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Balanced QSAR analysis to identify the structural requirements of ABBV-075 (Mivebresib) analogues as bromodomain and extraterminal domain (BET) family bromodomain inhibitor

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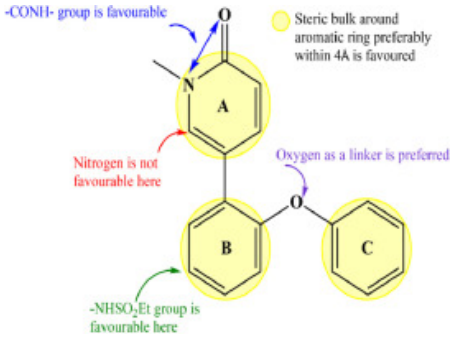
Highlights

- QSAR model has been built using **easily interpretable descriptors.**
- QSAR model has **excellent external predictive ability.**
- First attempt to develop QSAR for ABBV-075 (Mivebresib) analogues.
- A good number of structural features have been identified.

Abstract

ABBV-075 (Mivebresib) analogues were reported to have BET family bromodomain binding affinity Ki in nano-molar (nM) range (0.8 to 3000 nM). But future optimizations are required to achieve a drug-like molecule with retention of high binding affinity and optimum ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profile. This could be achieved by identifying the pharmacophoric features (salient and concealed) using modern techniques like CADD (Computer-Aided Drug Designing). Therefore, in the present work, QSAR (Quantitative structure-activity relationship) analysis, a thriving CADD branch, has been executed to achieve the determined objectives. The developed QSAR model is statistically acceptable with robust fitting, high internal and external predictive ability. The developed model fulfils the threshold values for a good number of statistical parameters like $R^2 = 0.80$, $R^2_{CV} = 0.77$, etc. The analysis reveals that non-ring Carbon/Nitrogen atoms, frequency of occurrence of specific combinations of Carbon/Nitrogen atoms with acceptor/donor atoms are important pharmacophoric features for BET binding affinity. Thus, the developed QSAR has a balance of quantitative and qualitative approaches. The results could be useful for future optimizations of Mivebresib analogues .

Graphical abstract



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Keywords

Bromodomain and extraterminal domain; Mivebresib; QSAR; Pharmacophoric patterns

Abbreviations

BET, bromodomain and extraterminal domain; GA, genetic algorithm; MLR, multiple linear regression; QSAR, quantitative structure-activity relationship; WHO, world health organization; ADME, absorption, distribution, metabolism, and excretion; OLS, ordinary least square; QSARINS, QSAR insubria; OECD, organisation for economic co-operation and development; CADD, computer aided drug designing

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