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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.

Nour Bou Karroum, Cindy Patinote, Adrien Chouchou, Georges Moarbess, Mona Diab-Assaf, Pierre Cuq, Carine Deleuze-Masquéfa, Issam Kassab, Pierre-Antoine Bonnet

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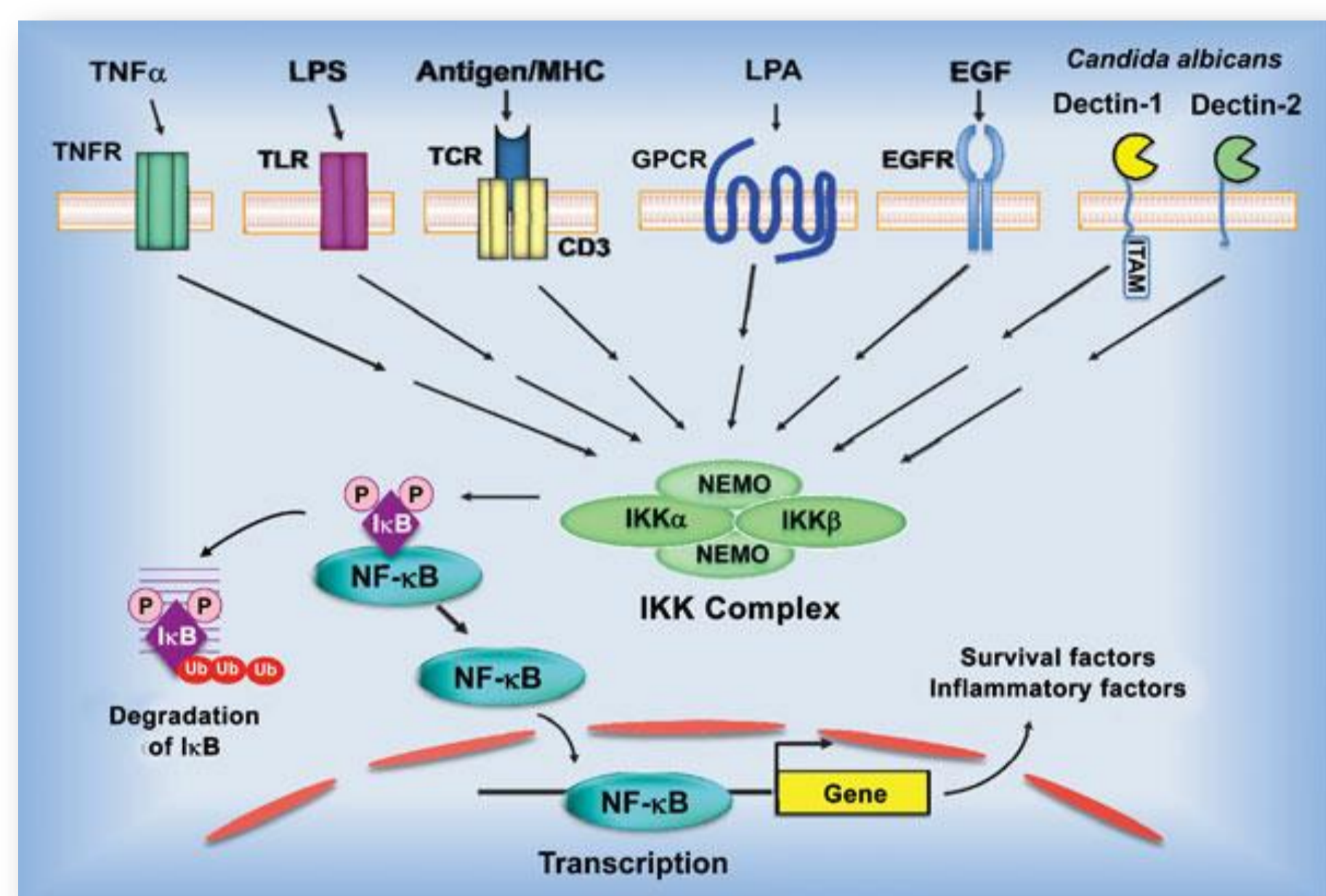
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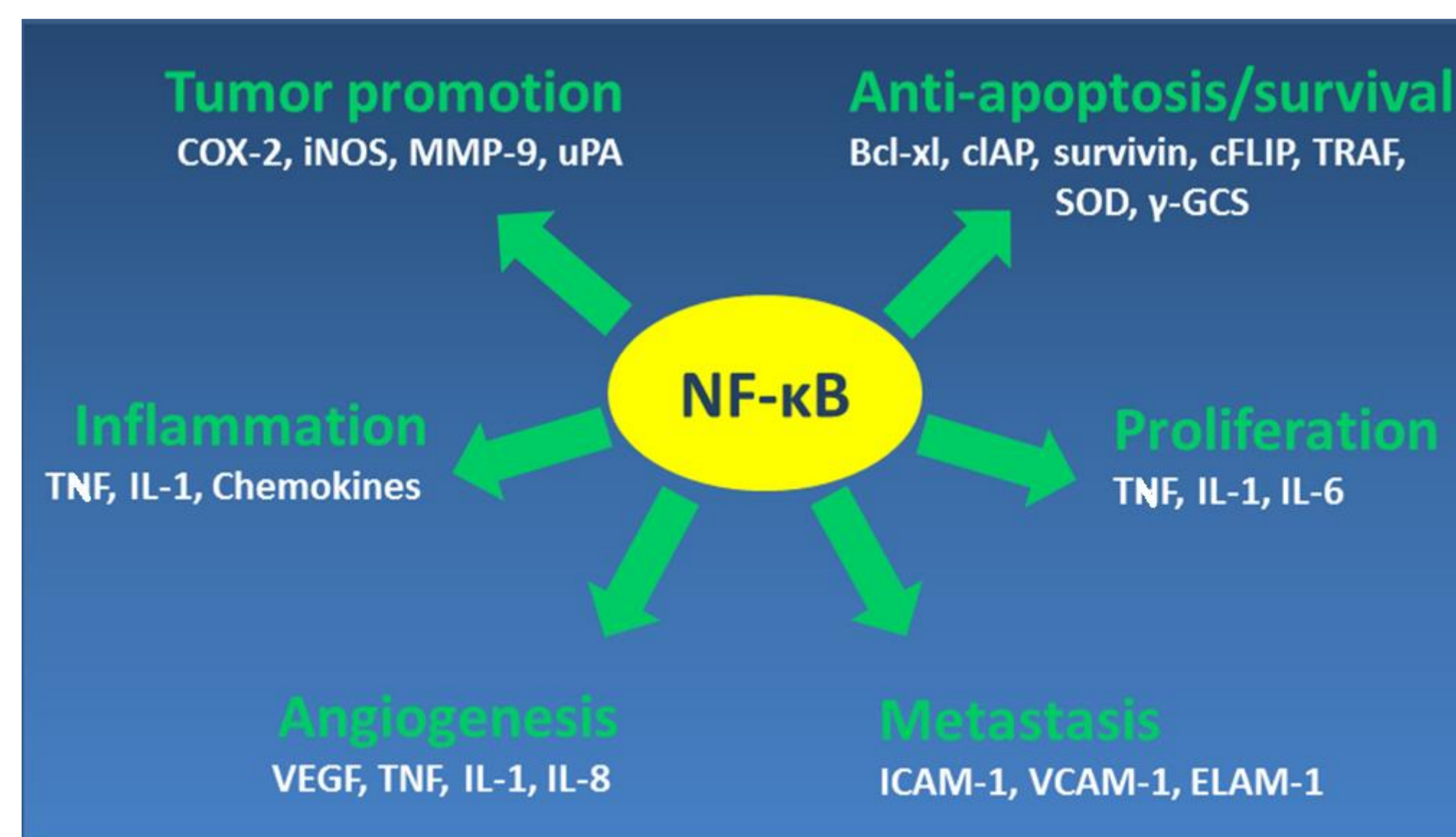
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Introduction

The transcription factor NF- κ B plays a key role in multiple cellular processes, including immune signaling, inflammation, development, proliferation and survival. Dysregulated NF- κ B activation is associated with autoimmunity¹, chronic inflammation² and cancer³. Activation of NF- κ B requires I κ B kinases: IKK α and IKK β .

