



US005935955A

United States Patent [19]

Ashworth et al.

[11] **Patent Number:** 5,935,955[45] **Date of Patent:** *Aug. 10, 1999[54] **PHARMACEUTICAL PIPERAZINE COMPOUNDS**[75] **Inventors:** Philip A. Ashworth; Sukhjit Hunjan; Ian A. Pretswell; Harnish Ryder, all of Slough, United Kingdom; Stephen J. Brocchini, Highland Park, N.J.[73] **Assignee:** Xenova Limited, Berkshire, United Kingdom[*] **Notice:** This patent is subject to a terminal disclaimer.[21] **Appl. No.:** 08/860,328[22] **PCT Filed:** Dec. 22, 1995[86] **PCT No.:** PCT/GB95/03029

§ 371 Date: Aug. 29, 1997

§ 102(e) Date: Aug. 29, 1997

[87] **PCT Pub. No.:** WO96/20180

PCT Pub. Date: Jul. 4, 1996

[30] **Foreign Application Priority Data**

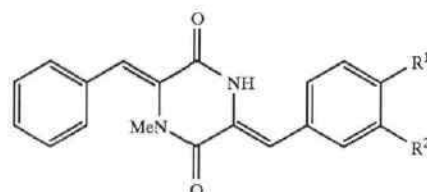
Dec. 23, 1994 [GB] United Kingdom 9426090

[51] **Int. Cl.⁶** A61K 31/495; C07D 241/02; C07D 401/12; C07D 403/14[52] **U.S. Cl.** 514/235.8; 514/252; 514/253; 514/255; 544/121; 544/295; 544/357; 544/360; 544/361; 544/363; 544/385[58] **Field of Search** 544/385, 121, 544/357, 295, 360, 361, 363; 514/252, 253, 255, 235.8[56] **References Cited****U.S. PATENT DOCUMENTS**5,700,804 12/1997 Collins et al. 514/255
5,750,530 5/1998 Bryans et al. 544/360**FOREIGN PATENT DOCUMENTS**WO 94/01408 1/1994 WIPO .
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95 21832 8/1995 WIPO .**OTHER PUBLICATIONS**Bellamy et al, *Cancer Investigations* 8 pp. 547-562, 1990.
Hill, *International Journal of Oncology* 9 197-203 1996
"Drug Resistance: An overview of the current state of the art".Dale et al, *British J. of Cancer* (1998) 78 (7), 885 to 892
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Annals of Oncology 7 (suppl. 1) Mar. 1996, No. 434, Luscombe et al.*Ann. Rev. of Biochemistry* 62 (1993) 385-427: Gottesman et al.

Prospectus for the public offering of shares in Xenova Limited Dec. 19, 1996 (cover, inside sheet and p. 51) by Xenova Limited.

Primary Examiner—Emily Bernhardt*Attorney, Agent, or Firm*—Nixon & Vanderhye P.C.[57] **ABSTRACT**

A piperazinedione of general formula (I):

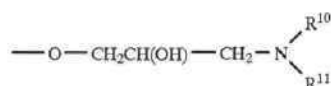


(I)

wherein R¹ is selected from
hydrogen;a group of formula $-(NH)_t-COR^3$ wherein t is 0 or 1
and R³ is an organic substituent as defined herein;

a group of formula (D):

(D)



and

a group of formula (E):

(E)

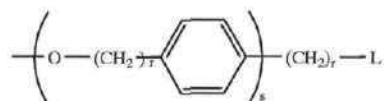
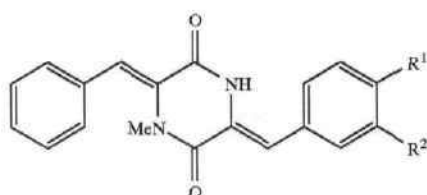
and the pharmaceutically acceptable salts thereof are
useful as modulators of multi-drug resistance.**18 Claims, No Drawings**

