Toward Resolving the Resveratrol Conundrum: Synthesis and *in Vivo* Pharmacokinetic Evaluation of BCP–ResveratrolYi Ling Goh,[†] Yan Ting Cui,[†] Vishal Pendharkar,[‡] and Vikrant A. Adsool^{*,†}[†]Institute of Chemical and Engineering Sciences (ICES), Agency for Science Technology and Research (A*STAR), 8 Biomedical Grove, Neuros, #07-01, Singapore 138665, Singapore[‡]Experimental Therapeutic Center (ETC), Agency for Science Technology and Research (A*STAR), 31 Biopolis way, Nanos, #03-01, Singapore 138669, Singapore

Supporting Information

ABSTRACT: Over the last few decades, resveratrol has gained significance due to its impressive array of biological activities; however, its true potential as a drug has been severely constrained by its poor bioavailability. Indeed, several studies have implicated this bioavailability trait as a major roadblock to resveratrol's potential clinical applications. To mitigate this pharmacokinetic issue, we envisioned a tactical bioisosteric modification of resveratrol to bicyclo[1.1.1]pentane (BCP) resveratrol. Relying on the beneficial bioisosteric potential demonstrated by the BCP-scaffold, we hypothesized that BCP–resveratrol would have an inherently better *in vivo* PK profile as compared to its natural counterpart. To validate such a hypothesis, it was necessary to secure a synthetic access to this novel structure. Herein we describe the first synthesis of BCP–resveratrol and disclose its PK properties.

KEYWORDS: Bioisostere, bicyclo[1.1.1]pentane, BCP, resveratrol, pharmacokinetic studies

Over the past two decades, resveratrol has become a topic of intense research in fields such as biology, chemistry, and medicinal chemistry. Indeed, the compound has shown many biological activities including antioxidant, anticancer, antidiabetic, cardioprotective, and even antiaging properties.¹ Importantly, these modern findings are in line with the traditional role of this compound, as an active principle, in Japanese and Chinese folk medicine used to treat ailments related to liver, skin, heart, and lipid metabolism.² However, despite this impressive array of biological and medicinal properties, poor bioavailability of resveratrol has severely restricted its application in human therapeutics. In fact, several studies on resveratrol, and its formulations in different rodent animal species and humans have repeatedly emphasized on this fact.³ Clearly, a resolution to this pharmacokinetic (PK) issue may hold the key to unlock the true medicinal potential of resveratrol and thereby facilitate its clinical applications.^{3,4}

A closer analysis of the low bioavailability of resveratrol reveals that its low plasma concentrations after oral administration is an outcome of rapid first-pass metabolism to glucuronide and sulfate conjugates.⁴ An obvious, and reported, approach to optimize the absorption and metabolism properties of resveratrol can be seen in manipulation of its phenolic functional groups.^{5–7} However, literature implication of the 4-OH group on the ring A of resveratrol (1, see Figure 1) in inhibition and cell proliferation properties warranted caution in designing of structure–activity relationship (SAR) studies.⁸ Indeed, the task of retaining the 4-

Figure 1. Resveratrol (1) and BCP–resveratrol (2).

OH group while eliminating the phenolic ring is challenging. To face this daunting task we decided to mandate the deployment of contemporary bioisostere tactics.⁹ Specifically, we were keen on deploying bicyclo[1.1.1]pentane (BCP) scaffold, a known bioisostere of 1,4-disubstituted aryl ring systems, as a replacement of the phenolic ring A in resveratrol (see Figure 1).^{10–12}

Our hypothesis was supported by strong literature precedents that allowed us to reasonably rationalize BCP–resveratrol (2) as a potential contender of the parent compound.^{10–12} On that premise, the broad range of biological activities showcased by resveratrol makes 2 a strong candidate for biological evaluation against all the successful targets reported for the natural product. However, we opined that performing an *in vivo* PK study on 2 first, to prove or disprove its *in vivo* PK advantage over 1, was

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essential to justify such an extensive effort. Additionally, given our previous experience with the synthesis of BCP derivatives, we were cognizant of the challenges offered by the nontrivial synthetic behavior of this uniquely strained scaffold.^{13–17} In this Letter, we now report the first synthesis of BCP derivative **2** and also disclose its PK studies.

