical or infectious shock, post-operative trauma, post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, *abruptio placenta, thrombotic thrombocytopenic purpura, snake venom or immune diseases*. A method of preparation of the inventive compounds consists of the condensation of different alkyl/aryl sulphonyl chlorides with dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate /dl -1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- amide to get the compounds of formula 1 (2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides) as shown in scheme 1 of the accompanying drawings.

The compounds of the present invention can be used as pharmaceutical compositions comprising compounds of the present invention with a suitable pharmaceutical carrier. Preferably, these compositions are used to produce intravascular antithrombotic activity and contain an effective amount of the compounds useful in the method of the invention. The most preferred compounds of the invention are

1. 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

2. 2[-4-methoxy benzene sulfonyl]-1, 2, 3, 4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
3. 2-[2-napthalene sulfonyl]-1, 2, 3, 4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

The reaction leading to 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters/ amides is shown in scheme 1 which represents the reaction sequence resulting in 2-alkyl aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido(3,4-b) indole -3- carboxylic acid esters /amides, according to the present invention.



Scheme 1

It will be noted that according to the foregoing scheme the methods that lead to the synthesis of 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters /amides of formula 1 as shown earlier are as follows

The method involves in the synthesis of the compounds of formula 1 wherein R is methyl ester comprises of condensation of an alkyl or aryl sulphonyl chloride with dimethyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate of formula 2 in the presence of a base selected from trimethylamine, potassium carbonate, pyridine in organic solvent selected from THF, DMF, acetone, dioxane at a temperature ranging from 30°C to 120°C for 8 to 24 hours to produce the corresponding 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters.

Two methods were used for the synthesis of 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amides.

The first method relates to a process for the synthesis of the above compounds by condensing a alkyl or aryl sulphonyl chloride with dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide formula 3 in the presence of a base selected from trimethylamine and an organic solvent DMF at temperature 30°C to 120°C for 8 to 12 hours to produce the corresponding 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amide of formula 1 wherein R=CONH₂.

The second method involves 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid esters synthesized as described previously, treated with methanolic ammonia for 24-32 hours at 32°C to obtain 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amide.

The compounds of the invention show marked antithrombotic activity and can be used as therapeutic agents for the treatment of intravascular thrombosis, myocardial ischemia and stroke as shown for instance by the following data of the compounds

- (i) 2-[2,5-dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3- carboxylic acid ester,
- (ii) 2-[4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3- carboxylic acid amide.
- (iii) 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide,

Pharmacological activity

(1) Methods:

1.1 Effect on mouse thrombosis: Pulmonary thromboembolism was induced by following a method of Diminno and Silver ⁽¹⁾. Test compounds (30µM/Kg) or vehicle were administered orally 60 min prior to the thrombotic challenge. A mixture of collagen (150 µg/ml) and adrenaline (50µg/mL) was administered by the rapid intravenous injection into the tail vein to induce hind limb paralysis or death. A group of 10 animals were used to evaluate the effect of test compound, while 5 mice were used to assess effect of a standard drug, aspirin and a group of vehicle treated (n=5) mice was also used in each experiment.

% Protection was expressed as:

$$\frac{(P_{\text{control}} - P_{\text{test}})}{P_{\text{control}}} \times 100$$

P_{test} is the number of animals paralyzed/dead in the test compound-treated group, and P_{control} is the number of animals paralyzed/dead in vehicle treated group.

1.2 Effect on mouse-tail bleeding time: Mice tail bleeding time was performed by method of Dejna et al, ⁽²⁾. The tail 2mm from tip was incised and the blood oozed was soaked with filter paper till the bleeding stops. The time elapsed from the tip incision to the stoppage of bleeding was determined as the bleeding time. Test compound (30µM/kg), aspirin or vehicle was given orally 60 min prior to the tail incision. Each group consisted of 5 mice.

1.3 Evaluation of compounds on platelet aggregation: Platelet aggregation was monitored according to the protocol described earlier ⁽³⁾. Sprague Dawley rats (wt 250-300 gm) were anaesthetized with ether and blood (9 mL) was drawn from the heart into a plastic syringe containing 1 ml of 1.9% tri-

Sodium citrate: The blood was centrifuged at 275xg for 20 min and the platelet rich plasma (PRP) was collected. The remaining blood was further centrifuged at 1500g for 15 min at 20°C to obtain platelet poor plasma (PPP). The platelet count in the PRP was adjusted to 2×10^8 cells/ml by using PPP. Adenosine-5'-diphosphate (ADP), thrombin, collagen, calcium ionophore A23187 or phorbol myristate ester (PMA) induced aggregation was monitored on a dual channel aggregometer (Chrono-log, USA). The test compound was incubated with PRP for 5 min before the addition of aggregation inducing agent. Percent inhibition of the test compounds at various concentrations was calculated as follows:

$$\% \text{ Inhibition} = \left[\frac{\text{Aggregation}_{\text{vehicle}} - \text{Aggregation}_{\text{test}}}{\text{Aggregation}_{\text{vehicle}}} \right] \times 100$$

1.4 Evaluation of coagulation parameters: Blood was collected by cardiac puncture from ether-anaesthetized rat using a syringe containing 3.2% tri-sodium citrate (9:1,v/v). Plasma was obtained by centrifugation of citrated blood at 2500xg for 15 min at 20°C. Stock solutions of the test compounds were prepared freshly in DMSO and were diluted in DMSO. Thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (aPTT) were evaluated according to manufacturer's instructions supplied with kits (Stago, France) and measured by Coagulometer (Stago, France) ⁽⁴⁾. In each set of experiment effect of DMSO on these parameters was also assessed and was used to calculate change in TT, PT or aPTT.

1.5 Rabbit venous thrombosis model: Experiments were performed on New Zealand white strain rabbits (2-3kg) either sex. *Escherichia coli* LPS strain 1055:B5 (Sigma Chemicals, USA) was injected intravenously via ear vein (1µg/kg) ^(5, 6). Jugular veins on both sides were exposed and dissected free from surrounding tissue. Two loose sutures were placed 1.5 cm apart and all collateral veins were ligated. Four hours after *E. Coli* endotoxin injection (animal is watched for any signs of hypersensitivity reaction during this period), stasis was established and maintained for 45 min by tightening the two sutures. Ligated segments were

removed and opened longitudinally and the thrombus was carefully removed and weighed. Heparin sodium (Beparine from beef intestinal mucosa ≥ 140 USP units/mg; Biological E. Limited, India) was given in doses of (0.5, 0.25, 0.1 mg/kg i.v., via ear vein) 5 min before stasis.

1.6 Effect of compound (i) on human platelet aggregation in vitro.: Platelet aggregation study was done on human platelets following isolation of PRP from the human blood as described above (1.3). Aggregation was induced by collagen (10 μ g/ml, 5 μ g/ml), ADP (10 μ M) and thrombin (0.5U/ml).

2. Results: Effect of test compounds is indicated in the following table (1) against collagen and epinephrine induced thrombosis in mice, which is a primary screening model to detect antithrombotic efficacy of the test agents. At the same dose these compounds were also evaluated for their effect on the bleeding time in mouse (Table 1).

