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Bibenzyls: Short Review on Their Synthesis and Biological Activities

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A class of chemical compounds which are obtainable from natural sources, known for their distinct molecular structure and wide range of biological actions are called bibenzyls. The synthesis, structural variety, and therapeutic qualities of bibenzyls are examined in this review, with an emphasis on their applicability to drug development and discovery. The reported synthesis shows promising yields in correspondence to different derivatives. The potential applications of bibenzyl derivatives in pharmaceutical research are highlighted through a discussion of the structural motifs and synthetic techniques utilized during their manufacture. In order to clarify their modes of action and therapeutic potential, bibenzyls' biological activities such as their antimicrobial, cytotoxic, enzyme assay and acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are also investigated. According to Wang et al. [17], antimicrobial activity shows potential as there was no bacteria growth in triplicate wells. Cytotoxic activity confirms that bibenzyls are able to cause apoptosis in various cancer cells. Enzyme assays show excellent tyrosinase inhibitory activity as it has an IC_{50} of 1.6 µm which is five times more potent than kojic acid. Acetylcholinesterase inhibitor is one of the most promising inhibitors with IC_{50} = 0.096 µm. The subject of bibenzyl research is finally summarized with an emphasis on future directions and present trends. This highlights the significance of ongoing research and innovation in order to fully utilize these chemicals for biological and pharmacological developments.

Keywords: Bibenzyls; synthesis; biological activity; enzymes

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Bibenzyls are prevalent in nature and have significant biological functions. The essential motif present in many different types of dihydrostilbenoids is bibenzyl [1]. They are especially found in lichens, fungi, and plants [2]. Since they both come from the phenylpropanol pathway, bibenzyls and flavonoids have a number of upstream stages in common [3]. Due to their unique chemical structures and wide range of prospective applications, bibenzyls, a type of organic compound consisting of two benzene rings joined by a single bond, have attracted significant interest from a variety of scientific professions [4, 5]. These compounds show pharmacological characteristics such as antibacterial, anti-inflammatory, antioxidant, and anticancer activities, which makes them appealing options for drug development and discovery [4].

According to Yang et al. [2], many synthetic techniques for their preparation have been developed due to the synthetic versatility of bibenzyls. The synthesis of bibenzyl derivatives with specific properties and functions has been made possible by organic chemists' innovative approaches, which have expanded the field of uses for these compounds in materials science and medical chemistry [5].

Studies have demonstrated that bibenzyl derivatives possess antibacterial properties against a range of pathogens, such as fungi and bacteria, indicating their potential for use in medicinal applications [6]. Additionally, bibenzyl compounds have demonstrated anticancer properties by inducing apoptosis and inhibiting the development of cancer cells [7]. It is also widely applicable in the production of flame retardants, ceramic superconductor forms, and magnetic recording media [8].

Cannabis contains bibenzyl compounds that are classified as phenyl-propanoid derivatives [9, 10], which contain cannflavins that are potentially useful as anti-inflammatory agents [11, 12].

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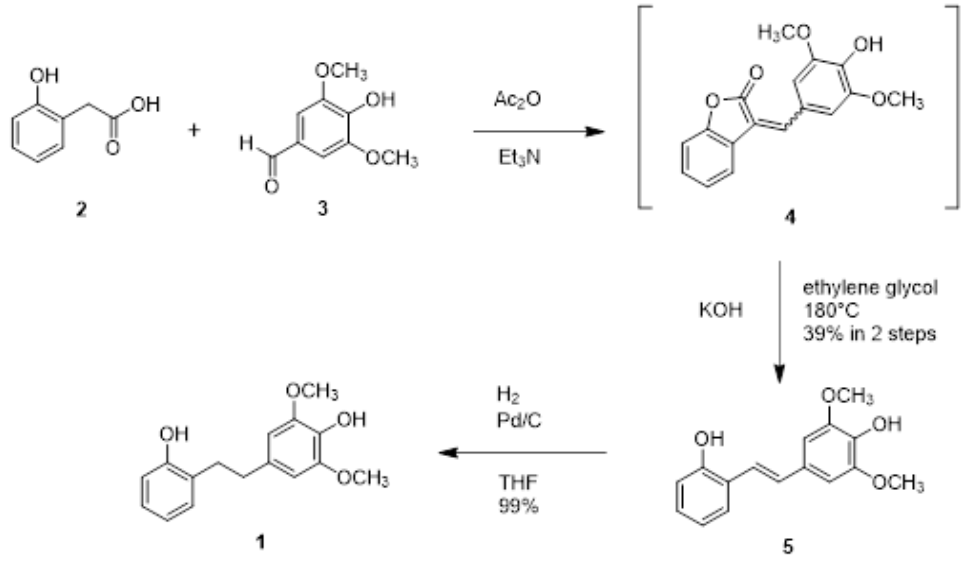


Figure 1. Synthesis of 4-(2-hydroxyphenethyl)-2,6-dimethoxyphenol.

