PharmaBlock

SCIENTIFIC INSIGHTS

Aliphatic Rings as Bioisosteres of Phenyl Ring in Drug Discovery

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Introduction

The phenyl ring is one of the most prevalent structural motifs in marketed drugs. However, its inherent aromaticity and potential for metabolic oxidation, poor solubility and low permeability can pose challenges in terms of stability and pharmacokinetics. Aliphatic rings, on the other hand, offer improved metabolic stability, reduced lipophilicity, increased solubility and enhanced membrane permeability, making them attractive alternatives to the phenyl ring (**Figure 1**). [1] By replacing the phenyl moiety with aliphatic rings, medicinal chemists can modulate the physicochemical properties of compounds while retaining or enhancing their biological activity.

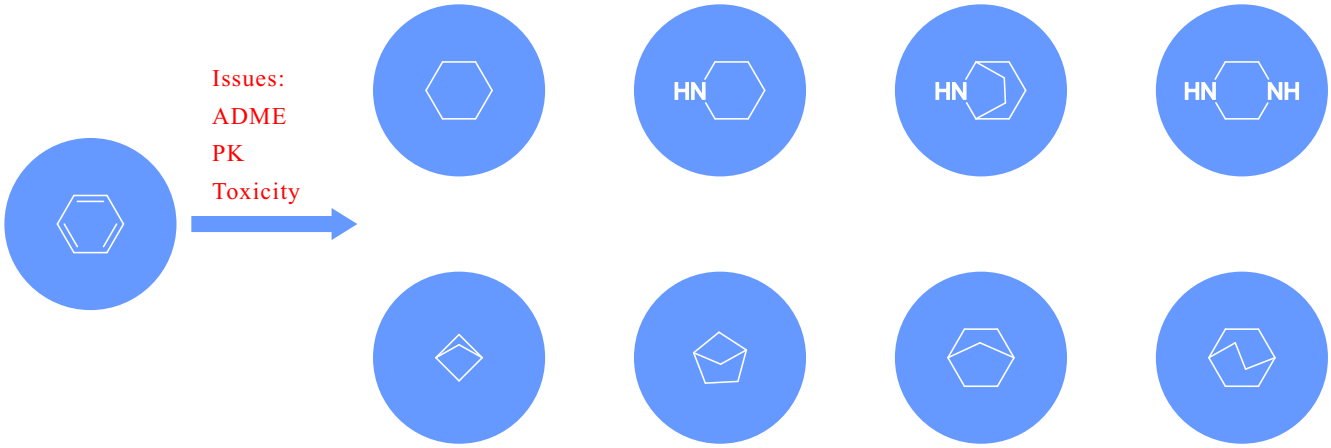


Figure 1. Widely used aliphatic rings as bioisosteres to replace the phenyl rings

Among the aliphatic rings as bioisosteres of the phenyl rings, bicylco[1.1.1]pentane (BCP) attracts more attention of the medicinal chemists because of the comparable dihedral angle, the similar distance and the linear disposition of the substituents (**Figure 2**) with significantly improved properties of the compounds (**Figure 3**). 1,3-disubstituted BCP can mimic a para-substituted phenyl ring.[1]

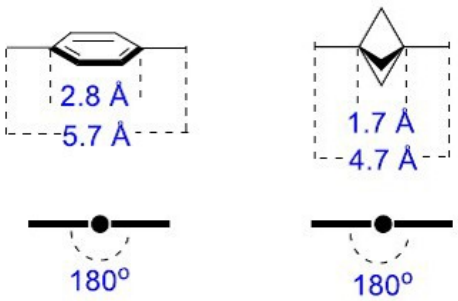


Figure 2. Geometrical parameters of phenyl ring and BCP ring

pIC_{50} = 9.65
Solubility pH6.5 (kinetic) = 0.60 (uM)
RRCK P_{app} (10^{-6} cm/s) = 5.52 RRCK
CL (Human Hep.) = 15.0 (uL/min/10^6 cells)

pIC_{50}=9.75
Solubility pH6.5 (kinetic) = 216 (uM)
P_{app} (10^{-6} cm/s) = 19.3
CL (Human Hep.) = <3.8 (uL/min/10^6 cells)