Since compound (i), (ii) and (iii) exhibited significant protection these compounds were further analysed in greater details for the anti-thrombotic activity in various test systems, as indicated below.

Effect on venous thrombosis model in rabbit: The selected compounds were evaluated at 10 μ M/Kg and 30 μ M/kg dose for their efficacy against stasis induced thrombosis in LPS treated rabbits. (i) was found to be most effective as it inhibited thrombus formation significantly at both 30 and 10 μ M/Kg, while n and a inhibited thrombus formations only at 30 μ M/Kg. heparin was used as standard drug in this model and the results obtained are shown in the Table 2.

Ex vivo effect of selective compounds on rat platelet aggregation: Blood was collected in sodium citrate to obtain PRP and evaluate the *ex vivo* effect of selective compounds ((i), (ii), (iii) at 30 μ M/kg administered by the ip route) against ADP, collagen, phorbol myristate ester (PMA) calcium ionophore (A23187), or thrombin induced aggregation. It was observed that all these compounds were consistent against collagen-induced platelet aggregation (Table 3). (iii) inhibited ADP(10 μ M), collagen (10 μ g/ml), PMA (1.5 μ M), and thrombin (0.64U/ml) induced platelet aggregation while no inhibition was found against calcium ionophore A23187 (2.5 μ g/ml) induced platelet aggregation. Compound (ii) inhibited only ADP (10 μ M), collagen (10 μ g/ml), PMA (1.5 μ M), and A23187 (2.5 μ g/ml) induced platelet aggregation however it did not inhibit thrombin (0.64U/ml) induced platelet aggregation. Compound(i) inhibited ADP (10 μ M), collagen (10 μ g/ml), and A23187 (2.5 μ g/ml) induced platelet aggregation but had no inhibitory effect against thrombin (0.64U/ml) and PMA (1.5 μ M) induced platelet aggregation.

Effect on clotting parameters: The selected compounds were also tested *in vitro* for their effect on thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (aPTT) at 100 µg/ml and 200 µg/ml *in vitro* (Table 4). The test compounds at 100 µg/ml had no significant effect of on these parameters. Some effect was though seen on PT at 200 µg/ml concentration, but the concentration seems to be quite high.

Effect of compound(i) on human platelet aggregation in human PRP *in vitro*: Since the compound(i) exhibited promising profile against venous thrombosis model in rabbits as well as in other test systems; it was therefore further studied for inhibition of aggregation in human platelet rich plasma (PRP). It was found to be a competitive inhibitor of collagen induced platelet aggregation, collagen (10 µg/ml) induced aggregation was not so significantly reduced in presence of compound(i), while response of low concentration of collagen (5 µg/ml) was reduced significantly (Fig 1).

Table 1: Antithrombotic Effect of the test compounds on mice model and bleeding time

Sl. no.	Compound No. (dose 30 µM/kg)	Antithrombotic activity (AT) (% protection)	Bleeding time (BT) % increase (1 hr)
	Control	0	-
1	A Compound(i)	60 ± 10 (n=4)	51 ± 14 (n=5)
2	b	20	31
3	c	0	18
4	d	20	0
5	e	0	13
6	f	20	25
7	g	20	0
8	h	0	0
9	i	0	0
10	j	56	150
11	k	50	0
12	o	40	31
13	p Compound(ii)	70 ± 10 (n=3)	33 ± 12 (n=3)
14	q	20	12
15	r	30	0
16	s	60	13
17	t	30	0
18	u	45	0
19	v	30	50
20	w Compound(iii)	70 ± 0 (n=3)	61 ± 16 (n=3)
	Aspirin (30mg/Kg)	38 ± 3 (n=24)	125 ± 6 (n=30)
	Indomethacin (10 mg/kg)	55 ± 15 (n=20)	-

n= number of groups

Number of mice used for AT testing were 10 in each group, while 5 mice were used in each group to evaluate BT. Values are mean ± SEM

Table 2: Effect of Test compounds on venous thrombosis model in rabbits:

Test compounds	10µM/Kg dose		30µM/Kg dose			
	Thrombus wt.	% Reduction	Thrombus wt.	% Reduction	Thrombus wt.	% Reduction
Control	43 ± 13					
(i)	26 ± 0	41	0.0 ± 0.0	100.0		
(ii)	79 ± 9	-67	5 ± 4	88		
(iii)	-	-	11 ± 5	57		
Heparin	0.5 mg/Kg dose		0.25 mg/Kg dose		0.1 mg/Kg dose	
	1 ± 0.2	98	2 ± 0.3	95	4 ± 0.5	91

Values are Mean ± s.d., Compound(i); n=2, Compound (ii); n=4, Compound (iii); n=4 [n is no. of observations in 2 or more animals at 10µM/Kg or 30µM/Kg p.o. administered 2 h prior to the stasis] or vehicle control [n=10 observations in five animals]. In heparin treated group n=6 observations for each dose in nine animals.

Table 3: Effect of Test compounds on the platelet aggregation

Aggregation Inducers	Compound(i)		Compound(ii)		Compound(iii)	
	% Aggregation	% Inhibition	% Aggregation	% Inhibition	% Aggregation	% Inhibition
ADP (10µM)	37 ± 4 n=12	17 ± 6 n=12	35 ± 5 n=8	26 ± 10 n=8	2 ± 0.4 n=4	94 ± 0.2 n=4
Thrombin (0.64U/ml)	45 ± 4 n=10	-9 ± 9 n=10	44 ± 10 n=4	4 ± 10 n=4	28 ± 3 n=6	40 ± 6 n=6
Collagen (10µg/ml)	22 ± 9 n=8	65 ± 13 n=8	5 ± 1 n=4	79 ± 7 n=4	2.5 ± 0 n=2	47 ± 13 n=2
A23187 (2.5µg/ml)	51 ± 4 n=8	11 ± 4 n=8	51 ± 5 n=6	54 ± 4 n=6	57 ± 6 n=4	-25 ± 2 n=4
PMA (1.5µM)	58 ± 6 n=6	-12 ± 9 n=6	44 ± 12 n=2	26 ± 0.3 n=2	38 ± 13 n=2	32 ± 5 n=2

n = number of experiments which consists of at least 6 or more observations

Table 4: Effect of test substances against clotting parameters

Compound	Compound (i)	Compound (ii)	Compound (iii)	Conc. (µg/ml)
	% Change			
Thrombin time (TT)	5 ± 5	9 ± 5	10 ± 4	100
	9 ± 5	9 ± 4	6 ± 1	200
Prothrombin time (PT)	19 ± 16	9 ± 5	-0.24 ± 0.8	100
	14 ± 3	14 ± 7	9 ± 0.2	200
Activated partial thromboplastin time (aPTT)	7 ± 5	13 ± 7	11 ± 4	100
	4 ± 3	11 ± 4	10 ± 8	200

Values are mean ± SEM (number of observation [n] = 3 in each case)

The following examples are provided by the way of illustration of the present invention.

