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Strategic Structural Diversification of Ibrutinib via Sulfonamide and Styrene Hybridization: Synthesis and Spectral Characterization of Novel Heterocyclic Derivatives

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Abstract: *Ibrutinib is a small molecule drug that targets Bruton's tyrosine kinase in B-cell malignancies and is highly efficient at killing mantle cell lymphoma and chronic lymphocytic leukemia. However, the anti-cancer activity of ibrutinib against solid tumors, such as non-small cell lung cancer (NSCLC).*

Keywords: Ibrutinib.

I. INTRODUCTION

Ibrutinib is a small molecule drug that targets Bruton's tyrosine kinase in B-cell malignancies and is highly efficient at killing mantle cell lymphoma and chronic lymphocytic leukemia. However, the anti-cancer activity of ibrutinib against solid tumors, such as non-small cell lung cancer (NSCLC), Ibrutinib isapotent covalent inhibitors of BKT the derivatives of ibrutinib has been well tolerated and has demonstrated profound anti-cancer activity in variety of hematologic malignancies.

Context of work:

We synthesized a series of ibrutinib derivatives, of which exhibited superior anti-cancer activity especially against B-Cell malignancies in cancer.which is effective towards the treatment in cancer.

Methodology:

In the present investigation, novel heterocyclic derivatives of ibrutinib were synthesized through sulfonamide coupling and styrene-based structural modifications. The reactions were carried out using ibrutinib free base in tetrahydrofuran under controlled low-temperature conditions followed by reaction with substituted sulfonyl chlorides and cinnamic acid derivatives. The synthesized compounds were purified by column chromatography and characterized by Mass spectrometry, ^1H NMR and ^13C NMR spectroscopy. Spectral analysis confirmed the successful formation of the desired derivatives. The incorporation of heterocyclic and electron-modifying substituents may contribute to improved biological interactions. The study provides a synthetic platform for further medicinal chemistry exploration of BTK inhibitors.

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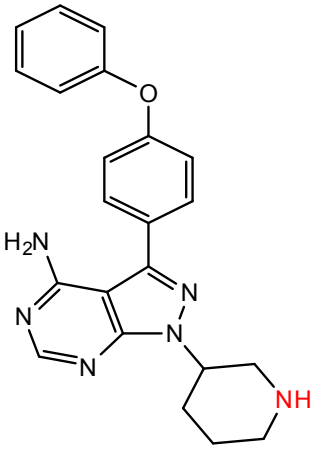
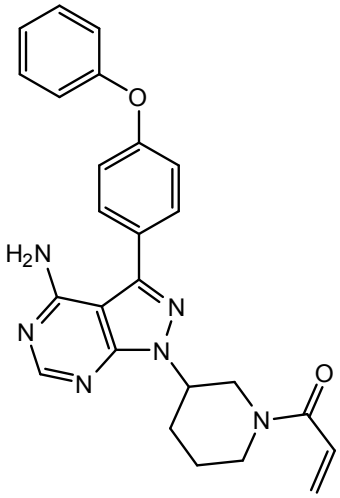
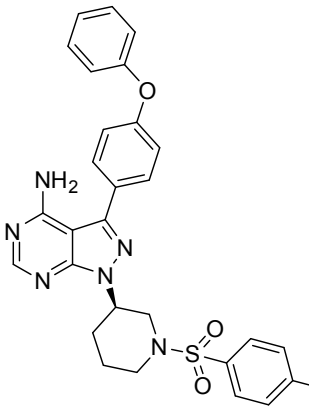


Ibrutinib free base



Ibrutinib

Direct Mass,^{1}HNMR of Sulfonamide Derivative



IA

Direct mass:m/z: 556.5

Proton NMR integration

□ 7.7 (2H), □ .7 (1H) □.27 (1H) □ 3.5(2H) □ 3.2(2H) □2.98(2H) □2.94(2H) 13 H Aromatic proton, □2.06 (2H), □1.8 (2H)

□1.5 (2H), □1.4 (2H), □3.83 (3H)

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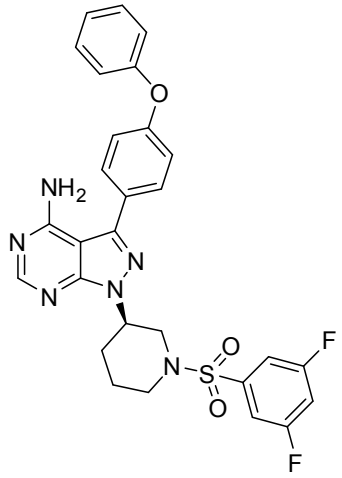
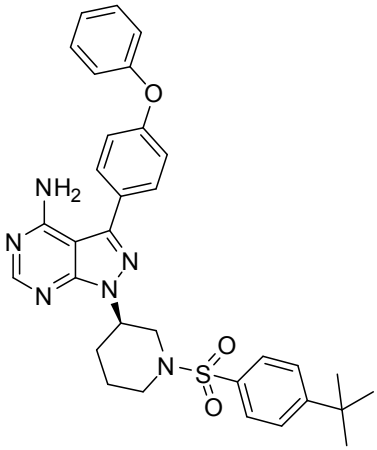


