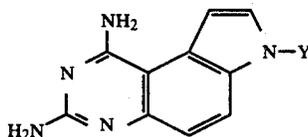


7-(SUBSTITUTED)-7H-PYRROLO[3,2-f]QUINAZOLINE-1,3-DIAMINES

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:

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

wherein:

R is 2,4-dichlorophenyl, 3-acetylphenyl, 3-carbomethoxyphenyl, 3-isopropylphenyl, 4-carboisopropoxyphenyl, 4-carbo-2-pentyloxyphenyl, 4-carbomethoxyphenyl, or 4-hydroxyphenyl;

and

R¹ is 4-pyridinyl, 2-(4-methylpyridinyl), 4-trifluoromethylphenyl, or 4-carbamoylphenyl.

The compounds of Formula I, wherein Y, R, and R¹ are as hereinbefore defined or the salts thereof, inhibit the growth of bacteria in vitro as demonstrated in a standard tube dilution test employing seed agar or Wellcotest Sensitivity Test Agar fortified with 5% hemolyzed horse blood as the growth medium. The compounds have shown activity in vitro against one or more of the following strains of bacteria: *S. aureus* Smith, *S. aureus* 53-180, *N. catarrhalis* 8193, *E. coli* 9637, *S. paratyphi* 11737, *K. pneumoniae* 10031, or *P. vulgaris* 6896.

The invention also provides compounds which will potentiate the antibacterial effects of sulfa drugs. When tested by the oral route of administration in mice, 7-(4-pyridinyl)-7H-pyrrolo[3,2-f]-quinazoline-1,3-diamine

gave a synergistic effect with sulfamethoxazole against bacterial infections.

In general, the compounds of Formula I having an N⁷-substituent are prepared by reacting 7H-pyrrolo[3,2-f]quinazoline-1,3-diamine with an alkali metal base to form the corresponding alkali metal salt, and the salt is reacted with the appropriate reagent, RCH₂-Z or R¹-Z, in order to attach the desired substituent, RCH₂- or R¹-, at the 7-position. The base employed in the first step must be of sufficient strength to remove the proton from the indolic nitrogen of the starting material. Examples of such bases are sodium and potassium hydride, potassium t-butoxide, and lithium or potassium amide.

In the reagents RCH₂-Z or R¹-Z, R and R¹ are as defined hereinbefore with respect to Formula I (except that R and R¹ cannot be a group which contains a free hydroxyl group as a substituent) and Z is a leaving group.

When the reagent is RCH₂-Z, the preferred leaving group Z is a chlorine, bromine, or iodine atom. When the reagent is R¹-Z, the preferred leaving group is a fluorine, bromine, chlorine, or iodine atom. Other examples, of appropriate leaving groups (Z) for RCH₂-Z are tosyloxy or mesyloxy. The reaction is conveniently carried out in an inert solvent, such as dimethylformamide (DMF) or dimethylacetamide (DMA). In a preferred method, the 7H-pyrrolo[3,2-f]quinazoline-1,3-diamine is treated with sodium-hydride in dimethylformamide and the appropriate reagent (RCH₂-Z or R¹-Z) is added to the reaction mixture. In the reaction employing the reagent R¹-Z, it is preferred to heat the reaction mixture at a temperature above 50° C.

7H-Pyrrolo[3,2-f]quinazoline-1,3-diamine is prepared by heating an acid addition salt of 5-aminoindole at a temperature of about 185°-215° C. with an alkali metal dicyanamide, such as sodium or potassium dicyanamide, in an aliphatic alcohol solvent. Best results are achieved if a >2:1 molar ratio of the dicyanamide to the 5-aminoindole acid addition salt is employed. A molar ratio of about 2.5:1 is preferred. The reaction is conveniently carried out by heating the reactants at the reflux temperature of the solvent. Aliphatic alcohols having a boiling point of about 185° C. to about 215° C. are preferred solvents. In a preferred method, the 5-aminoindole acid addition salt is heated at reflux temperature in 1-octyl alcohol with sodium dicyanamide until the reaction is complete.

When it is desired to prepare a compound of Formula I wherein $-\text{CH}_2-\text{R}$ or R¹ contain a free aromatic hydroxy group, such compound can be conveniently prepared by cleavage of a corresponding aromatic methoxy compound. For example, 7-[(4-hydroxyphenyl)methyl]-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine is prepared by cleaving 7-[(4-methoxyphenyl)methyl]-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine in the presence of boron tribromide.

The starting materials which are 5-aminoindole and the reagents RCH₂-Z and R¹-Z are either known compounds or can be prepared by known methods for analogous compounds or by obvious modifications of the known methods.

The compounds of Formula I may be isolated and purified either in the form of the free bases or the acid addition salts. Methods for converting one such form to another will be obvious to one skilled in the art of chemistry.