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Potent aromatase inhibitors and molecular mechanism of inhibitory action

Hongjun Kang^{a,1}, Xingqing Xiao^{b,1}, Chao Huang^c, Yan Yuan^d, Dongyan Tang^a, Xiaochang Dai^{a,*}, Xianghui Zeng^{a, e,*}

^a Key Laboratory of Medicinal Chemistry for Natural Resource, Yunnan University, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, P.R. China

^b Department of Chemical and Biomolecular Engineering, North Carolina State University, Raleigh, North Carolina 27695-7905, USA

^c Engineering Research Center of Biopolymer Functional Materials of Yunnan, Yunnan Minzu University, Kunming, 650500, P.R. China

^d School of Ethnic Medicine, Yunnan Minzu University, Kunming, 650504, P.R. China

^e Current address: Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen. DK-2100 Copenhagen, Denmark

¹ Co-first author

Correspondence: xchdai@ynu.edu.cn (X.D.), zeng_89@hotmail.com (X.Z.)

Highlights

- ▶ Discovery of novel non-steroidal inhibitors against aromatase
- ▶ Novel compounds demonstrate higher potencies in aromatase inhibitory than letrozole
- ▶ Computational models of aromatase with different substrates are built
- ▶ Binding mode of substrates to aromatase has significant impact on pharmacological effect

Abstract

Estrogen is a significant factor in the maintenance and progression of hormone-dependent breast cancer. As well known, aromatase mediates the production of estrogen. Thus, reduction of aromatase with chemical molecules has been considered to be an effective treatment for estrogen receptor-positive (ER+) breast cancer. In this work, we designed and synthesized a series of novel non-steroidal molecules containing 2-phenylindole scaffold and moiety of either imidazole or 1,2,4-triazole to enhance their binding capacity with the aromatase. Among these molecules, a compound named as **8o** was confirmed experimentally to have the highest inhibitory activity to aromatase. Further cell activity assay proved that compound **8o** has low cytotoxicity and is a promising lead for

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