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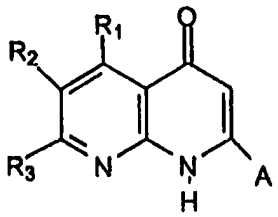
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(57) Abstract

The present invention provides compounds of Formula (I), wherein A and R_1–R_8 are defined herein. The compounds of Formula (I) inhibit the polymerization of tubulin and possess antimitotic activity. The compounds of Formula (I) may be useful for the treatment of psoriasis, gout, papiloma, warts, and a variety of tumors.



(I)

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
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2-ARYL-NAPHTHYRIDIN-4-ONES AS ANTITUMOR AGENTS

The present invention was made under grant number CA-17625 from the National Cancer Institute and grant number CHE-9412095 from the National Science Counsel. The United States government has rights in the instant invention.

Field of the Invention

The present invention relates to new compounds within the general class of 2-aryl-1,8-naphthyridin-4-ones. The present invention also relates to methods of inhibiting cellular mitosis and/or tumor growth.

Background of the Invention

The microtubule system of eukaryotic cells is an attractive target for the development of compounds useful in anticancer chemotherapeutics. Microtubules show highly dynamic instability and play an important role in

cellular mitosis. Chemicals that attack microtubules through their major structural component, tubulin, disrupt or suppress both microtubule structure and normal functions by inhibition or promotion of microtubule assembly. Inihibition or arrest of cellular mitosis is the result.

One example of conventional antimitotic agents includes the *vinca* alkaloids, which inhibit microtubule polymerization. Another example of conventional antimitotic agents includes the taxoids, which promote microtubule assembly.

Colchicine is another conventional antimitotic agent. Although colchicine has limited medicinal application due to its high toxicity, it has played a fundamental role in elucidation of the properties and functions of tubulin and microtubules.

Many natural products, such as cornigerine, podophyllotoxin, steganacin, and combretastatins, bind to the colchicine site of tubulin. Structurally, the compounds binding to this site are much simpler than those binding to *vinca* alkaloid or taxol domains. These compounds generally possess a "biaryl" system connected by a hydrocarbon bridge of variable length.

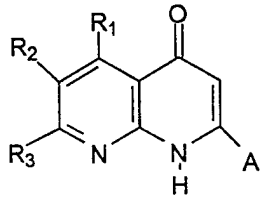
In the course of this group's search for novel plant-derived potent cytotoxic agents that are active against slow-growing solid tumors, we have isolated several flavonols as antitumor principles from a phytochemically and biologically heretofore uninvestigated plant, *Polanisia dodecandra*. Among these flavonols, 5,3'-dihydroxy-3,6,7,8,4'-pentamethoxyflavone showed remarkable cytotoxicity *in vitro* against panels of central nervous system, lung, ovarian, colon, and renal cancers and against melanoma and leukemia cell lines with GI_{50} values in the low micromolar to nanomolar concentration range. Flavonoids also possess the biaryl structural pattern of compounds binding to the colchicine site. We found that this compound is a strong inhibitor of tubulin polymerization with an IC_{50} value of 0.83 ± 0.2 μM and to be a potent inhibitor of radiolabeled colchicine binding to tubulin, showing 59% inhibition when present in an equimolar concentration with colchicine.

Paralleled with our studies of plant antitumor agents, we synthesized a large series of 2-aryl-1,8-naphthyridiones, which are the amino analogs of cytotoxic antimitotic flavonoids, and found that many of these compounds were cytotoxic and possess activitity against tubulin polymerization and colchicine binding.

There remains a need in the art for cytotoxic agents for use in cancer therapy. There remains a need in the art for agents capable of inhibiting cellular mitosis for use in cancer therapy. Further there remains a need in the art for methods of treating cancer and methods of providing cancer therapy.

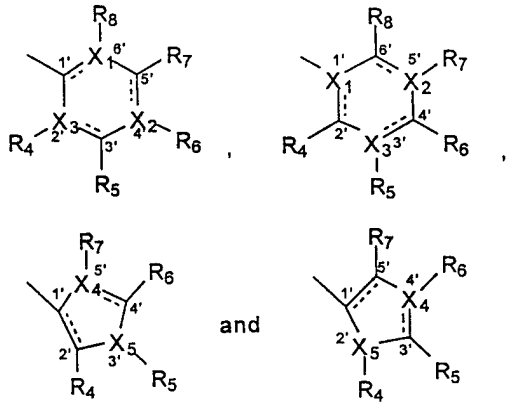
Summary of the Invention

As a first aspect, the present invention provides a compound of Formula the general Formula I:



I

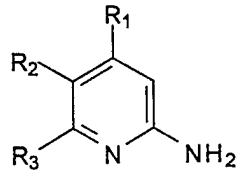
wherein A is an aromatic moeity selected from the the group consisting of:



wherein X_1, X_2, and X_3 are each individually selected from the group consisting of C, or N ; X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S; R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or

alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and the dashed line indicates that the bond may be a double bond or a single bond, with the provisos that when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected thereto are double bonds; when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent; when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent.

As a second aspect, the present invention provides a process for making compounds of Formula I. The process comprises (a) reacting a compound of Formula II:

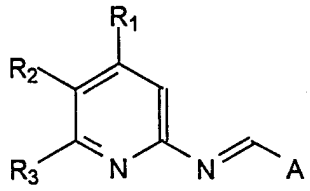


II

with a compound of Formula IV:

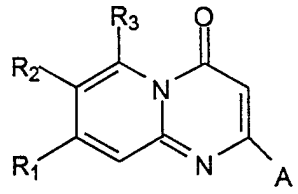
A—CHO IV

to produce a Schiff base intermediate of Formula VI:



VI

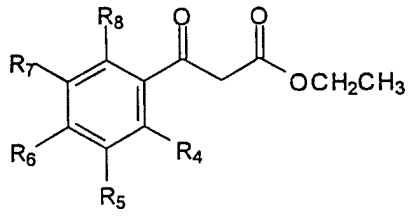
(b) cyclizing the Schiff base intermediate to give a pyridopyrimidinone intermediate of Formula V:



V

and (c) thermally converting the pyridopyrimidinone intermediate to a compound of Formula I.

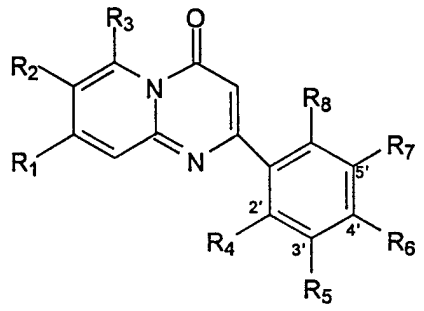
As a third aspect, the present invention provides another process for making compounds of Formula I wherein A is a six-member aromatic hydrocarbon ring. The process comprises the steps of (a) condensing a compound of Formula II with a compound of Formula III:



III

in the presence of polyphosphoric acid to produce a pyridopyrimidinone

intermediate of Formula V-A:



V-A

and (b) thermally converting the pyridopyrimidinone intermediate of Formula V-A to a compound of Formula I wherein A is a six-member aromatic hydrocarbon ring.

As a fourth aspect, the present invention provides a compound of Formula V.

As a fifth aspect, the present invention provides a compound of Formula VI.

As a sixth aspect, the present invention provides a method for treating a tumor. The method comprises administering to a subject in need of treatment, a compound of Formula I in an amount effective to treat a tumor.

As a seventh aspect, the present invention provides a method of inhibiting cellular mitosis. The method comprises contacting a cell with a compound of Formula I in an amount effective to inhibit cellular mitosis.

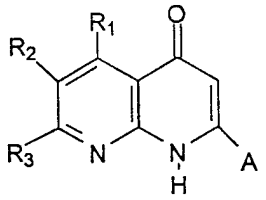
The foregoing and other aspects of the present invention are explained in detail in the detailed description and examples set forth hereinbelow.

Detailed Description of the Invention

As used herein the term "alkyl" refers to C_{1-20} inclusive, linear, branched, or cyclic, saturated or unsaturated hydrocarbon chains, including for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, octyl, ethenyl, propenyl, butenyl, pentenyl, hexenyl, octenyl, butadienyl, and allenyl groups. Thus, the term "alkyl" refers to C_{1-20} inclusive alkyls unless otherwise specified. The term "alkoxy" as used herein refers to C_{1-20} inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains,

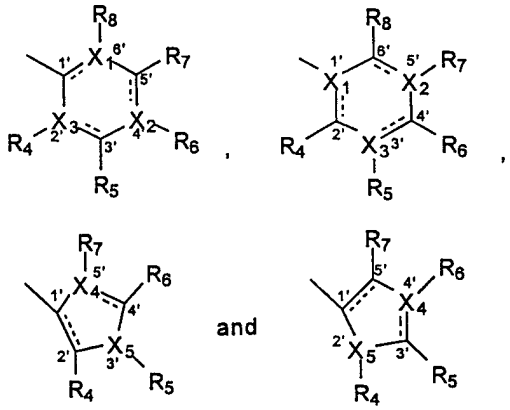
including for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, and pentoxy. The term "aryloxyl" as used herein refers to phenyloxyl and alkyl, halo, or alkoxyl substituted phenyloxyl. The terms "halo," "halide," or "halogen" as used herein refer to fluorine, chlorine, bromine, and iodine. The term "alkylamino" refers to a group of the general formula -NHR′, wherein R′ is alkyl. The term "dialkylamino" refers to a group of the general formula -NR′R″, wherein R′ and R″ are each the same of different alkyl groups. The term "heteroatom" as used herein refers to N, O, or S. The term "alkydienyl" refers to a group of the general formula -R′- where R′ is alkyl. The term "alkyleneoxy" refers to a group having the general formula -OR′- or -R′OR′- where each R′ is independently alkyl. The term "alkylenedioxy" refers to a group of the general formula -OR′O-, -OR′OR′-, or -R′OR′OR′- where each R′ is independently alkyl. The term "alkyleneimine" refers to a group having the general formula -NR′- or -R′NR′- where each R′ is independently alkyl. The term "alkylenediimine" refers to a group of the general formula -NR′N-, -NR′NR′-, or -R′NR′NR′- where each R′ is independently alkyl.

The present invention provides 2-aryl-1,8-naphthyridine-4-ones of the general Formula I:



I

wherein A is an aromatic moeity selected from the group consisting of:



and

wherein:

X_1, X_2, and X_3 are each individually selected from the group consisting of C, or N;

X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and

the dashed line indicates that the bond may be a double bond or a single bond,

with the provisos that:

when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected thereto are double bonds;

when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent;

when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and

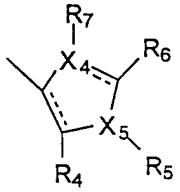
when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent.

More specifically, A is an aromatic moeity selected from the group consisting of six-member aromatic hydrocarbon rings, five-member aromatic heterocyclic rings containing 1 or 2 heteroatoms, and six-member aromatic heterocyclic rings containing 1, 2, or 3 heteroatoms, where any of these rings may include from 0 to 4 substiuents for five-member rings, or 0-5 substituents for six-member rings, which substituents are defined by variables R_4-R_8. Specific examples of suitable aromatic moeities within the scope of the definition of A of the Formula I of the present invention include, but are not limited to phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyrrole, imidazole, furan, thiophene, oxazole, thiazole, where any of those aromatic moeities may be substituted as represented by R_4-R_8 defined hereinabove.

The substituents R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 may be any of the species identified above, or two adjacent R groups (i.e., two R groups which are next to each other) may form a bridging group. More specifically, R_1 and R_2 may be a bridging group such that R_1 and R_2 together with the atoms to which they are attached may form a five- or six-member aromatic ring; R_2 and R_3 may be a bridging group such that R_2 and R_3 together with the atoms to which they are attached may form a five- or six-member aromatic ring; R_4 and R_5 may be a bridging group such that R_4 and R_5 together with the atoms to which they are attached may form a five- or six-member aromatic ring; R_5 and R_6 may be a bridging group such that R_5 and R_6 together with the atoms to which they are attached may form a five- or six-member aromatic ring; R_6 and R_7 may be a bridging group such that R_6 and R_7 together with the atoms to which they are attached may form a five- or six-member aromatic ring; R_7 and R_8 may be a bridging group such that R_7 and R_8 together with the atoms to which they are attached may form a five- or six-member aromatic ring. For example, the five or six-member rings which may be formed when adjacent R groups are defined as a bridging group include six-member aromatic hydrocarbon rings; which are defined when adjacent R groups are alkydienyl; five-member aromatic heterocyclic rings, which are defined when adjacent R groups are alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and six-member aromatic heterocyclic rings,

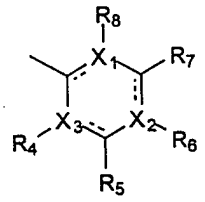
which are defined when adjacent R groups are alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine.

As is evident from the general Formula I and the definition of the aromatic moeity A, the compounds of Formula I may be substituted from 1 to 8 times. More specifically, the compounds of Formula I may be substituted from 1 to 3 times in the "A" ring (i.e., the first ring of the structure) and from 1 to 5 times in the "C" ring (i.e., the aromatic moeity defined by the variable A). The compounds of Formula I include compounds having substitutions in only the "A" or only the "C" ring or in both rings. As will be apparent to those skilled in the art, when the C ring is a six-member heterocyclic moeity, the R group substituent attached at the position of the heteroatom on the ring is absent in order to accomodate the valence requirements of the heteroatoms. Similarly, when the C ring is a five-member heterocyclic moeity containing an O or S, the R group substituent attached at the position of the O or S is absent in order to accomodate the valence requirements of that heteroatom. Thus, if A is a five-member heterocycle of the formula:



wherein X_4 is O or S, the dashed line connected to X_4 (i.e., between positions 4' and 5') is a single bond, the dashed line between positions 1' and 2' is a double bond, and R_7 is absent. In the embodiment wherein X_4 is N, the dashed line connected to X_4 (i.e., between positions 4' and 5') may be either a single bond or a double bond, the dashed line between positions 1' and 2' is a double bond, and if the dashed line connected to X_4 is a double bond, R_7 is absent. In the embodiment wherein X_5 is

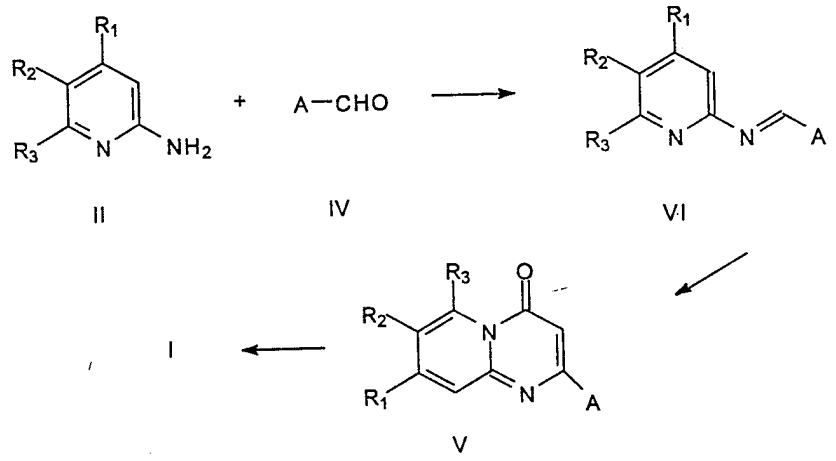
O or S, all dashed lines are double bonds and R_5 is absent. Similarly, when A is a heterocycle of the formula:



wherein X_3 is N and all dashed lines are double bonds, R_4 is absent. The other heterocyclic rings encompassed by the instant invention are similarly determined. One skilled in the art will readily appreciate the valence requirements of the different heteroatoms and will interpret the definitions of the variables in the present invention in a manner consistent with those requirements.

The compounds of Formula I wherein A is any of a six-member aromatic hydrocarbon ring, a five-member aromatic heterocycle, or a six-member aromatic heterocycle may be produced according to the following **Scheme I**.

Scheme I



wherein A and R_1-R_8 are as defined hereinabove.

The compounds of Formula IV above are commercially available and may be produced according to techniques known in the art. According to this method, the compounds of Formula II are reacted with the compounds of Formula IV in an organic solvent to yield the Schiff base intermediate of Formula VI. Typically, the reaction is carried out under heat, and preferably at the reflux

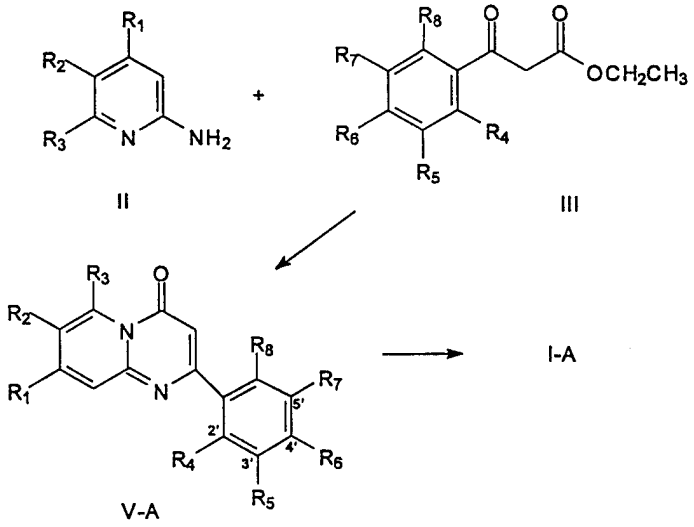
temperature of the solvent. Suitable solvents will be known to those skilled in the art, and include, for example, benzene, toluene, and m-xylene. The reaction is carried out until about 90-95% of the theoretical amount of water is recovered. The intermediates of Formula VI can be recovered by evaporating the organic solvent and distilling the residue. The compounds of Formula VI are then cyclized to the intermediate compounds of Formula V by reaction with a triethylamine and anhydrous chloroacetyl chloride. Typically the cyclization of the compounds of Formula VI to produce the compounds of Formula V is carried out in an appropriate organic solvent. Examples of suitable organic solvents include but are not limited to ethylether, methylene chloride, and tetrahydrofuran. Ethylether is currently the preferred organic solvent for the cyclization reaction.

The compound of Formula V (i.e., the pyridopyrimidinone intermediate) can be recovered using conventional recovery techniques including extraction with an organic solvent. Preferably, the compounds of Formula V are recovered by allowing the condensation reaction mixture, including the compounds of Formula V, to cool to room temperature, neutralizing the mixture with a base such as sodium hydroxide, extracting the compounds of Formula V with an appropriate organic solvent, such as methylene chloride, and passing the extract through a silica gel column.

The compounds of Formula V may then be thermally converted to the compounds of Formula I. The thermal conversion of the compounds of Formula V involves a rearrangment which forms the compounds of Formula I. The thermal conversion of the compounds of Formula V may be accomplished by adding the compound of Formula V to mineral oil, such as liquid paraffin, at a temperature of between about 300°C and about 400°C, preferably about 350°C. After the reaction is complete, the compounds of Formula I may be recovered using silica gel chromatography and eluting with a mixture of methylene chloride and ethylacetate.

Alternatively, the compounds of Formula I wherein A is a six-member hydrocarbon ring can also be produced according to the following **Scheme II**.

Scheme II



wherein R_1-R_8 are as defined above.

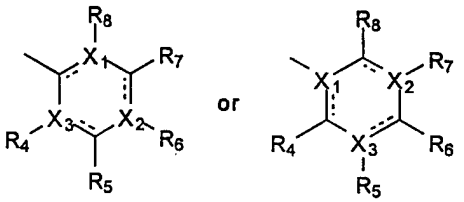
The starting substituted ethyl benzoylacetates of Formula III can be prepared according to techniques described in A. Krapcho, et al., *Organic Synthesis* 5:198 (1973), the disclosure of which is hereby incorporated by reference in its entirety. The substituted 2-aminopyridine of Formula II are commercially available. A compound of Formula II is combined with a compound of Formula III and polyphosphoric acid and heated to a temperature above about 100°C, preferably above about 110°C, and most preferably about 125°C at atmospheric pressure. Preferably, the condensation reaction is carried out while stirring the mixture. If desired, the progression of the condensation reaction can be monitered by thin layer chromatography using techniques known to those skilled in the art. The product of the condensation reaction is the pyridopyrimidine intermediate compound of Formula V-A.

The compound of Formula V-A may be recovered and subsequently thermally converted to the compounds of Formula I wherein A is a six-member aromatic hydrocarbon ring (i.e., compounds of Formula I-A), according to the techniques described hereinabove for converting compounds of Formula V to compounds of Formula I.

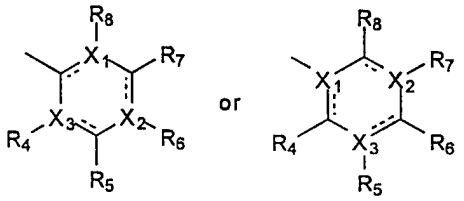
The compounds of Formula V and VI are useful intermediates for

the preparation of compounds of Formula I.

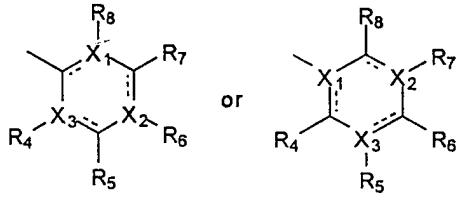
In one embodiment, preferred compounds of Formula I which are produced according to the methods of the present invention include compounds of Formula I wherein A is



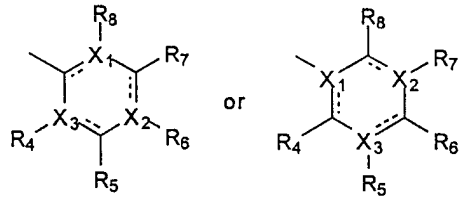
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_1 is alkyl. In another preferred embodiment of the compounds of Formula I wherein A is



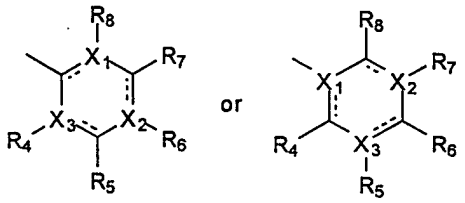
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_2 is alkyl. In another preferred embodiment, A is



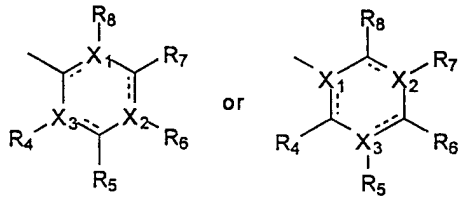
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_2 is halo. In another preferred embodiment A is



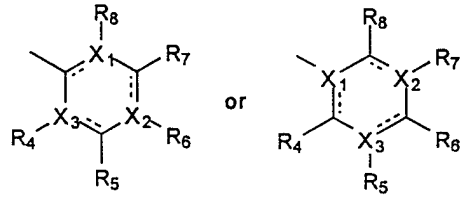
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_3 is alkyl. In another preferred embodiment A is



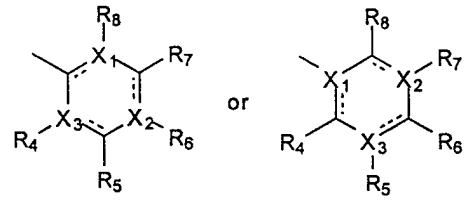
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_5 is alkoxyl. In another preferred embodiment, A is is



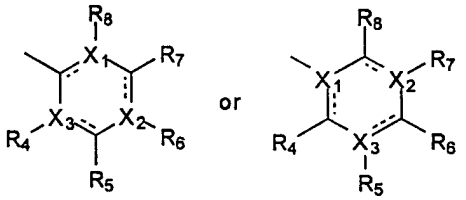
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_5 is halo. In yet another preferred embodiment, A is



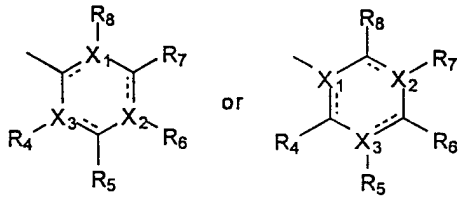
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds and R_5 is alkyl. In another preferred embodiment, A is



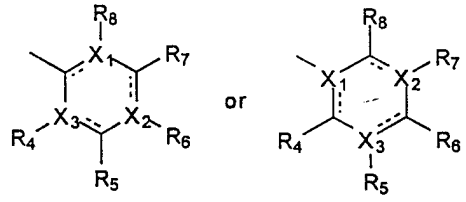
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_4 and R_5 together form a C_3-alkydienyl bridging group, and together with the atoms to which they are attached form a 6-member aromatic ring. In another preferred embodiment, A is



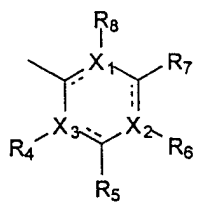
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_6 is alkoxyl. In another embodiment, A is



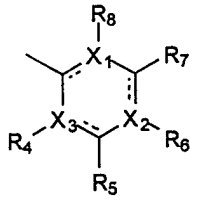
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_6 is halo. In another embodiment A is



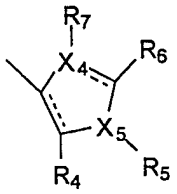
X_1, X_2, and X_3 are each C (i.e., A is a a six-member aromatic hydrocarbon), all dashed lines are double bonds, and R_6 is alkyl. In another preferred embodiment A is :



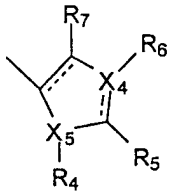
X_1 and X_2 are each C and X_3 is N (i.e., A is a a six-member aromatic heterocycle), all dashed lines are double bonds, R_2 and R_5 are each alkyl, and R_4 is absent. In another preferred embodiment A is



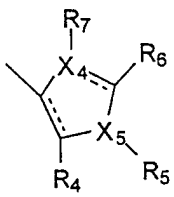
X_1 and X_3 are each C and X_2 is N (i.e., A is a a six-member aromatic heterocycle), all dashed lines are double bonds, R_3 is alkyl, and R_6 is absent. In another preferred embodiment, A is



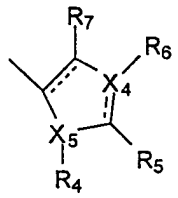
X_4 is C, X_5 is O (i.e., A is a a five-member aromatic heterocycle), all dashed lines are double bonds, R_2 is alkyl, and R_5 is absent. In another preferred embodiment, A is



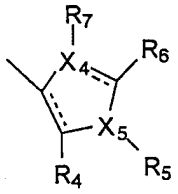
X_4 is C, X_5 is O (i.e., A is a a five-member aromatic heterocycle), all dashed lines are double bonds, R_2 is alkyl, and R_4 is absent. In another preferred embodiment, A is



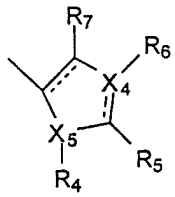
X_4 is C, X_5 is N (i.e., A is a a five-member aromatic heterocycle), all dashed lines are double bonds, R_2 is alkyl, and R_5 is absent. In another preferred embodiment, A is



X_4 is C, X_5 is N (i.e., A is a a five-member aromatic heterocycle), all dashed lines are double bonds, R_2 is alkyl, and R_4 is absent. In another preferred embodiment, A is

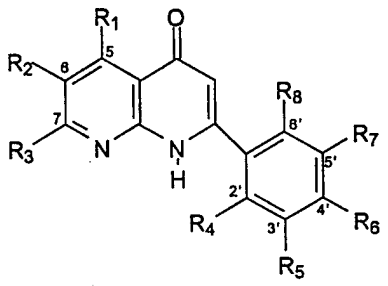


X_4 is C, X_5 is S (i.e., A is a a five-member aromatic heterocycle), all dashed lines are double bonds, R_2 is alkyl, and R_5 is absent. In another preferred embodiment, A is



X_4 is C, X_5 is S (i.e., A is a a five-member aromatic heterocycle), all dashed lines are double bonds, R_2 is alkyl, and R_4 is absent.

