Design, synthesis, biological evaluation and molecular docking of 1,7-dibenzyl substituted theophylline derivatives as novel BRD4-BD1 selective inhibitors

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Abstract

Bromodomain-containing protein 4 (BRD4), an epigenetic reader, has been recognized as a target with therapeutic potential in several types of cancer and cardiovascular diseases. In this study, a series of 1,7-dibenzyl substituted theophylline derivatives were synthesized and their BRD4 inhibitor activities were evaluated. Most of the compounds showed detectable activities with IC 50 values in the range of 2.51 – 10.50 μ M. Therein, compound 6e showed significant selectivity for two bromodomains of BRD4, the inhibition of BD1 (IC 50 = 2.51 μ M) was 20 times greater than that of BD2 (IC 50 > 50 μ M). Similarly, compounds 6b – 6d, 6f, 6j and 8a also displayed favorable BRD4-BD1 selectivity. In addition, molecular docking of compound 6e was performed to predict conceivable binding patterns of it with BRD4, prompting residue Ile146 might be crucial to the observed selectivity of BRD4-BD1. These findings will be of great value and significance for the development of novel BRD4-BD1 inhibitors.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures

A

Pan-BRD4 Inhibitors

OTX-015
Phase I clinical trial
Phase II clinical trial

CPI-0610
Phase I clinical trial
Phase II clinical trial

I-BET762
Phase I clinical trial

ABBV-075
Phase I clinical trial

BRD4-BD1 Inhibitors

A

MS402

LT052

BRD4-BD2 Inhibitors

RVX-208
Phase II clinical trial
Phase III clinical trial

ABBV-744
Phase I clinical trial

GSK973

Figure 1

(A) Structures of typical BRD4 inhibitors

Figure 2

(A) Docking conformation of compound 3a with BRD4-BD1, compound 3a in blue violet; (B) Docking conformation of compound 8a with BRD4-BD1, compound 8a in coffee

Figure 3

(A) Docking conformation of compound 6b with BRD4-BD1, 6b in pink, hydrogen bonds in yellow dotted lines, π-H and stacking interactions in blue dotted lines; (B) Docking conformation of compound 6e with BRD4-BD1, 6e in orange; (C) Docking conformation of compound 6d with BRD4-BD1, compound 6d in azure; (D) Docking conformation of compound 6c with BRD4-BD1, compound 6c in yellow; (E) Docking conformation of compound 6e with BRD4-BD2, compound 6e in orange

Supplementary Files

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- [GraphicalAbstract.png](#)