With approximately 9 million people developing active tuberculosis (TB) every year and 1.7 million deaths annually, TB is far from under control. Human immunodeficiency virus (HIV) infection dramatically increases the risk of developing active TB and is driving the TB epidemic in Africa. HIV renders tuberculosis more difficult to diagnose due to higher incidence of sputum negative disease, and to treat due to interactions and side effects. The increasing spread of multi drug-resistant TB (MDR-TB) and the recalcitrant nature of persistent infections pose additional challenges to treatment with currently available anti-TB drugs. The situation is exacerbated by the increasing emergence of extensively drug-resistant (XDR) TB.

The Global Alliance for TB Drug Development (TB Alliance) has played a critical role in changing the TB research and development landscape and is associated with approximately half of all compounds or projects aimed to identify candidate compounds in development. The main criteria established by the TB Alliance to select drug candidates for further development are: shortening of the current treatment regimen, activity against MDR-TB, and lack of interactions with antiretroviral drugs.

Among the major advances in basic research, molecular and genetic tools have become available for Mycobacterium tuberculosis and include targeted mutagenesis, array-based analysis of mutant libraries, techniques for conditional gene silencing, and global gene expression profiling. This has led to impressive improvements in the knowledge and understanding of the basic biology and physiology of M. tuberculosis. Despite these positive changes there are still problems that need to be tackled. There will need to be a sufficient number of promising compounds in the TB pipeline for a broadly effective new treatment combination to be developed. Many of the compounds currently in the pipeline are either derivatives of existing compounds or they target the same cellular processes as drugs currently in use. Whilst analogues and derivatives are far quicker to develop, they may be subject to cross-resistance, as has been the case with the new rifamycins and quinolones. Modern technologies and rational approaches to drug design such as creation of genomic libraries of M. tuberculosis conditional knock-out mutants for comprehensive target identification and validation, target-based drug discovery, or determination of three dimensional crystal structures of molecular targets, are still weakly implemented. Even the more promising candidate compounds currently in clinical development were identified serendipitously. There is also an urgent need for rational approaches aimed at
tackling the problem of mycobacterial persistence. The adaptations that allow *M. tuberculosis* to persist in the host despite a vigorous adaptive immune response likely contribute to the difficulty in curing TB with current chemotherapy.

In the search for novel leads with useful biological activities, synthesis and screening of the functionalized pyrimidines continues to be an area of active interest. The most common route to such pyrimidine derivatives is through the primary synthesis involving the condensation of 1,3-dicarbonyl compounds with amidines. A number of such fruitful condensations have been effected with a host of 1,3-dicarbonyl analogues to obtain the appropriately substituted pyrimidines. The ketene acetals have been used as 1,3-dicarbonyl variants in heterocyclization reactions to obtain the functionalized pyrimidines. The N-(carbethoxyacyanovinyl)amidines, the presumed intermediates in the pyrimidine synthesis have been isolated in the condensation of carbethoxyacyanoketene S,N-acetals with amidines. The cyanovinlamidines have been cyclised to 4-oxo- or 4-aminopyrimidines under appropriate conditions. Further, the cyanovinlamidines are found to undergo a novel, hydrogen chloride catalyzed cyclization to yield, directly, 4-chloropyrimidines. The displacement of the chlorine atom with appropriate nucleophilic reagents followed by cyclization reaction can be viewed as possible method for the construction of another heterocyclic ring system on the pyrimidine framework.

4-(Substituted amino)pyrimidines were found to exhibit potent antibacterial and antifungal activity. The 2,3-dihydroimidazo[1,2-c]pyrimidines have been studied as potential bioactive molecules, specifically as GABA<sub>A</sub> brain receptor ligands and antiviral activity. We successfully explored the antifungal and antimicrobial activity including antimycobacterial activity of several 2,3-dihydroimidazo[1,2-c]pyrimidines. Furthermore, a detailed 2-D QSAR study was also established.