Specific examples of preferred compounds of Formula I include compounds defined as follows:



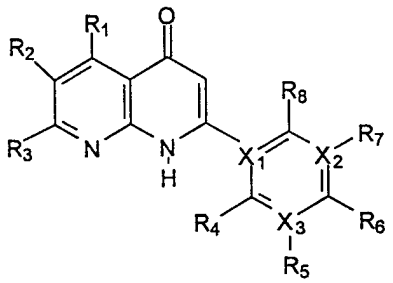
I-A

wherein:

R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
H	H	H	H	alkoxyl	H	H	H
alkyl	H	H	H	alkoxyl	H	H	H
H	alkyl	H	H	alkoxyl	H	H	H
H	H	alkyl	H	alkoxyl	H	H	H
alkyl	H	alkyl	H	alkoxyl	H	H	H
H	halo	H	H	alkoxyl	H	H	H
alkyl	H	H	H	H	alkoxyl	H	H
H	alkyl	H	H	H	alkoxyl	H	H
alkyl	H	H	H	H	halo	H	H
H	alkyl	H	H	H	halo	H	H
alkyl	H	H	H	H	alkyl	H	H
H	alkyl	H	H	H	alkyl	H	H
H	H	alkyl	H	H	alkyl	H	H
alkyl	H	alkyl	H	H	alkyl	H	H
H	alkyl	H	H	halo	H	H	H
H	H	alkyl	H	halo	H	H	H
alkyl	H	alkyl	H	halo	H	H	H
H	H	H	H	halo	H	H	H
alkyl	H	H	H	halo	H	H	H
H	alkyl	H	H	halo	H	H	H
H	H	alkyl	H	halo	H	H	H
alkyl	H	H	H	alkyl	H	H	H

R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
H	H	H	C_3 alkydienyl		H	H	H
alkyl	H	H	C_3 alkydienyl		H	H	H
H	alkyl	H	C_3 alkydienyl		H	H	H
H	H	alkyl	C_3 alkydienyl		H	H	H
alkyl	H	alkyl	C_3 alkydienyl		H	H	H

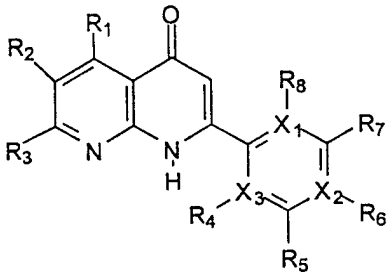
Another specific example of compounds of Formula I are defined as follows:



I-B

wherein X_1 and X_2 are C, X_3 is N, R_1, R_3, R_4, R_6, and R_8 are each H, R_2 and R_7 are each alkyl and R_5 is absent.

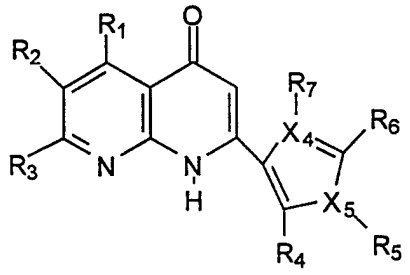
Another specific example of compounds of Formula I are defined as follows:



I-C

wherein X_1 and X_3 are C, X_2 is N, R_1, R_2, R_4, R_5, R_7, and R_8 are each H, R_3 is alkyl, and R_6 is absent.

Other specific examples of compounds of Formula I are defined as follows:

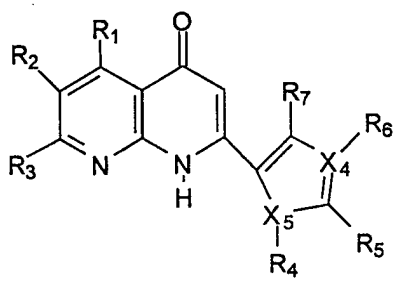


I-D

wherein

X_4	X_5	R_1	R_2	R_3	R_4	R_5	R_6	R_7
C	O	H	alkyl	H	H	absent	H	H
C	N	H	alkyl	H	H	absent	H	H
C	S	H	alkyl	H	H	absent	H	H
C	O	H	alkyoxl	H	H	absent	H	H
C	N	H	alkoxyl	H	H	absent	H	H
C	S	H	alkoxyl	H	H	absent	H	H

Other specific examples of compounds of Formula I are defined as follows:



I-E

wherein

X_4	X_5	R_1	R_2	R_3	R_4	R_5	R_6	R_7
C	O	H	alkyl	H	absent	H	H	H
C	N	H	alkyl	H	absent	H	H	H
C	S	H	alkyl	H	absent	H	H	H
C	O	H	alkyoxl	H	absent	H	H	H
C	N	H	alkoxyl	H	absent	H	H	H
C	S	H	alkoxyl	H	absent	H	H	H

The compounds of Formulas I-A, I-B, I-C, I-D, and I-E set forth hereinabove are encompassed by the scope of general Formula I hereinabove and are set forth herein for additional clarity.

Examples of specific compounds according to Formula I include but are not limited to:

2-(2'-Methoxyphenyl)-1,8-naphthyridin-4-one,

2-(2'-Methoxyphenyl)-5-methyl-1,8-naphthyridin-4-one,

2-(2'-Methoxyphenyl)-6-methyl-1,8-naphthyridin-4-one,

2-(2'-Methoxyphenyl)-7-methyl-1,8-naphthyridin-4-one,

2-(2'-Methoxyphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,

2-(3'-Methoxyphenyl)-1,8-naphthyridin-4-one,

2-(3'-Methoxyphenyl)-5-methyl-1,8-naphthyridin-4-one,

2-(3'-Methoxyphenyl)-6-methyl-1,8-naphthyridin-4-one,

2-(3'-Methoxyphenyl)-7-methyl-1,8-naphthyridin-4-one,

2-(3'-Methoxyphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(3'-Methoxyphenyl)-6-chloro-1,8-naphthyridin-4-one,
2-(3'-Methoxyphenyl)-6-bromo-1,8-naphthyridin-4-one,
2-(4'-Methoxyphenyl)-1,8-naphthyridin-4-one,
2-(4'-Methoxyphenyl)-5-methyl-1,8-naphthyridin-4-one,
2-(4'-Methoxyphenyl)-6-methyl-1,8-naphthyridin-4-one,
2-(4'-Methoxyphenyl)-7-methyl-1,8-naphthyridin-4-one,
2-(4'-Methoxyphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(4'-Fluorophenyl)-1,8-naphthyridin-4-one,
2-(4'-Fluorophenyl)-5-methyl-1,8-naphthyridin-4-one,
2-(4'-Fluorophenyl)-6-methyl-1,8-naphthyridin-4-one,
2-(4'-Fluorophenyl)-7-methyl-1,8-naphthyridin-4-one,
2-(4'-Fluorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(4'-Fluorophenyl)-6-chloro-1,8-naphthyridin-4-one,
2-(4'-Chlorophenyl)-1,8-naphthyridin-4-one,
2-(4'-Chlorophenyl)-5-methyl-1,8-naphthyridin-4-one,
2-(4'-Chlorophenyl)-6-methyl-1,8-naphthyridin-4-one,
2-(4'-Chlorophenyl)-7-methyl-1,8-naphthyridin-4-one,
2-(4'-Chlorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(4'-Methylphenyl)-5-methyl-1,8-naphthyridin-4-one,
2-(4'-Methylphenyl)-6-methyl-1,8-naphthyridin-4-one,
2-(4'-Methylphenyl)-7-methyl-1,8-naphthyridin-4-one,
2-(4'-Methylphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(3'-Fluorophenyl)-6-methyl-1,8-naphthyridin-4-one,
2-(3'- Fluorophenyl)-7-methyl-1,8-naphthyridin-4-one,
2-(3'- Fluorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(3'-Chlorophenyl)-1,8-naphthyridin-4-one,
2-(3'-Chlorophenyl)-5-methyl-1,8-naphthyridin-4-one,
2-(3'-Chlorophenyl)-6-methyl-1,8-naphthyridin-4-one,
2-(3'-Chlorophenyl)-7-methyl-1,8-naphthyridin-4-one,
2-(3'-Chlorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,

2-(3'-Methylphenyl)-1,8-naphthyridin-4-one,
2-(3'-Methylphenyl)-5-methyl-1,8-naphthyridin-4-one,
2-(3'-Methylphenyl)-6-methyl-1,8-naphthyridin-4-one,
2-(3'-Methylphenyl)-7-methyl-1,8-naphthyridin-4-one,
2-(3'-Methylphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(α-Naphthyl)-1,8-naphthyridin-4-one,
2-(α-Naphthyl)-5-methyl-1,8-naphthyridin-4-one,
2-(α-Naphthyl)-6-methyl-1,8-naphthyridin-4-one,
2-(α-Naphthyl)-7-methyl-1,8-naphthyridin-4-one,
2-(α-Naphthyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(β-Naphthyl)-1,8-naphthyridin-4-one,
2-(β-Naphthyl)-5-methyl-1,8-naphthyridin-4-one,
2-(β-Naphthyl)-6-methyl-1,8-naphthyridin-4-one,
2-(β-Naphthyl)-7-methyl-1,8-naphthyridin-4-one,
2-(β-Naphthyl)-5,7-dimethyl-1,8-naphthyridin-4-one,
2-(β-Naphthyl)-6-chloro-1,8-naphthyridin-4-one,
2-(5-Methylpyrid-3-yl)-6-methyl-1,8-naphthyridin-4-one,
2-(Pyrid-4-yl)-7-methyl-1,8-naphthyridin-4-one,
2-Fur-2-yl-6-methyl-1,8-naphthyridin-4-one,
2-Fur-3-yl-6-methyl-1,8-naphthyridin-4-one,
2-Pyrrol-2-yl-6-methyl-1,8-naphthyridin-4-one,
2-Pyrrol-3-yl-6-methyl-1,8-naphthyridin-4-one,
2-Thien-2-yl-6-methyl-1,8-naphthyridin-4-one, and
2-Thien-3-yl-6-methyl-1,8-naphthyridin-4-one.

The compounds of Formula I are useful as pharmaceutically active agents. The compounds of Formula I may be formulated for administration for the treatment of a variety of conditions. In the manufacture of a pharmacuetical formulation according to the invention, the compounds of Formula I and the physiologically acceptable salts thereof, or the acid derivatives of either thereof (hereinafter referred to as the "active compound") are typically admixed with, *inter alia*, an acceptable carrier. The carrier must, of course, be acceptable in the sense

of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.5% to 95% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may be administered by means of subcutaneous, intravenous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (*see*, for example, *Pharmaceutical Research* **3 (6)**:318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis\tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

The compounds of Formula I inhibit tubulin polymerization and have antimitotic activity. Such compounds are useful for the treatment of conditions including psoriasis, gout, papiloma, warts, and various tumors including

but not limited to non-small cell lung cancer, colon cancer, central nervous system cancers, melanoma, overian cancer, prostate cancer and breast cancer. Data regarding the activity of compounds of Formula I is provided in the Examples which follow.

Subjects to be treated by the methods of the present invention are typically human subjects although the methods of the present invention may be useful with any suitable subjects known to those skilled in the art, and particularly mammalian subjects including, in addition to humans, horses, cows, dogs, rabbits, fowl, sheep, and the like. As noted above, the present invention provides pharmaceutical formulations comprising the compounds of Formula I, or pharmaceutically acceptable salts thereof, in pharmaceutically acceptable carriers for oral, rectal, topical, buccal, parenteral, intramuscular, intradermal, or intravenous, and transdermal administration.

Obviously, the therapeutically effective dosage of any specific compound, the use of which is in the scope of present invention, will vary somewhat from compound to compound, patient to patient, and will depend upon the condition of the patient and the route of delivery. As a general proposition, a dosage from about 0.1 to about 50 mg/kg will have therapeutic efficacy, with still higher dosages potentially being employed for oral and/or aerosol administration. Toxicity concerns at the higher level may restrict intravenous dosages to a lower level such as up to about 10 mg/kg, all weights being calculated based upon the weight of the active base, including the cases where a salt is employed. Typically a dosage from about 0.5 mg/kg to about 5 mg/kg will be employed for intravenous or intramuscular administration. A dosage from about 10 mg/kg to about 50 mg/kg may be employed for oral administration.

The following Examples are provided to further illustrate the present invention, and should not be construed as limiting thereof. The present invention is defined by the claims which follow. Melting points were determined on a Fisher-John melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba EA 1108 elemental analyzer. Proton Nulear Magnetic Resonance (^{1}H NMR) spectra were measured on a Bruker AC-300

spectrometer with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ (ppm). Mass spectra (MS) were obtained on a TRIO 1000 mass spectrometer. Flash column chromatography was performed on silica gel (mesh 25-150 μm) using a mixture of CH_2Cl_2 amd EtOAc as eluant. Precoated silica gel plates (Kieselgel 60 F_{254} 0.25 mm, Merck) was used for thin layer chromatography (TLC) analysis. In these examples, "g" means grams, "mg" means milligrams, "mL" means milliliters, "min." means minute(s), "°C" means degress Centigrade.

EXAMPLE 1

Preparation of Substituted Ethyl Benzoylacetates

The substituted ethyl benzolylacetates were prepared according to procedures described in Krapcho et al., *Organic Synthesis* **5**:198 (1973). To a vigorously stirring suspension of NaH and $CO(OEt)_2$ in toluene was added dropwise a solution of substituted acetophenone in toluene under reflux. The mixture was allowed to reflux and was stirred for 20 min after the addition was complete. When cooled to room temperature, the mixture was acidified with glacial AcOH. After ice-cold water was added, the mixture wasa extracted with toluene. The extract was then dried over $MgSO_4$. After the toluene was evaporated at atmospheric pressure, the residue was distilled *in vacuo* to give the corresponding substituted ethyl benzoylacetates.

EXAMPLE 2

General Procedures for the Preparation of 2-Aryl-pyrido[1,2-a]pyrimidin-4-ones and 2-Aryl-1,8-naphthyridin-4-ones

Method 1. A mixture of substituted 2-aminopyridine (1), substituted ethyl benzoylacetate (2), and PPA was heated at 125 °C with stirring. The reaction was monitored by TLC. After the reaction was completed, the mixture was cooled to room temperature and neutralized with 4M NaOH. After extraction with Ch_2C1_2, the extract was passed through a silica gel column to give 2-phenyl-pyrido[1,2-*a*]pyrimidin-4-ones. The 2-phenyl-pyrido [1-2,*a*]pyrimidin-4-one was then added to liquid paraffin at 350°C for 2 hr after the addition was

complete. The cooled mixture was subjected to silica gel column chromatography. Elution with CH_2Cl_2-EtOAc gave the corresponding 2-phenyl-1,8-naphthyridin-4-ones.

Method 2. The substituted 2-aminopyridine and substituted aldehyde in equimolar concentration were heated in refluxing *m*-xylene until 90-95% of the theoretical amount of H_2O was collected in a Dean-Stark trap. After the *m*-xylene was evaporated at atmospheric pressure, the residue was distilled *in vacuo* to afford 2-arylideneaminopyridine. The 2-arylideneaminopyridine and Et^3N were dissolved in anhydrous Et_2OP; a solution of chloroacetyl chloride in anhydrous Et_2O was then added dropwise with stirring at -15 to -10°C. After the addition was complete, the mixture wa stirred for 1 hour. The precipitated triethylamine chloride was filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with CH_2Cl_2-EtOAc as eluant to give 2-phenyl-pyrido [1,2-*a*]pyrimidin-4-one, which was converted to the corresponding 2-phenyl-1,8-naphthyridin-4-one according to the procedures described in Method 1.

EXAMPLE 3

Data Regarding Specific 2-Phenyl-pyrido[1,2,*a*]pyrimidin-4-ones (Compounds 7-38)

•2-(2'-Methoxyphenyl)-pyrido[1,2-*a*]pyrimidin-4-one (7) is obtained from ethyl 2'-methoxybenzoylacetate and 2-aminopyridine. Characteristics: needles;, mp 148-149°C; ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 7.0 Hz, 1 H, H-6), 7.98 (dd, J = 7.5, 1.5 Hz, 1 H, H-6'), 7.78 (d, J = 7.0 Hz, 1 H, H-9), 7.74 (t, J = 7.0 Hz, 1 H, H-8), 7.44 (td, J = 7.5, 1.5 Hz, 1 H, H-4'), 7.15 (s, 1 H, H-3), 7.14 (t, J = 7.5 Hz, 1 H, H-5'), 7.12 (t, J = 7.0 Hz, 1 H-7), 7.04 (br. d, J = 8.5 Hz, 1 H, H-3'), 3.92 (s, 3 H, OCH_3-2'). MS *m/z* 252 (M^+).

•2-(2'-Methoxyphenyl)-8-methyl-pyrido [1,2-*a*]pyrimidin-4-one (8) is obtained from ethyl 2'-methoxybenzoylacetate and 2-amino-4-picoline. Characteristics: prisms; mp 154-155 °C; ^{1}H NMR ($CDCl_3$) δ 8.96 (d, J = 7.0 Hz, 1 H, H-6), 7.95 (dd, J = 7.5, 1.5 Hz, 1 H, H-6'), 7.57 (br. s, 1 H, H-9), 7.44 (td, J =

7.5, 1.5 Hz, 1 H, H-4'), 7.09 (t, J = 7.5 Hz, 1 H, H-5'), 7.05 (s, 1 H, H-3), 7.02 (br. d, J = 8.0 Hz, 1 H, H-7), 6.97 (dd, J = 7.5, 1.5 Hz, 1 H, H-3'), 3.90 (s, 3 H, OCH_3-2'), 2.49 (s, 3 H, CH_3-8). MS *m/z* 266 (M^+).

•2-(2'-Methoxyphenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(9)** is obtained from ethyl 2'-methoxybenzoylacetate and 2-amino-5-picoline. Characteristics: prisms; mp 148-149 °C; ^1H NMR ($CDCl_3$) δ 8.89 (s, 1 H, H-6), 7.96 (dd, J = 7.9, 1.9 Hz, 1 H, H-6'), 7.74 (d, J = 9.0 Hz, 1 H, H-9), 7.60 (dd, J = 9.0, 2.0 Hz, 1 H, H-8), 7.44 (td, J = 7.9, 1.9 Hz, 1 H, H-4'), 7.12 (s, 1 H, H-3), 7.10 (dt, J = 7.9 1.9 Hz, 1 H, H-5'), 7.03 (d, J = 7.9, Hz, 1 H, H-3'), 3.91 (s, 3 H, OCH_3-2'), 2.45 (s, 3 H, CH_3-7). MS *m/z* 266 (M^+).

•2-(2'-Methoxyphenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(10)** is obtained from ethyl 2'-methoxybenzoylacetate and 2-amino-6-picoline. Characteristics: prisms; mp 153-154 °C; ^1H NMR ($CDCl_3$) δ 7.99 (dd, J = 7.5, 1.7 Hz, 1 H, H-6'), 7.52 (d, J = 9.0 Hz, 1 H, H-9), 7.42 (t, J = 9.0, Hz, 1 H, H-8), 7.42 (td, J = 7.5, 1.7 Hz, 1 H, H-4'), 7.09 (t, J = 7.5 Hz, 1 H, H-5'), 7.01 (d, J = 7.5, Hz, 1 H, H-3'), 6.97 (s, 1 H, H-3), 6.64 (d, J = 9.0 Hz, 1 H, H-7), 3.91 (s, 3 H, OCH_3-2'), 3.09 (s, 3 H, CH_3-6). MS *m/z* 266 (M^+).

•2-(2'-Methoxyphenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(11)** is obtained from ethyl 2'-methoxybenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: prisms; mp 170-171 °C; ^1H NMR ($CDCl_3$) δ 7.96 (dd, J = 7.5, 1.7 Hz, 1 H, H-6'), 7.41 (td, J = 7.5, 1.7 Hz, 1 H, H-4'), 7.33 (br. s, 1 H, H-9), 7.08 (t, J = 7.5 Hz, 1 H, H-5'), 7.01 (d, J = 7.5, Hz, 1 H, H-3'), 6.88 (s, 1 H, H-3), 6.49 (br. s, 1 H, H-7), 3.90 (s, 3 H, OCH_3-2'), 3.06 (s, 3 H, CH_3-6), 2.34 (s, 3 H, CH_3-8). MS *m/z* 280 (M^+).

•2-(3'-Methoxyphenyl)-pyrido[1,2-*a*]pyrimidin-4-one **(12)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-aminopyridine. Characteristics: prisms; mp 156-157 °C; ^1H NMR ($CDCl_3$) δ 9.08 (d, J = 7,0 Hz, 1 H, H-6), 7.76 (d, J = 7.0 Hz, 1 H, H-9), 7.75 (t, J = 7.0 Hz, 1 H, H-8), 7.67 (s, 1 H, H-2'), 7.66 (d, J = 7.5, Hz, 1 H, H-6'), 7.42 (t, J = 7.5 Hz, 1 H, H-5'), 7.15 (ddd, J = 7.0, 7.0, 2.0 Hz, 1 H, H-7), 7.05 (td, J = 7.5 Hz, 1 H, H-4'), 6.92 (s, 1 H, H-3), 3.92 (s, 3 H, OCH_3-3'). MS *m/z* 252 (M^+).

•2-(3'-Methoxyphenyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(13)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-amino-4-picoline. Characteristics: plates; mp 136-137 °C; ^{1}H NMR ($CDCl_3$) δ 8.97 (d, J = 7.0 Hz, 1 H, H-6), 7.66 (br. s, 1 H, H-2'), 7.64 (d, J = 7.5, 1 H, H-6'), 7.54 (s, 1 H, H-9), 7.41 (t, J = 7.5 Hz, 1 H, H-5'), 7.04 (dd, J = 7.5, 2.0 Hz, 1 H, H-4'), 6.98 (d, J = 7.0 Hz, 1 H, H-7), 6.85 (s, 1H, H-3), 3.91 (s, 3 H, OCH_3-3'), 2.51 (s, 3 H, CH_3-8). MS *m/z* 266 (M^+).