Example 1: Preparation of 2-[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 2,5 dichlorobenzene sulphonyl chloride (0.541gm, 2.2mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml) during 15 min and was allowed to stir for 10hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[-2,5- dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3- carboxylic acid ester, crystallized with methanol, Yield= 0.650 gm (74.03%). m.p.=205°C. Mass (FAB) $m/z = 440 (M^+)$. IR (KBr cm^{-1}): 3412, 1730, 1600, 1446, 1343, 1271, 1162, 738. ^1H NMR (200 MHz, CDCl_3): δ 3.14-3.38 (m, 2H), δ 3.61 (s, 3H), δ 4.67-4.88 (m, 2H), δ 5.19 (d, 1H), δ 7.08-7.21 (m, 2H), δ 7.44- 7.49 (m, 3H), δ 7.79 (d, 1H), δ 8.16 (s, 1H). Molecular Formula = $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$.

Example 2: Preparation of 2-[-2,4,6, trimethyl benzenesulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 2,4,6, trimethyl benzene sulphonyl chloride (0.479 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stir for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[-2,4,6, trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3- carboxylic acid ester, crystallized with methanol, Yield= 0.521 gm (63.21%), m.p.= 160°C. Mass (FAB): $m/z = 413 (M^+)$. IR (KBr cm^{-1}): 3400, 2938, 1734, 1599, 1452, 1330, 1237, 1153, 738. ^1H NMR (200 MHz, CDCl_3): δ 2.29 (s, 3H), δ 2.63 (s, 6H), δ 3.05-3.39 (m, 2H), δ 3.64 (s, 3H), δ 4.50 (d, 1H), δ 4.79-4.93 (m, 2H), δ 6.95 (s, 2H), δ 7.05-7.20 (m, 2H), δ 7.45 (d, 1H), δ 7.78 (s, 1H). Molecular Formula = $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$.

Example 3: Preparation of 2[2, nitrobenzenesulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 2-nitrobenzenesulphonyl chloride (0.486 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml) during 15 min and was allowed to stir for 8 hours at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[-2, nitrobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-

carboxylic acid ester, crystallized with methanol, Yield= 0.42gm (50.6%), m.p.= 225-230°C. Mass (FAB) m/z =416 (M^+). IR (KBr cm^{-1}): 3424, 1743, 1598, 1363, 1229, 1166, 753. ^1H NMR (200 MHz, CDCl_3): δ 3.16-3.44(m, 2H), δ 3.55 (s, 3H), δ 4.83 (s, 2H), δ 5.20 (d, 1H), δ 7.04-7.19 (m, 2H), δ 7.33 (d, 1H), δ 7.45-7.47 (m, 1H), δ 7.69-7.79 (m, 3H), δ 8.10-8.18 (m, 1H). Molecular Formula= $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_6\text{S}$.

Example 4: Preparation of 2-[1-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 1-naphthylsulphonyl chloride (0.497 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stir for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[1-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield= 0.55gm (65%), m.p. =215°C. Mass (FAB) m/z =421 (M^+). IR (KBr cm^{-1}): 3402, 1736, , 1596, 1447, 1325, 1236, 1200, 1163, 733. ^1H NMR (200 MHz, CDCl_3): δ 3.09-3.29(m, 1H), δ 3.35-3.40(m, 4H), δ 4.76(s, 2H), δ 5.28(d, 1H), δ 7.03-7.19(m, 2H), δ 7.40-7.70(m, 5H), δ 7.90(d, 1H), δ 8.06 (d, 1H), δ 8.30 (d, 1H), δ 8.68 (d, 1H). Molecular Formula= $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$.

Example 5: Preparation of 2-[4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 4-methoxy benzene sulphonyl chloride (0.453 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stir for 8hours at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield=0.682gm (85.25%) m.p. =215°C. Mass (FAB) m/z =401 (M^+). IR (KBr cm^{-1}) 3426, 1748 , 1594, , 1450, 1344, 1256, 1155 , 741. ^1H NMR (200 MHz, CDCl_3): δ 3.05-3.37(m, 2H), δ 3.47(s, 3H), δ 3.84 (s, 3H), δ 4.59-4.86(m, 2H) δ 5.16(d, 1H), δ 6.92-7.46(m, 5H), δ 7.82 (d, 3H). Molecular Formula= $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$.

Example 6: Preparation of 2-[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 8-quinolinesulphonyl chloride (0.499 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml) during 15 min and was allowed to stir for 8 hours. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield=0.619gm (73.6%) , m.p.=235°C. Mass (FAB) $m/z = 422 (M^+)$. IR (KBr cm^{-1}) 3400, , 1733, 1621, 1564, 1446, 1327, 1213, 1161, 743. ^1H NMR (200 MHz, $CDCl_3$): δ 2.99-3.10 (m, 1H), δ 3.31-3.44 (m, 4H), δ 4.80-5.01 (m, 2H), δ 5.78 (d, 1H), δ 7.00-7.18 (m, 2H), δ 7.39-7.49 (m, 2H), δ 7.60- 7.80 (m, 2H), δ 8.02 (d, 1H), δ 8.20 (d, 1H), δ 8.56 (d, 1H), δ 9.00 (d, 1H). Molecular Formula = $C_{22}H_{19}N_3O_4S$.

Example 7: Preparation of 2-[dansyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 2-dansyl sulphonyl chloride (0.592 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stir for 8 hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[dansyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with acetone, Yield=0.364 gm (44.9%) m.p.=195°C

Mass (FAB) $m/z = 464 (M^+)$. IR (KBr cm^{-1}) : 3407, 1741, 1595, 1451, 1345, 1201, 1151, 744. ^1H NMR (200 MHz, $CDCl_3$) δ 2.85 (s, 6H), δ 3.08-3.18 (m, 1H), δ 3.33-3.45 (m, 4H), δ 4.71-4.77 (m, 2H), δ 5.28 (d, 1H), δ 7.10-7.16 (m, 3H), δ 7.39-7.58 (m, 3H), δ 7.75 (s, 1H), δ 8.29 (d, 2H), δ 8.51 (d, 1H). Molecular Formula = $C_{25}H_{25}N_3O_4S$.

Example 8: Preparation of 2-[2,4,6 tri isopropyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 2,4,6 tri isopropyl benzene sulphonyl chloride (0.664 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stir for 24 hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[2,4,6 tri isopropyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b]

indole-3-carboxylic acid ester, crystallized with acetone, Yield=0.310gm (31.25%) m.p.=200°C. Mass (FAB) $m/z = 497 (M^+)$. IR (KBr cm^{-1}): 3408, 2960, 1744, 1626, 1457, 1317, 1160, 1040, 934, 746. ^1H NMR (200 MHz, CDCl_3) δ 1.20-1.33(m, 18H), δ 2.81-2.98(m, 1H), δ 3.10-3.40(m, 2H), δ 3.65(s, 3H), δ 4.05-4.19(m, 2H), δ 4.45(d, 1H), δ 4.88(d, 1H), δ 5.12 (d, 1H), δ 7.05-7.17(m, 4H), δ 7.46 (d, 1H), δ 7.80 (s, 1H). Molecular Formula= $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_4\text{S}$.