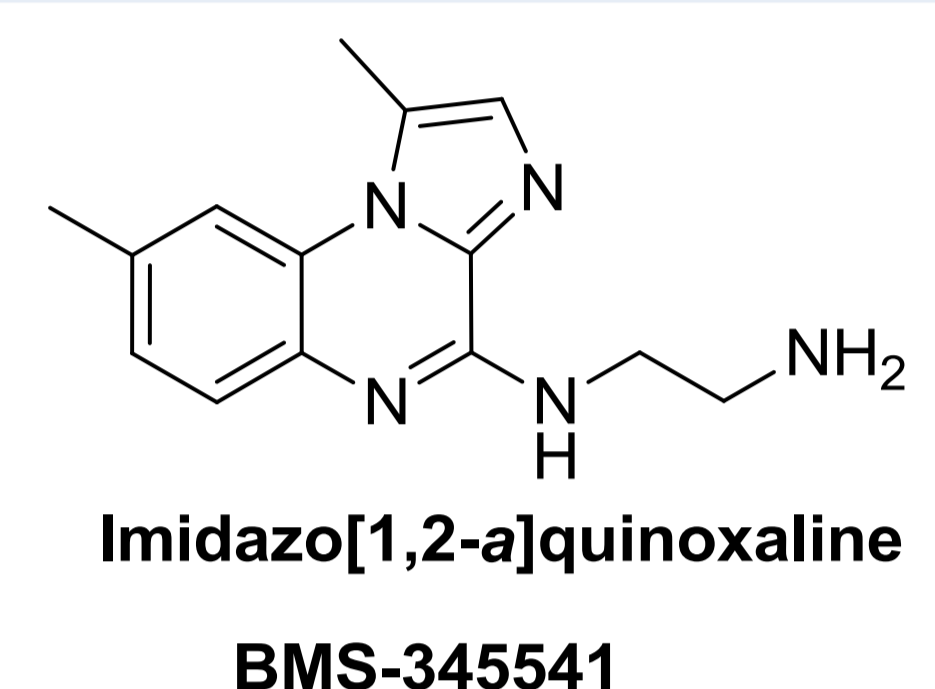


Stimulation of the surface receptors by different inducers initiates several proximal signaling events resulting in activation of the I κ B kinase complex⁴.



Representation of NF- κ B-dependent genes involved in inflammation and cancer (published by Mike Menkes listed in cancer, originally published in issue 220 - February 2015).

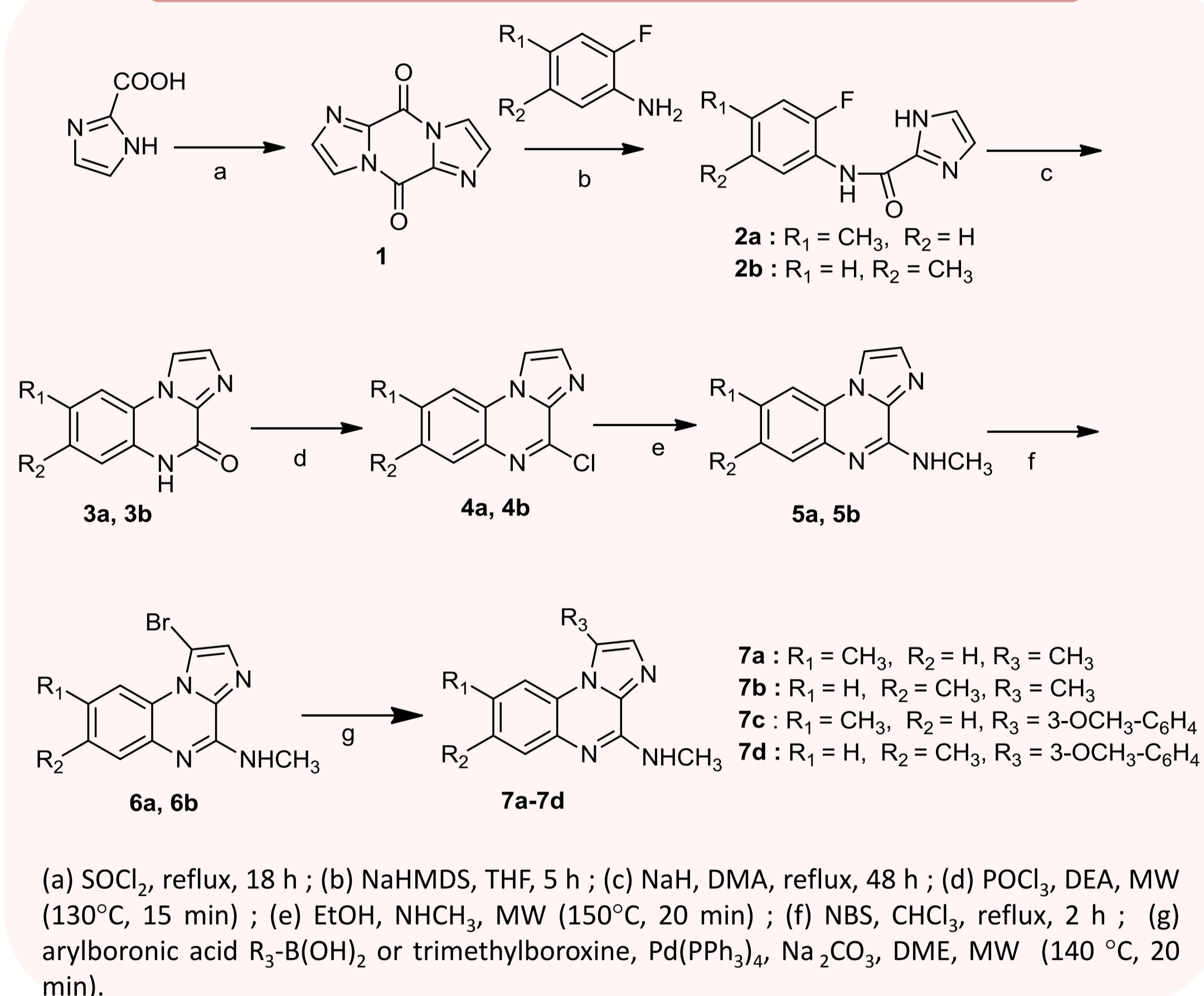
Targeting the activation of NF- κ B-dependent pathway by IKK inhibitors is becoming an increasingly popular avenue for the development of novel therapeutic interventions for inflammation and cancer. Many pharmaceutical companies are developing inhibitors that target IKK.