•2-(3'-Methoxyphenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(14)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-amino-5-picoline. Characteristics: prisms; mp 163-164 °C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H, H-6), 7.70 (d, J = 9.0 Hz, 1 H, H-9), 7.66 (d, J = 2.0 Hz, 1 H, H-2'), 7.65 (d, J = 7.8 Hz, 1 H, H-6'), 7.62 (dd, J = 9.0, 1.8 Hz, 1 H, H-8), 7.42 (t, J = 7.8, Hz, 1 H, H-5'), 7.04 (td, J = 7.8, 2.0 Hz, 1 H, H-4'), 6.90 (s, 1 H, H-3), 3.91 (s, 3 H, OCH_3-3'), 2.46 (s, 3 H, CH_3-7). MS *m/z* 266 (M^+).

•2-(3'-Methoxyphenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(15)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-amino-6-picoline. Characteristics: prisms; mp 115-116 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 1 H, H-2'), 7.61 (d, J = 7.5 Hz, 1 H, H-6'), 7.49 (d, J = 8.5, Hz, 1 H, H-9), 7.45 (dd, J = 8.5, 6.3 Hz, 1 H, H-8), 7.39 (t, J = 7.5 Hz, 1 H, H-5'), 7.02 (td, J = 7.5, 2.0 Hz, 1 H, H-4'), 6.72 (s, 1 H, H-3), 6.64 (d, J = 6.3 Hz, 1 H, H-7), 3.90 (s, 3 H, OCH_3-3'), 3.08 (s, 3 H, CH_3-6). MS *m/z* 266 (M^+).

•2-(3'-Methoxyphenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(16)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: prisms; mp 139-140 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (br. s, 1 H, H-2'), 7.60 (d, J = 7.5, Hz, 1 H, H-6'), 7.38 (t, J = 7.5 Hz, 1 H, H-5'), 7.28 (br. s, 1 H, H-9), 7.01 (dd, J = 7.5, 2.0 Hz, 1 H, H-4'), 6.64 (s, 1 H, H-3), 6.49 (br. s, 1 H, H-7), 3.89 (s, 3 H, OCH_3-3'), 3.05 (s, 3 H, CH_3-6), 2.34 (s, 3 H, CH_3-8). MS *m/z* 280 (M^+).

•2-(3'-Methoxyphenyl)-7-chloro-pyrido[1,2-*a*]pyrimidin-4-one **(17)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-amino-5-chloropyridine. Characteristics: needles; mp 172-173 °C; ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 1.5 Hz,

1 H, H-6), 7.67 (br. d, 1 H, H-2'), 7.66 (d, J = 10.0 Hz, 1 H, H-8), 7.65 (d, J = 10.0 Hz, 1 H, H-9), 7.63 (d, J = 7.7 Hz, 1 H, H-4'), 7.41 (t, J = 7.7, Hz, 1 H, H-5'), 7.05 (dd, J = 7.7, 2.0 Hz, 1 H, H-6'), 6.92 (s, 1 H, H-3), 3.91 (s, 3 H, OCH_3-3'). MS *m/z* 286 (M^+).

•2-(3'-Methoxyphenyl)-7-bromo-pyrido[1,2-*a*]pyrimidin-4-one **(18)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-amino-5-bromopyridine. Characteristics: needles; mp 197-198 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 2.0 Hz, 1 H, H-6), 7.77 (dd, J = 9.5, 2.0 Hz, 1 H, H-8), 7.64 (br. s, 1 H, H-2'), 7.63 (d, J = 7.7 Hz, 1 H, H-4'), 7.62 (dd, J = 9.0, 2.0 Hz, 1 H, H-9), 7.42 (t, J = 7.7, Hz, 1 H, H-5'), 7.05 (dd, J = 7.7, 2.0 Hz, 1 H, H-6'), 6.93 (s, 1 H, H-3), 3.91 (s, 3 H, OCH_3-3'). MS *m/z* 330 (M^+, 97%), 332 (M^+ + 2, 92%).

•2-(4'-Methoxyphenyl)-pyrido[1,2-*a*]pyrimidin-4-one **(19)** is obtained from ethyl 4'-methoxybenzoylacetate and 2-aminopyridine. Characteristics: needles; mp 153-154 °C; ^{1}H NMR ($CDCl_3$) δ 9.07 (d, J = 7.2 Hz, 1 H, H-6), 8.09 (d, J = 9.0 Hz, 2 H, H_2-2', 6'), 7.76 (d, J = 4.0 Hz, 2 H, H_2-8, 9), 7.12 (dd, J = 7.2, 4.0 Hz, 1 H, H-7), 7.04 (d, J = 9.0 Hz, 2 H, H_2-3' 5'), 6.88 (s, 1 H, H-3), 3.90 (s, 3 H, OCH_3-4'). MS *m/z* 252 (M^+).

•2-(4'-Methoxyphenyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(20)** is obtained from ethyl 4'-methoxybenzoylacetate and 2-amino-4-picoline. Characteristics: needles; mp 167-168 °C; ^{1}H NMR ($CDCl_3$) δ 8.96 (d, J = 7.2 Hz, 1 H, H-6), 8.08 (d, J = 8.8 Hz, 2 H, H_2-2', 6'), 7.55 (br. s, 1 H, H-9), 7.02 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.96 (dd, J = 7.2, 1.7 Hz, 1 H, H-7), 6.79 (s, 1 H, H-3), 3.89 (s, 3 H, OCH_3-4'), 2.51 (s, 3 H, CH_3-8). MS *m/z* 266 (M^+).

•2-(4'-Methoxyphenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(21)** is obtained from ethyl 4'-methoxybenzoylacetate and 2-amino-5-picoline. Characteristics: prisms; mp 197-198 °C; ^{1}H NMR ($CDCl_3$) δ 8.87 (s, 1 H, H-6), 8.07 (d, J = 8.8 Hz, 2 H, H_2-2', 6'), 7.67 (d, J = 9.0 Hz, 1 H, H-9), 7.60 (dd, J = 9.0, 2.0 Hz, 1 H, H-8), 7.02 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.85 (s, 1 H, H-3), 3.89 (s, 3 H, OCH_3-4'), 2.44 (s, 3 H, CH_3-7). MS *m/z* 266 (M^+).

•2-(4'-Methoxyphenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(22)** is obtained from ethyl 4'-methoxybenzoylacetate and 2-amino-6-picoline.

Characteristics: prisms; mp 143-144°C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 9.0 Hz, 2 H, H_2-2', 6'), 7.48 (dd, J = 8.7, 1.4 Hz, 1 H, H-9), 7.42 (dd, J = 6.8, 8.7 Hz, 1 H, H-8), 7.00 (d, J = 9.0 Hz, 2 H, H_2-3', 5'), 6.67 (s, 1 H, H-3), 6.62 (d, J = 6.8 Hz, 1 H, H-7), 3.88 (s, 3 H, OCH_3-4'), 3.08 (s, 3 H, CH_3-6). MS *m/z* 266 (M^+).

•2-(4'-Methoxyphenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(23)** is obtained from ethyl 3'-methoxybenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: amorphous; mp 187-188°C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 9.0 Hz, 2 H, H_2-2', 6'), 7.28 (br. s, 1 H, H-9), 7.00 (d, J = 9.0 Hz, 2 H, H_2-3', 5'), 6.60 (s, 1 H, H-3), 6.48 (br. s, 1 H, H-7), 3.88 (s, 3 H, OCH_3-4'), 3.06 (s, 3 H, CH_3-6), 2.35 (s, 3 H, CH_3-8). MS *m/z* 280 (M^+).

•2-(4'-Fluorophenyl)-pyrido[1,2-*a*]pyrimidin-4-one **(24)** is obtained from ethyl 4'-fluorobenzoylacetate and 2-aminopyridine. Characteristics: needles; mp 193-195°C; ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 7.2 Hz, 1 H, H-6), 8.12 (dd, J = 8.8, 5.2 Hz, 2 H, H_2-2', 6'), 7.79 (dd, J = 9.0, 1.5 Hz, 1 H, H-9), 7.75 (dd, J = 9.0, 6.5 Hz, 1 H, H-8), 7.20 (t, J = 8.8 Hz, 2 H, H_2-3' 5'), 6.88 (s, 1 H, H-3). MS *m/z* 240 (M^+).

•2-(4'-Fluorophenyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(25)** is obtained from ethyl 4'-fluorobenzoylacetate and 2-amino-4-picoline. Characteristics: amorphous; mp 191-193°C; ^{1}H NMR ($CDCl_3$) δ 8.97 (d, J = 7.3 Hz, 1 H, H-6), 8.10 (dd, J = 8.8, 5.7 Hz, 2 H, H_2-2', 6'), 7.53 (br. s, 1 H, H-9), 7.19 (t, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.99 (dd, J = 7.3, 2.0 Hz, 1 H, H-7), 6.80 (s, 1 H, H-3), 2.52 (s, 3 H, CH_3-8). MS *m/z* 254 (M^+).

•2-(4'-Fluorophenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(26)** is obtained from ethyl 4'-fluorobenzoylacetate and 2-amino-5-picoline. Characteristics: amorphous; mp 174-175°C; ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1 H, H-6), 8.10 (dd, J = 8.8, 5.7 Hz, 2 H, H_2-2', 6'), 7.67 (d, J = 9.0 Hz, 1 H, H-9), 7.63 (dd, J = 9.0, 2.0 Hz, 1 H, H-8), 7.19 (t, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.85 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-7). MS *m/z* 254 (M^+).

•2-(4'-Fluorophenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(27)** is obtained from ethyl 4'-fluorobenzoylacetate and 2-amino-6-picoline. Characteristics: prisms, mp 179-181°C; ^{1}H NMR ($CDCl_3$) δ 8.07 (dd, J = 8.8, 5.2

Hz, 2 H, H_2-2', 6'), 7.48 (dd, J = 8.5, 2.0 Hz, 1 H, H-9), 7.44 (dd, J = 8.5, 6.5 Hz, 1 H, H-8), 7.17 (t, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.67 (s, 1 H, H-3), 6.64 (dd, J = 6.5, 2.0 Hz, 1 H, H-7), 3.09 (s, 3 H, CH_3-6). MS *m/z* 254 (M^+).

•2-(4'-Fluorophenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(28)** is obtained from ethyl 3'-fluorobenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: prisms; mp 199-201°C; ^{1}H NMR ($CDCl_3$) δ 8.05 (dd, J = 8.7, 5.3 Hz, 2 H, H_2-2', 6'), 7.27 (br. s, 1 H, H-9), 7.16 (t, J = 8.7 Hz, 2 H, H_2-3', 5'), 6.61 (s, 1 H, H-3), 6.51 (br. s, 1 H, H-7), 3.06 (s, 3 H, CH_3-6), 2.36 (s, 3 H, CH_3-8). MS *m/z* 268 (M^+).

•2-(4'-Fluorophenyl)-7-chloro-pyrido[1,2-*a*]pyrimidin-4-one **(29)** is obtained from ethyl 4'-fluorobenzoylacetate and 2-amino-5-chloropyridine. Characteristics: prisms; mp 187-189°C; ^{1}H NMR ($CDCl_3$) δ 9.09 (s, 1 H, H-6), 8.10 (dd, J = 8.7, 5.6 Hz, 2 H, H_2-2', 6'), 7.70 (dd, J = 9.0, 2.0 Hz, 1 H, H-8), 7.67 (d, J = 9.0 Hz, 1 H, H-9); 7.20 (t, J = 8.7 Hz, 2 H, H_2-3', 5'), 6.89 (s, 1 H, H-3). MS *m/z* 274 (M^+).

•2-(4'-Chlorophenyl)-pyrido[1,2-*a*]pyrimidin-4-one **(30)** is obtained from ethyl 4'-chlorobenzoylacetate and 2-aminopyridine. Characteristics: amorphous; mp 202-203°C; ^{1}H NMR ($CDCl_3$) δ 9.10 (d, J = 7.0 Hz, 1 H, H-6), 8.07 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.90 (d, J = 9.0 Hz, 1 H, H-9), 7.83 (dd, J = 9.0, 6.5 Hz, 1 H, H-8), 7.50 (d, J = 8.5 Hz, 2 H, H_2-3' 5'), 7.21 (dd, J = 7.0, 6.5 Hz, 1 H, H-7), 6.88 (s, 1 H, H-3). MS *m/z* 256 (M^+).

•2-(4'-Chlorophenyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(31)** is obtained from ethyl 4'-chlorobenzoylacetate and 2-amino-4-picoline. Characteristics: needles; mp 211-213°C; ^{1}H NMR ($CDCl_3$) δ 8.98 (d, J = 7.3 Hz, 1 H, H-6), 8.04 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.56 (br. s, 1 H, H-9), 7.48 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 7.00 (dd, J = 7.3, 1.0 Hz, 1 H, H-7), 6.81 (s, 1 H, H-3), 2.53 (s, 3 H, CH_3-8). MS *m/z* 270 (M^+).

•2-(4'-Chlorophenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(32)** is obtained from ethyl 4'-chlorobenzoylacetate and 2-amino-5-picoline. Characteristics: needles; mp 195-196°C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H, H-6), 8.05 (d, J = 8.6 Hz, 2 H, H_2-2', 6'), 7.77 (d, J = 8.9 Hz, 1 H, H-9), 7.67 (dd, J =

8.9, 1.5 Hz, 1 H, H-8), 7.48 (d, J = 8.6 Hz, 2 H, H_2-3', 5'), 6.86 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-7). MS *m/z* 270 (M^+).

•2-(4'-Chlorophenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(33)** is obtained from ethyl 4'-chlorobenzoylacetate and 2-amino-6-picoline. Characteristics: needles; mp 154-156°C; ^1H NMR ($CDCl_3$) δ 8.02 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.51 (d, J = 8.5 Hz, 1 H, H-9), 7.47 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 7.46 (dd, J = 8.5, 6.3 Hz, 1 H, H-8), 6.69 (s, 1 H, H-3), 6.67 (d, J = 6.3 Hz, 1 H, H-7), 3.09 (s, 3 H, CH_3-6). MS *m/z* 266 (M^+).

•2-(4'-Chlorophenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(34)** is obtained from ethyl 3'-chlorobenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: needles; mp 210-212°C (decomposed); ^1H NMR ($CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.46 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 7.27 (s, 1 H, H-9), 6.61 (s, 1 H, H-3), 6.57 (s, 1 H, H-7), 3.07 (s, 3 H, CH_3-6), 2.39 (s, 3 H, CH_3-8). MS *m/z* 284 (M^+).

•2-(4'-Methylphenyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(35)** is obtained from ethyl 4'-methylbenzoylacetate and 2-amino-4-picoline. Characteristics: prisms; mp 176-177°C; ^1H NMR ($CDCl_3$) δ 8.96 (d, J = 7.3 Hz, 1 H, H-6), 7.99 (d, J = 8.2 Hz, 2 H, H_2-2', 6'), 7.54 (br. s, 1 H, H-9), 7.31 (d, J = 8.2 Hz, 2 H, H_2-3', 5'), 6.96 (dd, J = 7.3, 1.5 Hz, 1 H, H-7), 6.83 (s, 1 H, H-3), 2.50 (s, 3 H, CH_3-8), 2.43 (s, 3 H, CH_3-4'). MS *m/z* 250 (M^+).

•2-(4'-Methylphenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(36)** is obtained from ethyl 4'-methylbenzoylacetate and 2-amino-5-picoline. Characteristics: prisms; mp 171-172°C; ^1H NMR ($CDCl_3$) δ 8.88 (s, 1 H, H-6), 7.99 (d, J = 8.2 Hz, 2 H, H_2-2', 6'), 7.68 (d, J = 9.0 Hz, 1 H, H-9), 7.60 (dd, J = 9.0, 2.0 Hz, 1 H, H-8), 7.31 (d, J = 8.2 Hz, 2 H, H_2-3', 5'), 6.88 (s, 1 H, H-3), 2.44 (s, 3 H, CH_3-7), 2.43 (s, 3 H, CH_3-4'). MS *m/z* 250 (M^+).

•2-(4'-Methylphenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(37)** is obtained from ethyl 4'-methylbenzoylacetate and 2-amino-6-picoline. Characteristics: prisms; mp 140-141°C; ^1H NMR ($CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2 H, H_2-2', 6'), 7.50 (d, J = 8.3 Hz, 1 H, H-9), 7.42 (dd, J = 8.3, 6.5 Hz, 1 H, H-8), 7.30 (d, J = 8.2 Hz, 2 H, H_2-3', 5'), 6.71 (s, 1 H, H-3), 6.64 (d, J = 6.5 Hz, 1 H, H-

7), 3.08 (s, 3 H, CH_3-6), 2.42 (s, 3 H, CH_3-4'). MS *m/z* 250 (M^+).

•2-(4'-Methylphenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(38)** is obtained from ethyl 3'-methylbenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: amorphous; mp 196-198°C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2 H, H_2-2', 6'), 7.30 (s, 1 H, H-9), 7.29 (d, J = 9.0 Hz, 2 H, H_2-3', 5'), 6.64 (s, 1 H, H-3), 6.49 (s, 1 H, H-7), 3.06 (s, 3 H, CH_3-6), 2.42 (s, 3 H, CH_3-4'), 2.35 (s, 3 H, CH_3-8). MS *m/z* 264 (M^+).

EXAMPLE 4

Data Regarding Specific 2-phenyl-1,8-naphthyridin-4-ones (Compounds 39-70)

•2-(2'-Methoxyphenyl)-1,8-naphthyridin-4-one **(39)** is obtained from compound **(7)**. Characteristics: plates; ^{1}H NMR ($CDCl_3$) δ 8.65 (d, J = 8.0 Hz, 1 H, H-5), 8.62 (d, J = 4.5 Hz, 1 H, H-7), 7.64 (dd, J = 8.0, 1.7 Hz, 1 H, H-6'), 7.49 (td, J = 8.0, 1.7 Hz, 1 H, H-4'), 7.34 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 7.10 (t, J = 8.0 Hz, 1 H, H-5'), 7.06 (d, J = 8.0 Hz, 1 H, H-3'), 6.62 (s, 1 H, H-3), 3.94 (s, 3 H, OCH_3-2'). MS *m/z* 252 (M^+). Elemental Analysis: calculated C 7.42, H 4.79, N 11.10; found C 71.27, H 4.86, N 11.02.

•2-(2'-Methoxyphenyl)-5-methyl-1,8-naphthyridin-4-one **(40)** is obtained from compound **(8)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 10.45, (br. s, 1 H, NH-1), 8.19 (d, J = 5.0 Hz, 1 H, H-7), 7.65 (dd, J = 7.5, 1.0 Hz, 1 H, H-6'), 7.50 (td, J = 7.5, 1.0 Hz, 1 H, H-4'), 7.13 (t, J = 7.5 Hz, 1 H, H-5'), 7.04 (d, J = 7.5 Hz, 1 H, H-3'), 6.98 (d, J = 5.0 Hz, 1 H, H-6), 6.56 (s, 1 H, H-3), 3.89 (s, 3 H, OCH_3-2'), 2.99 (s, 3 H, CH_3-5). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 72.17, H 5.30, N 10.52; found C 72.21, H 5.33, N 10.38.

•2-(2'-Methoxyphenyl)-6-methyl-1,8-naphthyridin-4-one **(41)** is obtained from compound **(9)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 11.19, (br. s, 1 H, NH-1), 8.48 (d, J = 1.8 Hz, 1 H, H-5), 8.01 (d, J = 1.8 Hz, 1 H, H-7), 7.62 (dd, J = 8.0, 1.7 Hz, 1 H, H-6'), 7.52 (td, J = 8.0, 1.7 Hz, 1 H, H-4'), 7.13 (t, J = 8.0 Hz, 1 H, H-5'), 7.01 (d, J = 8.0 Hz, 1 H, H-3'), 6.59 (s, 1 H, H-3), 3.78 (s, 3 H, OCH_3-2'), 2.40 (s, 3 H, CH_3-6). MS *m/z* 266 (M^+). Elemental Analysis:

calculated C 72.17, H 5.30, N 10.52; found C 72.03, H 5.42, N 10.59.

•2-(2'-Methoxyphenyl)-7-methyl-1,8-naphthyridin-4-one **(42)** is obtained from compound **(10)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 10.66, (br. s, 1 H, NH-1), 8.57 (d, J = 8.0 Hz, 1 H, H-5), 7.63 (dd, J = 7.5, 1.5 Hz, 1 H, H-6'), 7.49 (td, J = 7.5, 1.5 Hz, 1 H, H-4'), 7.15 (d, J = 8.0 Hz, 1 H, H-6), 7.12 (t, J = 7.5 Hz, 1 H, H-5'), 6.95 (d, J = 7.5 Hz, 1 H, H-3'), 6.59 (s, 1 H, H-3), 3.73 (s, 3 H, OCH_3-2'), 2.42 (s, 3 H, CH_3-7). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 72.17, H 5.30, N 10.52; found C 72.10, H 5.51, N 10.29.

•2-(2'-Methoxyphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(43)** is obtained from compound **(11)**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 7.62 (dd, J = 7.5, 1.5 Hz, 1 H, H-6'), 7.47 (td, J = 7.5, 1.5 Hz, 1 H, H-4'), 7.10 (t, J = 7.5 Hz, 1 H, H-5'), 6.95 (d, J = 7.5 Hz, 1 H, H-3'), 6.84 (s, 1 H, H-6), 6.50 (s, 1 H, H-3), 3.77 (s, 3 H, OCH_3-2'), 2.95 (s, 3 H, CH_3-5), 2.35 (s, 3 H, CH_3-7). MS *m/z* 280 (M^+). Elemental Analysis: calculated C 71.69, H 5.84, N 9.84; found C 71.81, H 5.98, N 9.92.

•2-(3'-Methoxyphenyl)-1,8-naphthyridin-4-one **(44)** is obtained from compound **(12)**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 11.10, (br. s, 1 H, NH-1), 8.70 (dd, J = 8.0, 1.5 Hz, 1 H, H-5), 8.10 (dd, J = 4.5, 1.5 Hz, 1 H, H-7), 7.45 (t, J = 8.0 Hz, 1 H, H-5'), 7.31 (d, J = 8.0, Hz, 1 H, H-6'), 7.26 (br. s, 1 H, H-2'), 7.24 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 7.10 (dd, J = 8.0, 2.0 Hz, 1 H, H-4'), 6.60 (s, 1 H, H-3), 3.85 (s, 3 H, OCH_3-3'). MS *m/z* 252 (M^+). Elemental Analysis: calculated C 71.42, H 4.79, N 11.10; found C 71.31, H 4.84, N 11.07.

•2-(3'-Methoxyphenyl)-5-methyl-1,8-naphthyridin-4-one **(45)** is obtained from compound **(13)**. Characteristics: plates; ^{1}H NMR ($CDCl_3$) δ 10.74, (br. s, 1 H, NH-1), 7.84 (d, J = 5.0 Hz, 1 H, H-7), 7.43 (t, J = 8.0 Hz, 1 H, H-5'), 7.29 (d, J = 8.0 Hz, 1 H, H-6'), 7.22 (t, J = 2.5 Hz, 1 H, H-2'), 7.09 (dd, J = 8.0, 2.5 Hz, 1 H, H-4'), 6.93 (d, J = 5.0 Hz, 1 H, H-6), 6.52 (s, 1 H, H-3), 3.85 (s, 3 H, OCH_3-3'), 2.97 (s, 3 H, CH_3-5). MS *m/z* 266 (M^+). Elemental Analysis: calculated: C 72.17, H 5.30, N 10.52; found C 72.01, H 5.43, N 10.39.

•-(3'-Methoxyphenyl)-6-methyl-1,8-naphthyridin-4-one **(46)** is obtained from compound **(14)**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ

10.75, (s, 1 H, NH-1), 8.49 (d, J = 2.0 Hz, 1 H, H-5), 8.00 (d, J = 2.0 Hz, 1 H, H-7), 7.46 (t, J = 8.0 Hz, 1 H, H-5'), 7.29 (d, J = 8.0 Hz, 1 H, H-6'), 7.23 (t, J = 1.8 Hz, 1 H, H-2'), 7.11 (dd, J = 8.0, 1.8 Hz, 1 H, H-4'), 6.58 (s, 1 H, H-3), 3.85 (s, 3 H, OCH_3-3'), 2.39 (s, 3 H, CH_3-6). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 72.17, H 5.30, N 10.52; found C 72.32, H 5.51, N 10.41.

•2-(3'-Methoxyphenyl)-7-methyl-1,8-naphthyridin-4-one **(47)** is obtained from compound **(15)**. Characteristics: amorphous; ^1H NMR ($CDCl_3$) δ 9.13, (br. s, 1 H, NH-1), 8.57 (d, J = 8.0 Hz, 1 H, H-5), 7.45 (t, J = 8.0 Hz, 1 H, H-5'), 7.26 (d, J = 8.0 Hz, 1 H, H-6'), 7.21 (d, J = 8.0 Hz, 1 H, H-6), 7.20 (s, 1 H, H-2'), 7.08 (d, J = 8.0 Hz, 1 H, H-4'), 6.60 (s, 1 H, H-3), 3.88 (s, 3 H, OCH_3-3'), 2.60 (s, 3 H, CH_3-7). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 72.17, H 5.30, N 10.52; found C 72.28, H 5.49, N 10.36.

