PATENT SPECIFICATION (11) 1 602 684

1 602 684

(21) Application No. 37253/80 (22) Filed 26 May 1978
(62) Divided out of No. 1 602 683
(31) Convention Application No. 459 497
(32) Filed 4 June 1977 in
(33) Spain (ES)
(44) Complete Specification published 11 Nov. 1981
(51) INT CL³ C07D 221/14; A61K 31/435, 31/495, 31/535; C07D 401/02, 413/06; (C07D 401/02, 295/22); (C07D 413/06, 221/14, 295/04)
(52) Index at acceptance
C2C 1341 1532 1538 1562 1626 213 215 246 247 250 251 252 255 25Y 28X 305 30Y 323 32Y 332 341 34Y 351 352 620 621 626 650 670 671 72X 761 802 80Y AA KD LW ML

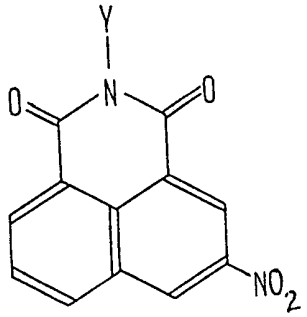
(19)

(54) SUBSTITUTED NAPHTHALIMIDES AND THEIR DERIVATIVES

(71) We, LABORATORIOS MADE, S.A., a Spanish body corporate of Avenida de Burgos 5Km850, Madrid, Spain, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to substituted naphthalimides and their derivatives which have great biological interest as anti-tumour agents, to processes for their preparation, and pharmaceutical compositions containing them.

According to one aspect of the invention there is provided a substituted naphthalimide of the general formula



or its salt of a pharmacologically acceptable acid, N-oxide or quaternary ammonium salt, wherein Y is 3-dimethylaminopropyl, 3-diethylminopropyl, 2-morpholinoethyl, 1-ethylpiperidin-3-yl, 3-(4-methyl-1-piperazinyl)propyl, dimethylamino, 1-pyrrolidinyl or —$NHCONH_2$.

The invention also provides a method of synthesis of these compounds by reaction of an activated derivative of the 3-nitro-substituted naphthalic acid with the corresponding compound of formula YNH_2, in a suitable solvent. The reaction temperature will be included between the freezing and boiling points of the solvent, but ambient temperature is sufficient in the majority of cases. Once the reaction is completed the resulting product may be filtered and crystallised from an appropriate solvent.

Compounds within the present invention include naphthalimides thought to be useful as anti-cancer agents which act as ADN and ARN-inhibiting agents.

For pharmaceutical use, at least one of the present compounds is incorporated in a pharmacologically active amount in a pharmaceutically acceptable carrier or excipient.

Specific non-limitative examples of the present invention will now be described.

The elemental analyses of the described compounds are within ± 0.4% in accordance with international standards.

Example 1.

$(Y=CH_2—CH_2—CH_2—N(CH_3)_2)$

In an Erlenmeyer flask of 100 ml capacity, provided with electromagnetic stirring, 2.43 g (0.01 mols) of 3-nitro-1,8-naphthalic anhydride and 20 ml of ethanol are placed, addition then being made and only once of 1.02 g (0.01 mols) of 3-dimethyl-aminopropylamine. The mixture is stirred for two hours and the solid thus formed is filtered and recrystallised from ethanol, obtaining 2.75 g (84% yield).

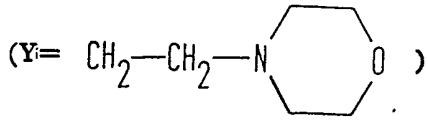
The N - (3 - dimethylaminopropyl) - 3 - nitro - 1,8 - naphthalimide is a yellow solid having a melting point of 99°C.

Example 2.

$(Y=CH_2—CH_2—CH_2N(CH_2—CH_3)_2)$

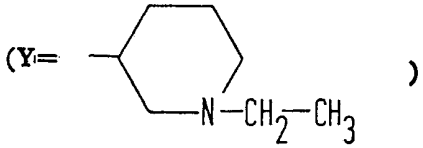
The same operation as in the preceding case, but using 1.30 g of 3-diethyl-amino-propylamine and obtaining 3.1 g (89%) of N - (3 - diethylaminopropyl) - 3 - nitro-1,8 - naphthalimide having a melting point of 105° (ethanol).

Example 3.



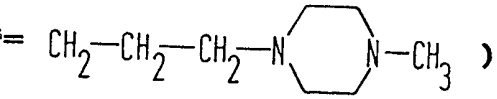
The same operation as in Example 1, but using 1.30 g (0.01 mols) of N-(2-aminoethyl)-morpholine, obtaining 2.35 g (68%) of N - 2 - (N - morpholin) - ethyl-3 - nitro - 1,8 - naphthalimide having a melting point of 189—90°C (DMF/water).

Example 4.



The same operation as in Example 1, but using 1.28 g (0.01 mols) of 1-ethyl-3-aminopiperidine, obtaining 1.31 g (37%) of N - 3 - (1 - ethylpiperidin) - 3 - nitro-1,8 - naphthalimide having a melting point of 157—58°C (DMF/water).

Example 5.



