IKK inhibitory activities of imidazo[1,2-a]pyrazine, imidazo[1,2-a]quinoxaline, imidazo[1,5-a]quinoxaline and pyrazolo[1,5-a]quinoxaline derivatives.


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IKK inhibitory activities of imidazo[1,2-α]pyrazine, imidazo[1,2-α]quinoxaline, imidazo[1,5-α]quinoxaline and pyrazolo[1,5-α]quinoxaline derivatives.

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Introduction
The transcription factor NF-κB plays a key role in multiple cellular processes, including immune signaling, inflammation, development, proliferation and survival. Disregulated NF-κB activation is associated with autoimmunity1, chronic inflammation2 and cancer3. Activation of NF-κB requires IκBα and IκBβ.

Synthesis of imidazo[1,2-α]quinoxalines

Synthesis of imidazo[1,5-α]quinoxalines

Synthesis of pyrazolo[1,5-α]quinoxalines

Conclusion
Four series of imidazo[1,2-α]pyrazines, imidazo[1,2-α]quinoxalines and pyrazolo[1,5-α]quinoxalines were efficiently synthesized with short reaction times by using microwave assistance. The compounds were evaluated for their IKKα and IKKβ inhibition. We found a good correlation between the biological activity as selective inhibitors on the IKKβ and the docking study performed. Compound 6a bearing a methyl group at the position 8 and a bromine group at position 1 showed remarkable activity.

References

Targeting the activation of NF-κB-dependent pathway by IKK inhibitors is becoming an increasingly popular avenue for the development of novel therapeutic interventions for inflammation and cancer. Many pharmaceutical companies are developing inhibitors that target IKK.

BMS-345541 was identified as a selective inhibitor of the catalytic subunits of IKK (IKKα: IC50 = 0.3 μM, IKKβ: IC50 = 4 μM). The aim of this study is to obtain new IKK inhibitors, analogues of BMS-345541.