Further understanding of the synthesis, structure-activity connections, and uses of bibenzyls is anticipated as this field of study develops, piquing interest in and exploration of this intriguing class of chemicals. In this review, we focus on the synthesis of bibenzyl primary structures, including the biological activity of bibenzyl-based compounds.

SYNTHESIS OF BIBENZYL DERIVATIVES

As reported by Oka et al. [13], the synthesis of 4-(2-hydroxyphenethyl)-2,6-dimethoxyphenol (**1**) begins with 2-hydroxyphenylacetic acid (**2**) and syringaldehyde (**3**) (Figure **1**). Compounds **2** and **3** are coupled using triethylamine and acetic anhydride, producing a mixture of E and Z-aurone **4**. Crude 4 minus purification was treated with potassium hydroxide in ethylene glycol at 180 °C. Hydrolysis of **4** along with decarboxylation of the resultant carboxylate occurred to give E-stilbene **5** in a 39% yield over two steps. Finally, hydrogenation of **5** gave a **1** in 99% yield. The ^{1}H NMR spectrum of synthetic **1** was identical to that of natural **1**.

Boddington et al. [14] reported that the bibenzyls in cannabis are derived from dihydrohydroxycinnamic acids, as the synthesis centres around the method of reducing the ethyl bridge connecting A and B aromatic rings. The synthesising process consists of three steps (Figure **2**). The conversion of CoA from different hydroxycinnamic acids is the first step in the synthesis of phenylpropanoids in all plants. Surprisingly, class-II members of plant 4CLs exhibit general enzymatic activity, which enables activation of carboxylic acids via CoA esterification. The next step would be the reduction of CoA esters by two double-bond reductases (p-coumaroyl-CoA and Caffeoyl-CoA) to form dihydro-CoA derivatives from preferred substrates. Two bibenzyl scaffolds, dihydropiceatannol and dihydroresveratrol, are created when a polyketide synthase specifically condenses malonyl-CoA with these dihydro-hydroxycinnamoyl-CoA derivatives, completing the bibenzyl backbone.

In a report written by Oozeki et al. [15], the structure in which two 4-substituted resorcinol moieties are found indicates that this substance would be a strong tyrosinase inhibitor. The bibenzyl xyloxide was synthesised by the Wittig reaction, implementing the trichloroimidate glycosylation procedure as a key step. This synthesis uses 2,4-dihydroxybenzaldehyde as the starting material, which is converted favourably to aldehyde **6** to only possess a benzyloxy moiety at 4-position, by using benzyl bromide and $NaHCO_3$ as a mild base. A phenolic hydroxyl at 2-position in **6** was protected as a methoxymethyl group to demonstrate the xylosylation selectivity at 2-position, from aldehyde **7** that was obtained in a quantitative yield. Chloride **8** was prepared from the same starting material through three consecutive steps, which are benzylation of two phenolic hydroxyls, aldehyde reduction, and chlorination of benzylic hydroxyls using $SOCl_2$. Phosphonium salt **9** is synthesised by the reflux of chloride **8** in toluene in the presence of triphenylphosphine. Stilbene **10** is produced via the Wittig reaction with ylide **9** and aldehyde **7** under basic conditions. Compound **10** undergoes hydrogenation to obtain bibenzyl **11** by using the Pd/C-ethylenediamine complex (Pd(en)/C) as a catalyst. The use of tosyl acid removed the methoxymethyl group in **11**, which led to the production of 2 bibenzyl **12**. To produce β-xyloxide **14**, bibenzyl **12**

is coupled with imidiate **13** that was prepared from D-xylose, both **12** and **13** were coupled with an adequate amount of tri-methylsilyl trifluoromethane-sulfonate (TMSOTf). Compound **15** is synthesized by a hydrogenation reaction using $Pd(OH)_2/C$ catalysts to remove benzyl moieties and an ester exchange reaction using sodium methoxide to remove acetyl moieties, which results in compound **15**. The overall synthesis to produce compound **15** is done in seven steps. (Figure **3**)

