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(57) Abstract

Polyhydroxylated naphthyl 2-carboxylate, and isoquinoline and quinoline 3-carboxylate derivatives are provided which possess protein tyrosine kinase inhibitory activity. Pharmaceutical compositions containing the compounds as well as methods of treating neoplastic and immune diseases, which diseases require protein tyrosine kinase for cell proliferation, are also provided.

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POLYHYDROXYLATED NAPHTHYL 2-CARBOXYLATE, AND QUINOLYL AND ISOQUINOLYL 3-CARBOXYLATE DERIVATIVES AS PROTEIN TYROSINE KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention is concerned with providing certain polyhydroxylated naphthyl 2-carboxylate, and quinolyl and isoquinolyl 3-carboxylate derivatives as protein tyrosine kinase inhibitors. The present invention is also concerned with certain novel and advantageous biological and pharmacological uses for such compounds, and with providing pharmaceutical compositions containing the same compounds.

BACKGROUND OF THE INVENTION

At the Fourth Chemical Congress of North America, held in New York, New York, on August 25-30, 1991, a paper was presented by Terrence R. Burke, Jr., et al. entitled "Carboxynaphthyl, -Quinolyl and -Isoquinolyl Compounds as Bicyclic Ring-Constrained Analogues of Styryl-Based Protein Tyrosine Kinase Inhibitors," disclosing certain of the compounds encompassed by the present invention. The presentation paper presented by Terrence R. Burke, Jr., et al. at the Fourth Chemical Congress of North America is incorporated herein by reference in its entirety.

Terrence R. Burke, Jr. in the publication "Drugs of the Future 1992," 17 (2): 119-131 (1992), provides a disclosure relating to protein/tyrosine kinase inhibitors. At pages 123-124 of the publication a disclosure of styryl-containing inhibitors is provided. The compound 6,7-dihydroxyisoquinoline-3-carboxamide is disclosed as a conformationally constrained memetic of a styryl-containing inhibitor. The publication of Terrence R. Burke, Jr. in "Drugs of the Future 1992" is incorporated herein by reference in its entirety.

Terrence R. Burke, Jr., et al. disclose in Heterocycles, Volume 34, No. 4, pages 757-764 (1992) a new synthetic method for the synthesis of hydroxylated

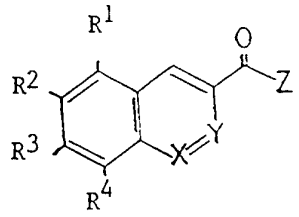
isoquinolines. More specifically, there is provided a preparation for methyl 6,7- and 7,8-dihydroxyiso-quinoline-3-carboxylates. The method is presented as a general procedure for the production of polyhydroxylated isoquinolines. The 6,7- and 7,8-dihydroxy-isoquinoline-3-carboxylates are disclosed to have potential protein-tyrosine kinase inhibitory activity. The publication of Terrence R. Burke, Jr. et al. in Heterocycles, Volume 34, No. 4, pages 757-764 (1992) is incorporated herein by reference in its entirety.

Terrence R. Burke, Jr., et al., in the publication "Arylamides of Hydroxylated Isoquinolines as Protein-Tyrosine Kinase Inhibitors," tested various hydroxylated isoquinolines for the inhibition of autophosphorylation of protein-tyrosine kinases (Terrence R. Burke, Jr., et al. Bioorg. Med. Chem. Lett. 2: 1771-1774 (November, 1992)). It was found that the aryl substitution on the amide nitrogen is necessary for potency in the epidermal growth factor receptor (EGFR) PTK. Specifically, the phenyl and benzyl substituted amides had significant potency ($IC_{50}(\mu M)$ of 5.6 and 3.1, respectively), while the primary amide had little potency ($IC_{50}(\mu M)$ of >100). The publication of Terrence R. Burke, Jr., et al. Bioorg. Med. Chem. Lett. 2: 1771-1774 (November, 1992) is incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