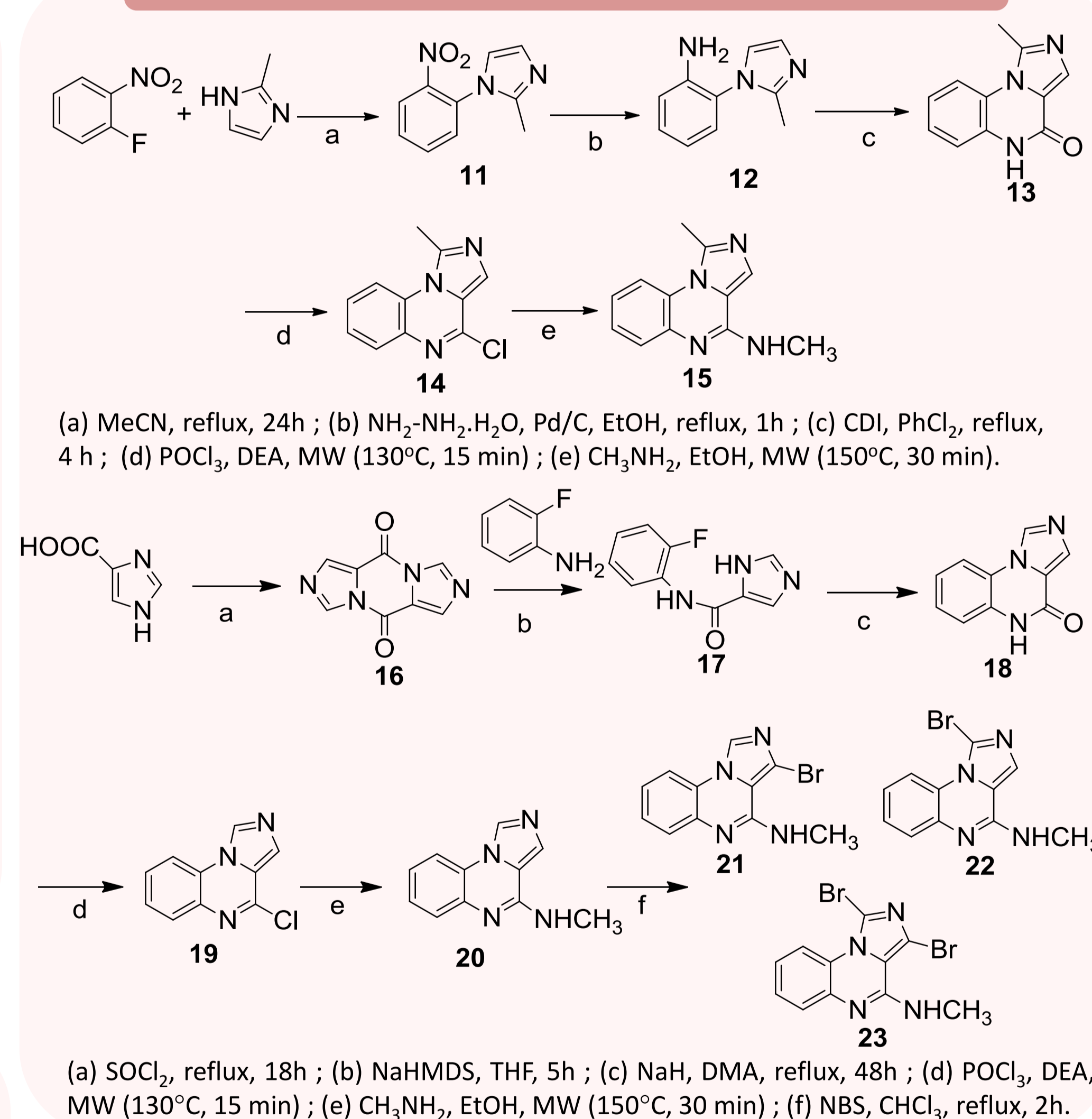
BMS-345541 was identified as a selective inhibitor of the catalytic subunits of IKK (IKK β : IC₅₀ = 0.3 μ M, IKK α : IC₅₀ = 4 μ M).⁵

The aim of this study is to obtain new IKK inhibitors, analogues of BMS-345541.