Figure 3. Effect on Potency and Developability Parameters of Bioisosteric Replacement of a phenyl ring of γ-Secretase Inhibitor with a BCP Moiety

The same effect was also observed on bicyclo[2.2.2]octane (BCO) ring system (**Figure 4**) and bridged piperidine ring system (**Figure 5**). [1]

Cellular IC_{50} = 510 (nM)
Solubility (LYSA) < 0.1 (μg/mL)

Cellular IC_{50} = 118 (nM)
Solubility (LYSA) = 15 (μg/mL)

Figure 4. Effect on Potency and Developability Parameters of Bioisosteric Replacement of a phenyl ring of γ-Secretase Modulator with a BCO Moiety

Cellular IC_{50} = 510 (nM)
Solubility (LYSA) < 0.1 (μg/mL)

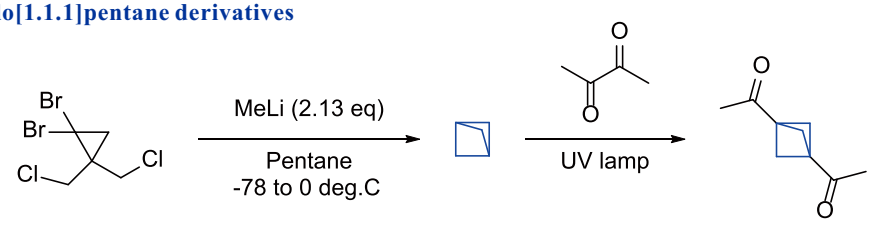
Cellular IC_{50} = 42 (nM)
Solubility (LYSA) = 104 (μg/mL)

Figure 5. Effect on Potency and Developability Parameters of Bioisosteric Replacement of a phenyl ring of γ-Secretase Modulator with a Bridged Piperidine Ring System

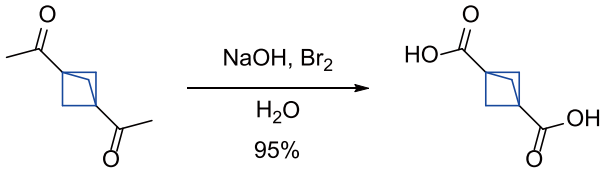
Aliphatic rings have emerged as valuable bioisosteres of phenyl rings in medicinal chemistry because of their unique characteristics to modulate drug properties while retaining or enhancing improved stability, reduced toxicity, and enhanced pharmacokinetic profiles. Continued exploration and optimization of aliphatic ring substituents hold promise for the development of novel and effective therapeutics across various therapeutic areas.