TABLE 10-continued

No.	Mol. Formula	Mass spec data		solvent/field	¹ H nmr data	
		mass (intensity)	mode		δ	
9163	C ₃₇ H ₂₆ N ₄ O ₃	585(100)	ESI	CDCl ₃ /400 MHz	7.04 (1H,m), 7.08-7.10 (2H,m), 7.22-7.29 (3H,m), 7.45 (1H,m), 7.52-7.60 (4H,m), 7.81 (1H,m), 7.95 (2H,s) 8.38 (1H,s)	
9176				CDCl ₃ /400 MHz	2.36(3H,s), 2.65 (2H,t), 2.95-3.10 (5H,m), 3.45 (2H,d), 4.20 (1H,t), 6.38 (1H,brs), 7.05-8.20 (22H,m)	
9177				CDCl ₃ /400 MHz	2.70-2.98 (8H,m), 3.00 (3H,s), 3.65 (2H,s), 3.82 (2x3H,s), 5.09 (2H,s), 6.53 (1H,s), 6.61 (1H,s), 7.00-7.10 (4H,m), 7.21-7.58 (7H,m), 7.82 (2H,d), 7.91 (1H,br s)	
9190	C ₃₉ H ₃₈ N ₄ O ₃	643(3)	CI	CDCl ₃ /400 MHz	2.62-2.89 (8H,m), 2.91 (3H,s), 3.57 (2H,s), 3.76 (2x3H,s), 4.97 (2H,s), 6.45 (1H,s), 6.51 (1H,s), 6.82-6.95 (3H,m), 7.12-7.38 (12H,m), 8.05 (1H,br s)	
9200	C ₃₇ H ₄₀ N ₄ O ₅	620(32)	EI	CDCl ₃ /400 MHz	2.70-3.04 (11H,m), 3.65 (2H,s), 3.85 (2x3H,s), 6.53 (1H,s), 6.60 (1H,s), 7.03 (1H,s), 7.15-7.50 (11H,m), 7.68-7.92 (5H,m)	
					1.05-2.00 (9H,m), 2.35-2.45(2Hd), 2.62-2.84 (4H,m), 3.2 (3H,s), 3.55 (2H,s), 3.84 (2x3H,s), 6.52 (1H,s), 6.60 (1H,s), 7.06 (1H,s), 7.20-7.55 (11H,m)	

We claim:

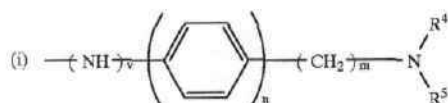
I. A piperazinedione of general formula (I):



wherein R¹ is selected from:

hydrogen

a group of formula —(NH)_t—COR³ wherein t is 0 and R³ is selected from:



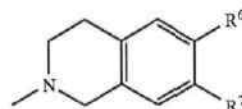
wherein v is 1; and wherein n is 0 or 1 and m is 0, 1, 2 or 3, at least one of n and m being other than 0, and either

- (a) R⁴ is H or C₁-C₆ alkyl and R⁵ is C₁-C₆ alkyl optionally substituted by one or two phenyl groups, the phenyl group or groups being optionally substituted by one or two C₁-C₆ alkoxy groups; or
- (b) R⁴ and R⁵, together with the nitrogen atom to which they are attached, form a heterocyclic group selected from (1) to (4):

25

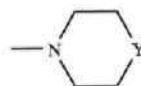
(I)

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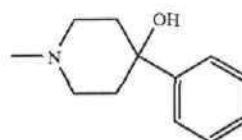
(1)

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(2)

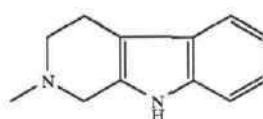
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(3)

(A)

45



(4)

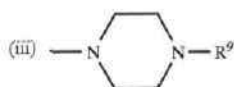
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wherein R⁶ and R⁷, which are the same or different, are H or C₁-C₆ alkoxy, or R⁶ and R⁷ together form a methylenedioxy group; Y is O or —NR⁸ wherein R⁸ is C₁-C₆ alkyl or a phenyl group optionally substituted by CF₃;