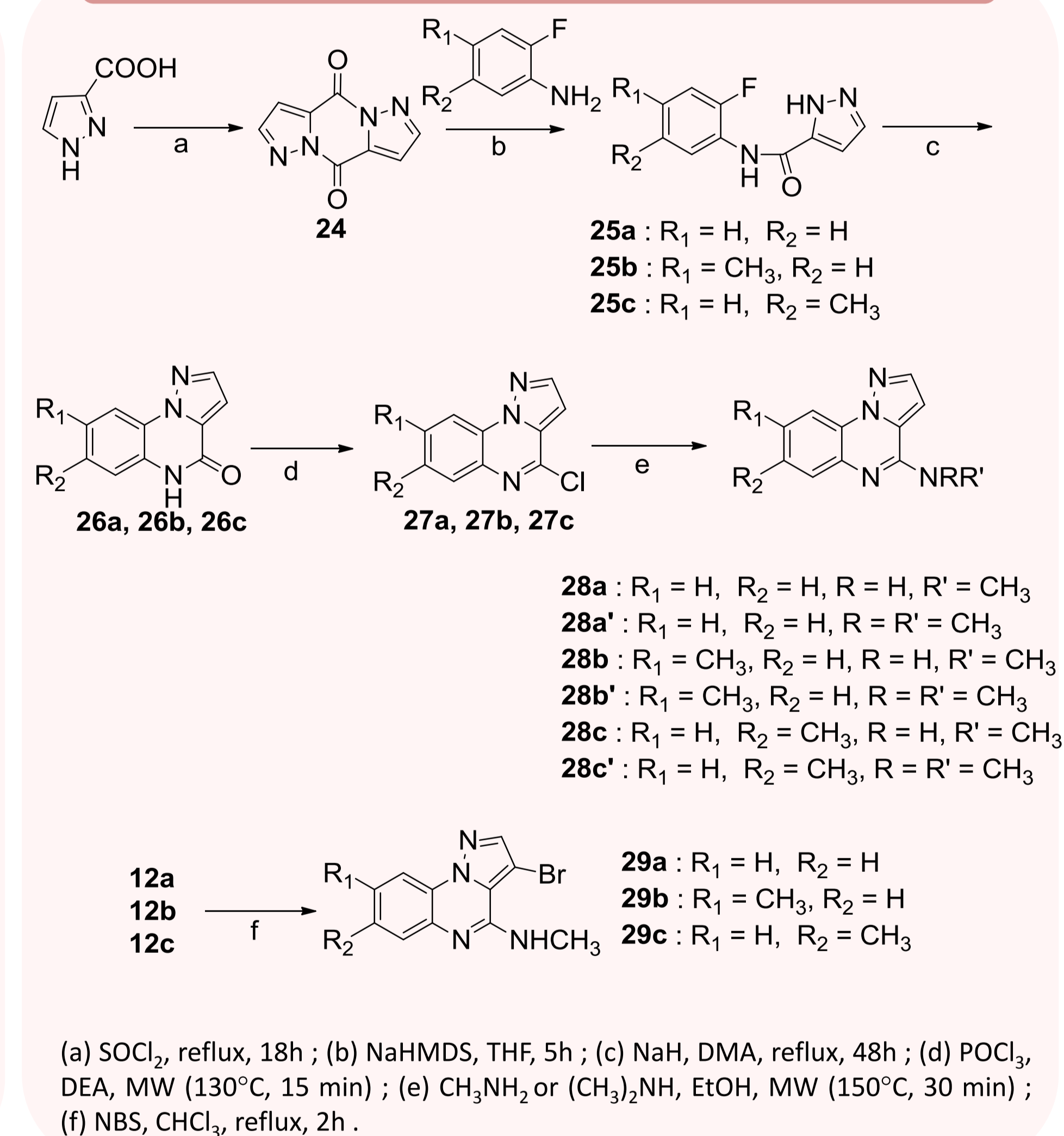
Synthesis of imidazo[1,2-*a*]quinoxalines



