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kind of national protection available): AE, AG, AL, AM,
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DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR,
KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,

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TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
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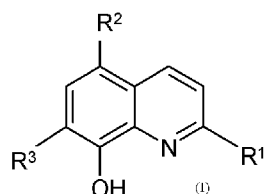
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(54) Title: MDR-REVERSING 8-HYDROXY-QUINOLINE DERIVATIVES



(57) Abstract: The present invention is related to 8-hydroxy-quinoline derivatives having mul-
tidrug-resistance reversing activity with improved selectivity and increased cytotoxicity towards
multidrug-resistant cancer cells, preparation thereof and use of the same in the treatment of can-
cer, especially multidrug-resistant variants thereof.



INTERNATIONAL SEARCH REPORT

International application No

PCT/HU2017/050009

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D215/36 C07D215/38 C07D401/04 C07D401/12
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A61P35/00

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)

C07D A61K A61P

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 practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/138686 A1 (US HEALTH [US]; INST OF ENZYMOLOGY BIOLOG RES CT HUNGARIAN ACADEMY OF) 2 December 2010 (2010-12-02) cited in the application claims 1, 4; compounds NSC693871, NSC693872 ----- -/--	1-15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family 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 application or patent 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

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/HU2017/050009

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TURK D ET AL: "Identification of compounds selectively killing multidrug-resistant cancer cells", CANCER RESEARCH, & 104TH ANNUAL MEETING OF THE AMERICAN-ASSOCIATION-FOR-CANCER-RESEARCH (AACR); WASHINGTON, DC, USA; APRIL 06 -10, 2013, vol. 69, no. 21, 1 November 2009 (2009-11-01), pages 8293-8301, XP002592581, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-09-2422 Supplementary table S1; figure 1; compound NSC693871 and NSC693872 & Dora Türk: "Supplement to Turk et al. "Identification of compounds selectively killing multidrug resistant cancer cells" Supplementary Tables", 1 November 2009 (2009-11-01), XP055377100, Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/canres/suppl/2009/10/16/0008-5472.CAN-09-2422.DC1/CAN_11-1-09_Turk.pdf [retrieved on 2017-05-30] -----	1-15
A	FR 2 160 718 A1 (ROUSSEL UCLAF) 6 July 1973 (1973-07-06) cited in the application example 1 -----	1-15
A	IZIDOR SOSIC ET AL: "Development of New Cathepsin B Inhibitors: Combining Bioisosteric Replacements and Structure-Based Design To Explore the Structure-Activity Relationships of Nitroxoline Derivatives", JOURNAL OF MEDICINAL CHEMISTRY, vol. 56, no. 2, 24 January 2013 (2013-01-24), pages 521-533, XP055376957, ISSN: 0022-2623, DOI: 10.1021/jm301544x cited in the application compound 13 ----- -/--	1-15

INTERNATIONAL SEARCH REPORT

International application No

PCT/HU2017/050009

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOHAMMED IDREES ET AL: "8-Hydroxyquinoline-based inhibitors of the Rce1 protease disrupt Ras membrane localization in human cells", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 24, no. 2, 30 November 2015 (2015-11-30), pages 160-178, XP029374720, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2015.11.043 compound 20	1-15
X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 4 April 2003 (2003-04-04), XP002770661, Database accession no. 501655-04-5 7-[[[(3,4-dichlorophenyl)methyl]amino]meth yl]-8-quinolinol	7,8
X	----- Pubchem: "CID 20667449 C17H15FN2O - PubChem", 5 December 2007 (2007-12-05), XP055377184, Retrieved from the Internet: URL:https://pubchem.ncbi.nlm.nih.gov/compo und/20667449#x291 [retrieved on 2017-05-30] 7-[(benzylamino)methyl]-5-fluoroquinolin-8 -ol	7,8
X	----- UTHAI SAKKE ET AL: "First Synthesis of 5-Chloro-7-[1,3]oxazolo[4,5-b]pyridin-2-yl quinolin-8-ol by Pd-Catalyzed Arylation", SYNTHETIC COMMUNICATIONS, vol. 39, no. 17, 29 July 2009 (2009-07-29) , pages 3031-3037, XP055408821, PHILADELPHIA, PA; US ISSN: 0039-7911, DOI: 10.1080/00397910902730861 compound 5	7
A	----- -/-	1-6,8-15