Example 9: Preparation of 2-[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 4-floro benzene sulphonyl chloride (0.427gm, 2.2mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate (0.46gm, 2.0mmol) and dry triethylamine (0.56ml, 4.0mmol) in dry acetone (8ml). during 15 min and was allowed to stirr for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vaccum, the residue was triturated with water (20 ml) to get 2-[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with acetone, Yield=0.666gm (67.19%) m.p.=190°C. Mass (FAB) $m/z = 389 (M^+)$. IR (KBr cm^{-1}) 3430, 1748, 1591, 1489, 1344, 1228, 1156, 742. ^1H NMR (200 MHz, CDCl_3) δ 3.08-3.19 (m, 1H), δ 3.32-3.47(m, 4H), δ 4.59-4.88(m, 2H), δ 5.16 (d, 1H), δ 7.10-7.32(m, 4H), δ 7.45 (d, 1H), δ 7.83-7.90- (m, 3H). Molecular Formula= $\text{C}_{19}\text{H}_{17}\text{FN}_2\text{O}_4\text{S}$.

Example 10: Preparation of 2-[2-tri floro methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) 2-tri floro methyl benzene sulphonyl chloride (0.537 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stirr for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vaccum, the residue was triturated with water (20 ml) to get 2-[2-tri floro methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester., crystallized with acetone, Yield=0.524gm (59.8%), m.p.=136°C. Mass (FAB) $m/z = 439 (M^+)$ IR (KBr cm^{-1}) 3400, 1741, 1563, 1449, 1347, 1308, 1272, 1218, 1169, 771. ^1H NMR (200 MHz, CDCl_3) : δ 3.18-3.24 (m, 1H), δ 3.40-3.50(m, 1H), δ 3.56(s, 3H), δ 4.75 (s, 2H), δ 5.20 (d, 1H), δ 7.11-7.15 (m, 2H), δ 7.46-7.49(d, 1H), δ 7.68-7.91- (m, 4H), δ 8.21-8.24(m, 1H). Molecular Formula= $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_4\text{S}$.

Example 11: Preparation of 2-[methane sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

i) Methane sulphonyl chloride (0.18 ml, 2.4 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stir for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[methyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with acetone. Yield=0.480gm (77.9%), m.p. =198°C. Mass (FAB) m/z =309 (M^+). IR (KBr cm^{-1}), 3384, 3026, 1736, 1632, 1278, 1234, 1152, 1016, 746. ^1H NMR (200 MHz, Acetone): δ 2.91(s,3H), δ 2.97-3.35(m, 2H), δ 3.51(s,3H), δ 4.52-4.74(m,2H), δ 4.99 (d,1H), δ 6.85-7.00(m ,2H), δ 7.22 (d ,1H), δ 7.34 (d,1H), δ 10.00(s,1H). Molecular Formula= $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$.

Example 12: Preparation of 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester .

i) 2-naphthyl sulphonyl chloride (0.497 gm, 2.2 mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56ml, 4.0 mmol) in dry acetone (10ml) during 15 min and was allowed to stir for 12 hours at room temperature 32°C. The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to give 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield= 0.714gm (85%).

m.p-210°C. Mass (FAB) m/z=421 (M^+). IR (KBr cm^{-1}): 3418, 1748, 1594, 1451, 1362, 1158, 751. ^1H NMR (200 MHz, CDCl_3): δ 3.08-3.36(m, 5H), δ 4.68-4.95 (m,2H), δ 5.24 (d,1H), δ 7.05-7.18 (m,2H) , δ 7.42(d,1H), δ 7.60-7.63 (m,2H), δ 7.77-7.98 (m,5H), δ 8.45 (s,1H). Molecular Formula= $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$.

ii) 2-naphthyl sulphonyl chloride (0.272 gm, 1.2mmol) in dry acetone (3ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.23 gm, 1.0 mmol) and dry pyridine (0.97ml, 1.2 mmol) in dry acetone (10ml) during 15 min and was allowed to stir for 12 hours at room temperature (32°C). The reaction mixture was concentrated under vacuum, water (10ml) was added to the residue and extracted with chloroform (3×10 ml). The extract was dried over Na_2SO_4 and concentrated over reduced pressure. to give 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield=0.227 gm (54%), m.p-210°C.

- iii) 2-naphthyl sulphonyl chloride (0.272 gm, 1.2 mmol) in dry acetone (3ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate (0.23gm, 1.0 mmol) and K_2CO_3 (0.13 gm, 1.2 mmol) in dry acetone (10ml) during 15 min and was allowed to stir for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, water (10ml) was added to the residue and extracted with chloroform (3×10 ml). The extract was dried over Na_2SO_4 and concentrated over reduced pressure to give 2-[2-naphthalene sulfonyl]-1,2,3,4-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield=0.29gm. (68%) m.p-210°C.
- iv) 2-naphthyl sulphonyl chloride (0.272 gm, 1.2 mmol) in dry acetone (3ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate (0.23gm, 1.0 mmol) and dry triethylamine (0.12 ml, 1.2 mmol) in THF (5ml) during 15 min and was allowed to stir for 8 hours at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get obtain 2-[2-naphthalene sulfonyl]-1,2,3,4-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield=0.32 gm. (75%), m.p-210°C.
- v) 2-naphthyl sulphonyl chloride (0.272 gm, 1.2 mmol) in dry acetone (3ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate (0.23 gm, 1.0 mmol) and dry triethylamine. (0.12 ml, 1.2 mmol) in DMF (3ml) during 15 min and was allowed to stir for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (10 ml) then extracted with chloroform (3×10 ml). The extract was dried over Na_2SO_4 and concentrated over reduced pressure to give 2-[2-naphthalene sulfonyl]-1,2,3,4-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester to get obtain 2-[2-naphthalene sulfonyl]-1,2,3,4-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield=0.21gm. (50%), m.p-210°C
- vi) 2-naphthyl sulphonyl chloride (0.272 gm, 1.2 mmol) in dry acetone (3ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate 0.23 gm, 1.0 mmol) and dry triethylamine (0.12 ml, 1.2 mmol) dry dioxane (5ml) during 15 min and was allowed to stir for 8 hours at room temperature (32°C). Water (10ml) was added to the residue and extracted with chloroform (3×10 ml). The extract was dried over Na_2SO_4 and concentrated over reduced pressure to give 2-[2-naphthalene sulfonyl]-1,2,3,4-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with methanol, Yield=0.29gm. (70%), m.p-210°C

vii) 2-naphthyl sulphonyl chloride (0.272 gm, 1.2 mmol) in dry THF (3ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.23 gm, 1.0 mmol) and backed K_2CO_3 (0.13 gm, 1.2 mmol) in dry THF and was allowed to stir for 12 hours at 80°C temperature. The reaction mixture was concentrated under vacuum, water (8ml) was added to the residue and extracted with chloroform (3×5 ml). The extract was dried over Na_2SO_4 and concentrated over reduced pressure to give 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester which was purified by column chromatography over silica gel using methanol chloroform as eluent. Yield=0.20 gm (48%), m.p-210°C.

viii) 2-naphthyl sulphonyl chloride (0.272 gm, 1.2 mmol) in dry DMF (3ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.23 gm, 1.0 mmol) and backed K_2CO_3 (0.13 gm, 1.2 mmol) in dry DMF and was allowed to stir for 8 hours at 120°C temperature. The reaction mixture was concentrated under vacuum, water (8ml) was added to the residue and extracted with chloroform (3×8 ml). The extract was dried over Na_2SO_4 and concentrated over reduced pressure to give 2-[2-naphthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester which was purified by column chromatography over silica gel using methanol chloroform as eluent. Yield=0.170 gm (40%), m.p-210°C.