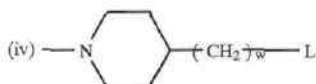
—NH—(CH₂)_p—Z

(B)

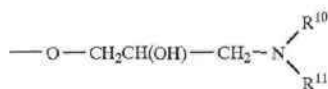
wherein p is 1 or 2 and Z is C₂-C₆ alkenyl or a phenyl group optionally substituted by C₁-C₆ alkoxy; and



wherein R^9 is C_1-C_6 alkyl, pyrimidinyl or a phenyl group optionally substituted by C_1-C_6 alkoxy;



or R^1 is selected from:
a group of the formula (D):



wherein each of R^{10} and R^{11} , which may be the same or different, is C_1-C_6 alkyl; and
a group of formula (E):



wherein s is 0, r is 1, 2 or 3 and L is a heterocyclic group of formula (1) as defined above; and R^2 is hydrogen or a group of formula $-COR^3$ as defined above, provided that one of R^1 and R^2 is hydrogen and the other is not hydrogen; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is hydrogen and R^2 is a group of formula $-COR^3$ as defined in claim 1 in which R^3 is a group of formula A.

3. A compound according to claim 1, wherein R^2 is hydrogen and R^1 is a group of formula $-COR^3$ as defined in claim 1 in which R^3 is a group of formula (A), a group of formula (B) wherein Z is ethenyl or phenyl substituted by two C_1-C_6 alkoxy groups, or a group of formula (C) wherein R^9 is methyl, pyrimidinyl or phenyl.

4. A compound according to claim 1 wherein, in formula (A), n is 0 and m is 2, or n is 1 and m is 0, 1, 2 or 3, or n is 1 and m is 0, and either

(a) R^4 is C_1-C_6 alkyl and R^5 is C_1-C_6 alkyl substituted on the terminal C atom by 2 unsubstituted phenyl groups or by one phenyl group which is disubstituted by C_1-C_6 alkoxy groups; or

(b) R^4 and R^5 form together with the nitrogen atom to which they are attached a heterocyclic group selected from groups of formula (1) wherein R^6 and R^7 are both H or both C_1-C_6 alkoxy, or together form a methylenedioxy group; formula (2) wherein Y is O or $-NR^8$ wherein R^8 is methyl, phenyl or trifluoromethylphenyl; formula (3); and formula (4).

5. A compound according to claim 1 wherein R^2 is hydrogen and R^1 is a group of formula (D) or (E) as defined in claim 1.

6. A compound selected from:

- (C) 1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(2-pyrimidyl)piperazine (9022);
- 5 1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-methylpiperazine, hydrochloride (9052);
- 1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(4-methoxyphenyl)piperazine, hydrochloride (9071);
- 10 N-Allyl-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9070);
- (F) N-(2-Diphenylmethylmethylaminoethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9076);
- 15 N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9116);
- N-(3,4-Dimethoxyphenethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9117);
- (D) 20 N-(4-(4-Phenyl-1-piperazinyl)methylphenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9104);
- N-(2-(4-Methyl-1-piperazinyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9007);
- 25 N-(2-Morpholinoethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9053);
- 30 N-(4-Morpholinophenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9054);
- N-(4-(2-(1,2,3,4-Tetrahydro- β -carbolin-2-yl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9080);
- 35 N-(4-(1,2,3,4-Tetrahydro- β -carbolin-2-yl)methylphenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9096);
- N-(4-(2-(4-Phenyl-1-piperazinyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9103);
- 40 N-(4-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9065);
- 45 N-(4-(2-(4-(3-Trifluoromethylphenyl)-1-piperazinyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9049);
- N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9006);
- 50 N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9008);
- N-(4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methylphenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9064);
- (3Z,6Z)-6-Benzylidene-3-(4-(3-dimethylamino-2-hydroxypropoxy)benzylidene)-1-methyl-2,5-piperazinedione (9023);
- (3Z,6Z)-6-Benzylidene-3-(4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)benzylidene)-1-methyl-2,5-piperazinedione (9115);
- N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9051);