•2-(3'-Methoxyphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(48)** is obtained from compound **(16)**. Characteristics: prisms; ^1H NMR ($CDCl_3$) δ 9.42, (br. s, 1 H, NH-1), 7.40 (t, J = 8.0 Hz, 1 H, H-5'), 7.22 (d, J = 8.0 Hz, 1 H, H-6'), 7.15 (t, J = 2.0 Hz, 1 H, H-2'), 7.05 (dd, J = 8.0, 2.0 Hz, 1 H, H-4'), 6.88 (s, 1 H, H-6), 6.50 (s, 1 H, H-3), 3.83 (s, 3 H, OCH_3-3'), 2.94 (s, 3 H, CH_3-5), 2.40 (s, 3 H, CH_3-7). MS *m/z* 280 (M^+). Elemental Analysis: calculated C 72.84, H 5.75, N 9.99; found C 72.62, H 5.91, N 9.87.

•2-(3'-Methoxyphenyl)-6-chloro-1,8-naphthyridin-4-one **(49)** is obtained from compound **(17)**; Charactertistics: needles; ^1H NMR (DMSO-d_6) δ 12.57, (s, 1 H, NH-1), 8.85 (d, J = 2.7 Hz, 1 H, H-5), 8.44 (d, J = 2.0 Hz, 1 H, H-7), 7.47 (t, J = 8.0 Hz, 1 H, H-5'), 7.41 (d, J = 8.0 Hz, 1 H, H-6'), 7.41 (br. s, 1 H, H-2'), 7.13 (br. d, J = 8.0, Hz, 1 H, H-4'), 6.49 (s, 1 H, H-3), 3.87 (s, 3 H, OCH_3-3'). MS *m/z* 286 (M^+). Elemental Analysis: calculated C 58.93, H 4.62, N 9.16; found C 59.11, H 4.90, N 9.27.

•2-(3'-Methoxyphenyl)-6-bromo-1,8-naphthyridin-4-one **(50)** is obtained from compound **(18)**. Characteristics: amorphous; ^1H NMR (DMSO-d_6) δ 12.54, (s, 1 H, NH-1), 8.90 (d, J = 2.3 Hz, 1 H, H-5), 8.55 (d, J = 2.3 Hz, 1 H, H-7), 7.46 (t, J = 7.8 Hz, 1 H, H-5'), 7.42 (d, J = 7.8 Hz, 1 H, H-6'), 7.41 (s, 1 H, H-2'), 7.12 (br. d, J = 7.8 Hz, 1 H, H-4'), 6.49 (s, 1 H, H-3), 3.87 s, 3 H, OCH_3-3').

MS *m/z* 330 (M^+, 100%), 332 ($M^+ + 2$, 94%). Elemental Analysis: calculated C 52.81, H 3.84, N 8.21; found C 52.97, H 4.08, N 8.02.

•2-(4'-Methoxyphenyl)-1,8-naphthyridin-4-one **(51)** is obtained from compound **(19)**. Characteristics: plates; ^{1}H NMR ($CDCl_3$) δ 8.69 (dd, J = 8.0, 2.0 Hz, 1 H, H-5), 8.35 (dd, J = 5.2, 2.0 Hz, 1 H, H-7), 7.70 (d, J = 8.8 Hz, 2 H, H_2-2', 6'), 7.30 (dd, J = 8.0, 5.2 Hz, 1 H, H-6), 7.06 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.61 (s, 1 H, H-3), 3.91 (s, 3 H, OCH_3-4'). MS *m/z* 252 (M^+). Elemental Analysis: calculated C 71.42, H 4.79, N 11.10; found C 71.18, H 4.93, N 11.01.

•2-(4'-Methoxyphenyl)-5-methyl-1,8-naphthyridin-4-one **(52)** is obtained from compound **(20)**. Characteristics: plates; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 4.8 Hz, 1 H, H-7), 7.67 (d, J = 8.8 Hz, 2 H, H_2-2', 6'), 7.05 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.98 (d, J = 4.8 Hz, 1 H, H-6), 6.51 (s, 1 H, H-3), 3.90 (s, 3 H, OCH_3-4'), 2.98 (s, 3 H, CH_3-5). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 72.17, H 5.30, N 10.52; found C 72.35, H 5.62, N 10.73.

•2-(4'-Methoxyphenyl)-6-methyl-1,8-naphthyridin-4-one **(53)** is obtained from compound **(21)**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1 H, H-5), 8.30 (s, 1 H, H-7), 7.69 (d, J = 8.7 Hz, 2 H, H_2-2', 6'), 7.07 (d, J = 8.7 Hz, 2 H, H_2-3', 5'), 6.63 (s, 1 H, H-3), 3.90 (s, 3 H, OCH_3-4'), 2.45 (s, 3 H, CH_3-6). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 72.17, H 5.30, N 10.52; found C 71.98, H 5.26, N 10.39.

•2-(4'-Methoxyphenyl)-7-methyl-1,8-naphthyridin-4-one **(54)** is obtained from compound **(22)**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, J = 8.0 Hz, 1 H, H-5), 7.68 (d, J = 8.8 Hz, 2 H, H_2-2', 6'), 7.23 (d, J = 8.0 Hz, 1 H, H-6), 7.07 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.61 (s, 1 H, H-3), 3.90 (s, 3 H, OCH_3-4'), 2.67 (s, 3 H, CH_3-7). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 72.17, H 5.30, N 10.52; found C 72.09, H 5.36, N 10.46.

•2-(4'-Methoxyphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(55)** is obtained from compound **(23)**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2 H, H_2-2', 6'), 7.02 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.89 (s, 1 H, H-6), 6.48 (s, 1 H, H-3), 3.88 (s, 3 H, OCH_3-4'), 2.94 (s, 3 H, CH_3-5), 2.47 (s, 3 H, CH_3-7). MS *m/z* 280 (M^+). Elemental Analysis: calculated C 70.57, H 5.92, N

9.68; found C 70.48, H 5.89, N 9.45.

•2-(4'-Fluorophenyl)-1,8-naphthyridin-4-one **(56)** is obtained from compound **(24)**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 8.66 (dd, J = 7.9, 1.5 Hz, 1 H, H-5), 8.62 (dd, J = 4.5, 1.5 Hz, 1 H, H-7), 7.74 (dd, J = 8.5, 5.0 Hz, 2 H, H_2-2', 6'), 7.36 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 7.23 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 6.56 (s, 1 H, H-3). MS *m/z* 240 (M^+). Elemental Analysis: calculated C 68.71, H 3.91, N 11.45; found C 68.49, H 4.16, N 11.23.

•2-(4'-Fluorophenyl)-5-methyl-1,8-naphthyridin-4-one **(57)** is obtained from compound **(25)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J = 4.7 Hz, 1 H, H-7), 7.71 (dd, J = 8.5, 5.0 Hz, 2 H, H_2-2', 6'), 7.21 (t, J = 8.5 Hz, 2 H, H_2-3', 5'), 7.04 (d, J = 4.7 Hz, 1 H, H-6), 6.47 (s, 1 H, H-3), 2.93 (s, 3 H, CH_3-5). MS *m/z* 254 (M^+). Elemental Analysis: calculated C 70.86, H 4.36, N 11.02; found C 70.94, H 4.51, N 11.16.

•2-(4'-Fluorophenyl)-6-methyl-1,8-naphthyridin-4-one **(58)** is obtained from compound **(26)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J = 2.0 Hz, 1 H, H-5), 8.45 (br. s, 1 H, H-7), 7.73 (dd, J = 8.8, 5.2 Hz, 2 H, H_2-2', 6'), 7.22 (t, J = 8.8 Hz, 2 H, H_2-3', 5'), 6.55 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-6). MS *m/z* 254 (M^+). Elemental Analysis: calculated C 70.86, H 4.36, N 11.02; found C 70.71, H 4.45, N 10.87.

•2-(4'-Fluorophenyl)-7-methyl-1,8-naphthyridin-4-one **(59)** is obtained from compound **(27)**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 9.04 (br. s, 1 H, NH-1), 8.58 (d, J = 8.0 Hz, 1 H, H-5), 7.71 (dd, J = 8.5, 5.0 Hz, 2 H, H_2-2', 6'), 7.26 (t, J = 8.5 Hz, 2 H, H_2-3', 5'), 7.23 (d, J = 8.0 Hz, 1 H, H-6), 6.55 (s, 1 H, H-3), 2.64 (s, 3 H, CH_3-7). MS *m/z* 254 (M^+). Elemental Analysis: calculated C 70.86, H 4.36, N 11.02; found C 70.59, H 4.54, N 11.11.

•2-(4'-Fluorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(60)** is obtained from compound **(28)**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 8.88 (br. s, 1 H, NH-1), 7.68 (dd, J = 8.7, 5.1 Hz, 2 H, H_2-2', 6'), 7.24 (t, J = 8.7 Hz, 2 H, H_2-3', 5'), 6.92 (s, 1 H, H-6), 6.45 (s, 1 H, H-3), 2.94 (s, 3 H, CH_3-5), 2.53 (s, 3 H, CH_3-7). MS *m/z* 268 (M^+). Elemental Analysis: calculated C 67.12, H 5.28, N 9.78; found C 67.33, H 5.45, N 9.91.

•2-(4'-Fluorophenyl)-6-chloro-1,8-naphthyridin-4-one **(61)** is obtained from compound **(29)**. Characteristics: prisms; ^{1}H NMR (DMSO-d_6) δ 12.58 (br. s, 1 H, NH-1), 8.85 (d, J = 2.4 Hz, 1 H, H-5), 8.44 (d, J = 2.4 Hz, 1 H, H-7), 7.92 (dd, J = 8.5, 5.5 Hz, 2 H, H_2-2', 6'), 7.40 (t, J = 8.5 Hz, 2 H, H_2-3', 5'), 6.45 (s, 1 H, H-3). MS *m/z* 274 (M^+). Elemental Analysis: calculated C 61.22, H 2.94, N 10.20; found C 61.09, H 3.13, N 10.03.

•2-(4'-Chlorophenyl)-1,8-naphthyridin-4-one **(62)** is obtained from compound **(30)**. Characteristics: plates; ^{1}H NMR ($CDCl_3$) δ 8.67 (dd, J = 4.5, 1.5 Hz, 1 H, H-7), 8.63 (dd, J = 8.0, 1.5 Hz, 1 H, H-5), 7.68 (d, J = 8.7 Hz, 2 H, H_2-2', 6'), 7.49 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 7.37 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.64 (s, 1 H, H-3). MS *m/z* 256 (M^+). Elemental Analysis: calculated C 65.51, H 3.53, N 10.91; found C 65.62, H 3.73, N 10.79.

•2-(4'-Chlorophenyl)-5-methyl-1,8-naphthyridin-4-one **(63)** is obtained from compound **(31)**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.36 (d, J = 5.0 Hz, 1 H, H-7), 7.68 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.49 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 7.06 (d, J = 5.0 Hz, 1 H, H-6), 6.57 (s, 1 H, H-3), 2.95 (s, 3 H, CH_3-5). MS *m/z* 270 (M^+). Elemental Analysis: calculated C 66.55, H 4.10, N 10.35; found C 66.78, H 4.41, N 10.53.

•2-(4'-Chlorophenyl)-6-methyl-1,8-naphthyridin-4-one **(64)** is obtained from compound **(32)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1 H, H-5), 8.41 (s, 1 H, H-7), 7.66 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.47 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 6.60 (s, 1 H, H-3), 2.44 (s, 3 H, CH_3-6). MS *m/z* 270 (M^+). Elemental Analysis: calculated C 66.55, H 4.10, N 10.35; found C 66.46, H 4.36, N 10.25.

•2-(4'-Chlorophenyl)-7-methyl-1,8-naphthyridin-4-one **(65)** is obtained from compound **(33)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 8.0 Hz, 1 H, H-5), 7.67 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.49 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 7.22 (d, J = 8.0 Hz, 1 H, H-6), 6.60 (s, 1 H, H-3), 2.64 (s, 3 H, CH_3-7). MS *m/z* 266 (M^+). Elemental Analysis: calculated C 66.55, H 4.10, N 10.35; found C 66.49, H 4.31, N 10.08.

•2-(4'-Chlorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(66)** is

obtained from compound **(34)**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 2 H, H_2-2', 6'), 7.52 (d, J = 8.5 Hz, 2 H, H_2-3', 5'), 6.95 (s, 1 H, H-6), 6.51 (s, 1 H, H-3), 2.96 (s, 3 H, CH_3-5), 2.56 (s, 3 H, CH_3-7). MS *m/z* 284 (M^+). Elemental Analysis: calculated C 67.49, H 4.60, N 9.84; found C 67.61, H 4.69, N 9.62.

•2-(4'-Methylphenyl)-5-methyl-1,8-naphthyridin-4-one **(67)** is obtained from compound **(35)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 4.9 Hz, 1 H, H-7), 7.61 (d, J = 8.2 Hz, 2 H, H_2-2', 6'), 7.34 (d, J = 8.2 Hz, 2 H, H_2-3', 5'), 6.95 (d, J = 4.9 Hz, 1 H, H-6), 6.52 (s, 1 H, H-3), 2.98 (s, 3 H, CH_3-5), 2.46 (s, 3 H, CH_3-4'). MS *m/z* 250 (M^+). Elemental Analysis: calculated C 76.78, H 5.64, N 11.19; found C 76.56, H 5.91, N 11.02.

•2-(4'-Methylphenyl)-6-methyl-1,8-naphthyridin-4-one **(68)** is obtained from compound **(36)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 10.61 (br. s, 1H, NH-1), 8.49 (d, J = 1.5 Hz, 1 H, H-5), 8.00 (d, J = 1.5 Hz, 1 H, H-7), 7.62 (d, J = 8.1 Hz, 2 H, H_2-2', 6'), 7.36 (d, J = 8.1 Hz, 2 H, H_2-3', 5'), 6.59 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-6), 2.39 (s, 3 H, CH_3-4'). MS *m/z* 250 (M^+). Elemental Analysis: calculated C 76.78, H 5.64, N 11.19; found C 76.73, H 5.69, N 11.03.

•2-(4'-Methylphenyl)-7-methyl-1,8-naphthyridin-4-one **(69)** is obtained from compound **(37)**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 8.57 (d, J = 8.0 Hz, 1 H, H-5), 7.59 (d, J = 8.2 Hz, 2 H, H_2-2', 6'), 7.33 (d, J = 8.8 Hz, 2 H, H_2-3', 5'), 7.19 (d, J = 8.0 Hz, 1 H, H-6), 6.59 (s, 1 H, H-3), 2.57 (s, 3 H, CH_3-7), 2.44 (s, 3 H, CH_3-4'). MS *m/z* 250 (M^+). Elemental Analysis: calculated C 76.78, H 5.64, N 11.19; found C 76.51, H 5.53, N 11.01.

•2-(4'-Methylphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(70)** is obtained from compound **(38)**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2 H, H_2-2', 6'), 7.31 (d, J = 8.1 Hz, 2 H, H_2-3', 5'), 6.89 (s, 1 H, H-6), 6.50 (s, 1 H, H-3), 2.93 (s, 3 H, CH_3-5), 2.48 (s, 3 H, CH_3-7), 2.44 (s, 3 H, CH_3-4'). MS *m/z* 264 (M^+). Elemental Analysis: calculated C 77.25, H 6.10, N 10.60; found C 77.43, H 6.214, N 10.52.

EXAMPLE 5

Cytotoxicity Assays of Compounds 39-70

Compounds **8-40** were assayed for *in vitro* cytotoxicity with a panel of human and murine tumor cell lines at the School of Medicine, University of North Carolina at Chapel Hill according to procedures described in K. H. Lee, *Planta Medica* **54**:308 (1988). The cell lines include human epidermoid carcinoma of the nasopharynx (KB), lung carcinoma (A-549), ileocecal carcinoma (HCT-8), melanoma (PRMI-7951), and medulloblastoma (TE-671), as well as one murine leukemia cell line (P-388).

Compounds **41-51** and **53-68** were submitted to NCI and assayed in the NCI's *in vitro* disease-oriented antitumor screen, which involves determination of a test compound's effects on the growth of approximately 60 human tumor cell lines. *See*, M. R. Boyd, et al. In *Cancer: Principles and Practice of Oncology Updates;* De Vita, V. T., Hellman, S., Rosenberg, S. A., Eds; J. B. Lippincoft: Philadelphia, pp 1-12 (1989); and A. Monks, et al. *J. Natl. Cancer Inst.* **83**:757 (1991). These lines include leukemia, non-small cell lung, colon, central nervous system (CNS), melanoma, ovarian, renal, prostate, and breast cancers. The cytotoxic effects of each compound were obtained as GI_{50} or TGI values, which represent the molar drug concentrations required to cause 50% inhibition or total growth inhibition, respectively.

The results of the cytotoxicity studies of Compounds **8-40** indicated that essentially all 2-phenyl-pyrido[1,2-*a*]pyrimidin-4-ones were inactive (EC_{50} >4 μg/ml); only a few compounds showed marginal activity.

The results of the cytotoxicity studies of the 2-aryl-1,8-naphthyridin-4-ones (Compounds **41-51** and **53-68**) are expressed in in **Table 1** as average log GI_{50} values for the entire panel of cell lines and in **Table 2** as log GI_{50} values for selected cell lines.

Table 1

Compound	ITP[1] HC_{50}(μM)±SD	ICB[2] (% Inhibition)	average[3] log GI_{50}	mp (°C)	Yield (%)[4]
39	>40		-4.39	196-197	27
40	20 ± 1		-5.55	199-200	23
41	18 ± 1		-4.50	202-203	38
42	>40		-4.10	198-199	48
43	>40		-4.24	203-204	38
44	0.96 ± 0.1	27 ± 1	-6.87	183-184	42
45	0.62 ± 0.1	28 ± 3	-7.23	208-209	40
46	0.08 ± 0.2	31 ± 4	-7.02	215-216	39
47	0.75 ± 0.2	29 ± 4	-7.24	213-214	63
48	0.88 ± 0.08	22 ± 2	-6.19	206-207	60
49	0.73 ± 0.2	35 ± 6	-7.01	264-265	30
50	1.5 ± 0.07		NT[5]	245-247	0.8
51	>40		-4.42	217-218	33
52	8.8 ± 3		-4.89	196-197	35
53	7.7 ± 0.7		-5.21	261-262	36
54	>40		-4.04	255-256	59
55	>40		-4.48	213-214	56
56	>40		-4.34	200-202	33
57	18 ± 2		-4.42	245-247	48
58	20 ± 0.2		-4.58	286-288	29
59	>40		-4.49	250-251	77
60	>40		-4.39	228-230	21
61	16 ± 3		-4.66	>300	31
62	22 ± 0.1		-4.41	>300	32
63	4.8 ± 1.4		-5.29	261-262	44
64	2.0 ± 0.01		-5.43	290-292	, 64
65	11 ± .07		-5.31	263-265	72
66	32 ± 8		-4.71	262-263	35
67	2.9 ± 0.7		NT[5]	218-220	35
68	2.4 ± 0.8		NT[5]	254-256	31

Compound	ITP[1] $HC_{50}(\mu M)\pm SD$	ICB[2] (% Inhibition)	average[3] log GI_{50}	mp (°C)	Yield (%)[4]
69	4.9 ± 0.2		NT[5]	255-257	61
70	9.8 ± 2		NT[5]	236-237	63
colchicine	0.80 ± 0.07				
podophyllotoxin	0.46 ± 0.02	76 ± 5			
combrtastatin A-4	0.53 ± 0.05	91 ± 2			

[1]Inhibition of Tubulin Polymerization, [2]Inhibition of colchicine binding (evaluated only when polymerization IC50≤1μM), [3]Data obtained from NCI's 60 human tumor cell line in vitro screen and calculated from all cell lines tested, [4]All yields were calculated form aminopyridines, [5]Not tested.

Table 2

Compound	Cytotoxicity log GI_{50} (M)[1]										
	HL-60(TB)[2]	NCI-H460	HCT-1.16	SF-295	U-251	SK-MEL-5	OVCAR-3	786-0	PC-3	MDA-MB-435	MDA-N
39	-4.41	-4.41	-4.56	-4.63	-4.17	-4.50	-4.32	-4.44	-4.53	-4.40	-4.70
40	-4.68	-4.62	-5.12	-4.63	-4.45	-4.65	-4.89	-4.22	-4.68	-5.19	-5.08
41	-5.02	-4.49	-4.37	-4.51	-4.56	-4.69	-4.71	-4.38	-4.57	-5.52	-5.35
42	-4.13	-4.01	-4.42	> -4	> -4	-4.29	> -4	> -4	> -4	-4.66	-4.70
43	-4.52	-4.15	-4.13	-4.27	> -4	-4.47	-4.19	> -4	-4.32	-4.49	-4.48
44	-7.79	-7.04	-7.44	-7.28	-7.26	-7.27	-7.26	7.21	-7.03	< -8.00	< -8.00
45	-7.89	-7.32	-7.35	-7.54	-7.23	-7.65	-7.59	-7.29	-7.58	< -8.00	< -8.00
46	-7.72	-7.36	-7.65	-7.43	-7.35	-7.59	-7.38	-7.43	-7.37	< -8.00	< -8.00
47	-7.74	-7.36	-7.33	-7.52	-7.27	-7.47	-7.65	-7.27	-7.48	< -8.00	-7.96
48	-6.76	-6.35	-6.39	-6.38	-6.77	-6.54	-6.60	-6.36	-6.51	< -8.00	< -8.00
49	-7.57	-7.20	-6.92	-7.22	-6.70	-6.90	-6.31	-6.37	-6.86	-7.49	-7.50
51	-4.89	-4.58	-4.75	-4.19	-4.27	-4.46	-4.52	-4.25	-4.50	-4.70	-4.68
52	-5.36	-5.21	-5.19	-4.71	-5.20	-5.41	-4.86	-4.60	-4.74	-5.62	-5.68
53	-5.64	-5.39	-5.38	-5.28	-5.38	-5.43	-5.53	-5.29	-5.27	-5.74	-5.77

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Compound	Cytotoxicity log GI_{50} (M)[1]										
	HL-60(TB)[2]	NCI-H460	HCT-1.16	SF-295	U-251	SK-MEL-5	OVCAR-3	786-0	PC-3	MDA-MB-435	MDA-N
54	> -4	> -4	> -4	-4.05	> -4	-4.32	> -4	> -4	> -4	-4.37	-4.26
55	-4.80	-4.39	-4.44	-4.37	-4.04	-4.75	-4.49	-4.23	-4.62	-4.54	-4.48
56	-4.89	-4.46	-4.37	-4.30	-4.32	-4.52	-4.34	-4.35	-4.34	-4.92	-4.85
57	-5.32	-4.49	-4.79	-4.10	-4.44	-4.79	-4.25	-4.47	-4.29	-5.54	-5.45
58	-5.62	-4.47	-4.62	-4.53	-4.60	-4.66	-4.65	-4.49	-4.59	-5.58	-5.52
59	-4.85	-4.47	-4.47	-4.43	-4.43	-4.50	-4.49	-4.38	-4.68	-5.23	-4.93
60	-4.81	-4.29	-4.30	-4.30	-4.02	-4.58	-4.36	-4.10	-4.52	-4.73	-4.60
61	-5.41	-4.52	-4.77	-4.67	-4.53	-5.18	-4.76	-4.49	-4.66	-5.59	-5.53
62	-4.78	-4.42	-4.49	-4.39	-4.40	-4.54	-4.63	-4.47	-4.32	-5.23	-5.08
63	-5.75	-5.43	-5.43	-5.27	-5.34	-5.46	-5.50	-5.40	-5.54	-6.12	-5.88
64	-5.65	-5.41	-5.55	-5.62	-5.52	-5.66	-5.65	-5.20	-5.94	-6.22	-6.25
65	-5.53	-5.35	-5.48	-5.34	-5.32	-5.36	-5.59	-5.20	-5.78	-6.04	-6.00
66	-4.60	-4.65	-4.83	-4.79	-4.52	-4.85	-4.74	-4.67	-5.20	-5.39	-5.44

[1]Log concentrations which reduced cell growth to 50% of level at start of experiment. [2]HL-60(TB): leukemia cell line; NC-H460: non-small cell lung cancer cell line; HCT-116: colon cancer cell line; SF-295 & U251: CNS cancer cell lines; SK-MEL-5: melanoma cell line; OVCAR-3: ovarian cancer cell line; 786-0: renal cancer cell line; PC-3: prostate cancer cell line; MDA-MB-435 & MDA-N: breast cancer cell lines. [3]Not tested.

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Among the compounds tested, **44-49** showed the strongest inhibitory effects against a variety of tumor cell lines, including leukemia, colon, CNS, melanoma, ovarian, renal, prostate, breast, and small cell lung cancer cell lines, with values in the low micromolar to nanomolar concentration range. It is notable that compounds **44, 46, 47,** and **49** show highly selective effects on several cell lines from the leukemia, breast, and non-small lung cancer panels at the TGI level. The log TGI values for these four compounds are -7.19 to -7.40 in the HL-60 cell line, -6.16 to -7.12 in the NCI-H226 cell line, and -7.40 to -7.67 in MDA-MB-435 and MDA-N cell lines. Growth of cells from more sensitive cell lines was arrested at a concentration approximately log 2.5-3.7 concentration lower than less sensitive cell lines.