Our retrosynthetic protocol for synthesis of BCP–resveratrol is shown in Scheme 1. We first dissected the target, **2**, at the olefin

Scheme 1. Retrosynthetic Analysis of **2**

to give us the aldehyde **4** as a reasonable starting point. In a forward sense, a Wittig reaction between the ylide **3** and **4** would generate the target compound. Next, we focused on the synthesis of **4** and envisioned it to originate from **9** via the application of classical reactions such as the Weinreb ketone synthesis, and the Baeyer–Villiger rearrangement. Thus, the onward synthesis would commence with the formation of the Weinreb amide from commercially available **9** to generate **8**. The amide in **8** could then be subjected to a stoichiometric amount of phenyl magnesium bromide to furnish the ketone **7**. Baeyer–Villiger oxidation of the latter would result in formation of the bis ester **6**, which in turn could be hydrolyzed to furnish **5**. Reduction of the carboxylic acid in the latter would give the aldehyde **4**.

In line with our retrosynthetic plan, we could access the bis ester **6** in a straightforward fashion.¹⁸ However, despite several attempts, hydrolysis of **6** proved to be difficult and resulted in a complex mixture of decomposition products (see Scheme 2). To

Scheme 2. Hydrolysis Attempts on **6** and **10**^a

^aReagents and conditions: (i) 1:1 1 N NaOH/EtOH, rt, 1 h.

test the viability of sequential hydrolysis, we also attempted hydrolysis of the carboxylic acid **10**. However, that attempt led to a similar outcome. It is possible that the hydroxide intermediate **I**, by the virtue of the electron-withdrawing effect of the carbonyl function in **6** or **10**, results in the ring-opening and subsequent disintegration of the BCP scaffold.

Above results indicated a need for a partial modification of our original retrosynthetic plan. To that end, we planned to postpone the liberation of the hydroxyl function to the last step of our planned synthetic sequence. However, to endorse this late-stage modification, especially in the light of our failed hydrolysis

attempts, we planned to study the deprotection of alcohol on a substrate with a noncarbonyl functional group at the 3-position of the BCP ring. To that end, the aryl-BCP-benzoate (**12**) was identified as an appropriate model substrate. The aryl derivative was promptly synthesized from **10** by first converting its carboxylic acid to perester **11**, and then subjecting the latter to the homolytic aromatic substitution conditions to afford **12** (see Scheme 3).¹⁸ Frustratingly, hydrolysis attempts on **12** resulted in

Scheme 3. Synthesis of **13**^a

^aReagents and conditions: (i) 70% *t*-BuOOH in water, EDCI, cat. DMAP, DCM, rt, 1 h, 89%; (ii) μ W, O₂, pyrazine, 125 °C, 5 h, 52%; (iii) 1.5 M MeLi-LiBr in ether, 0 °C to rt, 3 h, 61%. EDCI = 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide; DMAP = 4-dimethylamino-pyridine.

decomposition. Fortunately, however, we could secure the tertiary alcohol in **13** by treating **12** with MeLi-LiBr at a low temperature.

Equipped with a potential protocol to complete our endgame, we then ventured into the synthesis of BCP–resveratrol. Our sequence commenced with the reduction of the carboxylic acid in **9** to give **14**. Next, the primary alcohol in **14** was concealed as a TBS ether, and the ester was subjected to basic hydrolysis conditions to expose the acid and ultimately yield **15**. The carboxylic acid in **15** was transformed into the ketone, **16**, by employing the Weinreb protocol outlined above. Baeyer–Villiger oxidation of the ketone in **16** followed by TBAF promoted removal of the TBS group gave the primary alcohol **17**. The latter could then be easily oxidized to the aldehyde **18** (see Scheme 4). Notably, this reaction sequence could be repeated on gram-scale to generate aldehyde **18** in an overall yield of 30%.¹⁸

The endgame of the synthesis commenced with the Wittig olefination of **18** with the phosphine salt to secure **19** as a mixture of predominantly *E* olefin (*E*:*Z* = > 19:1 by ¹H NMR). Finally, by employing our conditions for removal of the benzoyl function, we secured the BCP–resveratrol (**2**) in a good yield of 80% (see Scheme 5).

Having BCP–resveratrol (**2**) in hand, we could experimentally determine, and compare, its key *in vitro* parameters such as thermodynamic solubility and lipophilicity with resveratrol (**1**). Thus, the thermodynamic solubility at pH 7.4 was found to be 619 ± 64 and 19 ± 2 μg/mL for **2** and **1**, respectively. Lipophilicity, measured as LogD (pH 7.4), was found to be 1.9 and 2.9 for **2** and **1**, respectively. Interestingly, the trend of higher solubility and lower lipophilicity of **2** as compared to **1**, was in line with Stepan's seminal findings on the use of BCP motif.¹² Encouraged by these observations, we tested **1** and **2** against available cancer cell lines; MDA-MB-231 (a metastatic breast cancer cell line), MiaPaCa2 (pancreatic cancer cell line), and SUDHL10 (B cell lymphoma cell line) (see Table 1). We were pleased to observe that both the compounds showed similar activities in all three cases.

