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New antibacterial agents targeting mycobacterial the ATP synthase

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Background: A set of 700 compounds found active after the whole cell screening of 20,000 compounds library against *Mycobacterium tuberculosis* H37Rv was screened in the ATP synthase assay. Three compounds showed promising IC50 and were further evaluated in the time kill assay and combination studies with first line anti-TB drugs against *M tuberculosis* H37Rv. The compounds were tested for cytotoxicity against HepG-2 cell lines

Methods & Materials: ATP synthase assay was performed using the inverted membrane vesicles of *Mycobacterium smegmatis* for the screening of the 700 compounds by estimating the ATP production. In-vitro activities of the selected compounds were done by microdilution method, cell toxicity profile using MTT assay in HepG2 cell line, in vitro time kill assay and combinational studies with first line drugs.

Results: Three compounds C1-C3 showing promising inhibitory activity (IC_{50} values 0.13-4.0 μM) in the in-vitro ATP synthase inhibition assay also exhibited potent anti-mycobacterial activity (MIC-0.06-2.0μg/ml). These compounds were nontoxic in HepG2 cell line, Compound C1 was bactericidal at 8X MIC (1 μg/ml) and exhibited synergistic activity with rifampicin.

Conclusion: ATP synthase screening of whole cell active compounds from IIIM repository led to the identification of three compounds showing good inhibitory activity against ATP synthase. All the compounds displayed promising anti-mycobacterial potential with no detected toxicity against mammalian cell line. Compound (C1) showed synergistic activity with rifampicin, which forms the backbone of anti-TB therapy. These compounds represents novel chemotypes against ATP synthase and can be taken up for medicinal chemistry efforts.

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Clinical profile and evaluation of diagnostic tests in culture positive childhood tuberculosis

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Background: Tuberculosis (TB) ranks among the ten major causes of mortality among children. The diagnosis of childhood TB remains quite challenging. Mycobacterial culture is the gold standard in diagnosis; however, positive cultures are seen only in 50%. The aim was to study the clinical profile and sensitivity of other diagnostic tests in culture-proven tuberculosis in children.

Methods & Materials: Retrospective chart review of children with culture-proven Tuberculosis diagnosed in the Department of Pediatrics, Christian Medical College, Vellore, India between January 2003 to January 2007.

Results: There were 61 cases of culture-confirmed TB (32 boys and 29 girls). The mean age at diagnosis was 7.8 ± 5 years. History of contact with TB was present in 14 children. The major presenting symptoms included fever (78%), cough (49%), loss of appetite (36%) and loss of weight (24%). Pulmonary Tb was seen in 22 children (36%) and extra-pulmonary TB in 39(64%). Disseminated TB was seen in 46%. Two children tested positive for HIV. Results of Drug susceptibility testing was available for only 41/61 children. Four children had MDR TB; none had XDR TB. All children were started on daily anti-tuberculous therapy. Of the 61 children, 26 were cured, 26 children were referred elsewhere for treatment, and 9 children died or were discharged in a moribund state (14.8%). There was no significant difference in treatment outcome between the pulmonary and extra pulmonary group (p=0.393). The sensitivity of ESR was 96% and Mantoux was 69.2% in the overall group. In culture-confirmed pulmonary TB, sensitivity of chest X-ray was 95.5% and AFB smear was 45.5%. In culture-confirmed extra-pulmonary TB, sensitivity of AFB smear was 38.5% and that of biopsy was 25%.

Conclusion: The majority of culture-confirmed TB at this tertiary care center was extra-pulmonary TB, with a high incidence of disseminated disease. Drug-resistant TB was seen in only a few children. The sensitivity of AFB smear, Mantoux and biopsy in making the diagnosis was quite low. ESR was highly sensitive but this test is highly nonspecific and elevated in many diseases.

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