

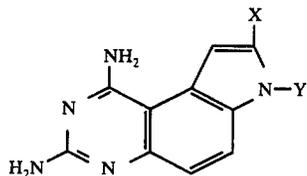
7-(SUBSTITUTED)-7H-PYRROLO[3,2-F]QUINAZOLINE-1,3-DIAMINES

This application is a continuation-in-part of copending application Ser. No. 784,987, filed Apr. 6, 1977, which in turn is a continuation-in-part of application Ser. No. 704,001, filed July 9, 1976, and Ser. No. 704,002, filed July 9, 1976, both now abandoned.

Various derivatives of 2,4-diaminoquinazoline and 2,4,6-triaminoquinazoline are described in the literature and are known to possess antifolic activity in bacterial systems. Such compounds are also known to exhibit antibacterial or antiprotozoal activity. For example, 2,4-diaminoquinazolines having an alkyl group at the 5-position and/or 6-position or having a trimethylene bridge between the 5- and 6-position possess antibacterial activity [see Hitchings et al., U.S. Pat. No. 2,945,859 or De Graw et al., J. Med. Chem., 17, 762 (1974)]. 2,4-Diamino-6-[(arylmethyl)amino]quinazolines; 2,4-diamino-6-[[substituted aryl]methyl]amino-quinazolines; and 2,4-diamino-6-[[heterocyclic]methyl]amino-quinazolines along with derivatives having a 5-alkyl substituent or N⁶-alkyl substituent exhibit antimalarial activity. [See Davoll et al., J. Med. Chem., 15, 812 (1972); Elslager et al., J. Med. Chem., 15, 1138 (1972); see also the review article by E. Elslager entitled, "New Perspectives on the Chemotherapy of Malaria, Filariasis, and Leprosy", Progress in Drug Research, 18, 99-172 (1974), in particular pages 111-116 and 152-154].

The pyrrolo[3,2-f]quinazoline-1,3-diamines of the invention differ from the known 2,4,6-triaminoquinazolines in that the 5-position and the N⁶ position of the latter are bridged by an ethylene moiety thus forming a novel tricyclic heterocycle.

The invention sought to be patented comprises compounds of the formula:



or a non-toxic acid addition salt thereof, wherein:

(a) X is hydrogen and

Y is $-\text{CH}_2\text{R}$ or $-\text{R}^1$

wherein:

R is hydrogen; methyl; ethyl; n-propyl; i-propyl; n-butyl; i-butyl; n-pentyl; n-hexyl; 2-methyl-1-propenyl; cyclobutyl; cyclopentyl; cyclohexyl; 2-phenylethyl; 2-phenylvinyl; phenyl; phenyl monosubstituted in the 2-, 3-, or 4-position by chlorine, bromine, iodine, fluorine, trifluoromethyl, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, methoxy, ethoxy, n-propoxy, trifluoromethoxy, cyano, methylsulfonyl, acetyl, propionyl, methylthio, ethylthio, carbethoxy, carboxyl, sodium carboxy, or potassium carboxy; phenyl monosubstituted in the 3-position by amino or nitro; phenyl disubstituted in the 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-positions by methyl, ethyl, n-propyl, methoxy, ethoxy, n-propoxy, chlorine, bromine, iodine, or fluorine; phenyl trisubstituted in the 2,4,6- or 3,4,5-positions by methyl, ethyl, methoxy, or ethoxy; 2,3,5,6-tetramethylphenyl; 3,4-(methylene dioxy)phenyl; 1-naphthalenyl; 2-naphthalenyl; 2-methyl-1-

naphthalenyl; 1-bromo-2-naphthalenyl; 2-pyridinyl; 3-pyridinyl; 4-pyridinyl; 2-quinolinyl; 8-quinolinyl; 2-thienyl; 3-thienyl; 4-thiazolyl; 3,5-dimethyl-4-isoxazolyl; tetrahydro-2-furanyl; or benzo[b]thien-3-yl;

and

R¹ is hydrogen; phenyl monosubstituted in the 2- or 4-position by amino, nitro, cyano, acetyl, propionyl, methylsulfonyl, trifluoromethyl, or carbethoxy; 2,4-dinitrophenyl; 2,4-diaminophenyl; 2-cyano-4-nitrophenyl; 2-cyano-4-aminophenyl; 3-methyl-4-nitrophenyl; 3-methyl-4-aminophenyl; 2-trifluoromethyl-4-nitrophenyl; 2-trifluoromethyl-4-aminophenyl; 2-thiazolyl; 2-pyridinyl; 5-nitro-2-pyridinyl; 2-pyrimidinyl; 2-pyrazinyl; 2-quinolinyl; 4-quinolinyl; 4-methyl-2-quinolinyl; 7-chloro-4-quinolinyl; 7-trifluoromethyl-4-quinolinyl; 2-methyl-4-quinolinyl; 3-methyl-2-quinoxalyl; 2-phenyl-4-quinolinyl; or 2-benzothiazolyl; 5-amino-2-pyridinyl; and

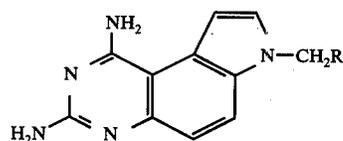
(b) X is methyl, phenyl, or chlorine; and

Y is hydrogen, methyl, benzyl, 3-cyanobenzyl, 4-cyanobenzyl, or 2,5-dimethylbenzyl; provided that when X is phenyl, Y may only be hydrogen or methyl, and when X is chlorine, Y may only be benzyl.

The terms "disubstituted" and "trisubstituted", as applied to substituents on the phenyl ring of the compounds of Formula I, refer to compounds wherein the substituents are identical for example, dichlorophenyl, dimethylphenyl, dimethoxyphenyl, trimethylphenyl, trimethoxyphenyl, or the like.

In subgeneric aspects, the invention comprises the following embodiments:

(a) A compound of the general formula:



or a non-toxic acid addition salt thereof, wherein:

R is hydrogen; methyl; ethyl; n-propyl; i-propyl; n-butyl; i-butyl, n-pentyl; n-hexyl; 2-methyl-1-propenyl; cyclobutyl; cyclopentyl; cyclohexyl; 2-phenylethyl; 2-phenylvinyl; phenyl; phenyl monosubstituted in the 2-, 3-, or 4-position by chlorine, bromine, iodine, fluorine, trifluoromethyl, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, methoxy, ethoxy, n-propoxy, trifluoromethoxy, cyano, methylsulfonyl, acetyl, propionyl, methylthio, ethylthio, carbethoxy, carboxyl, sodium carboxy, or potassium carboxy; phenyl monosubstituted in the 3-position by amino or nitro; phenyl disubstituted in the 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-positions by methyl, ethyl, n-propyl, methoxy, ethoxy, n-propoxy, chlorine, bromine, iodine, or fluorine; phenyl trisubstituted in the 2,4,6- or 3,4,5-positions by methyl, ethyl, methoxy, or ethoxy; 2,3,5,6-tetramethylphenyl; 3,4-(methylene dioxy)phenyl; 1-naphthalenyl; 2-naphthalenyl; 2-methyl-1-naphthalenyl; 1-bromo-2-naphthalenyl; 2-pyridinyl; 3-pyridinyl; 4-pyridinyl; 2-quinolinyl; 8-quinolinyl; 2-thienyl; 3-thienyl; 4-thiazolyl; 3,5-dimethyl-4-isoxazolyl; tetrahydro-2-furanyl; or benzo-[b]thien-3-yl;

(b) A compound of the general formula: