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Direct detection of rpoB and katG gene mutations in Mycobacterium tuberculosis from clinical samples

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Among the many infectious diseases, tuberculosis (TB) remains the world's leading cause of death. Worldwide, 37% of new cases went undiagnosed or were not reported. There are very few reports on direct detection of *rpoB* & *katG* gene mutations in Nepal. The vast majority of Rifampicin (RIF)-resistant *M. tuberculosis* clinical isolates have mutations in the gene *rpoB*, which encodes the β-subunit of RNA polymerase. However, most of the *INH* resistance mutations occurred in codon 315 and this was in agreement with other mentioned studies showing the major involvement of this codon in INH resistance all over the world. Most scrutinize literature was collected from different sources including PubMed, HINARI. 45 samples were collected from Annapurna Neurological Institute of Allied Sciences, Kathmandu Nepal and study was carried out in Decode Genomics and Research Center Pvt. Ltd Sinamangal, Kathmandu, Nepal. Among collected sample 27 were from male age ranged from 19-71 and 18 were female patients, age ranged from 22-71 years. Collected sample was first decontaminated by Petroffs modified method and following DNA was extracted. Out of 45, 6 samples were found to be AFB positive by ZN method-PCR was found to be positive for 31(68.88%) samples and 14 (31.11%) samples were found negative. Furthermore, *rpoB* mutation was found in 3 patients (6.66%) and *katG* gene mutation was also found in 3 patients (6.66%) of total sample. One sample shows both *katG* and *rpoB* gene mutation. We are now come to comprehend that from direct clinical samples mutation can be detected, this is even reliable when result need to disseminate fast for treatment. However, large sample size is needed to validate these findings.

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Addressing blood-brain barrier in CNS drug discovery using fragment based approach

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Central nervous system (CNS) related disorders affect over one billion people worldwide. The treatment cost in USA alone is expected to be over $600 billion per year with an economic impact exceeding over a trillion dollar. The two major challenges that impact the treatment of CNS diseases are: (i) effective delivery of drugs and (ii) discovery and development of drug molecules that can cross the blood-brain barrier. Given the fact, that CNS drugs require a more restricted profile of molecular properties (MW: <450Da; LogP: ≤4.0 and Polar Surface Area (PSA): ≤ 80Å2) than the Lipinski 'Rule of Five', hits identified using conventional compound library (MW: 500Da; LogP: 5.5 and Polar Surface Area: 140Å2) limits the possibility of evolving and optimizing them into promising lead candidates suitable for advancing into *in vivo* proof of concept and development studies. An efficient and alternate approach to overcome and address this limitation is to initiate the lead optimization starting with hits identified using fragment based approach and combine with rational structure-based drug design methods. We have used this approach to discover novel, potent and CNS permeable inhibitors of the molecular chaperone, Heat Shock Protein-90, which have demonstrated selective portioning into the CNS, target engagement and pharmacodynamics effects *in vivo*.

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