Example 13: 2[benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester

i) Benzene sulphonyl chloride (0.388gm, 2.2mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml). during 15 min and was allowed to stir for 8hrs. at room temperature (32°C). The reaction mixture was concentrated under vacuum, the residue was triturated with water (20 ml) to get 2-[benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with acetone. Yield=0.371gm (50%), m.p. =124°C. Mass (FAB) m/z =371 (M^+). IR (KBr cm^{-1}) : 3838, 3024, 1742, 1442, 1342, 1052, 746. ^1H NMR (200 MHz, $CDCl_3$): δ 3.04-3.42(m, 5H), δ 3.30-3.42(m, 4H), δ 4.61-4.89(m, 2H), δ 5.16(d, 1H), δ 7.05-7.19(m, 2H), δ 7.42-7.60(m, 4H), δ 7.83-7.91(m, 3H). Molecular Formula= $C_{19}H_{18}N_2O_4S$.

Example 14: 2-[4-methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester

i) 4-methyl benzene sulphonyl chloride (0.419gm, 2.2mmol) in dry acetone (5ml) was added to a stirred solution of dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-

carboxylate (0.46 gm, 2.0 mmol) and dry triethylamine (0.56 ml, 4.0 mmol) in dry acetone (8ml).during 15 min and was allowed to stirr for 8hrs. at room temperature(32°C). The reaction mixture was concentrated under vaccum, the residue was triturated with water (20 ml) to get 2-[4-methyl benzene sulphonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester, crystallized with acetone. Yield= 0.400gm (51%), m.p. =128°C. Mass (FAB) m/z =385 (M^+). IR (KBr cm^{-1}) : 3427, 1744, 1597, 1445, 1337, 1159, 1091, 1051, 1016, 935, 746. ^1H NMR (200 MHz, $CDCl_3$): δ 2.40(s, 3H), δ 3.05-3.45(m,5H), δ 4.60-4.87(m,2H), δ 5.15(d,1H), δ 6.96-7.46(m, 5H), δ 7.70-7.85(m,3H) . Molecular Formula= $C_{20}H_{20}N_2O_4S$.

Example 15: Preparation of 2-[2, 5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) 2,5 dichlorobenzene benzene sulphonyl chloride (0.590gm, 2.4mmol) in dry acetone(5ml) was added to a stirred solution of dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide (0.430 gm, 1.0mmol) and dry triethylamine (0.56 ml, 4.0mmol) in dry DMF(5ml).during 15 min and was allowed to stirr for 8hrs. at room temperature(32°C). Water was added to the reaction mixture and triturated to give 2-[2,5 dichlorobenzene benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide which was purified by column chromatography over silica gel using 2% methanol chloroform as eluent. Yield=0.400gm (47.17 %)

ii) 2-[2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester (0.220 gm, 0.5 mmol)was kept at room temperature (32°C) in methanolic ammonia(25ml) for 32 hours .The reaction mixture was then evaporated under vaccum to obtain to obtain 2-[2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide, crystallized in methanol chloroform solution(2:1) .Yield= 0.185gm (87.26%). m.p. =220°C. Mass (FAB) m/z = 425(M^+). IR (KBr cm^{-1}): 3456, 3332, 1693, 1602, 1450, 1337, 1160, 752. ^1H NMR (200 MHz, Acetone) δ 3.06-3.73 (m, 2H), δ 4.87(s, 2H), δ 4.97(d, 1H), δ 6.41(s, 1H), δ 7.01-6.84(m, 3H), δ 7.32-7.21(m, 2H), δ 7.60-7.48(m, 2H), δ 8.08-8.67(d,1H), δ 9.95(s,1H). Molecular Formula= $C_{18}H_{15}Cl_2N_3O_3S$.

Example 16: Preparation of 2-[4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) 4-methoxy benzene sulphonyl chloride (.495gm,2.4mmol) in dry acetone(5ml) was added to a stirred solution of dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide (0.430gm, 1.0 mmol) and dry triethylamine (0.56ml, 4.0 mmol) in dry DMF(5ml).during 15

min and was allowed to stir for 8hrs. at room temperature (32°C). Water was added to the reaction mixture and triturated to give 2-[4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide, which was purified by column chromatography over silica gel using 2% methanol chloroform as eluent. Yield=0.480gm (62.34%). m.p. =178-180°C

ii) 2-[4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester (0.200gm, 0.5mmol) was kept at room temperature (32°C) in methanolic ammonia (30ml) for 24 hrs. The reaction mixture was then evaporated under vacuum to obtain 2-[4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide, crystallized in methanol (5ml) Yield= 0.170gm (88%), m.p. =178-180°C. Mass (FAB) $m/z = 386 (M^+)$. IR (KBr cm^{-1}): 3375, 1698, 1595, 1495, 1447, 1342, 1256, 1151, 756. ^1H NMR (200 MHz, $CDCl_3$) δ 2.43-2.54(m, 1H), δ 3.43-3.77(s, 4H), δ 4.80-4.96(m, 3H), δ 6.81-6.86(d, 2H), δ 7.04-7.39(m, 6H), δ 7.67-7.72(d, 2H). Molecular Formula= $C_{19}H_{19}N_3O_4S$.

Example 17: Preparation of 2-[1-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) 2-[1-naphthylsulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester (0.210gm, 0.5mmol) was kept at room temperature (32°C) in methanolic ammonia (30ml) for 24 hrs. The reaction mixture was then evaporated under vacuum to obtain 2-[1-naphthylsulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide, Yield=0.174gm (85.7%). m.p. =145-150°C. Mass (FAB) $m/z = 406 (M^+)$. IR (KBr cm^{-1}) 3397, 1597, 1447, 1349, 1204, 1160, 799, 750. ^1H NMR (200 MHz, $CDCl_3$): δ 2.60-2.72 (m, 1H), δ 3.56 (d, 1H), δ 4.60-5.00 (m, 3H), δ 5.39(s, 1H), δ 6.61(s, 1H), δ 7.03-7.49 (m, 7H), δ 7.88(d, 1H), δ 8.06 (d, 1H), δ 8.30(d, 1H), δ 8.50(d, 1H). Molecular Formula= $C_{22}H_{19}N_3O_3S$.