In terms of average cytotoxicity, compounds substituted at the 4′-position were substantially less active than those substituted at the 3′-position, while compounds with a methoxy group at the 2′-position were the least active. Among the tested compounds with a 4′-substituent, only minor differences in cytotoxicity were obtained, suggestive of a potency order of chloro > methoxy > fluoro. The effects of substitutions at the 5, 6, and/or 7 positions in ring A depend on the substitution in ring C. All 3′-substituted compounds with different substituents in ring A showed potent cytotoxicity, indicating that the substitution(s) can be present at different position(s) in ring A without substantially affecting cytotoxicity. For 2′- and 4′-substituted compounds, substitution at the 5 or 6 position generated slightly greater activity than no substitution or substitution at the 7 or the 5 and 7 positions in ring A. Even the "less" active compounds showed moderate cytotoxicity on two breast cancer cell lines, MDA-MB-435 and MDA-N.

EXAMPLE 6

Materials for Tubulin Bioassays of Compounds 39-70

Electrophoretically homogeneous bovine brain tubulin was purified as described in E. Hamel, et al. *Biochemistry* **23**:4173 (1984). Combretastatin A-4 was a generous gift of Dr. G. R. Pettit, Arizona State University. [^{3}H]Colchicine was obtained from Dupont, nonradiolabeled colchicine from Sigma,

podophyllotoxin from Aldrich, and monosodium glutamate from USB.

Tubulin Polymerization Assay

The tubulin polymerization assay was performed as described in S. Kuo, et al. *J. Med. Chem.* **36**:1146 (1993); L. Li, et al. *J. Med. Chem.* **37**:1126 (1994); and L. Li, *J. Med. Chem.* **37**:3400 (1994). In brief, tubulin at 1.2 mg/ml (12 μM) was preincubated for 15 min at 26°C in a 0.24-ml volume of 0.8 M monosodium glutamate (pH 6.6 with NaOH in a 2 M stock solution) with varying drug concentrations. The drug stock solutions were in DMSO, and the final solvent concentration was 4 % (v/v). All concentrations are in terms of the final reaction volume (0.25 ml). The reaction mixtures were chilled on ice, and 10 μl of 10 mM GTP was added to each reaction mixture. Samples were transferred to cuvettes held at 0°C by an electronic temperature controller in Gilford spectrophotometers. Baselines were established at 350 nm, and polymerization initiated by a temperature jump to 26°C. The jump took about 50 sec to complete. After 20 min, turbidity readings were recorded, and the temperature controller was set to 0°C. When depolymerization was complete, turbidity readings were again recorded. Generally, turbidity readings were about 90% cold-reversible, and the cold-reversible turbidity was taken to represent the extent of assembly for each reaction mixture. IC_{50} values were obtained graphically from inhibition of polymerization by different drug concentrations. Four spectrophotometers were used for each experimental sequence, with two control reactions (no drug) in each set. Generally, the control reactions were within 5% of their average, and IC_{50} values obtained with this polymerization assay are usually highly reproducible. Generally, standard deviations were within 20% of the mean values, but in some cases, the standard deviations were 30-35% of the mean. Therefore, we can conservatively estimate that a 50% difference in IC_{50} values represents a difference in the relative activity of two agents.

The results are summarized in **Table 1**, with a comparison to previously obtained data with the potent antimitotic natural products colchicine, podophyllotoxin, and combretastatin A-4. With the most active compounds (**44-**

49) there was excellent correlation between cytotoxicity and inhibition of tubulin polymerization. These six strongly cytotoxic agents were the most potent inhibitors of assembly in the series. All had IC_{50} values below 1.0 μM, as did the three natural products. These six agents were also examined for inhibitory effects on the binding of [^{3}H]colchicine to tubulin (1.0 μM tubulin), with inhibitor and drug at equimolar concentrations (5.0 μM). Significant and similar inhibition was observed with all six compounds, although they were substantially less potent than podophyllotoxin or combretastatin A-4 (*See* **Table 1**).

Compounds **50**, **52**, **53**, **63**, **64**, and **67-70** showed reduced inhibitory effects on tubulin polymerization, with IC_{50} values ranging from 1.5 to 9.8 μM. Slight inhibition was observed with compounds **40**, **41**, **57**, **58**, **61**, **62**, **65**, and **66** (IC_{50} values ranging from 11 to 32 μM), while the remaining compounds (**39**, **42**, **43**, **51**, **54-56**, **59**, and **60**) were inactive, with IC_{50} values greater than 40 μM. Although it is not dramatic among these less active compounds, those with greater antitubulin activity (IC_{50} values < 10 μM) tend to be more cytotoxic than those with little or no antitubulin activity.

From the tubulin data, the 3′-substitution of a methoxy group was well-tolerated, while the 4′- and 2′-methoxy substituents resulted in large, progressive losses of activity or total loss of activity. On the other hand, the series of 4′-substituents indicate that the methyl and chloride groups are better tolerated than the methoxy group and that the fluoride group is equivalent to the methoxy substituent at position 4′. This suggests that a strong electron-withdrawing or a large electron-donating group at the 4′-position may be unfavorable for the drug-tubulin interaction.

The tubulin assay also yielded data of interest regarding A ring substituents. No clear pattern was observed in the potent 3′-methoxy-substituted subseries (compounds **44-50**), for a variety of substituents at different position(s) of ring A were well-tolerated. These substituents include both an electron-donating group (CH_3) and electron-withdrawing groups (Cl and Br). The size of the substituents (as small as hydrogen, compound **44**, and as large as two methyl groups, compound **48**) and their positions (no substitution or different positions of

both mono- and disubstitution) did not greatly affect relative compound activities.

However, a consistent pattern for A ring substitution emerged in the other five subseries (2′-methoxy, 4′-methoxy, 4′-fluoride, 4′-chloride, 4′-methyl). In all cases C-5 and C-6 substituents (generally methyl groups) enhanced activity relative to the unsubstituted derivative and to those bearing a C-7 substituent or two substituent groups.

EXAMPLE 7

Colchicine Binding Assay of Compounds 39-70

The binding of radiolabeled colchicine to tubulin was measured by the DEAE-cellulose filter technique, as described in S. Kuo, et al. *J. Med. Chem.* **36**:1146 (1993). In brief, each 0.1-ml reaction mixture contained 0.1 mg (1.0 μM) of tubulin, 1.0 M commercial monosodium glutamate (pH 6.6 with HCl), 1 mM $MgCl_2$, 0.1 mM GTP, 5.0 μM [^{3}H]colchicine, 5% (*v/v*) DMSO, and 5.0 μM inhibitor. Incubation was for 20 min at 37°C. Each reaction mixture was filtered under reduced vacuum through a stack of two DEAE-cellulose paper filters, washed with water, and radioactivity quantitated in a liquid scintillation counter.

The most active 2-phenyl-1,8-naphthyridin-4-ones approach colchicine in their potency as inhibitors of tubulin polymerization. While these compounds appear to interact at the colchicine binding site of tubulin, they only weakly inhibit the binding of radiolabeled colchicine to tubulin. This apparent discrepancy probably arises from a relatively slow binding and/or rapid dissociation reaction of these agents with tubulin relative to the binding and dissociation reactions of colchicine with the protein. These properties are similar to those of a structurally related class of antimitotic agents, the 2-phenyl-4-quinolones, which were developed in our laboratory. The 2-phenyl-1,8-naphthyridin-4-ones and 2-phenyl-4-quinolones together with other natural products, such as podophyllotoxin and combretastatin, fall into a group of colchicine site compounds that have two aryl ring systems connected by a hydrocarbon bridge of variable length. In both classes of compounds, derivatives with a methoxy at the 3'-position were the most active compounds within their

series and were much more active than isomers with the same substituent at the 2′- or 4′-position. However, unlike the 2-phenyl-4-quinolones, in which a 4′-methoxy group reduced activity more than a 2'-methoxy substituent, in the 2-phenyl-1,8-naphthyridin-4-ones, a 2′-methoxy group reduced activity more than did a 4′-methoxy substituent. Moreover, in the 2-phenyl-4-quinolone series, A ring substituents were optimal at positions 6 and 7, whereas in the 2-phenyl-1,8-naphthyridin-4-one series, it appears that A ring substituents are optimal at positions 5 and 6.

The COMPARE® computer program uses the patterns of cellular responsiveness in the NCI 60 cell line screen to calculate Pearson correlation coefficients between data for seed compounds and those for past agents in the database. The significance of these computations is that the observed correlation coefficients are greatest in pairs of compounds sharing common intracellular targets. COMPARE® computations for the six most potent compounds (**44-49**) against several known tubulin/microtubule binding agents are shown in **Table 3** at both the GI_{50} and TGI levels.

Table 3

Compd	Colchicine		Maytansine		Vincristine		Vinblastine		Rhizoxin		Paclitaxel	
	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI
44	0.66	0.55	0.65	0.64	0.58	0.45	0.47	0.67	0.60	0.60	0.36	0.63
45	0.69	0.47	0.73	0.37	0.61	0.41	0.60	0.53	0.58	0.40	0.30	0.47
46	0.73	0.53	0.69	0.62	0.58	0.44	0.56	0.62	0.54	0.58	0.40	0.53
47	0..79	0.47	0.74	0.45	0.71	0.43	0.64	0.56	0.61	0.45	0.41	0.55
48	0.71	0.55	0.71	0.51	0.62	0.48	0.65	0.64	0.65	0.51	0.46	0.61
49	0.70	0.58	0.63	0.69	0.62	0.55	0.51	0.77	0.55	0.62	0.31	0.65

Correlation coefficients > 0.6 at either level can be considered significant. These compounds display higher correlations with colchicine and maytansine than with the vinca alkaloids or rhizoxin, while correlations with paclitaxel (Taxol) are comparatively weak.

EXAMPLE 8

Data Regarding Specific 2-Aryl-pyrido[1,2,*a*]pyrimidin-4-ones (Compounds 5'-28')

•2-(3'-Fluorophenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(5')** is obtained from ethyl 3'-fluorobenzoylacetate and 2-amino-5-picoline. Characteristics: amorphous; mp 163-165°C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H, H-6), 7.85 (d, J = 8.5 Hz, 1 H, H-6'), 7.83 (s, 1 H, H-2'), 7.71 (d, J = 9.0 Hz, 1 H, H-9), 7.65 (dd, J = 9.0, 1.5 Hz, 1 H, H-8), 7.48 (m, 1 H, H-5'), 7.19 (dt, J = 2.0, 8.5 Hz, 1 H, H-4'), 6.88 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-7). MS *m/z* 254 (M^+).

•2-(3'-Fluorophenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(6')** is obtained from ethyl 3'-fluorobenzoylacetate and 2-amino-6-picoline. Characteristics: amorphous; mp 145-146°C; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 7.5, Hz, 1 H, H-6'), 7.80 (d, J = 1.5, Hz, 1 H, H-2'), 7.51 (d, J = 7.5 Hz, 1 H, H-9), 7.48 (m, 1 H, H-5'), 7.45 (dd, J = 7.5, 6.0 Hz, 1 H, H-8), 7.18 (dt, J = 2.5, 8.0 Hz, 1 H, H-4'), 6.72 (s, 1 H, H-3), 6.69 (d, J = 6.0 Hz, 1 H, H-7), 3.10 (s, 3 H, CH_3-6). MS *m/z* 254 (M^+).

•2-(3'-Fluorophenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(7')** is obtained from ethyl 3'-fluorobenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: amorphous; mp 162-164°C; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1 H, H-6'), 7.79 (d, J = 1.0 Hz, 1 H, H-2'), 7.45 (m, 1 H, H-5'), 7.30 (br. s, 1 H, H-9), 7.17 (dt, J = 2.5, 8.0 Hz, 1 H, H-4'), 6.64 (s, 1 H, H-3), 6.53 (br. s, 1 H, H-7), 3.07 (s, 3 H, CH_3-6), 2.37 (s, 3 H, CH_3-8). MS *m/z* 268 (M^+).

•2-(3'-Chlorophenyl)-pyrido[1,2-*a*]pyrimidin-4-one **(8')** is obtained from ethyl 3'-chlorobenzoylacetate and 2-aminopyridine. Characteristics: amorphous; mp 160-161°C; ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 7.2 Hz, 1 H, H-6), 8.15 (t, J = 1.5 Hz, 1 H, H-2'), 7.94 (td, J = 7.0, 1.5 Hz, 1 H, H-6'), 7.79 (m, 2 H, H_2-8, 9), 7.46 (m, 2 H, H_2-4', 5'), 7.17 (dt, J = 6.5, 1.5 Hz, 1 H, H-7), 6.90 (s, 1 H, H-3). MS *m/z* 256 (M^+).

•2-(3'-Chlorophenyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(9')** is obtained from ethyl 3'-chlorobenzoylacetate and 2-amino-4-picoline; prisms, mp

142-144°C; ^{1}H NMR ($CDCl_3$) δ 8.97 (d, J = 7.2 Hz, 1 H, H-6), 8.13 (t, J = 2.0, 1 H, H-2'), 7.92 (td, J = 7.5, 2.0 Hz, 1 H, H-6'), 7.54 (br. s, 1 H, H-9), 7.45 (m, 2 H, H_2-4', 5'), 7.00 (dd, J = 7.2, 2.0 Hz, 1 H, H-7), 2.52 (s, 3 H, CH_3-8). MS *m/z* 270 (M^+).

•2-(3'-Chlorophenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(10')** is obtained from ethyl 3'-chlorobenzoylacetate and 2-amino-5-picoline. Characteristics: prisms; mp 175-176°C; ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1 H, H-6), 8.13 (s, 1 H, H-2'), 7.92 (td, J = 7.0, 1.0 Hz, 1 H, H-6'), 7.69 (d, J = 9.0 Hz, 1 H, H-9), 7.64 (dd, J = 9.0, 1.5 Hz, 1 H, H-8), 7.45 (m, 2 H, H_2-4', 5'), 6.86 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-7). MS *m/z* 270 (M^+).

•2-(3'-Chlorophenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(11')** is obtained from ethyl 3'-chlorobenzoylacetate and 2-amino-6-picoline. Characteristics: needles; mp 150-152°C; ^{1}H NMR ($CDCl_3$) δ 8.10 (t, J = 1.5 Hz, 1 H, H-2'), 7.91 (td, J = 8.0, 1.5 Hz, 1 H, H-6'), 7.52 (d, J = 7.0 Hz, 1 H, H-9), 7.48 (dd, J = 8.0, 7.0 Hz, 1 H, H-8), 7.45 (m, 2 H, H_2-4', 5'), 6.70 (s, 1 H, H-3), 6.68 (d, J = 8.0 Hz, 1 H, H-7), 3.10 (s, 3 H, CH_3-6). MS *m/z* 270 (M^+).

•2-(3'-Chlorophenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(12')** is obtained from ethyl 3'-chlorobenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: prisms; mp 125-126°C; ^{1}H NMR ($CDCl_3$) δ 8.09 (t, J = 2.0 Hz, 1 H, H-2'), 7.89 (dd, J = 6.7, 2.0 Hz, 1 H, H-6'), 7.43 (m, 2 H, H_2-4', 5'), 7.31 (br. s, 1 H, H-9), 6.63 (s, 1 H, H-3), 6.53 (br. s, 1 H, H-7), 3.07 (s, 3 H, CH_3-6), 2.37 (s, 3 H, CH_3-8). MS *m/z* 284 (M^+).

•2-(3'-Methylphenyl)-pyrido[1,2-*a*]pyrimidin-4-one **(13')** is obtained from ethyl 3'-methylbenzoylacetate and 2-aminopyridine. Characteristics: needles; mp 118-120°C; ^{1}H NMR ($CDCl_3$) δ 9.09 (d, J = 7.0 Hz, 1 H, H-6), 7.94 (s, 1 H, H-2'), 7.87 (d, J = 7.5, Hz, 1 H, H-6'), 7.76 (d, J = 3.5 Hz, 2 H, H_2-8, 9), 7.41 (t, J = 7.5 Hz, 1 H, H-5'), 7.32 (d, J = 7.5 Hz, 1 H, H-4'), 7.15 (ddd, J = 7.0, 3.5, 1.5 Hz, 1 H, H-7), 6.92 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-3'). MS *m/z* 236 (M^+).

•2-(3'-Methylphenyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(14')** is obtained from ethyl 3'-methylbenzoylacetate and 2-amino-4-picoline.

Characteristics: amorphous; mp 146-148 °C; ^{1}H NMR ($CDCl_3$) δ 8.97 (d, J = 7.2 Hz, 1 H, H-6), 7.92 (s, 1 H, H-2'), 7.86 (d, J = 7.5, 1 H, H-6'), 7.54 (s, 1 H, H-9), 7.40 (t, J = 7.5 Hz, 1 H, H-5'), 7.31 (d, J = 7.5, Hz, 1 H, H-4'), 6.98 (d, J = 7.2 Hz, 1 H, H-7), 6.85 (s, 1H, H-3), 2.51 (s, 3 H, CH_3-8), 2.45 (s, 3 H, CH_3-3'). MS *m/z* 250 (M^+).

•2-(3'-Methylphenyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(15')** is obtained from ethyl 3'-methylbenzoylacetate and 2-amino-5-picoline. Characteristics: prisms; mp 158-160°C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H, H-6), 7.92 (s, 1 H, H-2'), 7.86 (d, J = 7.7, 1 H, H-6'), 7.69 (d, J = 9.0 Hz, 1 H, H-9), 7.62 (dd, J = 9.0, 2.0 Hz, 1 H, H-8), 7.40 (t, J = 7.7, Hz, 1 H, H-5'), 7.31 (d, J = 7.7, Hz, 1 H, H-4'), 6.90 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-7), 2.46 (s, 3 H, CH_3-3'). MS *m/z* 250(M^+).

•2-(3'-Methylphenyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(16')** is obtained from ethyl 3'-methylbenzoylacetate and 2-amino-6-picoline. Characteristics: prisms; mp 152-154°C; ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H, H-2'), 7.84 (d, J = 7.7, 1 H, H-6'), 7.51 (d, J = 8.5, Hz, 1 H, H-9), 7.46 (dd, J = 8.5, 6.4 Hz, 1 H, H-8), 7.39 (t, J = 7.5 Hz, 1 H, H-5'), 7.30 (d, J = 7.7, Hz, 1 H, H-4'), 6.73 (s, 1 H, H-3), 6.66 (d, J = 6.4 Hz, 1 H, H-7), 3.09 (s, 3 H, CH_3-6), 2.46 (s, 3 H, CH_3-3'). MS *m/z* 250(M^+).

•2-(3'-Methylphenyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(17')** is obtained from ethyl 3'-methylbenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: prisms; mp 145-147°C; ^{1}H NMR ($CDCl_3$) δ 7.88 (br. s, 1 H, H-2'), 7.82 (d, J = 7.5, Hz, 1 H, H-6'), 7.38 (t, J = 7.5 Hz, 1 H, H-5'), 7.35 (br. s, 1 H, H-9), 7.28 (d, J = 7.5, Hz, 1 H, H-4'), 6.66 (s, 1 H, H-3), 6.50 (br. s, 1 H, H-7), 3.07 (s, 3 H, CH_3-6), 2.45 (s, 3 H, CH_3-3'), 2.36 (s, 3 H, CH_3-8). MS *m/z* 264 (M^+).

•2-(α-Naphthyl)-pyrido[1,2-*a*]pyrimidin-4-one **(18')** is obtained from ethyl α-naphthylbenzoylacetate and 2-aminopyridine. Characteristics: amorphous; mp 169-170°C; ^{1}H NMR ($CDCl_3$) δ 9.19 (d, J = 7.0 Hz, 1 H, H-6), 8.24 (dd, J = 6.5, 2.5 Hz, 1 H, H-8'), 7.97 (d, J = 8.5 Hz, 1 H, H-2'), 7.95 (m, 1 H, H-5'), 7.81 (d, J = 2.5 Hz, 2 H, H_2-8, 9), 7.72 (d, J = 6.5 Hz, 1 H, H-4'), 7.58 (dd, J

= 8.5, 6.5 Hz, 1 H, H-3'), 7.52 (m, 2 H, H_2-6', 7'), 7.24 (m, 1 H, H-7), 6.80 (s, 1 H, H-3). MS *m/z* 272 (M^+).

•2-(α-Naphthyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(19')** is obtained from ethyl α-naphthylbenzoylacetate and 2-amino-4-picoline. Characteristics: needles; mp 146-148°C; ^{1}H NMR ($CDCl_3$) δ 9.08 (d, *J* = 7.2 Hz, 1 H, H-6), 8.24 (dd, *J* = 6.5, 2.5 Hz, 1 H, H-8'), 7.96 (d, *J* = 8.7 Hz, 1 H, H-2'), 7.93 (m, 1 H, H-5'), 7.71 (d, *J* = 6.8 Hz, 1 H, H-4'), 7.62 (br. s, 1 H, H-9), 7.58 (dd, *J* = 8.7, 6.8 Hz, 1 H, H-3'), 7.53 (m, 2 H, H_2-6', 7'), 7.08 (dd, *J* = 7.2, 1.5 Hz, 1 H, H-7), 6.72 (s, 1H, H-3), 2.54 (s, 3 H, CH_3-8). MS *m/z* 286 (M^+).

•2-(α-Naphthyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(20')** is obtained from ethyl α-naphthylbenzoylacetate and 2-amino-5-picoline. Characteristics: amorphous; mp 138-140°C; ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 1 H, H-6), 8.24 (dd, *J* = 6.5, 2.5 Hz, 1 H, H-8'), 7.96 (d, *J* = 8.7 Hz, 1 H, H-2'), 7.93 (m, 1 H, H-5'), 7.72 (d, *J* = 7.0 Hz, 1 H, H-4'), 7.70 (d, *J* = 9.0 Hz, 1 H, H-9), 7.66 (dd, *J* = 9.0, 1.5 Hz, 1 H, H-8), 7.56 (dd, *J* = 8.7, 6.8 Hz, 1 H, H-3'), 7.50 (m, 2 H, H_2-6', 7'), 6.77 (s, 1 H, H-3), 2.49 (s, 3 H, CH_3-7). MS *m/z* 286(M^+).

•2-(α-Naphthyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(21')** is obtained from ethyl α-naphthylbenzoylacetate and 2-amino-6-picoline. Characteristics: prisms; mp 149-150°C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, *J* = 5.0, 2.5 Hz, 1 H, H-8'), 7.95 (d, *J* = 8.3 Hz, 1 H, H-2'), 7.92 (m, 1 H, H-5'), 7.71 (d, *J* = 6.5 Hz, 1 H, H-4'), 7.56 (dd, *J* = 8.7, 6.8 Hz, 1 H, H-3'), 7.52 (m, 2 H, H_2-8, 9), 7.50 (m, 2 H, H_2-6', 7'), 6.74 (d, *J* = 5.5 Hz, 1 H, H-7), 6.61 (s, 1 H, H-3), 3.16 (s, 3 H, CH_3-6). MS *m/z* 286 (M^+).

•2-(α-Naphthyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(22')** is obtained from ethyl α-naphthylbenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: prisms; mp 160-162°C; ^{1}H NMR ($CDCl_3$) δ 8.27 (dd, *J* = 5.0, 2.5 Hz, 1 H, H-8'), 7.94 (d, *J* = 7.5 Hz, 1 H, H-2'), 7.92 (m, 1 H, H-5'), 7.70 (d, *J* = 7.5 Hz, 1 H, H-4'), 7.54 (t, *J* = 7.5 Hz, 1 H, H-3'), 7.51 (m, 2 H, H_2-6', 7'), 7.35 (br. s, 1 H, H-9), 6.60 (br. s, 1 H, H-7), 6.53 (s, 1 H, H-3), 3.13 (s, 3 H, CH_3-6), 2.39 (s, 3 H, CH_3-8). MS *m/z* 300 (M^+).

•2-(β-Naphthyl)-pyrido[1,2-*a*]pyrimidin-4-one **(23')** is obtained

from ethyl β-naphthylbenzoylacetate and 2-aminopyridine. Characteristics: amorphous; mp 201-202°C; ^{1}H NMR ($CDCl_3$) δ 9.11 (d, J = 7.0 Hz, 1 H, H-6), 8.68 (s, 1 H, H-1'), 8.18 (dd, J = 8.5, 1.0 Hz, 1 H, H-3'), 7.99 (m, 1 H, H-8'), 7.98 (d, J = 8.5 Hz, 1 H, H-4'), 7.91 (m, 1 H, H-5'), 7.81 (m, 2 H, H_2-8, 9), 7.57 (m, 2 H, H_2-6', 7'), 7.17 (dt, J = 7.0, 2.0 Hz, 1 H, H-7), 7.08 (s, 1 H, H-3). MS *m/z* 272 (M^+).

•2-(β-Naphthyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(24')** is obtained from ethyl β-naphthylbenzoylacetate and 2-amino-4-picoline. Characteristics: amorphous; mp 168-169°C; ^{1}H NMR ($CDCl_3$) δ 9.00 (d, J = 7.2 Hz, 1 H, H-6), 8.66 (s, 1 H, H-1'), 8.16 (d, J = 8.5 Hz, 1 H, H-3'), 7.99 (s, 1 H, H-9), 7.98 (m, 1 H, H-8'), 7.97 (d, J = 8.5 Hz, 1 H, H-4'), 7.90 (br. d, J = 7.0 Hz, 1 H, H-5'), 7.57 (m, 2 H, H_2-6', 7'), 7.01 (s, 1H, H-3), 6.99 (d, J = 7.2 Hz, 1 H, H-7), 2.54 (s, 3 H, CH_3-8). MS *m/z* 286 (M^+).