The present invention is concerned with providing novel polyhydroxylated naphthyl 2-carboxylate, and quinoline and isoquinoline 3-carboxylate derivatives which are active protein tyrosine kinase inhibitors. The present invention is also concerned with providing for the use of such compounds in a variety of pharmacological and biological settings, including the treatment of neoplastic and immune diseases (e.g., leukemias, lymphomas, breast cancer, ovarian cancer, prostate cancer, lung cancer, colon cancer, and the like wherein tyrosine kinase is a requirement for cell pro-

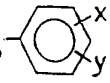
liferation) and auto-immune processes. The novel compounds encompassed by the present invention are represented within the structure of Formula I below



Formula I

wherein R^1, R^2, R^3 and R^4 are selected from the group consisting of hydrogen and hydroxy, wherein at least two of said R^1-R^4 groups are hydroxy;

X and Y are selected from the group consisting of N and CH, wherein at least one of X and Y is CH;

Z is C_{1-8} alkoxy, $-NH_2$, $-NHR^5$ or $-NH-(CH_2)_p-$  , wherein

R^5 is C_{1-8} alkyl, p is 0 to 3, and x and y are selected from the group consisting of hydrogen, hydroxy, halogen, carboxy and $-NH_2$, with the proviso that when Z is C_1-C_8 alkoxy, R^3 and R^4 are hydroxy; and pharmaceutically acceptable salts thereof.

Pharmaceutical compositions are also provided herein which contain a pharmacologically effective amount of a Formula I compound in combination with the pharmaceutically acceptable carrier therefor. Exemplary of such pharmaceutical compositions are those provided in the pharmacological section hereof. Preferably, such pharmaceutical compositions are formulated in order to be administered by intravenous administration. Such formulations preferably contain from about 0.5 μg to 5 mg of the active Formula I compound in its free form.

Preferred among the compounds encompassed by Formula I, are those compounds wherein R^3 and R^4 are hydroxy. Also preferred among compounds encompassed by Formula I, are the isoquinoline and naphthyl derivatives encompassed thereby, as well as the aryl-substituted amide derivatives.

As used in Formula I, the term "halogen" refers to

chlorine, bromine, fluorine and iodine.

As used in Formula I, the term "carboxy" refers to -COOH, and C_{1-8} alkyl esters thereof (e.g., $-COOCH_3$).

As used in Formula I, the term "C_{1-8} alkoxy" means $-O-C_{1-8}$ alkyl (e.g., methoxy).

As used in Formula I, the term "C_{1-8} alkyl" means straight or branched chain alkyl groups having 1-8 carbon atoms (e.g., methyl, ethyl, propyl, 2-propyl, butyl, t-butyl, and the like).

As used in Formula I, the term "pharmaceutically acceptable salts" refers to acid addition salts, hydrates, alkalates and salts of the compounds of Formula I which are physiologically compatible in warm blooded animals. The acid addition salts may be formed by either strong or weak acids. Representative of strong acids are hydrochloric, sulfuric, and phosphoric acids. Representative of weak acids are fumaric, maleic, succinic, oxalic, citric, tartaric, cyclohexamic, and the like.

Novel processes for preparing certain of the isoquinoline compounds encompassed by Formula I are also provided and discussed in the Detailed Description Section hereof.

DETAILED DESCRIPTION OF THE INVENTION

The following description is provided as an aid to those desiring to practice the present invention. Even so, the following description should not be construed to unduly limit the present inventive discoveries. In this regard, additional embodiments and methods other than those expressly disclosed herein may be readily utilized by those of ordinary skill in the art, without departing from the spirit or scope of the present inventive discoveries. As such, the present inventive discoveries are not to be limited by the specific embodiments and disclosures contained herein, but instead also include those variations and equivalents readily understood by those of ordinary skill in the art.

As indicated previously, a novel method exists for preparing certain of the isoquinoline Formula I compounds encompassed hereby. The method is fully disclosed in Heterocycles, Volume 34, No. 4, pages 757-764 (1992), and is utilized in preparing the isoquinolyl derivatives encompassed in the Examples hereof.

The quinolyl and naphthyl derivatives encompassed by Formula I may be readily prepared by those of ordinary skill in the art, utilizing procedures already known in the art for preparing quinolyl and naphthyl compounds. Naphthyl derivatives can also be prepared as shown in Example VI, if so desired.