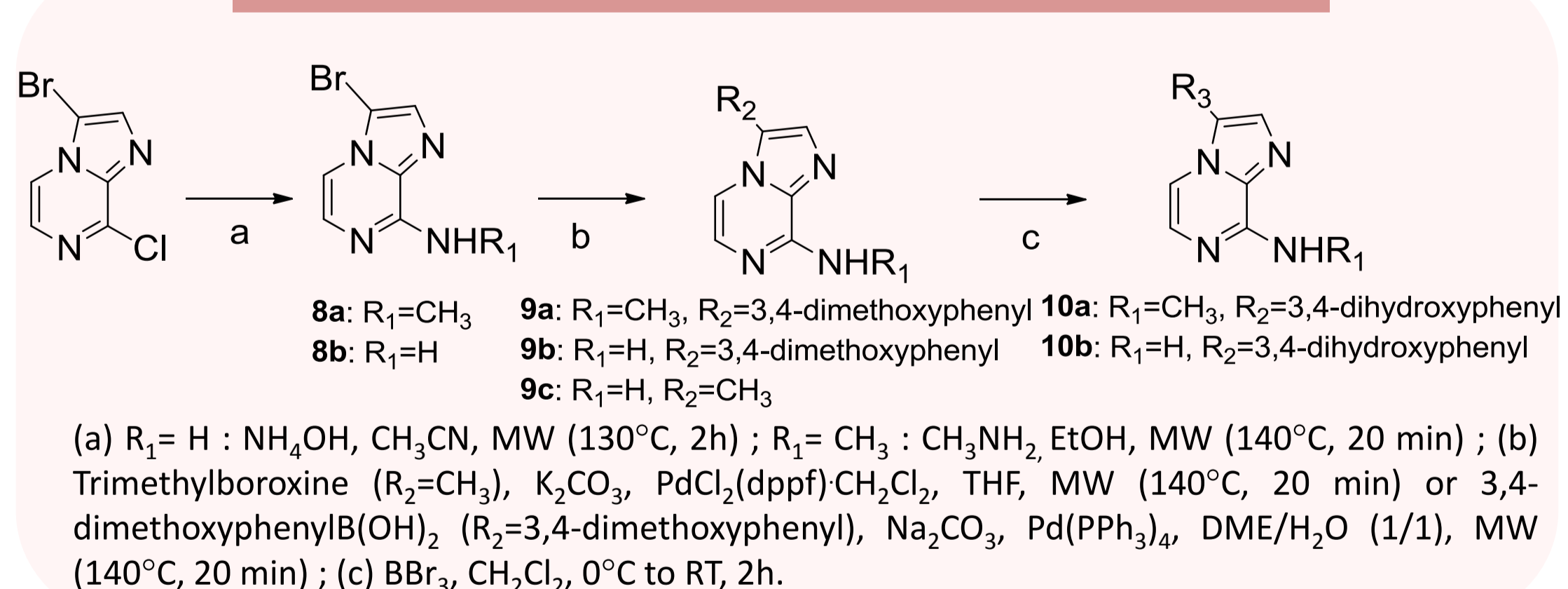
Synthesis of imidazo[1,5-*a*]quinoxalines