Example 18: Preparation of 2-[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) 2-[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester (0.211gm, 0.5mmol) was kept at room temperature (32°C) in methanolic ammonia (30ml) for 48 hrs. The reaction mixture was then evaporated under vacuum to obtain 2-[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide. This was purified by column chromatography over silica gel using 2% methanol chloroform as eluent. Yield=0.130gm (64.04%). m.p. =160°C

Mass (FAB) $m/z = 407 (M^+)$. IR (KBr cm^{-1}): 3426, 3338, 1686, 1617, 1493, 1450, 1328, 1161, 1139, 740. ^1H NMR (200 MHz, $CDCl_3$) δ 2.33-2.45(m, 1H), δ 3.33-3.59(m, 1H), δ 5.16-

5.48(m,3H), δ 6.96-7.42(m,6H), δ 7.61-7.83(m,2H), δ 8.18-8.63(m,2H), δ 8.56(d,1H), δ 8.80-8.32(d,1H). Molecular Formula= $C_{21}H_{18}N_4O_3S$.

Example 19: Preparation of 2-[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) 2-[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester (0.388gm, 0.5mol) was kept at room temperature (32°C) in methanolic ammonia (30ml) for 24 hrs. The reaction mixture was then evaporated under vacuum to obtain 2-[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide. Yield=0.300gm (80.41%). m.p. =220°C

Mass (FAB) m/z = 374 (M^+). IR (KBr cm^{-1}): 3461, 3371, 1690, 1598, 1488, 1454, 1330, 1167, 764. ^1H NMR (200 MHz, MeOH) δ 2.69-2.80(m,1H), δ 2.86-2.99(m,1H), δ 4.66-5.05(m,3H), δ 6.89-7.07(m,2H), δ 7.14-7.31(m,5H), δ 7.85-7.98(m,3H). Molecular Formula= $C_{18}H_{16}FN_3O_3S$.

Example 20: Preparation of 2-[methane sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) Methane sulphonyl chloride (0.18ml, 2.4mmol) was added to a stirred solution of dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide (0.430gm, 2.0mmol) and dry triethylamine (0.56ml, 4.0mmol) in dry DMF (8ml) during 15 min at room temperature 30°C. The reaction mixture was allowed to stir for 8hrs. at room temperature. Water (20ml) was added to the reaction mixture and extracted with chloroform (3×15 ml). The extract was dried over Na_2SO_4 and concentrated over reduced pressure to give 2-[methane sulphonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide which was purified by column chromatography over silica gel using 2% methanol chloroform as eluent. Yield=0.150gm (25.60%). m.p.=234°C. Mass (FAB) m/z =294 (M^+). IR (KBr cm^{-1}): 3483, 3361, 1685, 1610, 1446, 1325, 1148, 756. ^1H NMR (200 MHz, $CDCl_3$) δ 3.04(s,3H), δ 3.20-3.63(m,2H), δ 4.69-4.84(m,3H), δ 6.96-7.15(m,3H), δ 7.32-7.53(m,3H), δ 10.89(s,1H). Molecular Formula= $C_{13}H_{15}N_3O_3S$.

Example 21: Preparation of 2-[3-nitro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) 3-nitro benzene sulphonyl chloride (0.531gm, 2.4mmol) in dry acetone was added to a stirred solution of dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide (0.430gm, 2.0mmol) and dry triethylamine (0.56ml, 4.0mmol) in dry DMF (8ml) during 15 min and was allowed to stir for 8hrs. at room temperature. The reaction mixture was allowed to stir for 8hrs. at room temperature. Water (20ml) was added to the reaction

mixture and extracted with chloroform(3×15 ml).The extract was dried over Na₂SO₄ and concentrated over reduced pressure.to give 2-[3-nitro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide which was purified by column chromatography over silica gel using 2% methanol chloroform as eluent.Yield=0.400gm(50%). m.p.=252°C. Mass (FAB) m/z =401 (M⁺). IR(KBr cm⁻¹): 3459, 3378, 1692, 1618, 1528, 1353, 1173, 760. H¹NMR(200MHz,CDCl₃+DMSO-d₆): δ2.88(m,1H), δ3.33(d,1H), δ4.73(d,1H), δ4.93(d,1H), δ5.06(d,1H), δ6.41(s,1H), δ6.89-7.31(m,3H), δ7.63-7.71(m,3H), δ8.13-8.17(d,1H), δ8.30 (d,1H), δ8.59 (d,1H), δ 10.27(s, 1H). Molecular Formula=C₁₈H₁₆N₄O₅S.

Example 22: Preparation of 2-[2, 4, 6 trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

i) 2,4,6 trimethyl benzene sulphonyl chloride (0.524gm,2.4mmol) in dry acetone was added to a stirred solution of dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide (0.430gm,2.0mmol) and dry triethylamine (0.56 ml, 4.0mmol) in dry DMF (8ml).during 15 min and was allowed to stirr for 8hrs. at room temperature. Water (20ml) was added to the reaction mixture and extracted with chloroform(3×15 ml). The extract was dried over Na₂SO₄ and concentrated over reduced pressure to give 2-[2,4,6 trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide which was purified by column chromatography over silica gel using 2% methanol chloroform as eluent Yield=0.35gm(44.08%) m.p.=212°C. Mass (FAB) m/z = 398 (M⁺). IR(KBr cm⁻¹): 3394, 3299, 1668, 1596, 1455, 1324, 1155, 752. H¹NMR (200 MHz, DMSO d6) δ 2.30(s,3H), δ2.56-2.74(m,7H), δ3.55-3.62(d,1H), δ4.49-4.70(m,3H), δ5.17(s,1H), δ5.49(s,1H), δ6.96-7.77(m, 6H). Molecular Formula=C₂₁H₂₃N₃O₃S.

Example 23: Preparation of 2-[2-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.

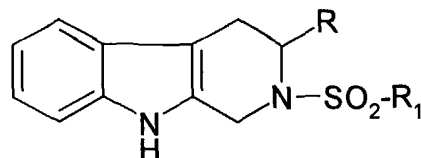
i) 2-[2-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester (0.210gm, 0.5mol)was kept at room temperature(32°C) in methanolic ammonia (30ml)for 24 hrs The reaction mixture was then evaporated under vaccum to obtain 2-[2-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amideYield=0.142gm(70%). m.p. =240°C. Mass (FAB) m/z = 406 (M⁺). IR (KBr cm⁻¹): 3489, 3372, 1694, 1604, 1444, 1328, 1160, 1078, 754. H¹NMR (200 MHz, Acetone): δ 3.17-3.28(m,2H), δ4.67-4.99(m,3H), δ6.35(s,1H), δ 6.76-6.91(m,3H), δ7.11-7.16(d,2H), δ7.48-7.55(m, 2H). δ7.67-7.97(m, 4H), δ8.40(s,1H), δ9.86(s,1H). Molecular Formula=C₂₂H₁₉N₃O₃S.

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We claim:

1. 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid esters/ amides having formula 1:

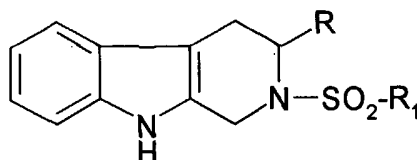


Formula 1

wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety

2. Compound as claimed in claim 1 comprising of 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
3. Compound as claimed in claim 1 comprising of 2[2,4,6, trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
4. Compound as claimed in claim 1 comprising of 2[2,nitrobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
5. Compound as claimed in claim 1 comprising of 2[1-naphthyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
6. Compound as claimed in claim 1 comprising of 2-4-metoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
7. Compound as claimed in claim 1 comprising of 2[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
8. Compound as claimed in claim 1 comprising of 2-[dansyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
9. Compound as claimed in claim 1 comprising of 2[2,4,6 tri isopropyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
10. Compound as claimed in claim 1 comprising of 2[4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
11. Compound as claimed in claim 1 comprising of 2[2-tri floro methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
12. Compound as claimed in claim 1 comprising of 2[methyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.