The following compound preparations are provided to further aid those desiring to practice the present invention.

Preparation I

Methyl 5-bromo-7,8-dihydroxytetrahydroisoquinoline-3-carboxylate hydrochloride.

To a solution of 2-bromo-4,5-dihydroxyphenyl-alanine (38.4 g, 139 mmol) in 1 N HCl (200 ml) is added formaldehyde (30 ml, 37% in H_2O) and the mixture is stirred at room temperature under argon overnight. The resulting suspension is reduced in volume to a slurry, mixed with ice-cold H_2O (50 ml), and filtered. The light brown filter cake is washed with ice-cold H_2O (2 x 50 ml), taken to dryness twice from anhydrous MeOH (2 x 200 ml), then refluxed with methanolic HCL (200 ml, 2 h). The resulting suspension is reduced in volume to a slurry, resuspended in MeOH (50 ml), filtered and the filter cake washed with MeOH (2 x 50 ml) to yield the title compound as off-white crystals; 19.6 g (42%), mp 221-223°C; m/z = 302/304 $(M+H)^+$; Anal. Calcd for $C_{11}H_{12}NO_4Br \cdot HCl \cdot CH_3OH$: C, 38.89; H, 4.62; N, 3.78. Found: C, 38.80; H 4.65; N, 3.72; ^{1}H-nmr δ: = 2.86 (dd, J = 16.9, 11.2 Hz, 1H, H-4_a), 3.12 (dd, J = 16.9, 5.2 Hz, 1H, H-4_b), 3.84 (s, 3H, OCH_3), 4.04 (d, J= 16.4 Hz, 1H, H-1_a), 4.27 (d, J = 16.4 Hz, 1H, H-1_b), 4.54 (dd, J = 11.2, 5.2 Hz, 1H, H-3),

7.08 (s, 1H, aromatic-H), 9.40 (s, 1H, OH), 9.99 (br s, 2H, NH_2), 10.13 (s, 1H, OH).

Preparation II

Methyl 7,8-dihydroxytetrahydroisoquinoline-3-carboxylate hydrochloride.

A suspension of methyl 5-bromo-7,8-dihydroxytetrahydroisoquinoline-3-carboxylate hydrochloride (Preparation I) (5.85 g, 17.3 mmol) in MeOH (250 ml) is hydrogenated in a Parr apparatus (600 mg of 10% Pd·C; 40 psi H_2 with replenishing of H_2 after 15 min). After 3 hours, the mixture is filtered through celite and taken to dryness. The resulting solid is re-evaporated from methanolic HCl (100 ml) then crystallized from MeOH/acetone to provide a white crystalline solid (2.72 g) which when combined with additional crystalline material obtained by working up the filtrate (1.69 g) yields the title compound as a white crystalline solid: (4.41 g, 97%), mp 216-218°C; m/z = 224 $(M+H)^+$; High resolution mass spectrum calculated for $C_{11}H_{14}NO_4$ $(M+H)^+$:224.092. Found: 224.096; ^{1}H-nmr δ: = 3.02 (dd, J = 16.4, 10.8 Hz, 1H, H-4_a), 3.15 (dd, J = 16.4, 5.0 Hz, 1H, H-4_b), 3.18 (s, 3H, OCH_3), 4.05 (d, J = 16.2 Hz, 1H, H-1_a), 4.24 (d, J = 16.2 Hz, 1H, H-1_b), 4.98 (dd, J = 10.8, 5.0 Hz, 1H, H-3), 6.55 (d, J = 8.2 Hz, 1H, aromatic-H), 6.76 (d, J = 8.2 Hz, 1H, aromatic-H), 9.03 (s, 1H, OH), 9.50 (s, 1H, OH), 10.00 (br s, 2H, NH_2).

Preparation III

Methyl 7,8-diacetoxyisoquinoline-3-carboxylate.