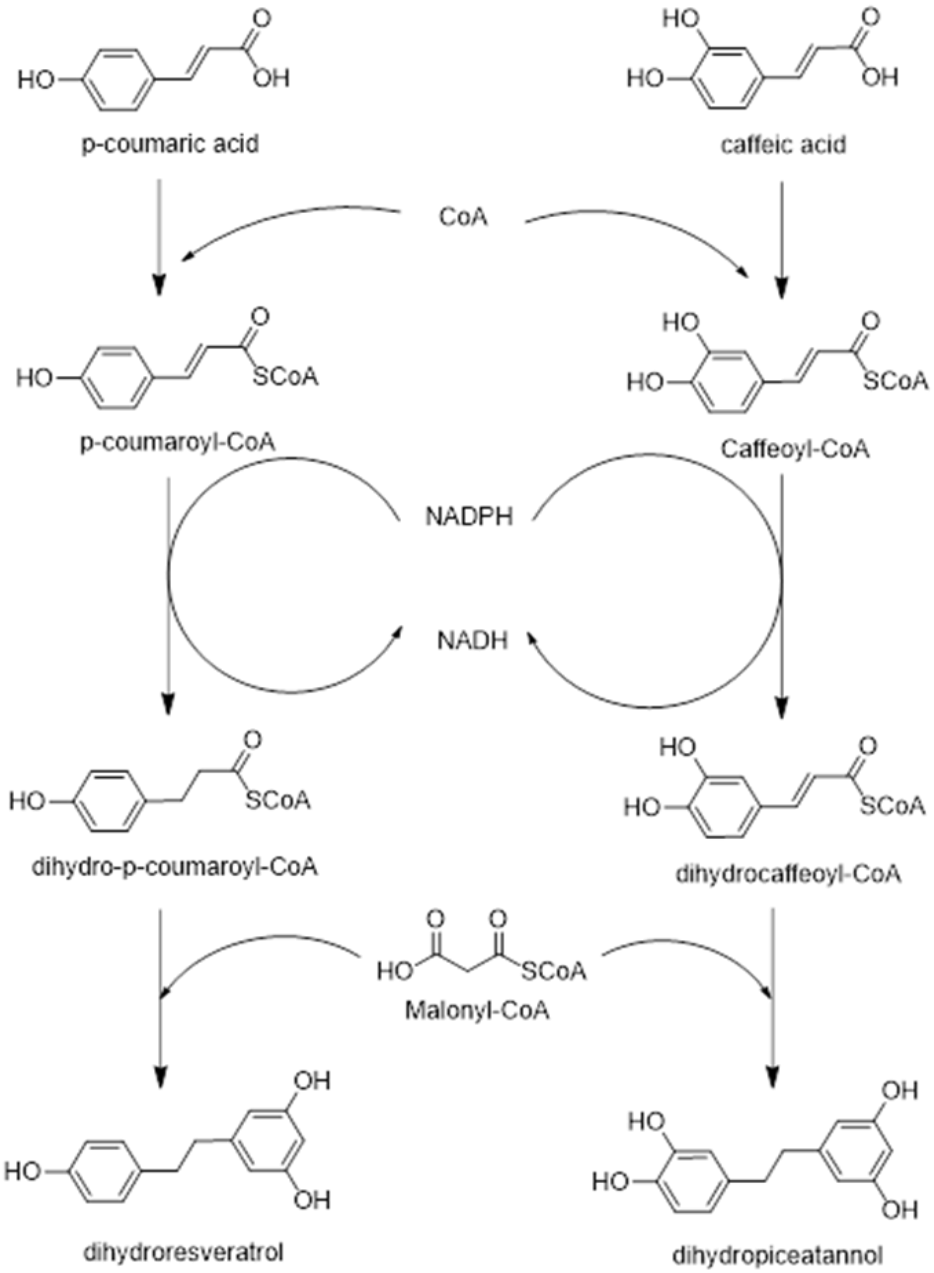


Figure 2. Conversion of CoA from different hydroxycinnamic acids, reduction of CoA esters and condensation of Malonyl-CoA with dihydro-hydroxycinnamoyl-CoA derivatives.

