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(54) **FORMULATIONS CONTAINING  
PYRIDAZINE COMPOUNDS**

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This patent is subject to a terminal dis-  
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**A61K 31/505**; **A61K 31/506**; **C07D 401/14**  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

2,857,384 A 10/1958 Druey  
4,169,158 A 9/1979 Laborit  
4,508,720 A 4/1985 Kan et al.  
4,654,343 A 3/1987 Albright  
4,710,499 A 12/1987 Wermuth  
4,721,711 A 1/1988 Chambon  
4,977,152 A 12/1990 Biziere

5,045,541 A 9/1991 Nakao  
5,484,940 A 1/1996 Grant  
8,367,672 B2 \* 2/2013 Watterson ..... 514/247  
8,933,076 B2 \* 1/2015 Watterson ..... 514/247

(Continued)

**FOREIGN PATENT DOCUMENTS**

EP 0072726 2/1983  
EP 0 094 038 11/1983

(Continued)

**OTHER PUBLICATIONS**

Shohami et al. "Inhibition of Tumor Necrosis Factor Alpha (TNFa)  
Activity in Rat Brain is Associated with Cerebroprotection After  
Closed Head Injury". Journal of Cerebral Blood Flow and Metabo-  
lism. 1996; 16:378-384.\*

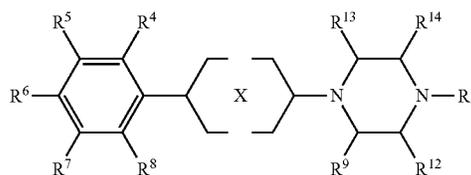
(Continued)

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(57) **ABSTRACT**

The invention relates to chemical compounds, compositions  
and methods of making and using the same. In particular, the  
invention provides selected pyridazine compounds of the formu-  
la I wherein R1, R4, R5, R6, R7, R8, R9, R12, R13 ET R14  
are independently hydrogen, hydroxyl, alkyl, alkenyl, alkyl-  
nyl, alkylene, alkenylene, alkoxy, alkenyloxy, cycloalkyl,  
cycloalkenyl, cycloalkynyl, cycloalkoxy, aryl, aryloxy, ary-  
lalkoxy, aroyl, heteroaryl, heterocyclic, acyl, acyloxy, amino,  
imino, azido, thiol, thioallyl, thioalkoxy, thioaryl, nitro,  
cyano, halo, sulfate, sulfonyl, sulfinyl, sulfonyl, sultanate,  
sulfoxide, silyl, silyloxy, silylalkyl, silylthio, =O, =S, phos-  
phonate, ureido, carboxyl, carbonyl, carbamoyl, or carboxa-  
mide; and X is optionally substituted pyrimidinyl or pyridazi-  
nyl, an isomer, a pharmaceutically acceptable salt, or  
derivative thereof. The invention additional relates to compo-  
sitions comprising the compounds, and methods of using the  
compounds and compositions for modulation of cellular  
pathways, for treatment or prevention of inflammatory dis-  
eases, for research, drug screening, and therapeutic applica-  
tions.



**10 Claims, 41 Drawing Sheets**