3-AMINO-1H-PYRAZOLE DERIVATIVES AS USEFUL SCAFFOLDS FOR THE GENERATION OF NEW KINASE INHIBITORS

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Sequencing of the human genome has revealed 518 protein kinases (PKs), which can be grouped into about 20 known families on the basis of their structural similarity. PKs are considered the second most important group of drug targets after G-protein-coupled receptors (GPCRs). Aberrant kinase activity is implicated in a variety of human diseases and members of the PK superfamily regulate key aspects of human neoplasia such as tumor cell proliferation, migration and survival .The ability to modulate kinase activity therefore represents an attractive therapeutic strategy for the treatment of human illness, such as cancer.

The vast majority of PKs are characterized by the presence of a highly homologous kinase catalytic domain (of about 250-300 amino acids residues), which folds into two lobes joined by a linker peptide coil of five to six residues, called the hinge region. The adenosine triphosphate (ATP) binding site, the common drugable feature of the kinase class, is situated at the interface of the two lobes.

As a part of our program towards the development of ATP-mimetic kinase inhibitors, we have designed new molecules based on the 3-aminopyrazole moiety, a well known adenino mimetic pharmacophore present in several classes of kinase inhibitors. The NH_2-C-N-NH pattern of the 3-aminopyrazole, which is stereochemically well suited to form hydrogen bonding interactions with the kinase hinge region of the ATP pocket, was embedded within the 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (A) and 1,4,5,7-6H-pyrazolo[3,4-c]pyridine (B) bicycles to give novel scaffolds endowed with additional diversity points.

An efficient solid-phase chemistry process, based on a novel linker to allow the attachment of pyrazoles to the resin, was developed for the combinatorial expansion of (A) and (B). Structural Chemistry information, including protein crystallography and computational modelling, was instrumental for a rapid and effective exploration of the high potential of (A) and (B) for the development of protein kinase inhibitors, as exemplified by the rapid identification of potent and selective Aurora and CDK2 inhibitors.