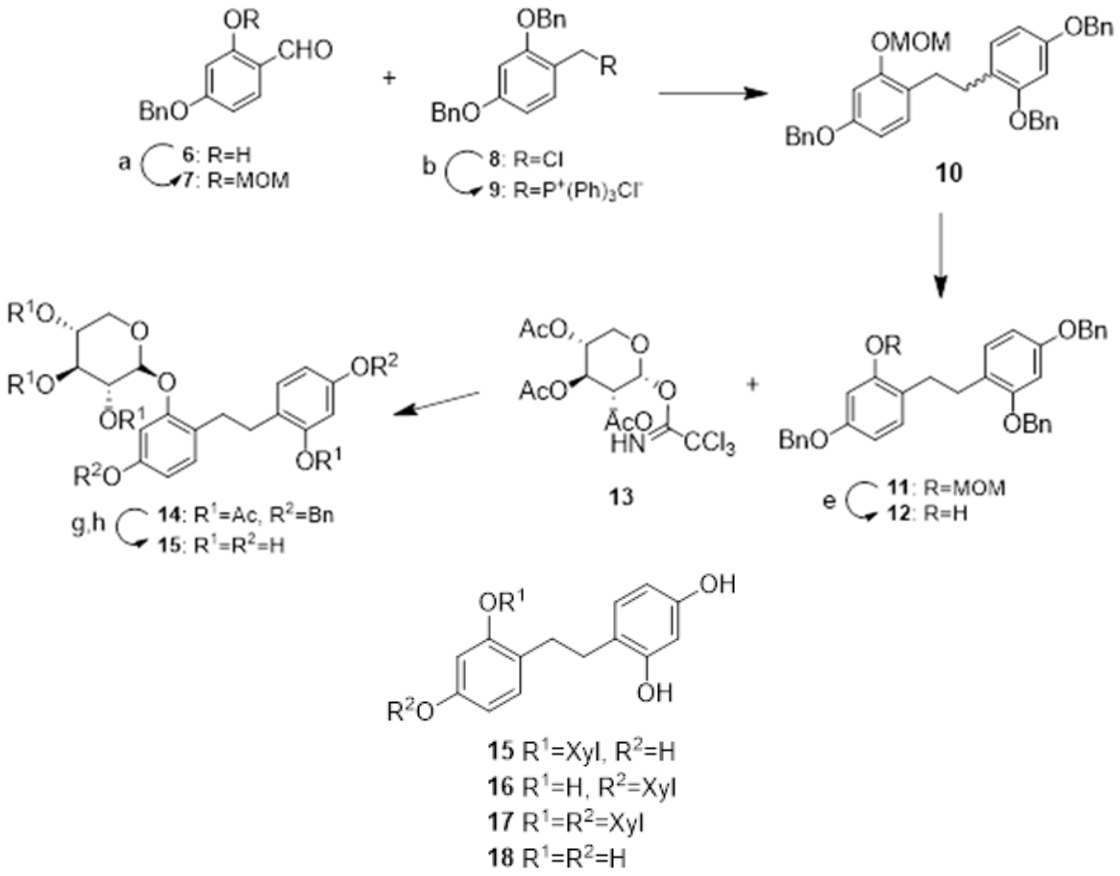


Figure 3. Synthetic route towards **15**. Aldehyde **6** is combined with phosphonium salt **9** to produce **10**. **10** undergo hydrogenation reaction produces **11**. Tosyl acid removes methoxymethyl group in **11** to form **12**. **12** is coupled with **13** to produce **14**. **14** undergo hydrogenation to produce **15**.

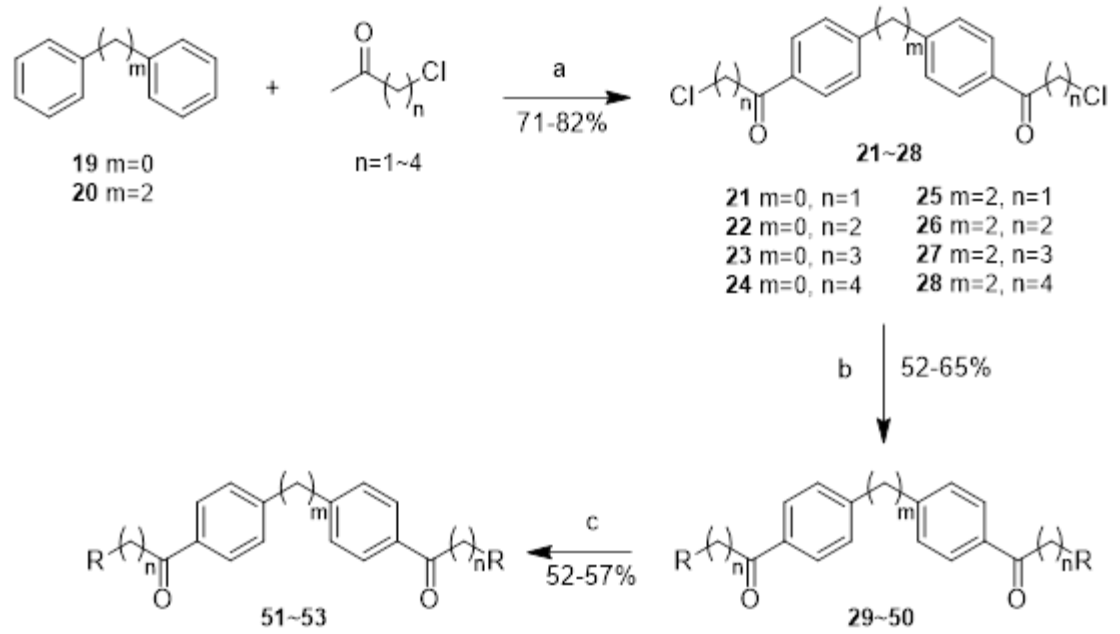
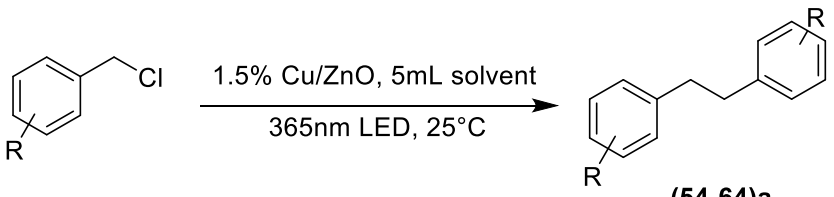


