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Extended Abstract

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Chemistry Congress: 2017 Synthesis, Characterization and in vitro Antitumor Evaluation of New Pyrazolo[3,4-d] Pyrimidine Derivatives - Hamada S Abulkhair

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Cancer is the most serious health problem and the second leading cause of death in developing countries. In addition, there have been no minor side effects with targeted non-toxic drugs over the past seven years and success in the development of new chemotherapeutic agents. Therefore, a new selective, potent and safe anti-tumor agent of the discovery is a must. The pyrazolo [3,4-d] pyrimidine nucleus is the purine bio-isostere. Therefore, ATP kinases enzymes competitive inhibition by an antitumor as promoting activity. Many pyrazolo [3,4-d] pyrimidine derivatives have been reported as anti-tumor agents. This compound of the cytotoxic activity can be characterized by several enzymes such as tyrosine kinase, Src kinase, and cyclin dependent kinase (CDK). the mammalian target of rapamycin (mTOR) and glycogen synthase kinase (GSK). In addition, the presence of a methylsulfanyl group in position 3 of the pyrazolo [3,4-d] pyrimidine nucleus would potentiate the antitumor activity of this nucleus.

For example, the compound exhibited excellent anti-tumor activity against the breast adenocarcinoma cell line MCF 7 with IC50 values of 12.0 and 7.50, respectively. In addition, Compound 3 showed enhanced cytotoxic activity against the A549 cell line with an IC50 Kb value of 5.28 μM. Based on these scientific facts and further exploration of new antitumor agents, we hypothesized that incorporating these structural features could result in potent antitumor agents. In this work, new derivatives 3- (methylthio) - 1-phenyl-1H-pyrazolo [3,4-d] pyrimidine 10-16 were synthesized, incorporated in the methylsulfanyl group of position 3 of pyrazolo.

synthetic route of pyrazolo [3,4-d] pyrimidin-4 (5H) -one starting 8 and 4-chloro-3- (methylthio) -1- phenyl-1H-pyrazolo [3,4-d] pyrimidine derivatives which were carried out by reacting malononitrile with carbon disulfide in the presence of sodium ethoxide followed by methylation of the product with dimethyl sulfate. The resulting 2 (bis (methylthio) methylene) malononitrile was then treated with phenylhydrazine in absolute ethanol. Cyclization of 5-amino-3-(methylthio) -1-phenyl-1Hpyrazole-4-carbonitrile gave the formic acid of action 3- (methylthio) -1-phenyl-1Hpyrazolo [3, 4-d] pyrimidine -4 (5H) -one [18]. The structure of the latter was confirmed by the characteristic absorption bands of C bN and NH in the IR spectrum of 5-amino1Hpyrazole-4-carbonitrile The phosphorus oxychloride with compound 8 of chlorination gave the derivative 4-chloro 9. The latter was authorized to react with different aliphatics and aromatics

Spectral data and elemental analyzes confirmed the formation of pyrazolo [3,4-d] pyrimidin-4-amine 10a-e, 11 and 12. The formation of compounds 10-12 was determined by the target derivatives of amines. The HNMR spectrum 1 of these derivatives exhibits a new exchangeable singlet signal D2 O at 8.48–8.60 ppm corresponding to the NH protons. These compounds of the mass spectra showed good m / z values with distinct molecular ions of peaks. Diagram 3 shows the target compounds of the route synthesis of 13a-h by the reaction of 3- (methylthio) -1-phenyl-1H-pyrazolo [3,4-d] pyrimidin-4 (5H) -one (8) with 2. - 3-chloro-N-phenylpropanamide of chloro-N-phenylacetamide or derivatives. These amides of the structures were confirmed based on spectral data and preliminary analyzes. The IR spectra show these compounds in the range of 3223-3317 cm-1 in the characteristic NH stretch bands. In addition, the same derivatives of the 1 HNMR spectra showed that the singlet signals correspond to the NH protons, 9.72-10.78 ppm

The human breast adenocarcinoma cell line MCF7 was purchased from the American Cell Culture Culture Collection of streptomycin, 100 units / ml of penicillin and 10% heat-inactivated fetal bovine serum in a humidified CO2 atmosphere. 5% (v / v) at 37 ° C.

The anti-tumor activity of newly synthesized pyrazolo [3,4-d] pyrimidines was measured in vitro using a human breast adenocarcinoma cell line MCF7 using the sulfoRhodamine-B - [4,5-dimethylthiazole-2 assay. -Yl] -2,5-dimethyltetrazolium bromide technique (MTT). The selected cancer cell line of exponentially cultured cells were trypsinized, counted and seeded at appropriate densities (2000–1000 cells / 0.33 cm2). The cells were then incubated in a humidified atmosphere for 24 h at 37 ° C. Then, the cells were exposed to different concentrations of the test compounds (0.1, 1, 10, 100, 1000 πM) for 72 h. After that, the viability of the treated cells was determined according to the MTT technique.

A series of novel 1-phenyl-3-methylsulfanylpyrazolo [3,4-d] pyrimidines 10-16 has been synthesized. This new series of antitumor activity has been studied in the human breast adenocarcinoma cell line MCF7. Ten of the test compounds showed moderate activity compared to that of doxorubicin. N-arylacetamide derivatives (13ah) showed better anti-tumor activity than all other series. Among this series, compound 13a exhibited the highest activity with an IC50 equivalent to 23 μM. As can be seen in Table 1 and Figure 2, increasing the linker length by one more CH2 unit of compounds 13a-h results in a dramatic drop-in activity. The presence of a hydrogen bonding donor in the aromatic ring of the new derivatives 16a, b is essential for the activity. This becomes clear by comparing the MIC values of 16a (above 326 μM) with those of 16b which are only 61 μM. More studies are needed to identify the mechanism of antitumor action and the identification of DAS from other positions in the pyrazolo [3,4-d] pyrimidine ring.