A suspension of methyl 7,8-dihydroxytetrahydroisoquinoline-3-carboxylate hydrochloride (Preparation II) (2.59 g, 10.0 mmol) in AcOH (50 ml) with 96% H_2SO_4 (2.04 g, 20 mmol) is warmed briefly until a solution is formed. To the still warm solution is added acetic anhydride (3.78 ml, 40 mmol) and the light yellow solution is stirred at room temperature (1 hour). The solution is diluted with ether (200 ml) and cooled on ice, providing a white precipitate

which is triturated with EtOAc (100 ml) and collected by filtration (2.80 g). The solid is partitioned between ice-cold aqueous $NaHCO_3$ (50 ml) and EtOAc (3 x 50 ml), dried ($MgSO_4$) and taken to dryness to yield crude methyl 7,8-diacetoxy-tetrahydroisoquinoline-3-carboxylate as an oil (2.38 g, 78%). A solution of 7,8-diacetoxy-tetrahydroisoquino-line-3-carboxylate (4.35 g, 14.2 mmol) in toluene (200 ml) is stirred at reflux temperature (1.5 hours) under argon with activated MnO_2 (14.2 g). The mixture is filtered hot through celite and taken to dryness, yielding a light brown crystalline solid (2.65 g). The crude product is taken up in $CHCl_3$ and filtered through a silica gel pad with the aid of additional $CHCl_3$, yielding the title compound as beige colored crystals; 1.92 g (35% overall), mp 162-164°C (ether); m/z = 304 $(M+H)^+$; Anal. Calcd for $C_{15}H_{13}NO_6 \cdot 1/4\ H_2O$: C, 58.44; H, 4.58; N, 4.54. Found: C, 58.76; H, 4.29; N, 4.55; ^{1}H-nmr: δ = 2.39 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 7.89 (d, J = 8.9 Hz, 1H, aromatic-H), 8.25 (d, J = 8.9 Hz, 1H, aromatic-H), 8.76 (s, 1H, aromatic-H), 9.49 (s, 1H, aromatic-H).

Example I

Methyl 7,8-dihydroxyisoquinoline-3-carboxylate hydrochloride.

Methyl 7,8-diacetoxyisoquinoline-3-carboxylate (Preparation III) (1.87 g, 6.17 mmol) is suspended in anhydrous MeOH (10 ml) and the mixture is saturated with HCl gas. The bright yellow solution is stirred at room temperature under argon overnight. The resulting thick suspension of yellow crystals is cooled on ice, filtered and washed with MeOH, yielding the title compound as yellow crystals: 1.50 g (95%), mp > 280°C (decomp); m/z = 220 $(M+H)^+$; Anal. Calcd for $C_{11}H_9NO_4 \cdot HCl$; C, 51.68; H, 3.94; N, 5.48. Found: C, 51.47; H, 3.98, N, 5.38; ^{1}H-nmr δ: = 3.99 (s, 3H, OCH_3), 7.81 (s, 2H, 2 aromatic-H), 8.78 (s, 1H, aromatic-H), 9.48 (s, 1H, aromatic-H).

Example II

3-carbamoyl-7,8-dihydroxyisoquinoline.

The title compound is prepared by reacting methyl 7,8-dihydroxyisoquinoline-3-carboxylate hydrochloride with ammonia at an elevated temperature to provide crude product. Thereafter, the crude product is purified utilizing high pressure liquid chromatography.

Example III

3-(N-phenylcarbamoyl)-7,8-dihydroxyisoquinoline.

The title compound is prepared by converting the compound of Example I (methyl 7,8-dihydroxyisoquinoline-3-carboxylate hydrochloride) to the free acid by heating with aqueous hydrochloric acid. Thereafter, the free acid is derivatized with ethyl chloroformate to yield an intermediate which is not isolated, but treated directly with aniline. Thereafter, the crude product is purified utilizing high pressure liquid chromatography to yield the title compound.

Example IV

3-(N-benzylcarbamoyl)-7,8-dihydroxyisoquinoline.

The title compound is prepared utilizing the same procedure set forth in Example III, except benzylamine is substituted for aniline.