Scheme 4. Synthesis of the Key Intermediate 18^a

^aReactions and conditions: (i) oxalyl chloride, cat. DMF, DCM, rt, 1 h; (ii) NaBH₄, MeCN, rt, 16 h, 97% (two steps); (iii) TBSCl, imidazole, DCM, rt, 2 h, 89%; (iv) NaOH, MeOH, 60 °C, 1 h, 81%; (v) CH₃NHOCH₃ HCl, EDCI, cat. HOBt, DIPEA, DCM, rt, 16 h; (vi) 3 M PhMgBr in THF, THF, 0 °C to rt; 66% (two steps); (vii) *m*-CPBA (77%), DCM, 50 °C, 27 h, 85%; (viii) 1 M TBAF in THF, THF, rt, 2 h, 92%; (ix) Dess–Martin periodinane, rt, 1 h, 84%. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt = 1-hydroxybenzotriazole; DIPEA = *N,N*-diisopropylethylamine.

Scheme 5. Completion of the Synthesis of 2^a

^aReactions and conditions: (i) lithium 5-((triphenyl-1^o-phosphanylidene)methyl)benzene-1,3-bis(olate), THF, −78 to 0 °C, 1.5 h, 31%; (ii) MeLi–LiBr in ether, THF, 0 °C to rt, 1.5 h, 80%.

Table 1. Biological Activities of Resveratrol and BCP–Resveratrol in Selected Cancer Cell Lines

cell line	% inhibition of cell proliferation at 30 μM ¹⁸		CC ₅₀ (μM)
	resveratrol	BCP–resveratrol	
MDA-MB-231	20	22	0.48
Mia-PaCa2	30	30	0.20
SU-DHL-10	46	41	0.11

Next, we dedicated our attention to determining the PK properties of BCP–resveratrol. At that end, we were cognizant of a few studies on resveratrol wherein a sensitive bioanalytical method such as LC–MS/MS was employed.¹⁹ Based on this, we decided to perform *in vivo* PK studies of BCP–resveratrol in rat and then attempt the bioanalysis using LC–MS/MS. Our final task was to equate the outcome of our studies with the reported PK data on resveratrol. For this comparison, we identified the work reported by Asensi and co-workers as most suitable.²⁰ Thus, during the course of their extensive investigations on the anticancer and PK properties of resveratrol, the authors have reported resveratrol to reach plasma levels of 273 ng/mL after oral administration at 20 mg/kg, with *T*_{max} at 5 min. Additionally, in a more recent study, Kapetanovic and co-workers carried out similar experiments in rats, albeit with a much higher dose of 50 mg/kg delivered every 24 h for 14 days.²¹ Interestingly, they registered a *C*_{max} of 76.7 ng/mL on day 1 and that of 176 ng/mL on day 14 prove that the plasma levels of 1 do not increase significantly despite repetitive dosing.

Pleasingly, our studies revealed that BCP–resveratrol achieved *C*_{max} of 942 ng/mL, a 3-fold increase over resveratrol, and an AUC_{0–4h} of 587 ng·h/mL, a 10-fold increase over the reported values for resveratrol (for PK parameters see Table 2). Moreover,

Table 2. Comparison of PK Parameters of BCP–Resveratrol with Reported Values of Resveratrol

PK parameter ^a	BCP–resveratrol	resveratrol (estimated from the published data ²⁰)
<i>C</i> _{max} (ng/mL)	942	273
<i>T</i> _{max} (h)	0.067	0.083
AUC _{0–last} (ng·h/mL)	587	47.5
<i>t</i> _{1/2} (h)	2.6	0.19
CL/F (L/h/kg)	21.8	409

^aMean *C*_{max} of BCP–resveratrol was 942 ng/mL, 5 min after oral administration of 20 mg/kg. Mean AUC_{0–last} of BCP–resveratrol was 587 ng·h/mL.

whereas the plasma levels of resveratrol seemed to deplete beyond the scope of reasonable measurement after an hour in Asensi's study,²⁰ BCP–resveratrol concentration could be easily measured up to 4 h with the mean plasma concentrations observed (in three rats) to be 85 ng/mL at this time point.

Clearly, a comparison of the reported PK studies on resveratrol with our finding on BCP–resveratrol (see Figure 2) suggests that the latter has an unambiguous PK advantage, in both absorption and metabolic stability, over resveratrol.