•2-(β-Naphthyl)-7-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(25')** is obtained from ethyl β-naphthylbenzoylacetate and 2-amino-5-picoline. Characteristics: needles; mp 228-229°C; ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1 H, H-6), 8.66 (s, 1 H, H-1'), 8.17 (dd, J = 8.7, 1.0 Hz, 1 H, H-3'), 7.99 (m, 1 H, H-8'), 7.97 (d, J = 8.7 Hz, 1 H, H-4'), 7.90 (m, 1 H, H-5'), 7.75 (d, J = 9.0 Hz, 1 H, H-9), 7.65 (dd, J = 9.0, 1.2 Hz, 1 H, H-8), 7.56 (m, 2 H, H_2-6', 7'), 7.06 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-7). MS *m/z* 286(M^+).

•2-(β-Naphthyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4-one **(26')** is obtained from ethyl β-naphthylbenzoylacetate and 2-amino-6-picoline. Characteristics: prisms; mp 160-162°C; ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1 H, H-1'), 8.14 (d, J = 8.6 Hz, 1 H, H-3'), 7.99 (m, 1 H, H-8'), 7.96 (d, J = 8.6 Hz, 1 H, H-4'), 7.90 (m, 1 H, H-5'), 7.55 (m, 2 H, H_2-6', 7'), 7.53 (d, J = 8.8 Hz, 1 H, H-9), 7.49 (dd, J = 8.8, 6.5 Hz, 1 H, H-8), 6.88 (s, 1 H, H-3), 6.68 (d, J = 6.5 Hz, 1 H, H-7), 3.12 (s, 3 H, CH_3-6). MS *m/z* 286 (M^+).

•2-(β-Naphthyl)-6,8-dimethyl-pyrido[1,2-*a*]pyrimidin-4-one **(27')** is obtained from ethyl β-naphthylbenzoylacetate and 2-amino-4,6-dimethylpyridine. Characteristics: needles; mp 189-190°C; ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1 H, H-1'), 8.12 (d, J = 8.9 Hz, 1 H, H-3'), 7.98 (m, 1 H, H-8'), 7.94 (d, J = 8.9 Hz, 1 H, H-4'),

7.89 (m, 1 H, H-5'), 7.55 (m, 2 H, H_2-6', 7'), 7.36 (br. s, 1 H, H-9), 6.81 (s, 1 H, H-3), 6.53 (br. s, 1 H, H-7), 3.09 (s, 3 H, CH_3-6), 2.38 (s, 3 H, CH_3-8). MS *m/z* 300 (M^+).

•2-(β-Naphthyl)-7-chloro-pyrido[1,2-*a*]pyrimidin-4-one **(28')** is obtained from ethyl β-naphthylbenzoylacetate and 2-amino-5-chloro-pyridine. Characteristics: amorphous; mp 227-229°C; ^{1}H NMR ($CDCl_3$) δ 9.12 (d, J = 2.0 Hz, 1 H, H-6), 8.66 (s, 1 H, H-1'), 8.15 (dd, J = 8.7, 1.5 Hz, 1 H, H-3'), 8.00 (m, 1 H, H-8'), 7.97 (d, J = 8.7 Hz, 1 H, H-4'), 7.90 (m, 1 H, H-5'), 7.75 (d, J = 9.3 Hz, 1 H, H-9), 7.70 (dd, J = 9.3, 2.0 Hz, 1 H, H-8), 7.57 (m, 2 H, H_2-6', 7'), 7.09 (s, 1 H, H-3). MS *m/z* 306(M^+).

EXAMPLE 9

Data Regarding Specific 2-phenyl-1,8-naphthyridin-4-ones (Compounds 29'-51')

•2-(3'-Fluorophenyl)-6-methyl-1,8-naphthyridin-4-one **(29')** is obtained from compound **(5')**. Characterisitics: needles; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.48 (d, J = 2.0 Hz, 1 H, H-5), 8.47 (d, J = 2.0 Hz, 1 H, H-7), 7.52 (m, 2 H, H_2-2', 5'), 7.45 (dd, J = 8.0, 2.0 Hz, 1 H, H-6'), 7.25 (m, 1 H, H-4'), 6.57 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-6). MS *m/z* 254 (M^+). Elemental Analysis: calculated C 70.86, H 4.36, N 11.02; found C 70.69, H 4.48, N 10.91.

•2-(3'- Fluorophenyl)-7-methyl-1,8-naphthyridin-4-one **(30')** is obtained from compound **(6')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.90, (br. s, 1 H, NH-1), 8.56 (d, J = 8.0 Hz, 1 H, H-5), 7.52 (m, 2 H, H_2-2', 5'), 7.41 (d, J = 9.5 Hz, 1 H, H-6'), 7.29 (m, 1 H, H-4'), 7.23 (d, J = 8.0 Hz, 1 H, H-6), 6.57 (s, 1 H, H-3), 2.64 (s, 3 H, CH_3-7). MS *m/z* 254 (M^+). Elemental Analysis: calculated C 70.86, H 4.36, N 11.02; found C 70.99, H 4.62, N 10.97.

•2-(3'- Fluorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(31')** is obtained from compound **(7')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.86, (br. s, 1 H, NH-1), 7.50 (m, 2 H, H_2-2', 5'), 7.39 (dd, J = 9.3, 1.8 Hz, 1 H, H-6'), 7.24 (m, 1 H, H-4'), 6.92 (s, 1 H, H-6), 6.49 (s, 1 H, H-3), 2.93 (s, 3 H, CH_3-5), 2.51 (s, 3 H, CH_3-7). MS *m/z* 268 (M^+). Elemental Analysis: calculated C 71.63,

H 4.88, N 10.44; found C 71.82, H 5.01, N 10.21.

•2-(3'-Chlorophenyl)-1,8-naphthyridin-4-one **(32')** is obtained from compound **(8')**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 8.66 (dd, J = 4.5, 2.0 Hz, 1 H, H-5), 8.63 (dd, J = 8.0, 2.0 Hz, 1 H, H-7), 7.72 (t, J = 1.5 Hz, 1 H, H-2'), 7.61 (td, J = 7.0, 1.5 Hz, 1 H, H-6'), 7.48 (m, 2 H, H_2-4', 5'), 7.36 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.58 (s, 1 H, H-3). MS *m/z* 256 (M^+). Elemental Analysis: calculated C 65.51, H 3.53, N 10.91; found C 65.28, H 3.65, N 10.67.

•2-(3'-Chlorophenyl)-5-methyl-1,8-naphthyridin-4-one **(33')** is obtained from compound **(9')**. Characteristics: needles; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.37 (d, J = 5.0 Hz, 1 H, H-7), 7.70 (t, J = 2.0 Hz, 1 H, H-2'), 7.59 (td, J = 7.2, 2.0 Hz, 1 H, H-6'), 7.46 (m, 2 H, H_2-4', 5'), 7.02 (d, J = 5.0 Hz, 1 H, H-6), 6.49 (s, 1 H, H-3), 2.91 (s, 3 H, CH_3-5). MS *m/z* 270 (M^+). Elemental Analysis: calculated C 66.55, H 4.10, N 10.35; found C 66.82, H 4.45, N 10.43.

•2-(3'-Chlorophenyl)-6-methyl-1,8-naphthyridin-4-one **(34')** is obtained from compound **(10')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.49 (d, J = 2.0 Hz, 1 H, H-5), 8.42 (d, J = 2.0 Hz, 1 H, H-7), 7.72 (t, J = 1.5 Hz, 1 H, H-2'), 7.61 (td, J = 7.2, 1.5 Hz, 1 H, H-6'), 7.48 (m, 2 H, H_2-4', 5'), 6.57 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-6). MS *m/z* 270 (M^+). Elemental Analysis: calculated C 66.55, H 4.10, N 10.35; found C 66.26, H 4.41, N 10.22.

•2-(3'-Chlorophenyl)-7-methyl-1,8-naphthyridin-4-one **(35')** is obtained from compound **(11')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.54 (d, J = 8.0 Hz, 1 H, H-5), 7.72 (t, J = 2.0 Hz, 1 H, H-2'), 7.61 (td, J = 6.8, 2.0 Hz, 1 H, H-6'), 7.50 (m, 2 H, H_2-4', 5'), 7.23 (d, J = 8.0 Hz, 1 H, H-6), 2.64 (s, 3 H, CH_3-7). MS *m/z* 270 (M^+). Elemental Analysis: calculated C 66.55, H 4.10, N 10.35; found C 66.38, H 4.37, N 10.11.

•2-(3'-Chlorophenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(36')** is obtained from compound **(12')**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 7.67 (t, J = 1.5 Hz, 1 H, H-2'), 7.58 (td, J = 7.0, 1.5 Hz, 1 H, H-6'), 7.50 (m, 2 H, H_2-4', 5'), 6.93 (s, 1 H, H-6), 6.49 (s, 1 H, H-3), 2.94 (s, 3 H, CH_3-5), 2.53 (s, 3 H, CH_3-7). MS *m/z* 284 (M^+). Elemental Analysis: calculated C 67.49, H 4.60, N 9.84; found C 67.31, H 4.72, N 9.66.

•2-(3'-Methylphenyl)-1,8-naphthyridin-4-one **(37')** is obtained from compound **(13')**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 10.57, (br. s, 1 H, NH-1), 8.70 (dd, J = 8.0, 2.0 Hz, 1 H, H-5), 8.18 (dd, J = 4.5, 2.0 Hz, 1 H, H-7), 7.54 (d, J = 1.5 Hz, 1 H, H-2'), 7.53 (d, J = 7.5 Hz, 1 H, H-6'), 7.45 (t, J = 7.5, Hz, 1 H, H-5'), 7.40 (d, J = 7.5 Hz, 1 H, H-4'), 7.27 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.60 (s, 1 H, H-3), 2.44 (s, 3 H, CH_3-3'). MS *m/z* 236 (M^+). Elemental Analysis: calculated C 76.25, H 5.12, N 11.86; found C 76.35, H 5.41, N 11.93.

•2-(3'-Methylphenyl)-5-methyl-1,8-naphthyridin-4-one **(38')** is obtained from compound **(14')**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 9.77, (br. s, 1 H, NH-1), 8.10 (d, J = 4.8 Hz, 1 H, H-7), 7.52 (s, 1 H, H-2'), 7.50 (br. d, J = 6.0 Hz, 1 H, H-6'), 7.43 (t, J = 7.5, Hz, 1 H, H-5'), 7.37 (d, J = 7.5 Hz, 1 H, H-4'), 6.98 (d, J = 4.8 Hz, 1 H, H-6), 6.52 (s, 1 H, H-3), 2.98 (s, 3 H, CH_3-5), 2.45 (s, 3 H, CH_3-3'). MS *m/z* 250 (M^+). Elemental Analysis: calculated C 76.78, H 5.64, N 11.19; found C 76.52, H 5.75, N 11.01.

•2-(3'-Methylphenyl)-6-methyl-1,8-naphthyridin-4-one **(39')** is obtained from compound **(15')**. Characteristics: prisms; ^{1}H NMR ($CDCl_3$) δ 10.78, (s, 1 H, NH-1), 8.50 (d, J = 2.0 Hz, 1 H, H-5), 7.92 (d, J = 2.0 Hz, 1 H, H-7), 7.52 (br. s, 2 H, H_2-2', 6'), 7.45 (t, J = 7.5, Hz, 1 H, H-5'), 7.40 (d, J = 7.5 Hz, 1 H, H-4'), 6.57 (s, 1 H, H-3), 2.43 (s, 3 H, CH_3-3'), 2.38 (s, 3 H, CH_3-6). MS *m/z* 250 (M^+). Elemental Analysis: calculated C 75.42, H 5.74, N 10.99; found C 75.31, H 5.63, N 10.84.

•2-(3'-Methylphenyl)-7-methyl-1,8-naphthyridin-4-one **(40')** is obtained from compound **(16')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.23, (br. s, 1 H, NH-1), 8.57 (d, J = 8.0 Hz, 1 H, H-5), 7.49 (br. s, 2 H, H_2-2', 6'), 7.42 (t, J = 7.2, Hz, 1 H, H-5'), 7.36 (d, J = 7.2 Hz, 1 H, H-4'), 7.20 (d, J = 8.0 Hz, 1 H, H-6), 6.60 (s, 1 H, H-3), 2.58 (s, 3 H, CH_3-7), 2.43 (s, 3 H, CH_3-3'). MS *m/z* 250 (M^+). Elemental Analysis: calculated C 76.78, H 5.64, N 11.19; found C 76.61, H 5.78, N 11.11.

•2-(3'-Methylphenyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(41')** is obtained from compound **(17')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.14, (br. s, 1 H, NH-1), 7.47 (br. s, 2 H, H_2-2', 6'), 7.40 (t, J = 7.5, Hz, 1 H, H-5'),

7.34 (d, J = 7.5 Hz, 1 H, H-4'), 6.89 (s, 1 H, H-6), 6.50 (s, 1 H, H-3), 2.94 (s, 3 H, CH_3-5), 2.42 (s, 3 H, CH_3-7), 2.47 (s, 3 H, CH_3-3'). MS *m/z* 264 (M^+). Elemental Analysis: calculated C 77.25, H 6.10, N 10.60; found C 77.51, H 6.38, N 10.71.

•2-(α-Naphthyl)-1,8-naphthyridin-4-one **(42')** is obtained from compound **(18')**. Characteristics: plates; ^{1}H NMR ($CDCl_3$) δ 8.67 (dd, J = 8.0, 1.5 Hz, 1 H, H-5), 8.08 (d, J = 8.0 Hz, 1 H, H-2'), 7.99 (d, J = 8.0 Hz, 1 H, H-8'), 7.97 (d, J = 8.0 Hz, 1 H, H-5'), 7.68 (d, J = 8.0 Hz, 1 H, H-4'), 7.62 (t, J = 8.0 Hz, 1 H, H-3'), 7.57 (d, J = 8.0 Hz, 1 H, H-6'), 7.52 (d, J = 8.0 Hz, 1 H, H-7'), 7.49 (d, J = 4.5 Hz, 1 H, H-7), 7.11 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.56 (s, 1 H, H-3). MS *m/z* 272 (M^+). Elemental Analysis: calculated C 79.40, H 4.44, N 10.29; found C 79.52, H 4.64, N 10.32.

•2-(α-Naphthyl)-5-methyl-1,8-naphthyridin-4-one **(43')** is obtained from compound **(19')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 11.37, (br. s, 1 H, NH-1), 8.06 (d, J = 7.8 Hz, 1 H, H-2'), 7.97 (d, J = 8.5 Hz, 2 H, H-5', 8'), 7.65 (br. d, J = 6.5 Hz, 1 H, H-4'), 7.62 (t, J = 7.8 Hz, 1 H, H-3'), 7.56 (d, J = 7.5 Hz, 1 H, H-6'), 7.48 (d, J = 7.5 Hz, 1 H, H-7'), 7.00 (d, J = 4.8 Hz, 1 H, H-7), 6.71 (d, J = 4.8 Hz, 1 H, H-6), 6.46 (s, 1 H, H-3), 2.93 (s, 3 H, CH_3-5). MS *m/z* 286 (M^+). Elemental Analysis: calculated C 79.70, H 4.93, N 9.78; found C 79.55, H 5.12, N 9.51.

•2-(α-Naphthyl)-6-methyl-1,8-naphthyridin-4-one **(44')** is obtained from compound **(20')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, J = 1.0 Hz, 1 H, H-5), 8.10 (dd, J = 7.5, 1.5 Hz, 1 H, H-2'), 7.99 (d, J = 8.0 Hz, 1 H, H-8'), 7.88 (d, J = 8.0 Hz, 1 H, H-5'), 7.66 (br. d, J = 7.0 Hz, 1 H, H-4'), 7.65 (d, J = 1.0 Hz, 1 H, H-7), 7.63 (t, J = 7.5 Hz, 1 H, H-3'), 7.54 (t, J = 7.5 Hz, 1 H, H-6'), 7.44 (t, J = 7.5 Hz, 1 H, H-7'), 6.50 (s, 1 H, H-3), 2.12 (s, 3 H, CH_3-6). MS *m/z* 286 (M^+). Elemental Analysis: calculated C 79.70, H 4.93, N 9.78; found C 79.49, H 5.21, N 9.48.

•2-(α-Naphthyl)-7-methyl-1,8-naphthyridin-4-one **(45')** is obtained from compound **(21')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 10.78, (br. s, 1 H, NH-1), 8.48 (d, J = 8.0 Hz, 1 H, H-5), 7.97(d, J = 8.0 Hz, 1 H, H-2'), 7.92 (d, J = 8.0 Hz, 1 H, H-8'), 7.85 (d, J = 8.0 Hz, 1 H, H-5'), 7.58 (dd, J = 7.0, 1.0 Hz,

1 H, H-4'), 7.51 (t, J = 8.0 Hz, 1 H, H-3'), 7.43 (dt, J = 7,0, 1.0 Hz, 1 H, H-6'), 7.32 (dt, J = 7.0, 1.0 Hz, 1 H, H-7'), 6.93 (d, J = 8.0 Hz, 1 H, H-6), 6.50 (s, 1 H, H-3), 2.06 (s, 3 H, CH_3-7). MS *m/z* 286 (M$^+$). Elemental Analysis: calculated C 77.27, H 5.12, N 9.49; found C 77.12, H 5.45, N 9.17.

•2-(α-Naphthyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(46')** is obtained from compound **(22')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 7.5 Hz, 1 H, H-2'), 7.95 (d, J = 8.0 Hz, 1 H, H-8'), 7.88 (d, J = 8.0 Hz, 1 H, H-5'), 7.60 (dd, J = 6.5, 1.0 Hz, 1 H, H-4'), 7.53 (t, J = 7.5 Hz, 1 H, H-3'), 7.49 (dt, J = 6.0, 2.0 Hz, 1 H, H-6'), 7.38 (dt, J = 7.0, 1.0 Hz, 1 H, H-7'), 6.69 (s, 1 H, H-6), 6.45 (s, 1 H, H-3), 2.91 (s, 3 H, CH_3-5), 2.10 (s, 3 H, CH_3-7). MS *m/z* 300 (M$^+$). Elemental Analysis: calculated C 79.98, H 5.37, N 9.33; found C 79.74, H 5.56, N 9.18.

•2-(β-Naphthyl)-1,8-naphthyridin-4-one **(47')** is obtained from compound **(23')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.98 (br. s, 1H, NH-1), 8.71 (dd, J = 8.0, 1.5 Hz, 1 H, H-5), 8.44 (d, J = 4.5 Hz, 1 H, H-7), 8.24 (d, J = 1.0 Hz, 1 H, H-1'), 8.04 (d, J = 8.5 Hz, 1 H, H-4'), 7.94 (m, 2 H, H_2-5', 8'), 7.80 (dd, J = 8.5, 2.0 Hz, 1 H, H-3'), 7.63 (m, 2 H, H_2-6', 7'), 7.28 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.76 (s, 1 H, H-3). MS *m/z* 272 (M$^+$). Elemental Analysis: calculated C 79.40, H 4.44, N 10.29; found C 79.62, H 4.71, N 10.37.

•2-(β-Naphthyl)-5-methyl-1,8-naphthyridin-4-one **(48')** is obtained from compound **(24')**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 10.09, (br. s, 1 H, NH-1), 8.21 (d, J = 1.0 Hz, 1 H, H-1'), 8.08 (d, J = 5.0 Hz, 1 H, H-7), 8.01 (d, J = 8.5 Hz, 1 H, H-4'), 7.93 (m, 2 H, H_2-5', 8'), 7.79 (dd, J = 8.5, 2.0 Hz, 1 H, H-3'), 7.61 (m, 2 H, H_2-6', 7'), 6.93 (d, J = 5.0 Hz, 1 H, H-6), 6.67 (s, 1 H, H-3), 2.99 (s, 3 H, CH_3-5). MS *m/z* 286 (M$^+$). Elemental Analysis: calculated C 79.70, H 4.93, N 9.78; found C 79.79, H 5.15, N 9.56.

•2-(β-Naphthyl)-6-methyl-1,8-naphthyridin-4-one **(49')** is obtained from compound **(25')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 1 H, H-5), 8.21 (d, J = 1.0 Hz, 1 H, H-1'), 8.03 (d, J = 8.5 Hz, 1 H, H-4'), 7.97 (m, 2 H, H_2-5', 8'), 7.87 (d, J = 1.0 Hz, 1 H, H-7), 7.79 (dd, J = 8.5, 2.0 Hz, 1 H, H-3'), 7.62 (m, 2 H, H_2-6', 7'), 6.72 (s, 1 H, H-3), 2.24 (s, 3 H, CH_3-6). MS *m/z*

286 (M$^+$). Elemental Analysis: calculated C 79.70, H 4.93, N 9.78; found C 79.66, H 4.98, N 9.86.

•2-(β-Naphthyl)-7-methyl-1,8-naphthyridin-4-one **(50')** is obtained from compound **(26')**. Characteristics: needles; ^{1}H NMR ($CDCl_3$) δ 9.32, (br. s, 1 H, NH-1), 8.59 (d, J = 8.0 Hz, 1 H, H-5), 8.19 (d, J = 2.0 Hz, 1 H, H-1'), 8.01 (d, J = 8.5 Hz, 1 H, H-4'), 7.92 (m, 2 H, H_2-5', 8'), 7.76 (dd, J = 8.5, 2.0 Hz, 1 H, H-3'), 7.61 (m, 2 H, H_2-6', 7'), 7.21 (d, J = 8.0 Hz, 1 H, H-6), 6.74 (s, 1 H, H-3), 2.60 (s, 3 H, CH_3-7). MS *m/z* 286 (M$^+$). Elemental Analysis: calculated C 79.70, H 4.93, N 9.78; found C 79.83, H 5.05, N 9.69.

•2-(β-Naphthyl)-5,7-dimethyl-1,8-naphthyridin-4-one **(51')** is obtained from compound **(27')**. Characteristics: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.20, (br. s, 1 H, NH-1), 8.17 (d, J = 1.5 Hz, 1 H, H-1'), 7.99 (d, J = 8.5 Hz, 1 H, H-4'), 7.92 (m, 2 H, H_2-5', 8'), 7.75 (dd, J = 8.5, 1.5 Hz, 1 H, H-3'), 7.60 (m, 2 H, H_2-6', 7'), 6.90 (s, 1 H, H-6), 6.65 (s, 1 H, H-3), 2.96 (s, 3 H, CH_3-5), 2.50 (s, 3 H, CH_3-7). MS *m/z* 300 (M$^+$). Elemental Analysis: calculated C 70.48, H 3.61, N 9.13; found C 70.61, H 3.93, N 9.25.

EXAMPLE 10

Cytotoxicity assays of Compounds 5'-51'

Compounds **5'-28'** were assayed for *in vitro* cytotoxicity in a panel of human and murine tumor cell lines using the same techniques as in **Example 5**. The cell lines include human epidermoid carcinoma of the nasopharynx (KB), lung carcinoma (A-549), ileocecal carcinoma (HCT-8), melanoma (PRMI-7951), and medulloblastoma (TE-671), as well as one murine leukemia cell line (P-388). The results demonstrated that essentially all 2-phenyl-pyrido[1,2-*a*]pyrimidin-4-ones **(5'-28')** were inactive (EC_{50} >4 μg/ml); only a few compounds showed marginal activity.

Compounds **29'-51'** were submitted to NCI and assayed in the NCI's *in vitro* disease-oriented antitumor screen, using the techniques described in **Example 5**. This assay involves determinations of a test agent's effect on growth parameters against a panel of approximately 60 human tumor cell lines, derived

largely from solid tumors, including non-small cell lung, colon, central nervous system, renal, ovarian, prostate, and breast cancers, plus a few leukemia cell lines. The cytotoxic effects of each compound are obtained as GI_{50} or TGI values, which represent the molar drug concentrations required to cause half growth inhibition and total growth inhibition, respectively. The results are expressed for each cell line as average log GI_{50} values in **Table 4**, as log GI_{50} values in **Table 5**, and as log TGI values and average log TGI values in **Table 6**.