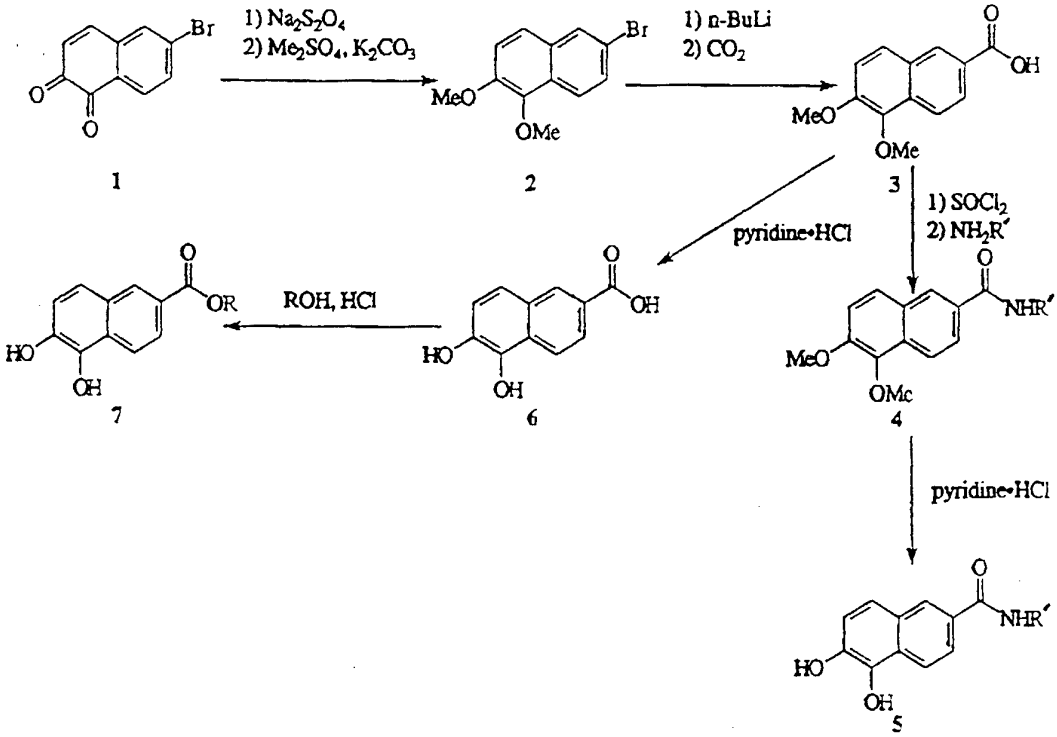
Example V

3-[N-(2-phenylethyl)carbamoyl]-7,8-dihydroxyisoquino-line.

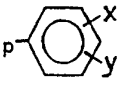
The title compound is prepared utilizing the same procedure as set forth in Example III, except 2-phenyl-ethylamine is substituted for aniline.

Example VI

Preparation of 5,6-dihydroxynaphthalene-2-carboxylates.



R = C_{1-8} straight or branched alkyl;

R′ = hydrogen, C_{1-8} alkyl, or $-(CH_2)_p$-  , wherein p, x and y are as defined in Formula I.

Synthesis of 5,6-dihydroxynaphthalene-2-carboxylate esters 7 and amides 5 can be synthesized from their common novel intermediate 3 using standard chemical techniques. The synthesis of 3 can start from known (R.W.A. Oliver, et al., Tetrahedron 24: 4067-4072 (1968)). 6-bromo-1,2-naphthoquinone 1, which is reduced (any of a variety of reducing agents can be used; sodium thiosulfate is one example (J.D. McDermed, et al., J. Med. Chem. 18: 362-368 (1975)) and methylated in situ (using standard methylating agents; for example, dimethyl sulfate (J.D. McDermed, et al., J. Med. Chem. 18: 362-368 (1975)). Conversion to an amide 4 can be achieved using standard techniques (converting to the acid chloride using thionyl chloride, followed by reaction with the appropriate amine, is exemplary). Demethylation (by heating with pyridine·HCl) yields the final products 5 (other agents, such as BBr_3 can

also be used to demethylate). Alternatively, demethylation of 3 to the dihydroxy 4, followed by esterification (heating the appropriate alcohol with acid is an example) can provide the final esters 7.