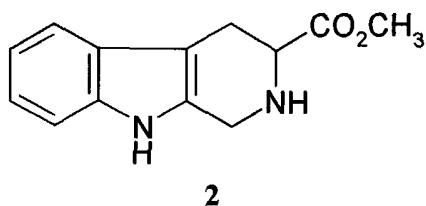
13. Compound as claimed in claim 1 comprising of 2-[2-napthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
14. Compound as claimed in claim 1 comprising of 2[benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
15. Compound as claimed in claim 1 comprising of 2[4-methyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
16. Compound as claimed in claim 1 comprising of 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
17. Compound as claimed in claim 1 comprising of 2[-4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
18. Compound as claimed in claim 1 comprising of 2[-1-napthylsulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
19. Compound as claimed in claim 1 comprising of 2[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
20. Compound as claimed in claim 1 comprising of 2[-4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
21. Compound as claimed in claim 1 comprising of 2[methane sulphonyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
22. Compound as claimed in claim 1 comprising of 2[3-nitro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
23. Compound as claimed in claim 1 comprising of 2[2,4,6 trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
24. Compound as claimed in claim 1 comprising of 2-[2-napthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
25. A process for the preparation of a 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid ester of formula 1



1

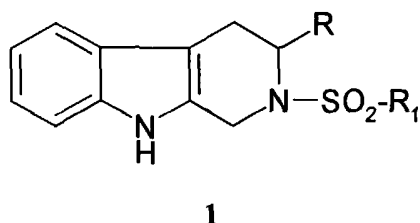
wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety, the process comprising condensing an

alkyl or aryl sulphonyl chloride with dimethyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3- carboxylate Formula 2

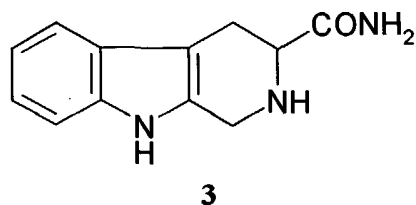


in the presence of a base and an organic solvent to obtain a corresponding 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid ester of formula 1.

26. A method as claimed in claim 25 wherein the aryl is selected from the group consisting of substituted phenyl substituted by hydrogen, halogen, alkyl or alkoxy, substituted naphthyl substituted by hydrogen or dimethyl amino; and heteroaryl.
27. A method as claimed in claim 26 wherein the heteroaryl is quinoline.
28. A method as claimed in claim 25 wherein the reaction is carried out at a temperature in the range of 30°C to 120°C and for 8 to 24 hours
29. A method as claimed in claim 26 wherein the halogen is selected from the group consisting of chlorine, bromine fluorine, iodine, and mixtures thereof; alkoxy is selected from the group consisting of C₁-C₁₀ oxy; alkyl is selected from the group consisting of C₁-C₁₀ alkyl, and heteroaryl is selected from the group consisting of C₄-C₁₀ heteroaryl.
30. A method for the preparation of 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid amide of formula 1

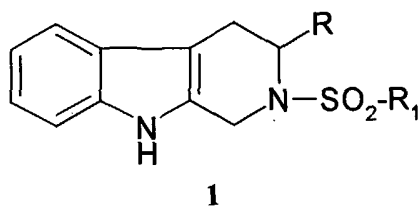


wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety by condensing an alkyl or aryl sulphonyl chloride wherein aryl is selected from the group consisting of substituted phenyl substituted by hydrogen, halogen, alkyl or alkoxy; substituted naphthyl substituted by hydrogen or di methyl amino; and heteroaryl consisting of quinoline with dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide formula 3



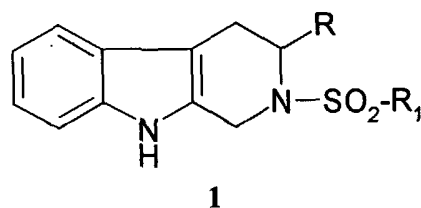
- in the presence of a base and an organic solvent to obtain a corresponding 2-alkyl/aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amide.
31. A method as claimed in claim 30 wherein the reaction is carried out at a temperature in the range of 30°C to 120°C for 8 to 24 hours.
 32. A method as claimed in claim 30 wherein the halogen is selected from the group consisting of chlorine, bromine fluorine, iodine, and mixtures thereof; alkoxy is selected from the group consisting of C₁-C₁₀ oxy; alkyl is selected from the group consisting of C₁-C₁₀ alkyl, and heteroaryl is selected from the group consisting of C₄-C₁₀ heteroaryl.
 33. A method for the preparation of 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amides comprising reacting a 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid ester with methanolic ammonia for 24 to 48 hours hrs to obtain the corresponding 2-alkyl/ aryl sulphonyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3,4-b) indole -3- carboxylic acid amide.
 34. A process as claimed in claim 25 wherein the reaction is carried out in the presence of a solvent selected from the group consisting of acetone, DMF, THF and dioxane; a base selected from the group consisting of TEA, K₂CO₃, Na₂CO₃, pyridine or any combination thereof and at a temperature in the range of 30°C to 120°C and a period of 8 to 24 hours.
 35. A process as claimed in claim 25 wherein molar ratio of substituted sulphonyl chloride to dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate/ dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole-3-amide is 1:2.
 36. A process as claimed in claim 34 wherein the amount of solvent is in the range of 0.8-2.2 ml per mmol.
 37. A process as claimed in claim 34 wherein molar ratio of the base to the dl methyl-1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-carboxylate / dl 1, 2, 3, 4-tetrahydro-9H-pyrido (3, 4-b) indole -3-amide is 1:4.

38. A pharmaceutical composition comprising a pharmaceutically effective amount of 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid ester/amide of formula 1



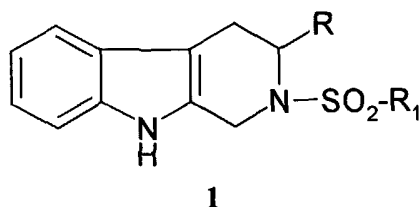
wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety, and a pharmaceutically acceptable carrier.