Synthesis of Aliphatic Rings

1) Synthesis of bicyclo[1.1.1]pentane derivatives

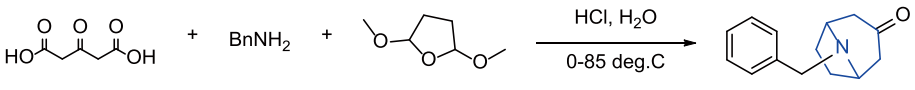


Journal of Medicinal Chemistry, **2012**, *55*, 3414-3424

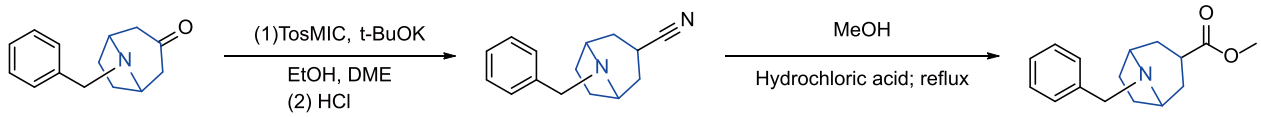


Organic Syntheses, **2000**, *77*, 249-253

2) Synthesis of 8-azabicyclo[3.2.1]octane derivatives

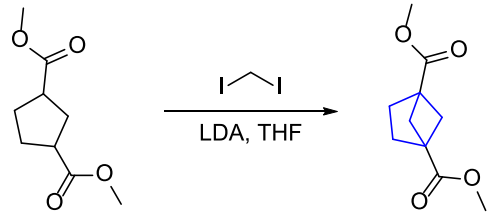


US2007/117796

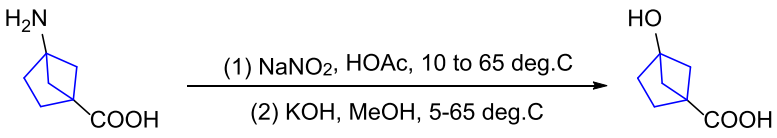


Huaxue Xuebao, **2015**, *73*, 679-684

3) Synthesis of bicyclo[2.1.1]hexane derivatives



Chemistry - A European Journal, **2002**, *8*, 4506-4509



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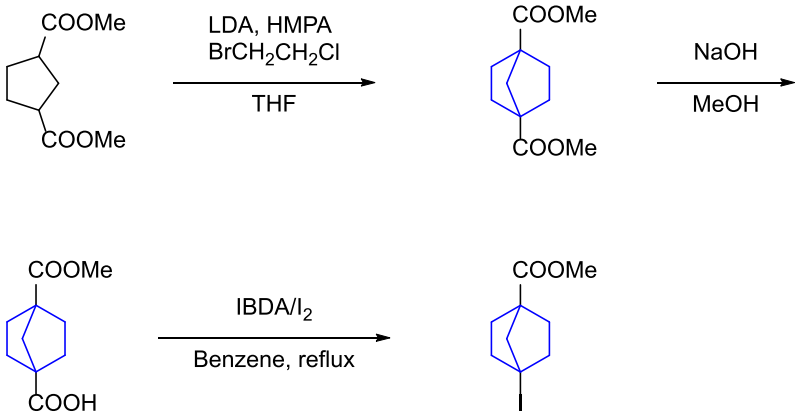
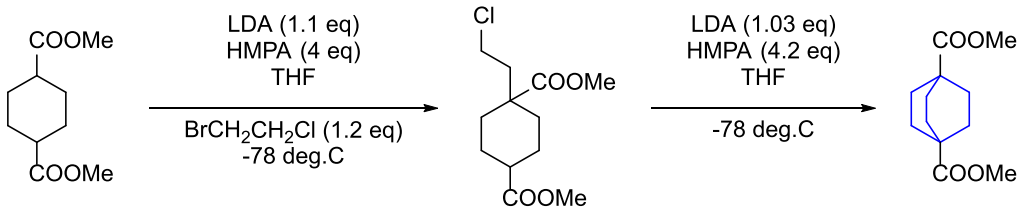
4) Synthesis of bicyclo[2.2.1]heptane derivatives