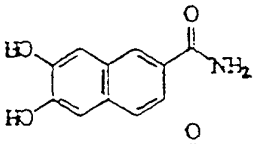
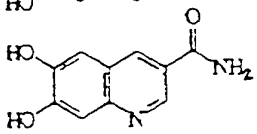
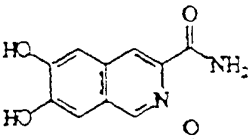
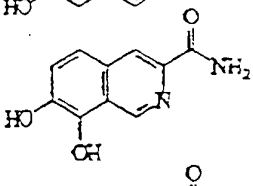
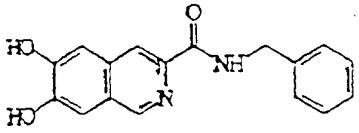
Pharmacology

Compounds encompassed by Formula I were tested for tyrosine kinase inhibitory activity utilizing an *in vitro* kinase assay similar to that described by Zhen-Hong Li, et al. in Biochemical and Biophysical Research Communications, Volume 180, pages 1048-1056 (1991), and utilizing T-cell leukemia cell lines for $p56^{lck}$ and B-cell leukemia cell lines for $p56^{lyn}$ protein tyrosine kinase. Results obtained with each test compound are shown below. In the following Table IC_{50} refers to the concentration causing 50% inhibition of tyrosine kinase in lysed test cells.

Test Compound	IC_{50} (μm)	
	$p56^{leu}$	$p56^{lyn}$
Ex. 1	0.1	100
Ex. 2	0.1	100
Ex. 4	0.1	100

The above test results evidence the ability of the Formula I compounds to inhibit protein tyrosine kinase activity, and further evidence the utility of such compounds in the present inventive methods and pharma-ceutical compositions.

Some additional compounds encompassed by the present invention as well as certain comparative compounds were tested for tyrosine kinase inhibitory activity again utilizing an in vitro test method such as described by Zhen-Hong Li et al, and utilizing T-cell leukemia cell lines for $p56^{lck}$ and B-cell leukemia cell lines for $p56^{lyn}$ protein tyrosine kinase, results obtained are shown below. In the Table "ND" means "no data" was collected.

Test Compound	IC_{50} (μm) $p56^{lck}$	$p56^{lyn}$
	50	ND
	10	ND
	10	ND
	≥0.1	100
	>1000	>1000
Herbimycin	>10	10

Pharmaceutical Compositions

The compounds of Formula I may be advantageously formulated into pharmaceutical compositions. Such compositions are useful in treating conditions such as neoplastic diseases and immune diseases having protein tyrosine kinase as a requirement for cell proliferation, in a patient in need of such treatment.

Preferably, pharmaceutical compositions encompassed by the present invention should be formulated for intravenous administration to a patient in need thereof. Such formulations preferably contain an effective amount of a Formula I compound in combination with a pharmaceutically acceptable sterile carrier (e.g., water or arachis oil).

Pharmaceutical compositions encompassed by the present invention may also be formulated as therapeutic compositions suitable for oral, parenteral, subcutaneous, intramuscular, intraperitoneal administration. For example, compositions for oral administration may take the form of elixors, capsules, tables or coated tablets containing carriers conveniently used in the pharmaceutical art. Exemplary of solid carriers, including tableting and capsulating excipients, are lactose, sucrose, potato and maize starches, talc, gelatin, agar, pectin or acacia, stearic and silicic acids, magnesium stearate, terra alba and polyvinyl pyrrolidone.

For parenteral administration, the carrier or excipient can be composed of sterile parentally acceptable liquid, e.g., water or arachis oil contained in ampules.

The pharmaceutical compositions used in the present invention should preferably contain from about 0.5 μg to 10 mg of active ingredients therein.

When administered, the composition of the present invention should be formulated so that from about 0.1 μg/kg to about 0.5 mg/kg body weight, preferably 0.1 mg/kg body weight or less is administered per day.