Table 4

Compound	ITP[1] HC_{50}(μM)±SD	ICB[2] (% Inhibition)	average[3] log GI_{50}	mp (°C)	Yield (%)[4]
29'	0.63 ± 0.2	43 ± 1	-7.30	>300	57
30'	0.53 ± 0.08	41 ± 2	-7.37	270-272	48
31'	0.74 ± 0.06	29 ± 1	-7.07	236-238	57
32'	1.5 ± 0.1		-6.64	295-297	26
33'	1.0 ± 0.03	32 ± 1	-6.80	260-262	21
34'	0.72 ± 0.08	33 ± 2	-6.57	290-292	49
35'	0.89 ± 0.09	38 ± 1	-6.77	255-257	17
36'	0.77 ± 0.2	22 ± 2	-6.46	232-234	49
37'	3.3 ± 0.6		-7.02	205-207	33
38'	1.8 ± 0.5		-7.24	175-177	32
39'	1.5 ± 0.3		-6.19	223-225	36
40'	1.9 ± 0.5		-7.01	193-195	52
41'	2.3 ± 0.2		-4.42	197-198	55
42'	1.1 ± 0.3		-7.45	282-283	27
43'	0.93 ± 0.2	37 ± 4	-7.45	228-230	27
44'	0.55 ± 0.05	46 ± 3	-7.72	236-238	25
45'	0.66 ± 0.1	40 ± 4	-7.18	240-242	34

Compound	TTP[1] IC_{50}(μM)±SD	ICB[2] (% Inhibition)	average[3] log GI_{50}	mp (°C)	Yield (%)[4]
46'	0.78 ± 0.2	15 ± 10	-5.98	276-278	37
47'	14 ± 2		-5.09	259-261	38
48'	1.8 ± 0.06		-5.92	217-219	29
49'	2.1 ± 0.5		-6.13	255-257	34
50'	5.1 ± 0.9		-5.34	244-246	45
51'	> 40		-4.87	149-151	59
52'	2.5 ± 0.5		-5.24	> 300	51
colchicine	0.08 ± 0.07				
podophyllotoxin	0.46 ± 0.02	76 ± 5			
combretstatinA-4	0.53 ± 0.05	91 ± 2			

[1]Inhibition of Tubulin Polymerization, [2]Inhibition of colchicine binding (evaluated only when polymerization IC50 < 1μM), [3]Data obtained from NCI's 60 human tumor cell line in vitro screen and calculated from all cell lines tested, [4]All yields were calculated form aminopyridines, [5]Not tested.

Table 5

Compound	Cytotoxicity log GI_{50} (M)[a]										
	HL-60(TB)[a]	NCI-H460	HCT-1.16	SF-295	U-251	SK-MEL-5	OVCAR-3	786-0	PC-3	MDA-MB-435	MDA-N
29'	-7.69	-7.41	-7.62	-7.56	-7.39	-7.55	-7.87	-7.55	-7.46	< -8.00	-7.93
30'	-7.65	-7.48	-7.55	-7.54	-7.42	-7.65	-7.71	-7.34	-7.46	-7.91	-7.84
31'	-7.43	-7.27	< -8.00	-7.48	-7.19	-7.43	-7.74	-7.45	-7.21	< -8.00	-7.89
32'	-7.98	-7.06	-7.54	-7.20	-6.84	-7.28	-7.34	-7.25	-7.65	< -8.00	-7.76
33'	-8.00	-7.41	-7.80	-7.39	-7.28	-7.38	-7.50	-7.48	-7.81	< -8.00	-7.93
34'	-7.51	-7.30	-7.52	-7.60	-7.16	-7.15	-7.65	-7.37	> -4.00	< -8.00	> -4.00
35'	-7.54	-7.38	-7.59	-7.64	-7.19	-7.50	< -8.00	-7.38	> -4.00	< -8.00	> -4.00
36'	-7.13	-6.65	-6.77	-7.32	-6.53	-6.93	-6.77	-6.69	-7.56	-7.88	-7.72
37'	-7.72	-7.59	-7.65	-7.43	-7.35	-7.59	-7.38	-7.43	-7.37	<- 8.00	<-8.0
38'	-7.74	-7.44	-7.33	-7.52	-7.27	-7.47	-7.65	-7.27	-7.48	< -8.00	-7.96
39'	-6.76	-6.41	-6.39	-6.38	-6.77	-6.54	-6.60	-6.36	-6.51	<- 8.00	<-8.0
40'	-7.57	-7.75	-6.92	-7.22	-6.70	-6.90	-6.31	-6.37	-6.86	-7.49	-7.50
41'	-4.89	-4.35	-4.75	-4.19	-4.27	-4.46	-4.52	-4.25	-4.50	-4.70	-4.68

Compound	Cytotoxicity log GI_{50} (M)[1]									
	HL-60(TB)[2]	NCI-H460	HCT-116	SF-295	U-251	SK-MEL-5	OVCAR-3	786-0	PC-3	MDA-MB-435	MDA-N
42'	< -8.00	-7.41	< -8.00	< -8.00	-7.99	< -8.00	< -8.00	-7.82	-7.75	< -8.00	< -8.00
43'	< -8.00	< -8.00	< -8.00	-7.97	< -8.00	< -8.00	< -8.00	-7.92	-7.70	< -8.00	< -8.00
44'	< -8.00	< -8.00	< -8.00	< -8.00	< -8.00	< -8.00	< -8.00	< -8.00	< -8.00	< -8.00	< -8.00
45'	< -8.00	-7.76	< -8.00	-7.62	-7.81	-7.86	< -8.00	-5.22	-7.52	< -8.00	< -8.00
46'	-6.61	-6.20	-6.42	-6.23	-6.43	-6.33	-6.46	-5.02	-6.12	-6.72	-6.63
47'	-5.74	-5.42	-5.42	-5.04	-5.36	-5.46	-5.08	-5.25	-4.98	-5.75	-5.78
48'	-6.69	-5.98	-6.37	-5.83	-6.19	-6.36	-5.89	-5.62	-5.86	-6.69	-6.69
49'	-6.85	-6.40	-6.33	-6.26	-6.33	-6.44	-6.45	-6.21	-6.39	-6.98	-6.88
50'	-5.75	-5.42	-5.40	-5.42	-5.34	-5.48	-5.44	-5.27	-5.58	-5.80	-5.71
51'	-5.46	-4.88	-4.90	-4.83	-4.80	-5.66	-4.70	-4.29	-5.26	-5.53	-5.49
52'	-5.75	-5.39	-5.40	-5.26	-5.32	-5.53	-5.58	-5.12	-5.51	-6.07	-5.81

[1]Log concentrations which reduced cell growth to 50% of level at start of experiment. [2]HL-60(TB): leukemia cell line; NC-H460: non-small cell lung cancer cell line; HCT-116: colon cancer cell line; SF-295 & U251: CNS cancer cell lines; SK-MEL-5: mehanoma cell line: OVCAR-3: ovarian cancer cell line;'786-0: renal cancer cell line: PC-3: prostate cancer cell line: MDA-MB-435 & MDA-N: breast cancer cell lines. [3]Not tested.

Table 6

	Cytotoxicity log TGI (M)[1] per compound							
Cell line	**29'**	**30'**	**31'**	**32'**	**33'**	**34'**	**35'**	**36'**
average	-5.29	-5.33	-5.25	-4.62	-4.59	-4.51	-4.67	-4.58
leukemia	-5.57	-5.56	-5.61	-4.41	> -4.00	-4.14	> -4.00	-4.09
non-small cell lung cancer	-4.79	-5.24	-5.60	-4.07	> -4.00	-4.35	-4.61	> -4.00
colon cancer	-6.49	-6.26	-5.93	-4.79	-4.92	-5.02	-5.51	-4.54
CNS cancer	-5.51	-5.65	-5.01	-4.78	-4.74	-5.72	-5.71	-5.30
melanoma	-4.49	-4.62	-4.86	-4.01	-4.15	-4.32	-4.16	-4.14
ovarian cancer	-4.57	-4.99	-5.26	-4.50	-4.56	-4.80	-4.89	-4.52
renal cancer	-4.26	-4.19	-4.31	-4.31	-4.16	-4.06	> -4.00	-4.23
prostate cancer	-6.16	-5.80	-4.31	-5.58	-5.63	> -4.00	> -4.00	-5.51
breast cancer	-6.27	-6.24	-6.00	-5.93	-6.09	-4.89	-5.42	-5.91

[1]log molar concentrations required to cause total growth inhibition.

All compounds had cytotoxic activity (log GI_{50} < -4.00) against all cell lines tested. Among the three subseries of 2-phenyl-1,8-naphthyridin-4-ones, only compound **41'** had limited activity, for compounds **29'-40'** were inhibitory toward most cell lines in the submicromolar (log GI_{50}'s of -7 to -6) to nanomolar (log GI_{50}'s of -8 to -7) range. Ignoring compound **41'**, and considering only the average log GI_{50} values, which takes into account all the cell lines tested (not just those shown in **Table 5**), the agents with 3'-fluoride and methyl groups were slightly more cytotoxic than those with a 3'-chloride group. The 3'-fluoride compounds, in particular, have cytotoxicity comparable to that reported earlier for agents bearing a 3'-methoxy substituent.

A fairly dramatic difference was observed between the 2-(α-naphthyl) compounds (**42'-46'**) and the 2-(β-naphthyl) compounds (**47'-52'**) derivatives. In the former group, except for compound **46'**, low nanomolar GI_{50} values (log < -8) were observed with many cell lines. In the latter group, in contrast, submicromolar GI_{50} values were rarely obtained with any agent except compound **49'**. Note, moreover, that 2-(β-naphthyl) compound **49'** was at least 50-fold less active than its 2-(α-naphthyl) congener compound **44'**.

As in **Example 5** above substituents in the C ring altered substituent effects in the A ring. With a 3′-halogen, cytotoxicity was apparently unaffected by A ring substituents, within the limited range of available compounds. With a 3′-methyl group and with both 2-naphthyl series, cytotoxicity was unfavorably affected by methyl groups at both position 5 and position 7. With a 3′-methyl group, a methyl group at position 6 was less favorable than either no substituent or a methyl group at positions 5 or 7. In the α-naphthyl series, a methyl substituent at position 5, 6, or 7 was equivalent, and cytotoxicity differed little from that of the unsubstituted compound. In the β-naphthyl series, greater activity was observed in the compounds with methyl groups at positions 5 or 6 than in the unsubstituted agent or that bearing a methyl group at position 7.

Interestingly, all 3′- halogenated compounds showed different selectivity in the tested tumor panels at the total growth inhibition (TGI) levels. Growth of cells from more sensitive panels was arrested at a concentration approximately 1-2 log concentrations lower than was growth of less sensitive panels. As summarized in **Table 6**, all 3′-halogenated compounds, except for compound **34'**, exhibited a highly selective effect at the TGI level on the breast cancer panel. In the 3′-fluoro analogs, the compound with a methyl group at position 6 (**29'**) showed high selectivity for the colon, prostate, and breast panels; the analog with a methyl group at position 7 (**30'**) demonstrated high selectivity for the colon and breast panels and moderate selectivity for the prostate panel; and the compound with methyl groups at positions 5 and 7 (**31'**) exhibited highly selective effects on the colon and breast panels. In the 3′-chloro compounds, substitution of a methyl group at position 5 (**32'**) or no substitution (**33'**) in ring A produced high selectivity for the prostate and breast panels; a methyl at position 6 (**34'**) conferred high selectivity for the CNS panel and moderate selectivity for the colon, ovarian, and breast panels; a methyl substituent at position 7 (**35'**) gave highly selective effects on the colon, CNS, and breast panels; and methyl groups at positions 5 and 7 (**36'**) produced high selectivity for the CNS, prostate, and breast panels.

EXAMPLE 11

Antimicrotubule Assay of Compounds 29'-51'

Electrophoretically homogeneous bovine brain tubulin was purified as described in **Example 6**. Combretastatin A-4 was a generous gift of Dr. G. R. Pettit, Arizona State University.

The tubulin polymerization assay was performed as described in **Example 6**. Data presented in **Table 4** demonstrate that the new agents described here, both the new 2-phenyl-1,8-naphthyridin-4-ones and the 2-naphthyl derivatives, also interact with tubulin, with good correlation between their cytotoxic properties and their relative activity as inhibitors of tubulin assembly.

Among the compounds examined here, only one compound was inactive (**51'**; IC_{50} value >40 μM), one weakly active (**47'**; IC_{50} value, 14 μM), and one moderately active (**50'**; IC_{50} value, 5.1 μM). These three compounds were among the least cytotoxic agents, in terms of the average log GI_{50} values. At the opposite extreme, eleven compounds (**29'-31'**, **33'-36'**, and **43'-46'**) were highly potent inhibitors of tubulin polymerization, with IC_{50} values of 1.0 μM or less. This is the group that has activity comparable to that observed with the natural products colchicine, podophyllotoxin, and combretastatin A-4. Six of these agents had average log GI_{50} values below -7, and the remainder fell between -7 and -6. The remaining ten compounds (**32'**, **37'-42'**, **48'**, **49'**, and **52'**) inhibited tubulin assembly with IC_{50} values of 1.1 to 3.3 μM. Four of these compounds (**37'**, **38'**, **40'**, and **42'**) were among the most cytotoxic agents (log GI_{50} values of -7 or less), three (**32'**, **39'**, and **49'**) were moderately cytotoxic with log GI_{50} values between -7 and -6, and three (**41'**, **48'**, and **52'**) had little cytotoxicity (log GI_{50} values > -6).

Considering structure-activity aspects solely from the point of view of inhibition of tubulin polymerization, the 3′-fluoride and 3′-chloride substituents appeared to be equivalent, differed little in their activity from the previously described 3′-methoxy series, and were more active than the analogous derivatives with the 3′-methyl substituent. With the 3′-halogen series and the 3′-methyl series, derivatives with different methyl substituents in the A ring all had nearly equivalent activity. In the chloride and methyl series the data suggest that the

derivatives that are unsubstituted in the A ring (compounds **32'** and **37'**) were less active than those bearing methyl substituent(s).

The 2-(α-naphthyl) compounds (**42'-46'**) were comparable in activity to the 3'-halogen derivatives. In this series, too, substituents in the A ring had little effect on inhibitory activity. It was only in the less active 2-(β-naphthyl) compounds (**47'-52'**) that A ring substitution affected the apparent interaction with tubulin. A methyl substituent at either position 5 (**48'**) or 6 (**49'**) decreased the IC_{50} value 7-fold relative to the value obtained with the unsubstituted compound **47'**, while a methyl substituent at position 7 decreased the IC_{50} value 3-fold. In contrast, two methyl groups at positions 5 and 7 abolished activity. In the 2-(β-naphthyl) compounds, we found no significant difference between methyl and chloride substituents at position 6.

EXAMPLE 12

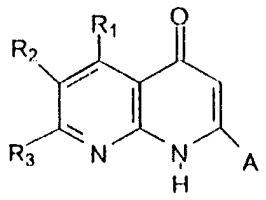
Colchicine Binding Assay of Compounds 29'-51'

The binding of radiolabeled colchicine to tubulin was measured by the DEAE-cellulose filter technique, as described in **Example 7**.

All compounds that inhibited tubulin assembly with IC_{50} values of 1.0 μM or less were compared with podophyllotoxin and combretastatin A-4 for inhibitory effects on the binding of [^{3}H]colchicine to tubulin (data summarized in **Table 4**). In these experiments inhibitor and colchicine were equimolar and in 5-fold molar excess over tubulin. All agents, except possibly compound **46'**, significantly inhibited colchicine binding to tubulin, but none was as potent as either podophyllotoxin or combretastatin A-4. Without wishing to be bound by any particular theory, we suspect that the quantitative differences between the assembly assay and the [^{3}H]colchicine assay result from differences in relative rates of drug binding and dissociation from tubulin and from the stoichiometric character of the [^{3}H]colchicine assay versus the cooperative character of the assembly assay. However, the [^{3}H]colchicine binding assay does detect reduced activity in the 5,7-dimethyl derivatives that was not apparent in either the cytotoxicity or polymerization assays (*cf.* results with **31'** *vs.* **29'** and **30'**; with **36'** *vs.* **33'-35'**; and with **46'** *vs.* **43'-45'**).

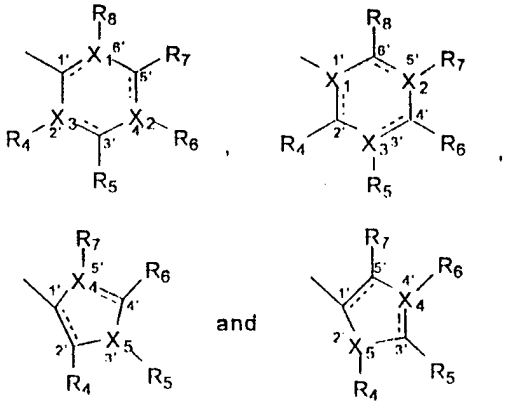
That Which Is Claimed Is:

1. A compound of Formula I:



I

wherein A is an aromatic moeity selected from the the group consisting of:



wherein:

X_1, X_2, and X_3 are each individually selected from the group consisting of C, or N;

X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkylenoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and

the dashed line indicates that the bond may be a double bond or a single bond,

with the provisos that:

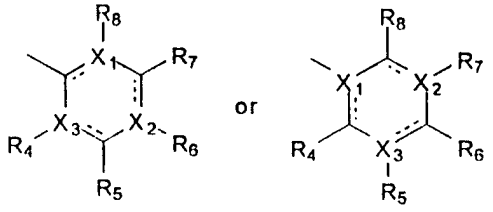
when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected thereto are double bonds;

when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent;

when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and

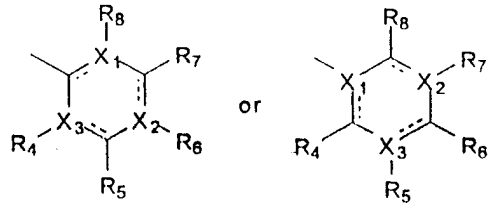
when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent.

2. The compound according to Claim 1, wherein A is



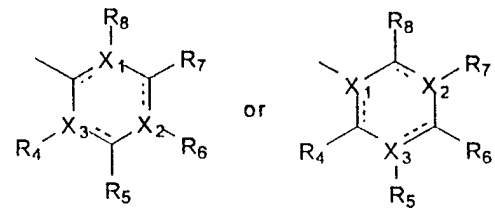
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_4 is alkoxy.

3. The compound according to Claim 1, wherein A is



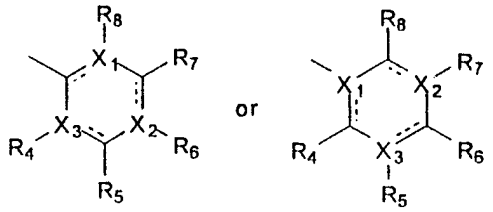
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 is alkoxy.

4. The compound according to Claim 1, wherein A is



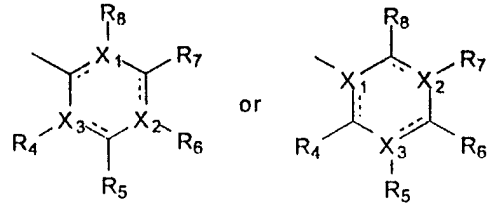
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is alkoxy.

5. The compound according to Claim 1, wherein A is



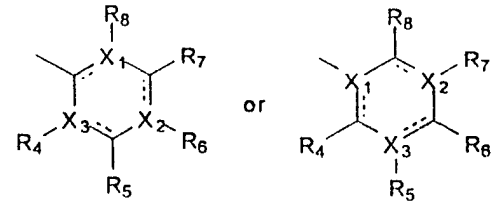
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is halo.

6. The compound according to Claim 1, wherein A is



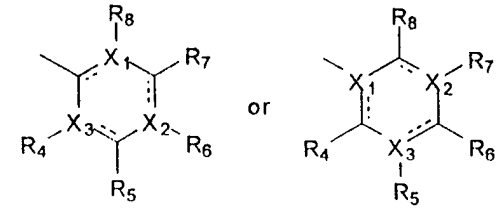
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is halo.

7. The compound according to Claim 1, wherein A is



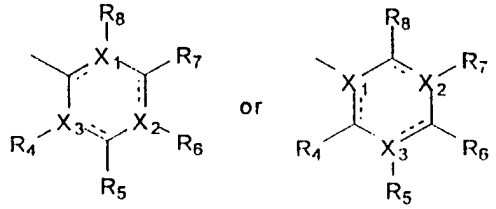
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 is alkyl.

8. The compound according to claim 1, wherein A is



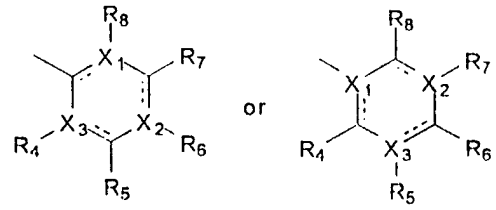
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and at least one of R_1, R_2, R_3, and R_4 is alkyl.

9. The compound according to Claim 1, wherein A is



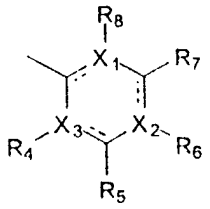
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_4 and R_5 together form an alkydienyl bridging group.

10. The compound according to Claim 1, wherein A is



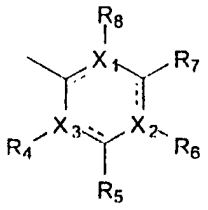
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 and R_6 together form an alkydienyl bridging group.

11. The compound according to Claim 1, wherein A is



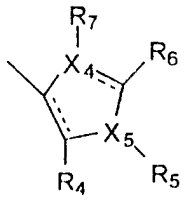
X_1 and X_2 are each C, X_3 is N, all dashed lines are double bonds, R_5 and R_6 are each alkyl, and R_4 is absent.

12. The compound according to Claim 1, wherein A is



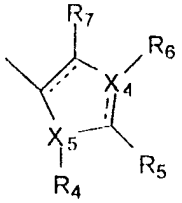
X_1 and X_3 are each C, X_2 is N, all dashed lines are double bonds, R_3 is alkyl, and R_6 is absent.

13. The compound according to Claim 1, wherein A is



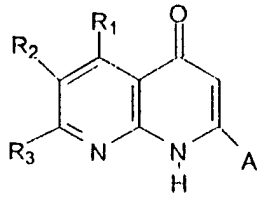
X_4 is C, X_5 is selected from the group consisting of O, S, and N, all dashed lines are double bonds, and R_2 is alkyl and R_5 is absent.

14. The compound according to Claim 1, wherein A is

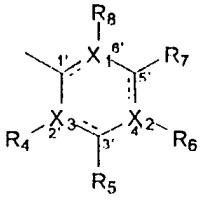
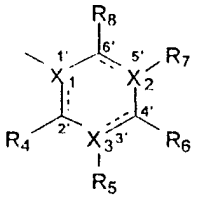
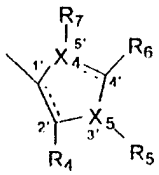
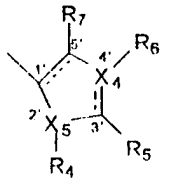


X_4 is C, X_5 is selected from the group consisting of O, S, and N, all dashed lines are double bonds, R_3 is alkyl, and R_4 is absent.

15. A process for making compounds of Formula I:



wherein A is an aromatic moeity selected from the group consisting of:




and


wherein:

X_1, X_2, and X_3 are each individually selected from the group consisting of C, or N;

X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and

the dashed line indicates that the bond may be a double bond or a single bond,

with the provisos that:

when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected

thereto are double bonds;

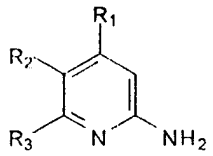
when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent;

when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and

when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent.;

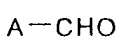
said process comprising:

(a) reacting a compound of Formula II:



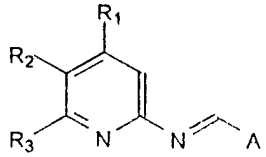
II

with a compound of Formula IV:



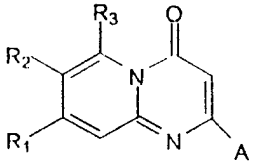
IV

to produce a Schiff base intermediate of Formula VI:



VI

(b) cyclizing the Schiff base intermediate to give a pyridopyrimidinone intermediate of Formula V:



V

and

(c) thermally converting said pyridopyrimidinone intermediate to a compound of Formula I.

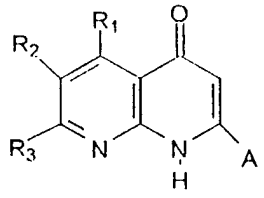
16. The process according to Claim 15, wherein said step (a) of reacting said compound of Formula II with said compound of Formula IV is carried out with heating in the presence of an organic solvent.

17. The process according to Claim 15, wherein said step (a) of reacting said compound of Formula II with said compound of Formula IV is carried out in the presence of an organic solvent and at the reflux temperature of said solvent.

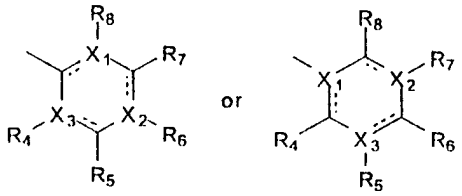
18. The process according to Claim 15, wherein said step (b) of cyclizing said Schiff base intermediate of Formula VI is carried out in the presence of chloroacetyl chloride and triethylamine.

19. The process according to Claim 15, wherein said step (c) of thermally converting said pyridopyrimidinone intermediate of Formula V to said compound of Formula I comprises heating said pyridopyrimidinone intermediate of Formula V to a temperature of between about 300°C and about 400°C in mineral oil.