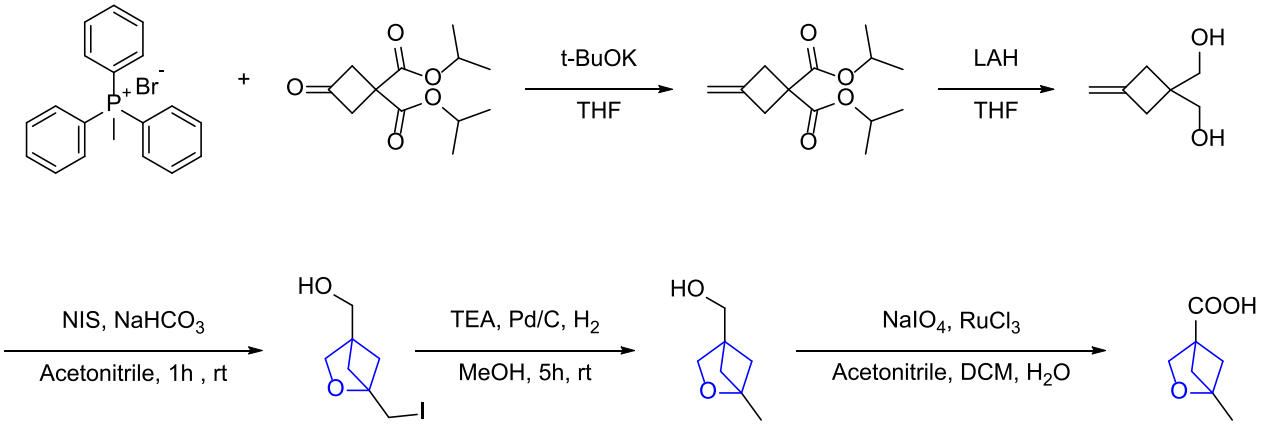
Synthetic Communications, **2007**, *37*, 1267-1272

5) Synthesis of bicyclo[2.2.2]octane derivatives



Journal of Medicinal Chemistry, **2011**, *54*, 3480-3491

6) Synthesis of 2-oxabicyclo[2.1.1]hexane derivatives



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Building Blocks as Bioisosteres of Phenyl Rings

PharmaBlock has conducted a systematic study of clinical and preclinical drug molecules, and our chemists continue to pay attention to the latest research, design and synthesize a large number of bioisosteres of phenyl rings, which can be used to explore structure-activity relationship (SAR) and structure-property relationship (SPR). We offer more than 3000 unique bioisosteres of phenyl rings, ranging from grams to kilograms, most of which are in stock (**Figure 6**)