39. A method for the treatment of intravascular thrombosis in mammals comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition consisting of a pharmaceutically effective amount of 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid amide of formula 1



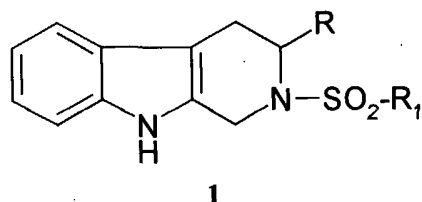
wherein R is selected from methyl ester and amide; and R₁ is selected from group consisting of alkyl, aryl, and heteroaryl moiety, with a pharmaceutically acceptable carrier

40. A method for the treatment of myocardial ischemia in mammals, comprising by administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition consisting of a pharmaceutically effective amount of 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid ester/amide of formula 1



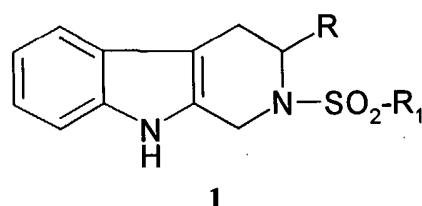
wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety, with a pharmaceutically acceptable carrier

41. A method for the treatment of stroke in mammals, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition consisting of a pharmaceutically effective amount of 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid ester/amide of formula 1



wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety, with a pharmaceutically acceptable carrier.

42. Use of of 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid ester/amide of formula 1



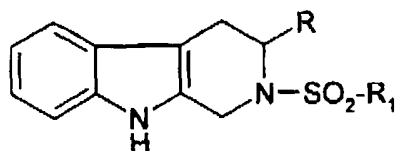
wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety, with or without a pharmaceutically acceptable carrier, for the treatment of myocardial ischemia, intravascular thromboses and stroke.

43. Method as claimed in claim 39 to 41 wherein the amount of compound of formula 1 is in the range of 10μM to 30μM per kilogram body weight of subject.
44. Use as claimed in claim 43 wherein the amount of compound of formula 1 is in the range of 10μM to 30μM per kilogram body weight of subject.

AMENDED CLAIMS

received by the International Bureau on 02 February 2006 (02.02.06)

13. Compound as claimed in claim 1 comprising of 2-[2-napthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
14. Compound as claimed in claim 1 comprising of 2[benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid ester.
15. Compound as claimed in claim 1 comprising of 2[-2,5 dichlorobenzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
16. Compound as claimed in claim 1 comprising of 2[-4-methoxy benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
17. Compound as claimed in claim 1 comprising of 2[-1-napthylsulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
18. Compound as claimed in claim 1 comprising of 2[8-quinoline sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
19. Compound as claimed in claim 1 comprising of 2[-4-floro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
20. Compound as claimed in claim 1 comprising of 2[methane sulphonyl sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
21. Compound as claimed in claim 1 comprising of 2[3-nitro benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
22. Compound as claimed in claim 1 comprising of 2[2,4,6 trimethyl benzene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
23. Compound as claimed in claim 1 comprising of 2-[2-napthalene sulfonyl]-1,2,3,4,-tetra hydro-9H-pyrido[3,4-b] indole-3-carboxylic acid amide.
24. A process for the preparation of a 2-alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid ester of formula 1



1

wherein R is selected from methyl ester and amide; and R₁ is selected from the group consisting of alkyl, aryl, and heteroaryl moiety, the process comprising condensing an

STATEMENT UNDER ARTICLE 19 (1)

The subject matter of the present invention is novel and inventive over all the documents cited in the International Search Report except for the compound as claimed in claim 15 of the present invention ; PCT/IN2004/00417. Accordingly, the said claim has been deleted from the present application. This has resulted in renumbering of the originally filed claims 1 to 44 as 1 to 43.

1/1

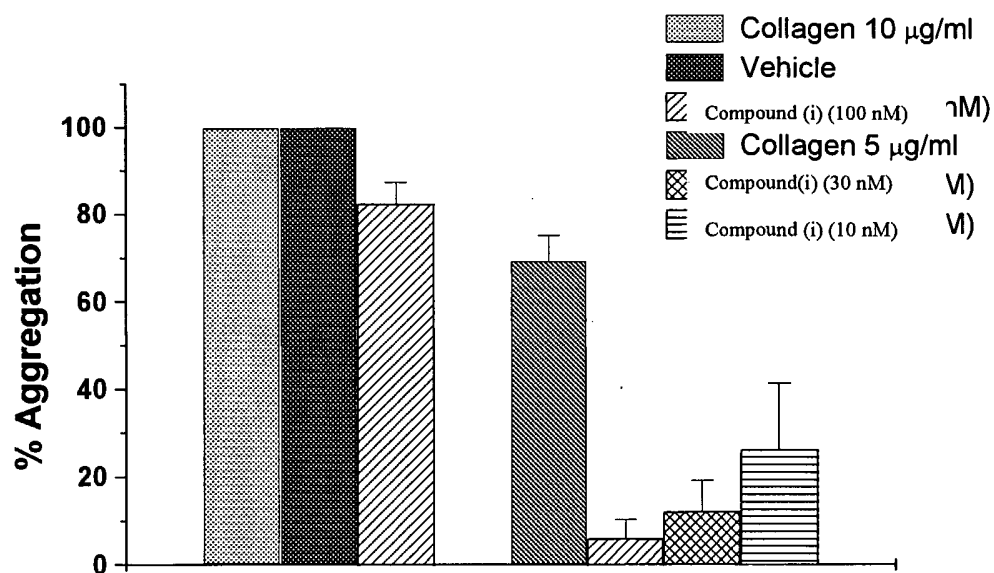


Fig 1: Effect of Compound (i) on human platelet aggregation

Values are mean $\pm$ SEM (number of experiments =3 in each set)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2004/000417

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/4035 A61K31/407 A61K31/437

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TRIPATHI, RAVISH C. ET AL: "Synthesis and SAR studies in 2-substituted 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acids - a new class of potent antiulcer agents" INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY, 28B(4), 333-7 CODEN: IJSBDB; ISSN: 0376-4699, 1989, XP009052431 page 334; table 1; compounds 7,12,25,30	1,38
A	WO 97/37658 A (BOEHRINGER MANNHEIM ITALIA S.P.A; SPINELLI, SILVANO; MENTA, ERNESTO; K) 16 October 1997 (1997-10-16) page 8, line 21 claim 1	1-44
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 August 2005

Date of mailing of the international search report

29/08/2005

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Authorized officer

Samsam Bakhtiary, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2004/000417

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/87883 A (DARWIN DISCOVERY LIMITED) 22 November 2001 (2001-11-22) page 12, line 21 claim 1 -----	1-44
A	WO 2004/000842 A (JANSSEN PHARMACEUTICA, N.V.; JIANG, WEIQIN; SUI, ZHIHUA) 31 December 2003 (2003-12-31) page 4, paragraphs 1,3 claim 1 -----	1-44
A	WO 98/51301 A (PIERRE FABRE MEDICAMENT; HALAZY, SERGE; PEREZ, MICHEL; VALENTIN, JEAN-) 19 November 1998 (1998-11-19) claim 1 -----	1-44
A	MATTER ET AL: "Affinity and Selectivity of Matrix Metalloproteinase Inhibitors: A Chemometrical Study from the Perspective of Ligands and Proteins" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 42, no. 22, 1999, pages 4506-4523, XP002162629 ISSN: 0022-2623 page 4508; table 1; compounds 1,2,4,7 -----	1,38
A	DE 196 12 298 A1 (HOECHST AG, 65929 FRANKFURT, DE) 2 October 1997 (1997-10-02) page 12; table 1; compounds 2,3 -----	1,38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2004/000417

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 39-44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2004/000417

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INTERNATIONAL SEARCH REPORT

International Application No
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