Figure 2. Comparison of plasma levels of BCP–resveratrol with reported plasma levels of resveratrol during a 1 h time frame.²⁰

Additionally, we also performed *in vitro* metabolic stability tests on both BCP–resveratrol and resveratrol (see Table 3). In

Table 3. Metabolic Stability Studies, of Resveratrol and BCP–Resveratrol, in Human and Rat Hepatocytes

compound	human hepatocytes		rat hepatocytes	
	<i>t</i> _{1/2} (min) mean ± SD	CL _{int, app} (μL/min/10 ⁶ cells) mean ± SD	<i>t</i> _{1/2} (min) mean ± SD	CL _{int, app} (μL/min/10 ⁶ cells) mean ± SD
BCP–resveratrol	90.4 ± 11.7	7.7 ± 1.0	24.2 ± 0.5	57.4 ± 1.3
resveratrol	23.2 ± 1.6	29.9 ± 2.1	<7.5 ^a	>184.8 ^a

^aHalf-life and intrinsic clearance of resveratrol would not be quantified owing to its very fast metabolism in rat hepatocytes.

human hepatocytes study we observed that the former had >3-fold higher metabolic stability. In accordance with our *in vivo* studies, BCP–resveratrol was seen to have significantly more metabolic stability than the natural product in rat hepatocytes.

It is also worth reporting that formation of glucuronide and sulfate conjugates in human hepatocytes studies was signifi-

cantly higher for resveratrol compared to BCP–resveratrol (Figure 3), thus confirming the efficiency of the phenyl ring replacement.

Figure 3. Formation of glucuronide and sulfate conjugates of resveratrol and BCP–resveratrol in human hepatocytes.

While we were delighted by the pharmacokinetic profile of **2**, we were aware of the significance of our synthetic efforts in enabling this study and were keen to facilitate similar biological evaluation of novel and potentially ‘bioisosteric natural products’. In line with this commitment, we are actively pursuing synthetic development of such compounds in our laboratories. One such synthetic study that deserves to be introduced at this stage especially, given its synthetic relevance to **2**, is a BCP–tyrosine derivative, **23**. Thus, our synthesis (unoptimized) of this compound originates from an advanced intermediate **18**, used in the synthesis of **2**. The sequence commenced with a straightforward transformation of **18** to α,β -unsaturated ester **20** by employing Wittig reaction conditions (see Scheme 6).

Scheme 6. Synthesis of ($\pm$) BCP–Tyrosine Ethyl Ester (**23**)^a

^aReactions and conditions: (i) ethyl 2-(diethoxyphosphoryl)acetate, 60% NaH, THF, 0 °C to rt, 2 h, 87%; (ii) di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate, Mn(dpm)₃, PhSiH₃, IPA, 0 °C to rt, 2 h, 71%; (iii) TFA, DCM, 0 °C to rt, 16 h; (iv) 0.1 M SmI₂ in THF, 0 °C to rt, 6 h, 45% (2 steps); (v) 37% HCl, EtOH, 80 °C, 48 h, 64%. dpm = 2,2,6,6-tetramethyl-3,5-heptanedionato; IPA = isopropyl alcohol.

Next, in the key-step of this protocol, the olefin in **20** was subjected to Carreira hydrohydrazination conditions to generate the diazo compound **21**.²² Deprotection of the Boc functionality with trifluoroacetic acid gave the hydrazine intermediate, which in turn could be converted to the amine **22** with the help of samarium diiodide. Finally, acid hydrolysis of **22** yielded the hydrolyzed product **23** to complete our racemic synthesis of the tyrosine–BCP ethyl ester. Given the aforementioned bioisosteric properties of BCP motif, it would be interesting to compare **23** with its tyrosine counterpart **24**.²³

To conclude, we have disclosed a tactical application of the BCP motif to generate BCP–resveratrol (**2**), a potential

bioisostere of resveratrol, and established its superior *in vivo* PK properties over the parent compound. In doing so, we have provided an intriguing approach that may potentially allow clinical exploitation of the beneficial activities shown by resveratrol and thus resolve the longstanding conundrum around its application. We have also demonstrated the synthesis of BCP–tyrosine ester (**23**) and thus opened the avenue for its applications in pharmaceutical and other fields. It is also worth mentioning that, the strategic disposition of the BCP motif in **2** and **23** can render these building blocks, and the scaffolds employing them, the cogency to mitigate intellectual property and compound attrition related issues.²⁴ Lastly, our *in vivo* PK studies on **2** strongly justify its biological testing in many of the targets that have shown promise for resveratrol. We hope that this report will initiate such enquiries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00018.

Synthesis details, characterization data for all new compounds, and PK protocols (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. Project leader, V.A.; Synthetic chemists, Y.L., Y.T., V.A.; Biological studies, V.P.

Notes

The authors declare no competing financial interest.

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