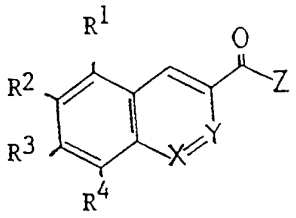
In all of the above, it is only necessary that a suitable effective dosage be utilized. Accordingly, the

exact individual dosages, as well as daily dosages, will be determined according to standard medical principles under the direction of a physician or veterinarian.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims. Each of the publications and patents referred herein above are expressly incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:

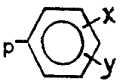


Formula I

wherein

R^1, R^2, R^3 and R^4 are selected from the group consisting of hydrogen or hydroxy, wherein at least of two said R^1-R^4 groups are hydroxy;

X and Y are selected from the group consisting of N and CH, wherein at least one of X and Y is CH;

Z is C_{2-8} alkoxy, $-NHR^5$ or $-NH-(CH_2)_p$-  ,

wherein R^5 is C_{1-8} alkyl, p is 0 to 3 and x and y are selected from the group consisting of hydrogen, hydroxy, halogen, carboxy and $-NH_2$, with the proviso that when Z is C_{1-8} alkoxy then R^3 and R^4 are hydroxy; and the pharmaceutically acceptable salts thereof.

2. A compound as recited in claim 1, wherein X is CH and Y is N.

3. A compound as recited in claim 2, which is methyl 7,8-dihydroxyisoquinoline-3-carboxylate, or a pharmaceutically acceptable salt thereof.

4. A compound as recited in claim 2, which is 3-(N-phenylcarbamoyl)-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

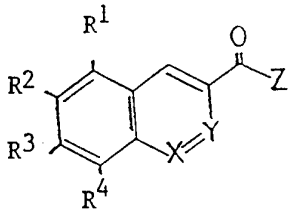
5. A compound as recited in claim 2, which is 3-(N-benzylcarbamoyl)-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

6. A compound as recited in claim 2, which is 3-[N-(2-phenylethyl)carbamoyl]-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

7. A compound as recited in claim 1, wherein X and Y are each CH.

8. A compound as recited in claim 1, wherein X is N and Y is CH.

9. A pharmaceutical composition containing a pharmacologically effective amount of a compound of Formula I:

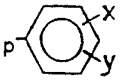


Formula I

wherein

R^1, R^2, R^3 and R^4 are selected from the group consisting of hydrogen or hydroxy, wherein at least of two said R^1-R^4 groups are hydroxy;

X and Y are selected from the group consisting of N and CH, wherein at least one of X and Y is CH;

Z is C_{2-8} alkoxy $-NHR^5$ or $-NH-(CH_2)_p$-  ,

wherein R^5 is C_{1-8} alkyl, p is 0 to 3 and x and y are selected from the group consisting of hydrogen, hydroxy, halogen, carboxy and $-NH_2$, with the proviso that when Z is C_{1-8} alkoxy then R^3 and R^4 are hydroxy; and the pharmaceutically acceptable salts thereof;

and a pharmaceutically acceptable carrier therefor.

10. A pharmaceutical composition as recited in claim 9, wherein X is CH and Y is N.

11. A pharmaceutical composition as recited in claim 9, wherein the Formula I compound is methyl 7,8-dihydroxyisoquinoline-3-carboxylate, or a pharmaceutically acceptable salt thereof.

12 A pharmaceutical composition as recited in claim 10, wherein said Formula I compound is 3-(N-phenylcarbamoyl)-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

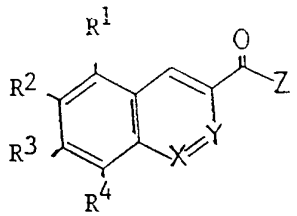
13. A pharmaceutical composition as recited in claim 10, wherein said Formula I compound is 3-(N-benzylcarbamoyl)-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition as recited in claim 10, wherein said Formula I compound is 3-[N-(2-phenylethyl)carbamoyl]-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

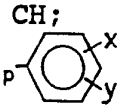
15. A pharmaceutical composition as recited in claim 9, wherein X and Y are each CH.