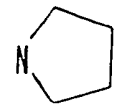
The same operation as in Example 1, but using 1.57 g (0.01 mols) of 1-(3-amino-propyl)-4-methylpiperazine, obtaining 2.80 g (74.8%) of N - (3 - (4 - methyl - 1-piperazin) - propyl - 3 - nitro - 1,8 - naphthalimide having a melting point of 154—55°C (ethanol/water).

Example 6.

$(Y=NCH_3)_2)$

In a flask of 100 ml capacity, provided with magnetic stirring and reflux coolant, 2.43 g (0.01 mols) of 3-nitro-1,8-naphthalic anhydride, 0.48 g (0.01 mols) of N,N-dimethylhydrazine and 50 ml of ethanol are placed, and are reflux heated with stirring for 10 hours. At the end of this time a brown solid is precipitated which is crystallised from ethanol, obtaining 2.0 g (70.2%) of N - dimethylamino - 3 - nitro - 1,8 - naph-thalimide having a melting point of 233—34°C.

Example 7.

(Y=  .)

The same operation as in the preceding Example, but using 0.2 g (0.0023 mols) of N-aminopyrrolidine, obtaining 0.25 g (40%) of N - (1 - pyrrolidin) - 3 - nitro-1,8 - naphthalimide of a melting point of 227—28°C (DMF/water).

Example 8.

(Y=$NHCONH_2$)

The same operation as in Example 6, but using 0.75 g of semicarbazide, obtaining 2.7 g (90%) of N - ureido - 3 - nitro - 1,8 - naphthalimide of a melting point of >300° (DMF).

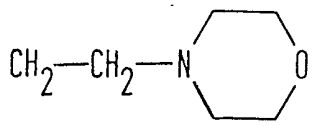
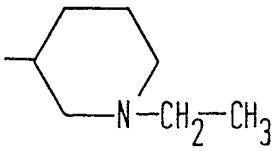
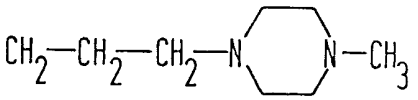
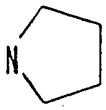
As has been indicated, the most important biological activity of compounds within this invention is its anti-cancer action, and to determine this "screening" tests have been made of the cytotoxic activity of the compounds on the so-called Hela cellular line, cultivated in monolayer on glass bottles.

Testing commences from a culture having approximately 125,000 cells per millilitre. They were dispersed with trypsin and maintained in suspension by stirring, until the moment of their distribution in tubes to which addition was made, after the cells have become stuck to the wall, of the tested compound in different concentrations. Apart from blank control tubes, controls are used to which the compound 6-mercaptopurine was added, from which the 50% inhibitory dose (ID_{50}) was known, that is, the dose which inhibits cellular growth by 50%.

After 72 hours the results were read.

First an optical reading was made under microscope, which gives an idea of the proportion in which the compounds have affected the cellular culture. Then the proteins were determined (Lowry method modified by Dyama and Eagle: Proc. Soc. Exper. Biol. Med. 305, 1956) in each culture tube and the results compared with those obtained in the control tubes, to which compound had not been added. With these data a graph can be made in which the microgram concentrations of the compound are represented in relation to the percentage of inhibition of cellular growth, thereby obtaining the ID_{50}.

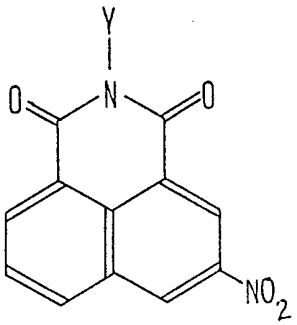
The data obtained as to the values of ID_{50} are given in the following table, in which Y has the significance indicated previously.

Example	Y	ID_{50}
1	$CH_2-CH_2-CH_2-N(CH_3)_2$	1
2	$CH_2-CH_2-CH_2-N(CH_2-CH_3)_2$	5
3		20
4		6
5		2
6	$N(CH_3)_2$	>100
7		>100
8	$NHCONH_2$	>100

It is noted that certain 3-nitronaphthalimide compounds and a process for their preparation are disclosed in our prior British Patent Specification No. 1,435,238.

WHAT WE CLAIM IS:—

1. A substituted naphthalimide of the general formula



or its salt of a pharmacologically acceptable acid, N-oxide or quaternary ammonium salt, wherein Y is 3-dimethylaminopropyl, 3-diethylminopropyl, 2-morpholinoethyl, 1-ethylpiperidin-3-yl, 3-(4-methyl-1-piperazinyl)propyl, dimethylamino, 1-pyrrolidinyl or $-NHCONH_2$.

2. A substituted naphthalimide or derivative according to claim 1, substantially as herein exemplified.

3. A process for the preparation of a substituted naphthalimide as claimed in claim 1 which includes reacting an active derivative of 3-nitro-substituted naphthalic

acid with a compound of formula YNH_2 wherein Y is as defined in claim 1, in a suitable solvent.

4. A process for the preparation of a substituted naphthalimide as claimed in claim 1, substantially as herein described or as described in any one of the Examples.

5. A substituted naphthalimide whenever prepared by a process as claimed in claim 3 or claim 4.

6. A pharmaceutical composition containing at least one compound as claimed in claim 1 in a pharmacologically active amount in a pharmaceutically acceptable carrier or excipient.

MATHISEN, MACARA & CO.,
Chartered Patent Agents,
Lyon House, Lyon Road,
Harrow, Middlesex, HA1 2ET.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.