INTERNATIONAL SEARCH REPORT

International application No

PCT/HU2017/050009

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ISTVÁN SZATMÁRI ET AL: "Solvent-Free Synthesis of 1-(Hydroxyquinolyl)- and 1-(Hydroxyisoquinolyl)-1,2,3,4-tetrahydroisoquinolines by Modified Mannich Reaction", SYNTHESIS, vol. 2011, no. 05, 3 February 2011 (2011-02-03), pages 745-748, XP055408824, STUTTGART, DE. ISSN: 0039-7881, DOI: 10.1055/s-0030-1258423 compounds 7a, 7b, 9a	1-15
A	ISTVÁN ILISZ ET AL: "High-performance liquid chromatographic enantioseparation of naphthol-substituted tetrahydroisoquinolines on polysaccharide-based chiral stationary phases : HPLC enantioseparation of tetrahydroisoquinoline analogs", BIOMEDICAL CHROMATOGRAPHY., vol. 28, no. 1, 30 July 2013 (2013-07-30), pages 142-151, XP055408830, GB ISSN: 0269-3879, DOI: 10.1002/bmc.3002 compounds 12-15	1-15
X	PADALKAR VIKAS S ET AL: "Excited-state intramolecular proton transfer (ESIPT) inspired azole-quinoline based fluorophores: Synthesis and photophysical properties study", JOURNAL OF LUMINESCENCE, vol. 155, 19 June 2014 (2014-06-19), pages 58-64, XP029042115, ISSN: 0022-2313, DOI: 10.1016/J.JLUMIN.2014.06.018 compound 10	7
A		1-6,8-15
X	KHALIL Z H ET AL: "SYNTHESIS OF SOME OXAZOLO-, IMIDAZOLO-, SELENADIAZOLO-, THIADIAZOLOAZETIDINONO- AND THIAZOLIDINONO-8-HYDROXYQUINOLINES", JOURNAL OF THE INDIAN CHEMICAL SOCIETY, IN, vol. 64, no. 1, 1 January 1987 (1987-01-01), pages 42-45, XP002040517, ISSN: 0019-4522 compounds 4b, 4f	7
A		1-6,8-15
	-/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/HU2017/050009

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 6 June 2008 (2008-06-06), XP002774164, Database accession no. 1025921-59-8	7,8
A	5-iodo-7-(1-piperidinylmethyl)-8-quinolino 1	1-6,9-15
A	----- AI-YU SHEN ET AL: "Synthesis and cytotoxicity evaluation of some 8-hydroxyquinoline derivatives", JOURNAL OF PHARMACY AND PHARMACO, JOHN WILEY & SONS LTD, LONDON; GB, vol. 51, no. 5, 1 January 1999 (1999-01-01), pages 543-548, XP009127966, ISSN: 0022-3573 7-pyrrolidinomethyl-8-hydroxyquinoline hydrochloride, 7-piperidinomethyl-8-hydroxyquinoline hydrochloride -----	1-15
A	AUGUSTO RIVERA ET AL: "7-(Imidazolidin-1-ylmethyl)quinolin-8-ol: An Unexpected Product from a Mannich-type Reaction in Basic Medium", HETEROCYCLES COMMUNICATION SPECIAL ISSUE, vol. 68, no. 3, 1 January 2006 (2006-01-01), page 531, XP055409017, JP ISSN: 0385-5414, DOI: 10.3987/COM-05-10642 compound 3 -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU2017/050009

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

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

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/HU2017/050009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010138686	A1	02-12-2010	NONE
FR 2160718	A1	06-07-1973	NONE