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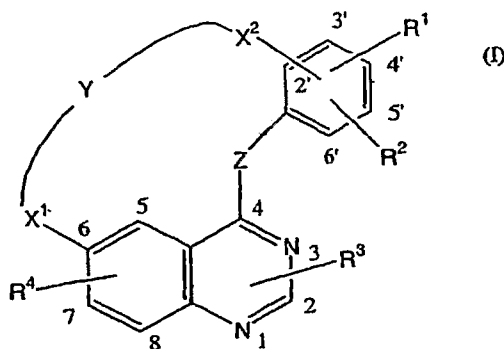
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— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,

[Continued on next page]

(54) Title: MACROCYCLIC QUINAZOLINE DERIVATIVES AS ANTIPROLIFERATIVE AGENTS



(57) Abstract: The present invention concerns the compounds of formula (I) the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein Z represents O, CH₂, NH or S; in particular Z represents NH; Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₃₋₉alkynyl-, -C₃₋₇alkyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino or C₁₋₄alkyloxycarbonylamino-, -C₃₋₇alkenyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino- or C₁₋₄alkyloxycarbonylamino-, C₁₋₅alkyl-oxy-C₁₋₅alkyl-, -C₁₋₅alkyl NR¹³-, -C₁₋₅alkyl-, -C₁₋₅alkyl-NR¹⁴-CO-C₁₋₅alkyl-, -C₁₋₅alkyl-CO NR¹⁵-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-, -C₁₋₃alkyl-NH-CS-Het²⁰-, -C₁₋₃alkyl-NH-CO-Het²⁰-, -C₁₋₂alkyl-CO-Het²¹-CO-, -Het²²-CH₂-CO-NH-C₁₋₃alkyl-, -CO-NH-C₁₋₆alkyl-, -NH-CO-C₁₋₆alkyl-, -CO-C₁₋₇alkyl-, -C₁₋₇alkyl-CO-, -C₁₋₆alkyl-CO-C₁₋₆alkyl-, -C₁₋₂alkyl-NH-CO-CR¹⁶R¹⁷-NH-, -C₁₋₂alkyl-CO-NH-CR¹⁸R¹⁹-CO-, -C₁₋₂alkyl-CO-NR²⁰-C₁₋₃alkyl-CO-, C₁₋₂alkyl-NR²¹-CH₂-CO-NH-C₁₋₃alkyl-, or -NR²²-CO-C₁₋₃alkyl-NH-; X¹ represents a direct bond, O or -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹¹-, -NR¹¹-C₁₋₂alkyl-, CH₂-, -O-N=CH- or -C₁₋₂alkyl-; X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹²-, -NR¹²-C₁₋₂alkyl-, -CH₂-, -O-N=CH- or -C₁₋₂alkyl-. The growth inhibitory effect anti-tumour activity of the present compounds has been demonstrated *in vitro*, in enzymatic assays on the receptor tyrosine kinase EGFR.



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