Direct mass: m/z: 562.59

Proton NMR integration

□ 7.7 (2H), □ .7 (1H) □.27 (1H) □ 3.5 (2H) □ 3.2(2H) □2.98 (2H) □2.94 (2H) 13 H Aromatic proton, □2.06 (2H), □1.8 (2H)
□1.5 (2H), □1.4 (2H)

IC



Direct mass: m/z: 583.48
Proton NMR integration
□ 7.7 (2H), □ .7 (1H) □.27 (1H) □ 3.5 (2H) □ 3.2(2H) □2.98 (2H) □2.94 (2H) 13 H Aromatic proton, □2.06 (2H), □1.8 (2H)
□1.5 (2H), □1.4 (2H), □1.35 (9H)

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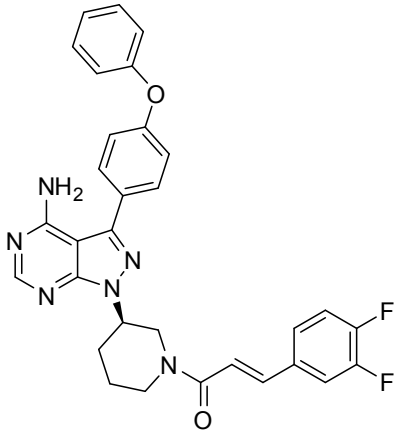
Styrene Derivatives

IIA



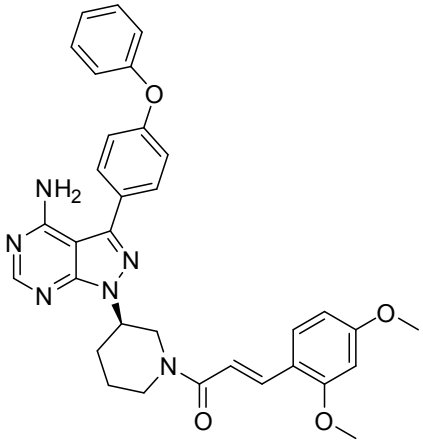
Direct mass: m/z: 552.57

Proton NMR integration

□ 7.7 (2H), □ .7 (1H) □.27 (1H) □ 3.5 (2H) □ 3.2(2H) □2.98 (2H) □2.94 (2H) 12 H Aromatic proton, □2.06 (2H), □1.8 (2H)

□1.5 (2H), □1.4 (2H), □7.3 (1H), □7.03 (1H),

IIB



Direct mass: m/z: 576.64

Proton NMR integration

□ 7.7 (2H), □ .7 (1H) □.27 (1H) □ 3.5 (2H) □ 3.2(2H) □2.98 (2H) □2.94 (2H) 12 H Aromatic proton, □2.06 (2H), □1.8 (2H)

□1.5 (2H), □1.4 (2H), □7.3 (1H), □7.03 (1H), □3.8 (3H), □3.8(3H)

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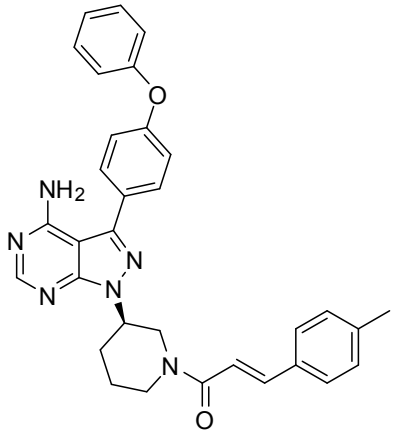

Direct mass: m/z: 530.62
Proton NMR integration
□ 7.7 (2H), □ .7 (1H) □.27 (1H) □ 3.5 (2H) □ 3.2(2H) □2.98 (2H) □2.94 (2H) 12 H Aromatic proton, □2.06 (2H), □1.8 (2H)
□1.5 (2H), □1.4 (2H), □7.3 (1H), □7.03 (1H), □2.3 (3H)

Results and Discussion*

The synthetic strategy successfully yielded several novel heterocyclic derivatives of ibrutinib. The reactions proceeded smoothly under controlled temperature conditions.
Mass spectral analysis confirmed the expected molecular ion peaks corresponding to the proposed molecular weights.
^1H NMR spectra showed characteristic aromatic proton signals along with aliphatic proton integration consistent with the proposed structures.
^13C NMR spectra further confirmed carbon skeleton integrity and functional group incorporation.
The introduction of sulfonamide and styrene moieties may influence electron distribution and binding potential toward BTK enzyme targets. Structural modification through heterocyclic incorporation may enhance pharmacodynamic properties and warrants further biological investigation.

II. CONCLUSION

Novel sulfonamide and styrene-based heterocyclic derivatives of ibrutinib were successfully synthesized and characterized using spectral techniques. The study demonstrates effective structural diversification of ibrutinib, providing a foundation for future pharmacological and SAR investigations in medicinal chemistry.

ACKNOWLEDGEMENT

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