Synthesis of pyrazolo[1,5-*a*]quinoxalines



Synthesis of imidazo[1,2-*a*]pyrazines



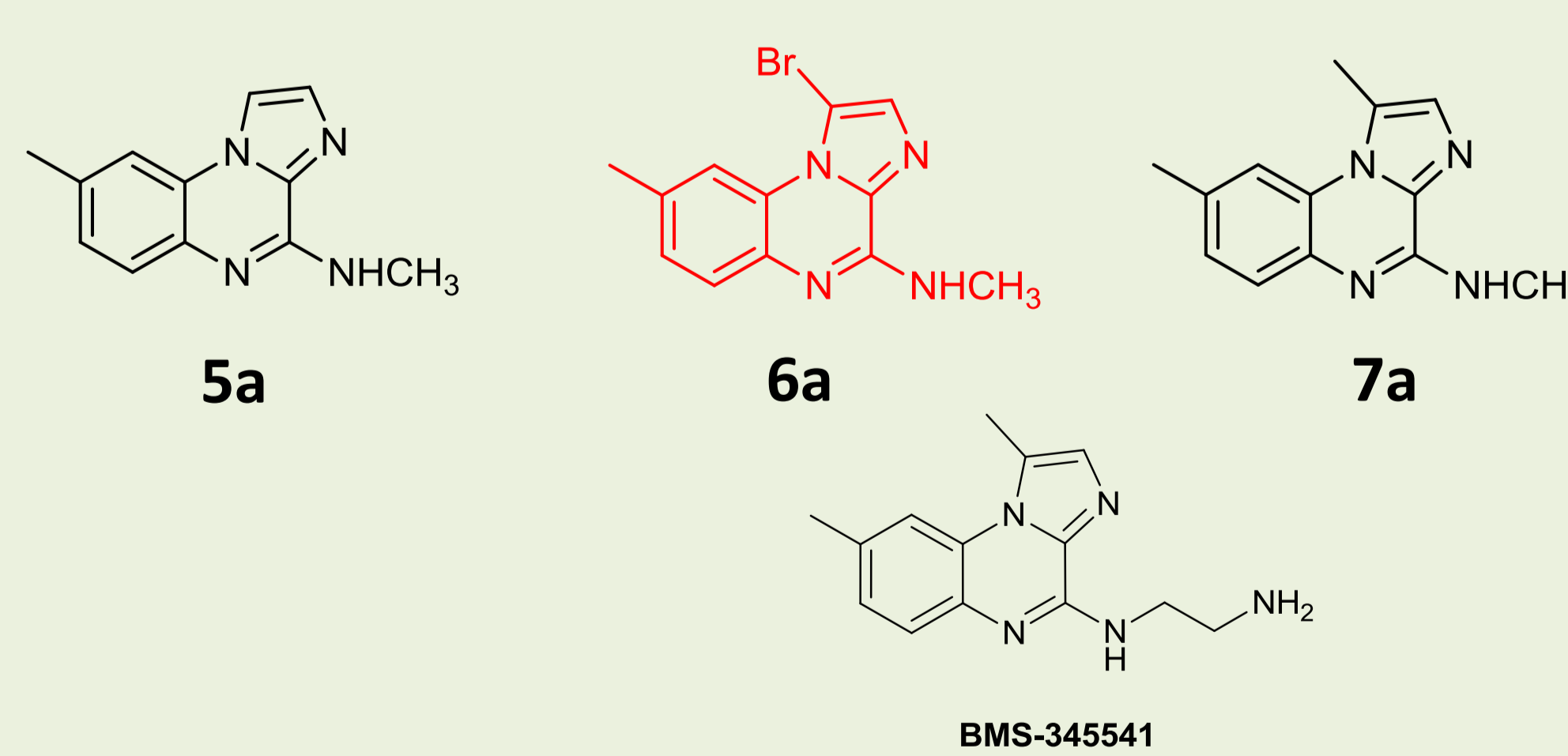
Conclusion

Four series of imidazopyrazines, imidazoquinoxalines and pyrazoloquinoxalines were efficiently synthesized with short reaction times by using microwave assistance. The compounds were evaluated for their IKK α and IKK β inhibition. We found a good correlation between the biological activity as selective inhibitors on the IKK β 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.

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IKK inhibitory activities and docking study

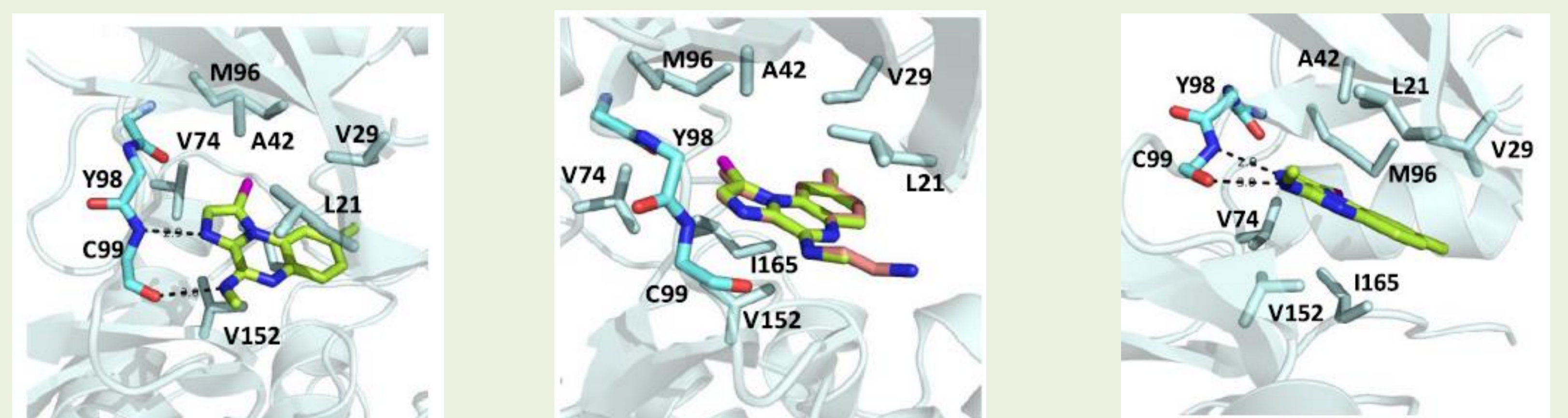


Inhibitory potencies of novel derivatives on IKK β

Compounds	IC ₅₀ ^a (nM)
5a	579 ± 56
6a	324 ± 48
7a	773 ± 160
BMS-345541	644 ± 97

^a IC₅₀: 50% inhibitory concentration of IKK β (mean ± SE of two independent experiments).

IKK α inhibition activities are less than 20 % at 10 μ M for all compounds.



Compound **6a** in the ATP binding pocket of IKK β .