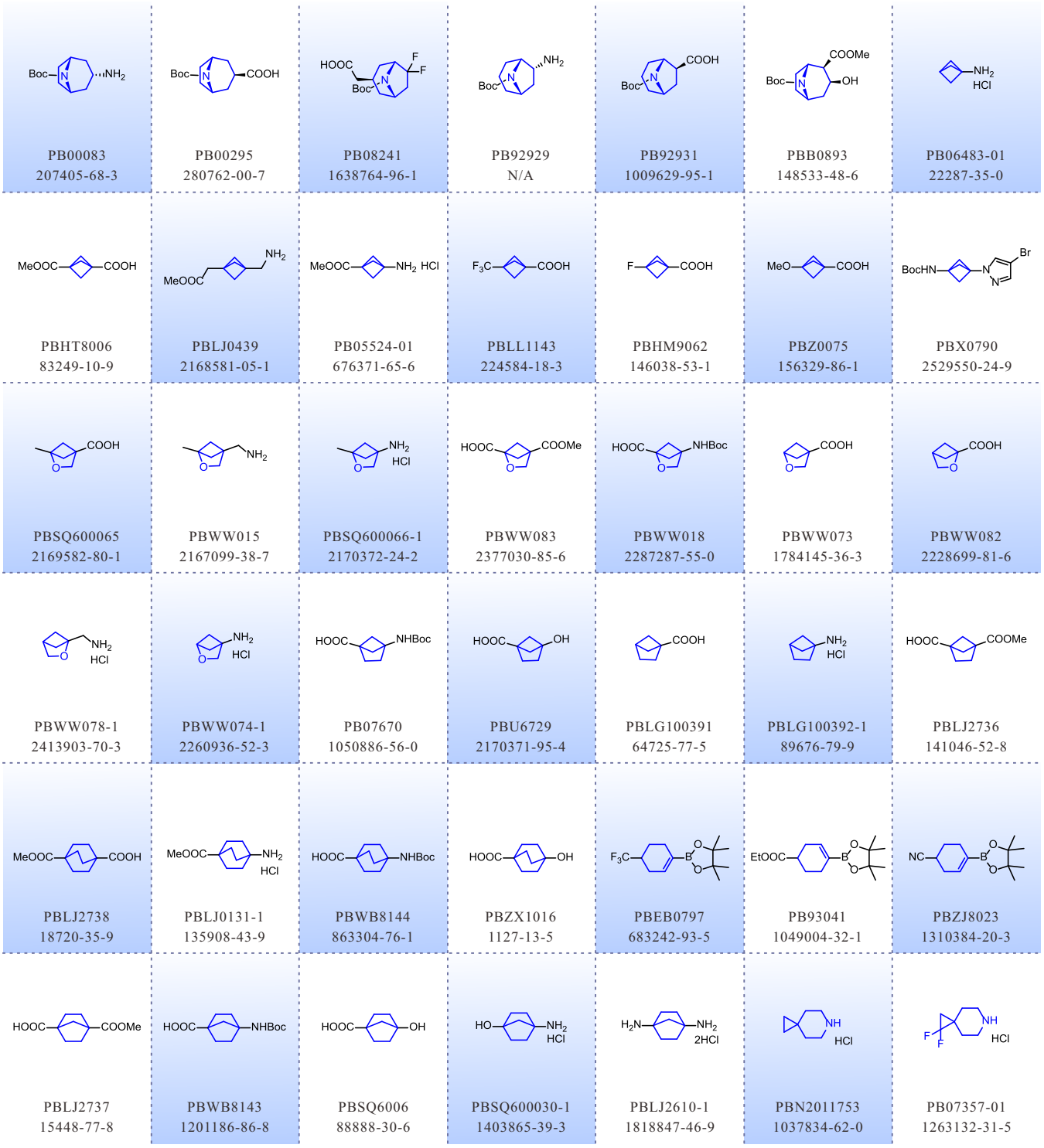

Figure 6. Representative bioisosteres of phenyl rings at PharmaBlock

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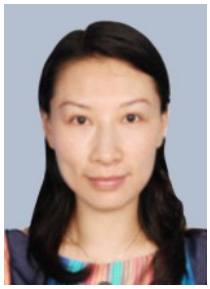
[9] Design, Synthesis, Radiolabeling, and in Vitro and in Vivo Evaluation of Bridgehead Iodinated Analogues of N-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-N-(pyridin-2-yl)cyclohexanecarboxamide (WAY-100635) as Potential SPECT Ligands for the 5-HT1A Receptor. Al Hussainy, Rana; Verbeek, Joost; *J. Med. Chem*., **2011**, *54(10)*, 3480-3491
[10] WO2019126505

About Authors



Dr. Lisha Wang
Director of CADD

Ph.D., Shanghai Institute of Organic Chemistry Chinese Academy
Postdoc in Aaron Diamond AIDS Research Center (ADARC), the Rockefeller University,
Research Investigator & Project leadership member, CADD, Roche R&D Center (China)
Principal Scientist, CADD, Roche Basel (Switzerland)
60 publications including 40 patents
Email: wang_lisha@pharmablock.com

Dr. Shanbao Yu
Executive Director
Synthetic Chemistry

10+ years' experience in organic chemistry and medicinal chemistry
PhD degree from East China Normal University
15+ papers and patents published
Email: yu_shanbao@pharmablock.com

Aihua Xia
Senior Director

M.D., Zhejiang University
15+ years' experience in organic chemistry and medicinal chemistry
Served at ChemPartner
6+ patents and papers published
Email: xia_aihua@pharmablock.com

Jin Li
Senior Director

10+ years' experience in organic chemistry and 3+ year's experience in medicinal chemistry
10+ patents and papers published
Inventor of 2 clinical candidates
Email: li_jin@pharmablock.com

Contact Us

PharmaBlock Sciences (Nanjing), Inc.
Tel: +86-400 025 5188
Email: sales@pharmablock.com

PharmaBlock (USA), Inc.
Tel (PA): +1 (877) 878-5226 Tel (CA): +1 (267) 649-7271
Email: salesusa@pharmablock.com

Find out more at www.pharmablock.com

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