20. A process for making compounds of Formula I:



wherein A is:



wherein

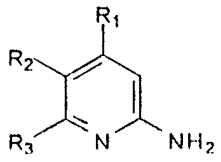
X_1, X_2, and X_3 are each C;

all dashed lines are double bonds; and

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkylenedioxy, alkylenedioxy, alkyleneimine, and alkylenediimine bridging groups;

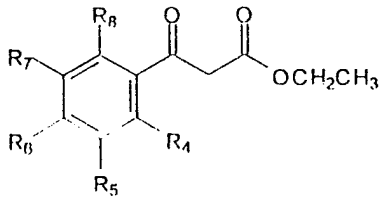
said process comprising:

(a) condensing a compound of Formula II:



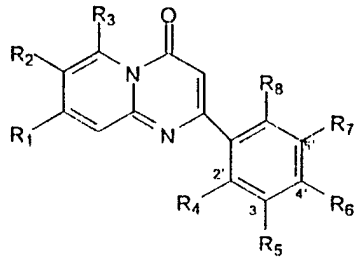
II

with a compound of Formula III:



III

in the presence of polyphosphoric acid to produce a pyridopyrimidinone intermediate of Formula V-A:



V-A

and

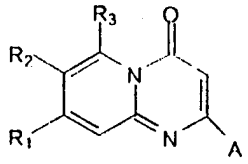
(b) thermally converting said pyridopyrimidinone intermediate to a compound of Formula I.

21. The process according to Claim 20, wherein said step (a) of condensing said compound of Formula II with said compound of Formula III comprises heating a mixture of said compound of Formula II and said compound of Formula III in the presence of polyphosphoric acid.

22. The process according to Claim 20, wherein said step (a) of condensing said compound of Formula II with said compound of Formula III comprises heating a mixture of said compound of Formula II and said compound of Formula III in the presence of polyphosphoric acid.

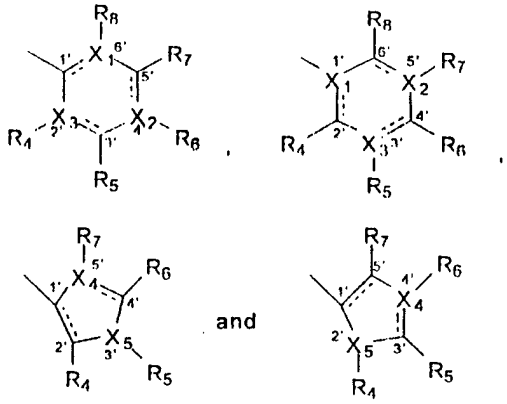
23. The process according to Claim 20, wherein said step (b) of thermally converting said pyridopyrimidinone intermediate to said compound of Formula I comprises heating said pyridopyrimidinone intermediate to a temperature of between about 300°C and about 400°C in mineral oil.

24. A compound of Formula V:



V

wherein A is an aromatic moeity selected from the group consisting of:



wherein:

X_1, X_2, and X_3 are each individually selected from the group consisting of C, or N;

X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and

the dashed line indicates that the bond may be a double bond or a single bond,

with the provisos that:

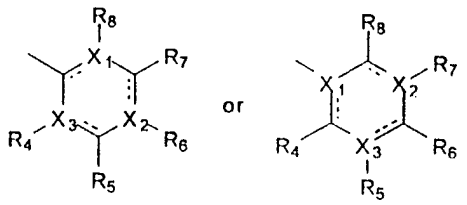
when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected thereto are double bonds;

when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent;

when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and

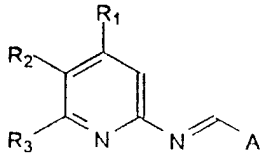
when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent.

25. The compound according to Claim 24, wherein A is:



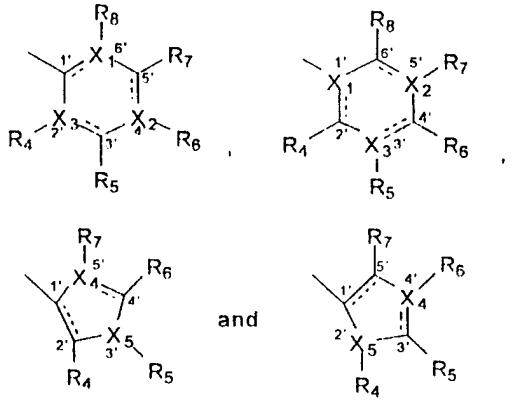
wherein X_1, X_2, and X_3 are each C and all dashed lines are double bonds.

26. A compound of Formula VI:



VI

wherein A is an aromatic moeity selected from the group consisting of:



wherein:

X_1, X_2, and X_3 are each individually selected from the group

consisting of C, or N;

X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and

the dashed line indicates that the bond may be a double bond or a single bond,

with the provisos that:

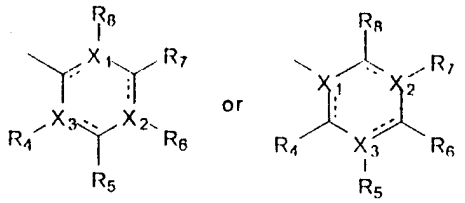
when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected thereto are double bonds;

when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent;

when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and

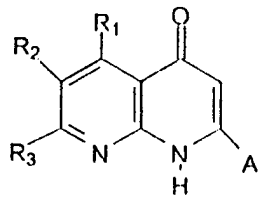
when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent..

27. The compound according to Claim 26, wherein A is:



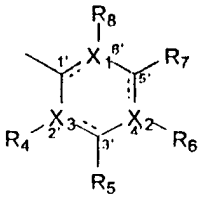
wherein X_1, X_2, and X_3 are each C, and all dashed lines are double bonds.

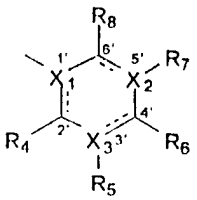
28. A method for treating a tumor, said method comprising administering to a subject in need of treatment, a compound of Formula I:

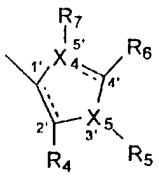


I

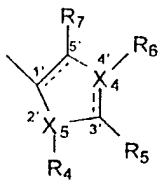
wherein A is an aromatic moeity selected from the group consisting of:







and



wherein:

X_1, X_2, and X_3 are each individually selected from the group consisting of C, or N;

X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and

the dashed line indicates that the bond may be a double bond or a single bond,

with the provisos that:

when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected thereto are double bonds;

when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent;

when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and

when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent;

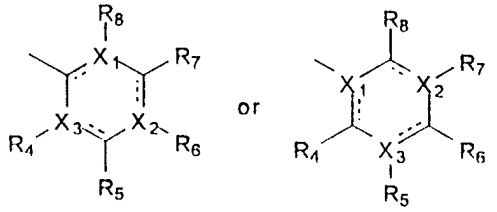
in an amount effective to treat a tumor.

29. The method according to Claim 28, wherein said tumor is selected from the group consisting of non-small cell lung cancer, colon cancer, central nervous system cancers, melanoma, ovarian cancer, prostate cancer and breast cancer.

30. The method according to Claim 28, wherein said tumor is breast cancer.

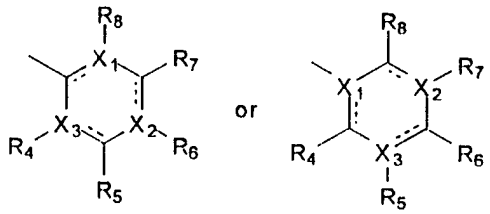
31. The method according to Claim 28, wherein said tumor is prostate cancer.

32. The method according to Claim 28, wherein A is



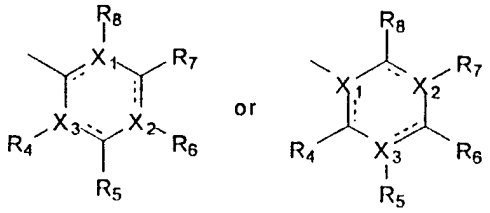
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_4 is alkoxy.

33. The method according to Claim 28, wherein A is



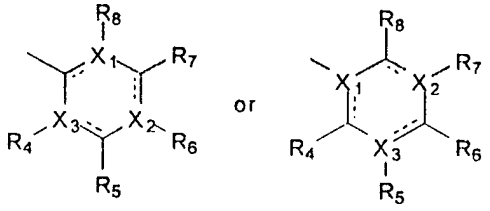
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 is alkoxy.

34. The method according to Claim 28, wherein A is



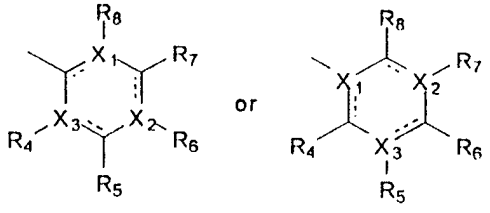
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is alkoxy.

35. The method according to Claim 28, wherein A is



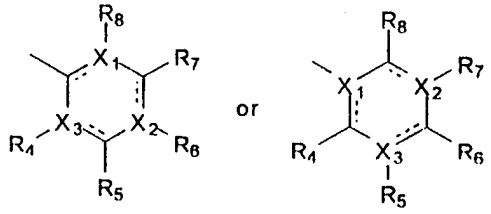
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is halo.

36. The method according to Claim 28, wherein A is



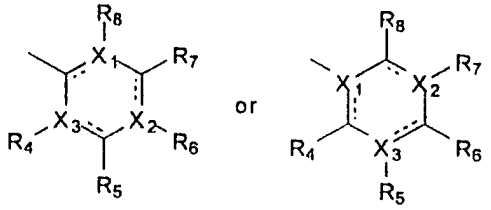
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 is halo.

37. The method according to Claim 28, wherein A is



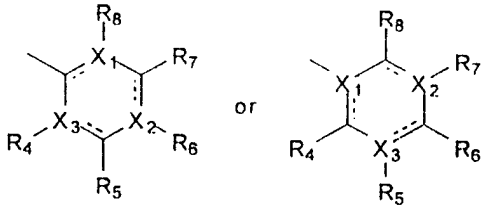
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is alkyl.

38. The method according to Claim 28, wherein A is



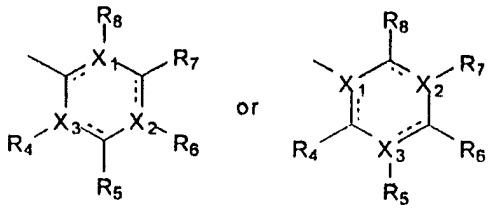
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and at least one of R_1, R_2, R_3, and R_4 is alkyl.

39. The method according to Claim 28, wherein A is



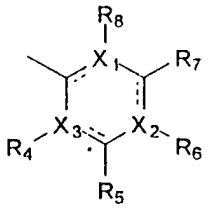
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and and R_4 and R_5 together form an alkydienyl bridging group.

40. The method according to Claim 28, wherein A is



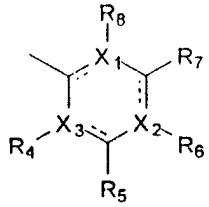
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 and R_6 together form an alkydienyl bridging group.

41. The method according to Claim 28, wherein A is



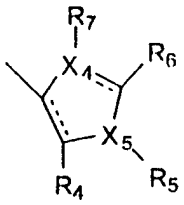
X_1 and X_2 are each C, X_3 is N, all dashed lines are double bonds, R_2 and R_5 are each alkyl, and R_4 is absent.

42. The method according to Claim 28, wherein A is



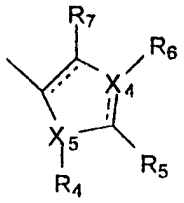
X_1 and X_3 are each C, X_2 is N, all dashed lines are double bonds, R_3 is alkyl, and R_6 is absent.

43. The method according to Claim 28, wherein A is



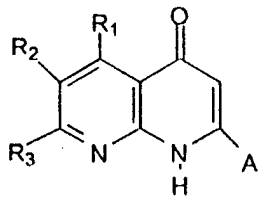
X_4 is C, X_5 is selected from the group consisting of O, S, and N, all dashed lines are double bonds, R_2 is alkyl, and R_5 is absent.

44. The method according to Claim 28, wherein A is



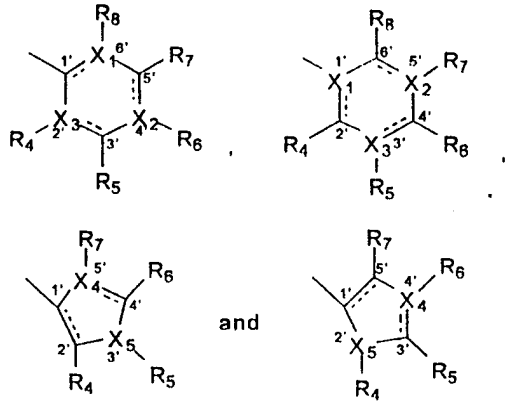
X_4 is C, X_5 is selected from the group consisting of O, S, and N, all dashed lines are double bonds, R_2 is alkyl, and R_4 is absent.

45. A method of inhibiting cellular mitosis, said method comprising contacting a cell with a compound of Formula I:



I

wherein A is an aromatic moeity selected from the group consisting of:



wherein:

X_1, X_2, and X_3 are each individually selected from the group consisting of C, or N;

X_4 and X_5 are each individually selected from the group consisting of C, N, O, and S wherein at least one of X_4 and X_5 is N, O, or S;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are each independently selected from the group consisting of H, alkyl, hydroxyl, alkoxyl, aryloxyl, halo, amino, alkylamino, dialkylamino, or nitro, or alterantively, two adjacent R groups together may form a bridging group selected from the group consisting of alkydienyl, alkyleneoxy, alkylenedioxy, alkyleneimine, and alkylenediimine; and

the dashed line indicates that the bond may be a double bond or a single bond,

with the provisos that:

when any of X_1, X_2, X_3, X_4 or X_5 is C, the dashed lines connected thereto are double bonds;

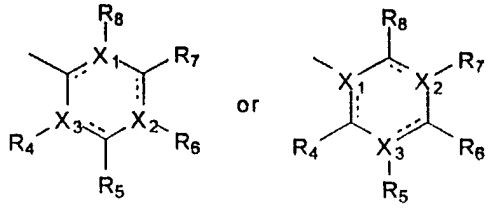
when any of X_1, X_2, or X_3 is N, the dashed lines connected thereto are double bonds and the R group attached at that position is absent;

when either X_4 or X_5 is N, the dashed lines connected thereto may be single bonds or double bonds, and when the dashed line is a double bond, the R group attached at that position is absent; and

when either X_4 or X_5 is O or S, the dashed lines connected thereto are single bonds and the R group attached at that position is absent;

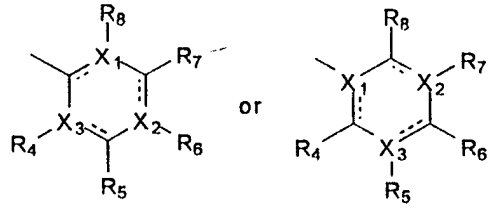
in an amount effective to inhibit cellular mitosis.

46. The method according to Claim 45, wherein A is



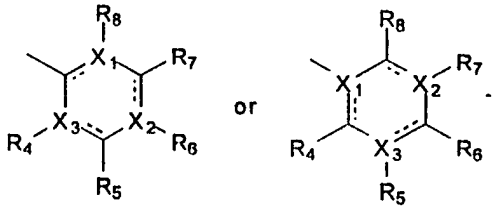
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_4 is alkoxy.

47. The method according to Claim 45, wherein A is



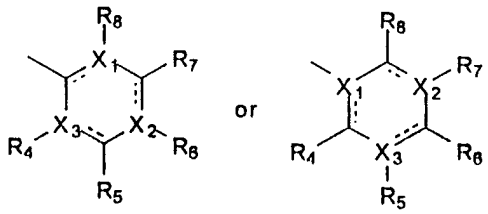
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_4 is alkoxy.

48. The method according to Claim 45, wherein A is



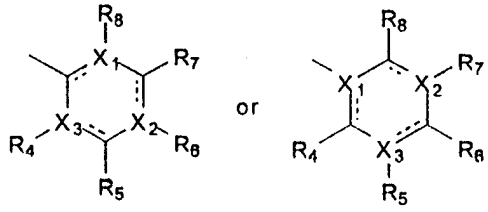
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is alkoxy.

49. The method according to Claim 45, wherein A is



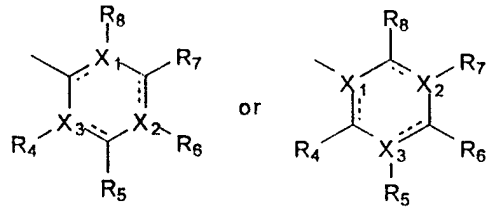
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_6 is halo.

50. The method according to Claim 45, wherein A is



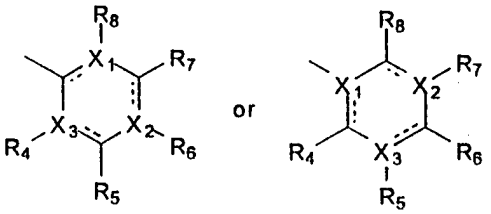
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 is halo.

51. The method according to Claim 45, wherein A is



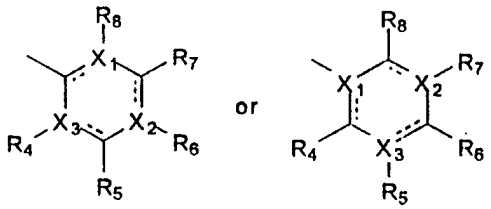
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 is alkyl.

52. The method according to Claim 45, wherein A is



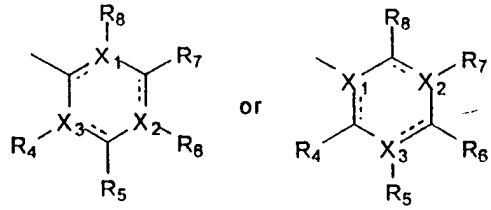
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and at least one of R_1, R_2, R_3, and R_4 is alkyl.

53. The method according to Claim 45, wherein A is



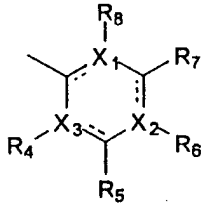
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_4 and R_5 together form an alkydienyl bridging group.

54. The method according to Claim 45, wherein A is



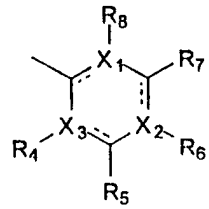
X_1, X_2, and X_3 are each C, all dashed lines are double bonds, and R_5 and R_6 together form an alkydienyl bridging group.

55. The method according to Claim 45, wherein A is



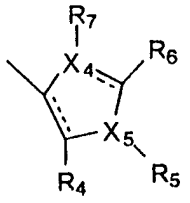
X_1 and X_2 are each C, X_3 is N, all dashed lines are double bonds, R_2 and R_5 are each alkyl, and R_4 is absent.

56. The method according to Claim 45, wherein A is



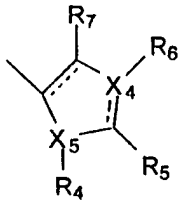
X_1 and X_3 are each C, X_2 is N, all dashed lines are double bonds, R_3 is alkyl, and R_6 is absent.

57. The method according to Claim 45, wherein A is



X_4 is C, X_5 is selected from the group consisting of O, S, and N, all dashed lines are double bonds, R_2 is alkyl, and R_5 is absent.

58. The method according to Claim 45, wherein A is



X_4 is C, X_5 is selected from the group consisting of O, S, and N, all dashed lines are double bonds, R_2 is alkyl, and R_4 is absent.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 C07D213/74 A61K31/435 //(C07D471/04,C07D213:00, C07D213:00)

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T. R. KELLY ET AL.: J. AMER. CHEM. SOC., vol. 112, no. 22, 1990, pages 8024-8034, XP002069221 * Compound of formula 53 * ---	1-14
X	N. KATAGIRI ET AL.: "Studies on Ketene and Its Derivatives. Part 119. Reactions of Haloketenes with 2-Arylideneaminopyridines" J. HETEROCYCL. CHEM., vol. 21, no. 2, 1984, pages 407-412, XP002069222 see tables I,,II --- -/--	1-14,24, 25

[X] Further documents are listed in the continuation of box C.

[X] 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
30 June 1998	03.07.98

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	Herz, C

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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.
X	P. L. FERRARINI ET AL.: "Synthesis of some Substituted Pyrido[1,2-a]pyrimidin-4-ones and 1,8-Naphthyridines" J. HETEROCYCL. CHEM., vol. 20, no. 4, 1983, pages 1053-1057, XP002069223 see tables I,II	1-14,24, 25
X	WO 92 07468 A (IMPERIAL CHEMICAL INDUSTRIES PLC) 14 May 1992 * Scheme A, B * see claims 7-9; examples 1-26; table 1	1-25
X	H. L. YALE: "9-Hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 9-Methyl-2-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one, Ethyl 9-Hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one-3-carboxylate and Their Derivatives" J. HETEROCYCL. CHEM., vol. 12, 1975, pages 427-431, XP000562848 see table I	24,25
X	P. L. FERRARINI ET AL.: "One Step Synthesis of Pyrimido[1,2-a][1,8]naphthyridinones, Pyrido[1,2-a]pyrimidinones and 1,8-Naphthyridinones. Antihypertensive Agents. V" J. HETEROCYCL. CHEM., vol. 27, no. 4, 1990, pages 881-886, XP002069225 see table I	24,25
X	A. HORVATH, I. HERMECZ: "Nitrogen Bridgehead Compounds. Part 65. Vilsmeier-Haack Formylation of 4H-Pyrido[1,2-a]pyrimidin-4-ones. Part 6" J. JETEROCYCL. CHEM., vol. 23, no. 5, 1986, pages 1295-1298, XP002069226 see table 2	24,25
X	M. SHUR, S. S. ISRAELSTAM: "The Reaction of Amino Heterocycles with Reactive Esters. I. 2-Aminopyridines" J. ORG. CHEM., vol. 33, no. 8, 1968, pages 3015-3020, XP002069227 see table I	24,25

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R. ADAMS, I. J. PACHTER: "Ultraviolet Specra and Structures of the Pyrido[1,2-a]pyrimidones" J. AMER. CHEM. SOC., vol. 74, 1952, pages 5491-5497, XP002069228 * Compound of formula XXIV *	24,25
Y	US 4 042 765 A (EXXON RESEARCH AND ENGINEERING CO.) 16 August 1977 * Compounds of formula i and II *	24,25
Y	US 3 929 787 A (E. R. SQUIBB & SONS, INC.) 30 December 1975 * Compounds of formula IV *	24,25
X	I. A. KAYE ET AL.: "N,N-Dimethyl-N'-benzohydryl-N'-(2-pyridyl)-ethylenediamine and Related Compounds as Histamine Antagonists" J. AMER. CHEM. SOC., vol. 74, 1952, pages 403-407, XP002069229 see table I	26,27
X	US 2 713 048 A (ABBOTT LABORATORIES) 12 July 1955 see column 2, line 43 - line 53	26,27
X	DE 406 209 C (CHEMISCHE FABRIK AUF ACTIEN (VORM. E. SCHERING)) 15 November 1924 see column 2, line 56 - line 63	26,27
X	K. FEIST: "Über einige Derivate des 2-Amino-pyridins" ARCH. PHARM (WEINHEIM GER.), vol. 272, 1934, pages 101-113, XP002069230 see page 106	26,27
X	CHEMICAL ABSTRACTS, vol. 52, no. 12, 1959 Columbus, Ohio, US; abstract no. 1334b, I. A. SAVICH ET AL.: "Synthesis of a series of Schiff bases formed from aromatic hydroxy aldehyes and heterocyclic amines" XP002069233 see abstract & VESTNIK MOSKOV. UNIV. 11, SER. MAT. MEKH., ASTRON., FIZ., KHIM., no. 1, 1956, pages 225-231,	26,27

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P. CHERUBIM ET AL.: "Synthesis and biological evaluation of phenanthrene-derived carboxamides as cytotoxic agents" ANTI-CANCER DRUG DESIGN, vol. 8, 1993, pages 429-438, XP002069231 * entire document * ---	1-58
P,X	YI XIA ET AL.: "Antitumor Agents. 178. Synthesis and Biological Evaluation of Substituted 2-Aryl-1,8-naphthyridin-4(1H)-ones as a Antitumor Agents That Inhibit Tubulin Polymerization" J. MED. CHEM., vol. 40, no. 19, 1997, pages 3049-3056, XP002069232 * entire document * -----	1-58

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INTERNATIONAL SEARCH REPORT

International application No.
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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:

2. ☒ Claims Nos.: 26-27
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 26-27

In view of the large number of several hundred novelty-destroying compounds, which are defined by the general definition in this independent claim, the search had to be restricted for economic reasons. The search was limited to the compounds mentioned in the claims and examples and reasonable generalization thereof. (see Guidelines, Chapter III, paragraph 2.3).

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 98/04325

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9207468 A	14-05-1992	AU 8640891 A	26-05-1992
US 4042765 A	16-08-1977	NONE	
US 3929787 A	30-12-1975	NONE	
US 2713048 A	12-07-1955	NONE	
DE 406209 C		NONE	