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NATURE’S FIRST LEAD IN THE FIGHT AGAINST MESOTHELIOMA:
THE TOTAL SYNTHESIS AND BIOLOGICAL EVALUATION OF JBIR-23 AND RELATED COMPOUNDS

Rendicontazione

Informazioni relative al progetto

JBIR-23

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Progetto chiuso

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Final Report Summary - JBIR-23 (NATURE'S FIRST LEAD IN THE FIGHT AGAINST MESOTHELIOMA: THE TOTAL SYNTHESIS AND BIOLOGICAL EVALUATION OF JBIR-23 AND RELATED COMPOUNDS)

Executive Summary:

Human malignant pleural mesothelioma (MPM) is an aggressive lung cancer which is always associated with previous asbestos exposure. Typically symptoms do not appear until 35-40 years after the original exposure, with life expectancy then 12-18 months. Given the great use of asbestos during the 20th century (before its long overdue ban in 1985) and this long latency period, it is no surprise that cases of MPM continue to rise, with a peak not expected until 2015-2020. At present, there are ca. 2450 deaths in the UK per annum from mesothelioma, and ca. 10,000 in the USA, with both countries showing a 50% increase in cases per year. There is no known cure for MPM, and traditional chemotherapeutic cancer treatments, such as cis-platin or Pemetrexed/cis-Platin1-4 have had little impact on the disease; radiotherapy and partial pleurectomy have only very limited impact on life expectancy.5 However, mesothelioma research is frequently not considered to be a 'big enough market' (currently accounting for <1% of all cancers in the U.K.) there have been no reported good lead compounds as a starting point for the drug discovery process and consequently there are currently no drugs in development for this disease.

First isolated from Streptomyces sp. AK-AB27 in 2008, JBIR-23 possesses a unique structural architecture, hitherto unobserved in Streptomyces extracts.6 Furthermore, JBIR-23 is the first natural product to be isolated to exhibit activity against human MPM (with IC50 values of 10 and 20 #M against the two main human mesothelioma cell lines).6 These cell lines have demonstrated resistance to all clinical anticancer agents. This is an amazing breakthrough: the isolation of the first natural product to be highly active against mesothelioma is crucial, providing a precious lead compound for investigation. An analogue, JBIR-24, has also been isolated from the same Streptomyces species, although showed this demonstrated slightly lower activity against mesothelioma cell lines.6 Interestingly, the side chain of JBIR-23 is also observed in Cuevaenes A and B,7 two metabolites isolated from Streptomyces sp. HKI0180 and it is not too difficult to imagine that these three compounds may have the same or similar biosynthetic

origin. The latter two compounds had not been tested against mesothelioma cell lines. None of these three compounds have any ‘structure-activity studies’ been performed.

The aim of the project was twofold: to investigate the synthesis of JBIR-23, cuevaenes and theiranalogues, and to study their anti-mesothelioma activity in order to get a better knowledge of their structure-activity relationship.

The synthesis of analogues of JBIR-23 was performed by dissecting JBIR-23 into two independent portions: the synthesis of the fused three-ring system which was done by the fellow, and the side chain whose analogues were synthesized by a graduate student. This approach made possible to assay all the intermediates prepared en route to the final targets, thus determining the minimal pharmacophore required for activity against the MPM cell lines. Firstly, a library of analogues of the three membered ring system of Cuevaene A was prepared. Then, the synthesis of analogues of the tricyclic part of JBIR-23 was approached with the aim of obtaining simpler, more “drug-like” compounds, analogues of the tricyclic part of JBIR-23. Every analogue as well as the intermediates was biologically tested.

All the compounds prepared were tested by the Fellow with the help of Dr Szlosarek’s research group at the Barts Cancer institute for assay against the MPM cell line MSTO. The occurrence of activity of some of the compounds gave us a clue to the key structural features and functional groups required for anti-mesothelioma activity. A colorimetric assay (MTS assay) was performed on the intermediates and analogues prepared, as well as on a sample of Cuevaene A, which was kindly provided to us by Prof. Richard Taylor from the University of York.

Poor or no activity was observed in the side chain analogues, nor did Cuevaene A or its analogues show much activity; in fact there was not much difference observed between the activities of the analogues of the three membered ring of Cuevaene A, and the whole molecule including the side chain. However, interesting activity could be seen in some substituted quinones, which was enhanced in the case of their correspondent epoxyquinones; this gave us an idea of the epoxy group being important in the activity of JBIR-23.

Interestingly, a couple of compounds, which are substituted quinones, showed an activity similar to that described for JBIR-23, with IC values around 10 – 15 μM against MSTO cell line. These compounds are currently under further evaluation and therefore their structure cannot be fully disclosed.

Given the very limited laboratory-based mesothelioma research taking place in the world, the achievements of this project have opened a new field of study and have the potential to set a basis on which further research can be done against mesothelioma. With this project, we have helped establish European competitiveness in this field in which not many research groups are pioneers. This will lead to a direct continuation of the project by the host group, as well as indirectly by the Fellow whose knowledge acquired in this area will be transferable to her further career.

Documenti correlati

final1-publishable-summary-of-project-jbir23.docx

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