New aza- and polyaza-naphthalenyl ketones useful in the treatment of e.g. infection by HIV (Eng)

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NOVELTY
Aza- and polyaza-naphthalenyl ketones or their salts are new.

DETAILED DESCRIPTION

alkynyl-CH3(N(R),N(R)), N(R),C(N(R)),N(R), or 1-6C (fluorinated) substituted with R6, -O-(1-6Calkyl), -R6, -N(R),R6, -N(R),C(N(R)),N(R), or 1-6C (fluorinated) substituted with R6, -O-(1-6Calkyl), -R6, -N(R),C(N(R)),N(R), or 1-6C (fluorinated)

T = H, 1-6Calkyl, 1-6Cfluoroalkyl, CH3, -O-(1-6Calkyl), CH3, CH2, -O-(1-6Cfluoroalkyl), halo, CH;

T = 1-6Calkyl, -O-(1-6Calkyl), -O-(1-6Calkyl), halo, CH;

R1 and R2 = H, 1-6Calkyl, -O-(1-6Calkyl), halo, CH3, -O-(1-6Calkyl), halo, CH2, -O-(1-6Cfluoroalkyl), halo, CH;

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ANTIVIRAL SPECIFICITY

pectrum of antiviral activity of structurally related compounds.

ACTIVITY

Anti-HIV, Viruside.

MECHANISM OF ACTION

HIV integrase and HIV replication inhibitors.

USE

In the treatment or prevention of infection by HIV; treating, preventing or delaying onset of AIDS (claimed) or AIDS related complications (ARC). The compounds are also useful in the preparation and execution of screening assay for antiviral compounds; for isolating enzyme mutants; and in establishing or determining the binding site of other antiviral to HIV integrase e.g. by competitive inhibition. The compounds have highly specific inhibition capacity of HIV

ADVANTAGE

The compounds have highly specific inhibition capacity of HIV

(2002-09-22 1996)

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SPECFIC COMPOUNDS

25 compounds are specifically claimed as (I) e.g. 1-(3-benzylphenyl)-1-(8-hydroxyquinolin-7-yl)methane (IA)

hydroxynoline (5 g) in chloroform (10 ml). The addition mixture was stirred for 1 hour, warmed to ambient temperature, diluted with ethyl acetate (200 ml) and extracted. The organic extracts were dried, filtered and purified to give 7-bromoquinolinol-8-ol (A). (A) (3.1 g), disopropylammonium (7.23 ml) and methyl chloride (100 ml) were added. MEM chloride (1.90 ml) was added and the reaction was stirred for 18 hours. After which another MEM chloride (0.95 ml) was added. This mixture was stirred for 1 hour, water (50 ml) was added and the organic solvent removed in vacuum. The residue was extracted, washed dried and filtered to give 7-bromo-8-2(methoxyethoxy)ethylbenzoinol-quinoline (B). (B) (0.765 g) and tetrahydrofuran (THF) (10 ml) were added in flask. The flask was cooled to -78°C and to it was added t-butyllithium (3.6 ml of a 1.5M solution in pentane, 5.4 mmol). The reaction was stirred for 15 minutes than N-methyl-N-methoxy-3-benzylphenylbenzincarbonyamide (0.626 g THF (5 ml) was added at 74°C. This mixture was stirred for 5 minutes, warmed to ambient temperature and the reaction was quenched by the addition of saturated aqueous NH4Cl. The solution was extracted, washed, dried and filtered to give 1-(3-benzylphenyl)-8-(2-methoxyethoxy)ethylbenzoinol-quinoline (C). (C) (0.2 g), MeOH (3 ml) and trifluoroacetic acid (1.08 ml) were added and the reaction was stirred for 3 days, after which it was poured into aqueous saturated NaHCO3 (20 ml) and extracted, dried, filtered and purified to give 1-(3-benzylphenyl)-1-(8-hydroxyquinolin-7-yl)methane (IA).

DEFINITIONS

Preferred Definitions:
X = N;
Y = C-O;
Z1 = C=O;
Z2 = C=O;
Z3 = CH;
Q1 and Q1 = H;
R1 = R2 = (CH3)2 or -OR2, -O-(CH2)n-R2;
R3 = H, methyl, ethyl, CF3, methoxy, etoxy, OCF3, F, Cl, Br, CN, -CH2OR, -CO2R, -SR2, -N(R2)2, -(CH3)2-N(R2)=O, -OR2, -(CH3)2-OR2 or -O-(
(CH3)2-CH3);
S1 = S2 = S3 = S4 = or S5;
S1 = phenyl (optionally mono- to tetra-substituted by T1, S-CH3).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation - (I) are prepared by treating (II) with alkylthiium, followed by coupling of (II) with carboxylic derivative of (III) to provide ketone of formula (I).

G1 = alkyl;
H1 = halogen; and
G2 = OH, alkoxy, halide, NMe(OH).
Preferred Compound: The ketones are of formula (1a) (preferably (1b), especially (1c)).

A' = phenyl, a fused carbocyclic ring selected from indane, 1-H indene, naphthalene, 1,2-dihydro-naphthalene, 1,2,3,4-tetrahydro-naphthalene, 6,7,8,9-tetrahydro-5H-benzocycloheptene, 6,7-dihydro-5H-benzocycloheptene, 9H-fluorene, anthracene, or 9,10-Dihydro-anthracene, 5- or 6-membered optionally saturated monocyclic heterocycle containing 1 - 4 N atoms, or 0 - 2 O or S atoms with at least one of the ring atoms being carbon (all optionally substituted by R1 - R3);
Q1 = H or 1-CN alkyl;
Q2 = Ti, Ti, 2-CN alkyl. C equivalent to C-CH3N(R2)2, -C-