16. A pharmaceutical composition as recited in claim 9, wherein X is N and Y is CH.

17. A method of treating a neoplastic or immune disease in a patient, which disease requires protein tyrosine kinase for cell proliferation, said method comprising administering to the patient an effective amount of a compound of Formula I for treating said disease:



Formula I

wherein
R^1, R^2, R^3 and R^4 are selected from the group consisting of hydrogen or hydroxy, wherein at least two of said R^1-R^4 groups are hydroxy;
X and Y are selected from the group consisting of N and CH, wherein at least one of X and Y is CH;
Z is C_{2-8} alkoxy, $-NHR^5$ or $-NH-(CH_2)_p$- 

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wherein R^5 is C_{1-8} alkyl, p is 0 to 3, and x and y are selected from the group consisting of hydrogen, hydroxy, halogen, carboxy and $-NH_2$, with the proviso that when Z is C_{1-8} alkoxy then R^3 and R^4 are hydroxy; and the pharmaceutically acceptable salts thereof.

18. The method of claim 17, wherein X is CH and Y is N.

19. The method of claim 18, wherein the Formula I compound is methyl 7-8-dihydroxyisoquinoline-3-carboxylate, or a pharmaceutically acceptable salt thereof.

20. The method of claim 18, wherein the Formula I compound is 3-(N-phenylcarbamoyl)-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

21. The method of claim 18, wherein the Formula I compound is 3-(N-benzylcarbamoyl)-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt there-of.

22. The method of claim 18, wherein the Formula I compound is 3-[N-(2-phenylethyl)carbamoyl]-7,8-dihydroxyisoquinoline, or a pharmaceutically acceptable salt thereof.

23. A compound as recited in claim 17, wherein X and Y are each CH.

24. A compound as recited in claim 17, wherein X is N and Y is CH.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/07575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D217/26 C07D215/48 C07C69/94 C07C235/66 A61K31/47
A61K31/165 A61K31/235

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 5 C07D C07C

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HETEROCYCLES vol. 34, no. 4 , 1992 pages 757 - 764 TERRENCE R. BURKE ET AL 'A new synthetic method for the synthesis of hydroxylated isoquinolines:preparation of methyl 6,7- and 7,8-dihydroxy isoquinoline-3-carboxylates,potential protein-tyrosine kinase inhibitors' see the whole document --- -/--	1-3, 9-11, 17-19

[X] 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	Date of mailing of the international search report
3 November 1993	15. 11. 93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	HENRY, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JOURNAL OF MEDICINAL CHEMISTRY. vol. 16, no. 4 , 19 February 1993 , WASHINGTON US pages 425 - 432 TERRENCE R. BURKE ET AL 'Bicyclic compounds as ring-constrained inhibitors of protein-tyrosine kinase p56(lck)' see the whole document and footnote 1	1-24
O,X	& FOURTH CHEMICAL CONGRESS OF NORTH-AMERICA ,25-30 AUGUST 1991 , NEW YORK TERRENCE R. BURKE ET AL 'Carboxy naphthyl,-quinolyl and -isoquinolyl compouds as bicyclic ring-constrained analogues of styryl-based protein-tyrosine kinase inhibitors'	1-24

X	CHEMICAL ABSTRACTS, vol. 117, no. 23, 7 December 1992, Columbus, Ohio, US; abstract no. 233627j, page 831 ; see abstract & JP,A,04 154 736 (GREEN CROSS CORP.) 27 May 1992	1,7,9,15

A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 27, no. 5 , May 1984 , WASHINGTON US pages 564 - 570 FILADELFO GUZMAN ET AL 'Biomimetic approach to potential benzodiazepine receptor agonists and antagonists' see page 566,compounds 3	1,2,9,10

P,X	BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS vol. 2, no. 12 , 1992 pages 1771 - 1774 TERRENCE R. BURKE ET AL 'Arylamides of hydroxylated isoquinolines as protein-tyrosine kinase inhibitors' see the whole document	1,2,4,5, 8,10, 12-14, 17,18, 20-22

3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/07575

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 17-22 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

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 II Observations where unity of invention is lacking (Continuation of item 2 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 searches 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

formation on patent family members

International application No.
PCT/US 93/07575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP-A-04154736	27-05-92	NONE	