Figure 4. Synthetic route for target compounds **29**-**50**. Reagents, conditions, and yields: (a) $Cl(CH_2)nCOCl$, CS_2; 40–50 °C, 4–8 h; 71%−82%; (b) secondary amines or heterocyclic amines, CH_3CN, K_2CO_3, KI; 50 °C, 20 min; 52%−65%; (c) $NaBH_4$, THF; 50 °C, 6 h; 52%–57%.

According to Wang et al. [16], the biphenyl scaffold is an uncommon structure [17] that exists in 4.3% of commercially obtainable drugs [18]. According to Figure **4**, to synthesise target compounds **29**-**50**, the chlorine in the intermediates **21**-**28** is substituted with secondary alkyl amines or heterocyclic amines. Intermediates **21**-**28** are added 20 minutes after the mixture of secondary alkyl amines or heterocyclic amines reacts with K_2CO_3 and KI in acetonitrile. This would then produce compounds **29**-**50** with the yield ranging between 52% - 65%. Next, to synthesise compounds **51**-**53**, sodium borohydride was added to a stirred solution of compounds (**36**,**37** and **47**) in anhydrous THF. The target alcohols (**51**-**53**) are produced with yields of 52% - 57%.

In a report by Yang et al. [19], the synthesis of bibenzyl is obtained by homo-coupling. Dihydrostilbenoids have numerous biological and chemical applications [20]. However, the process often demands extreme conditions, which include high temperatures and expensive catalysts focused on metals, to achieve huge yields with a particular level of selectivity for bibenzyls [21]. Various metals were tested for their photocatalytic activity towards homo-coupling of benzyl chloride as the conversions of benzyl chloride, contributed to the increase in the rate of recombination. Several metals, such as Ir, Ni, Rh, and Pt, show excellent results in alcohol dehydrogenation [22]. Increased interactions between metals like Fe, Co, and Ru and halides cause co-catalysts to become poisoned and exhibit reduced activity [23]. Indium (In) exhibits a high tendency towards bibenzyl at 75%. This is because the lower charge separation and transfer efficiency in the photocatalytic process only converts 38% of the benzyl chloride. Copper (Cu) shows promising potential as it has a high conversion rate of 99% and selectivity of 93% towards bibenzyl. Comparing Cu to Pd, Pd has a -0.43 eV that is measuring the adsorption energy of hydrogen atoms. It is more negative compared to Cu, which exhibits 0.05 eV. This shows that the low selectivity shown by Pd is related to a high amount of surface-adsorbed protons. This converts the intermediate (benzyl radical) into toluene, a dehydrogenated product. This explains the low selectivity of Pd towards bibenzyl at 55% compared to 93%. However, the addition of more Cu does not increase the conversion of benzyl chloride, and it decreases the selectivity of bibenzyl.

According to Iraji et al. [24], a dark macromolecular pigment known as melanin is what gives skin its colour and UV protection [25]. However, hyperpigmentation disorders are one of the reasons that lead to undesirable medicinal conditions, especially in elderly individuals [26]. Tyrosinase inhibitors contribute to autoimmune diseases [27], including neurodegenerative disease and dopamine toxicity [28]. One of the natural ligands of tyrosinase is tyrosine (Tyr), and it has been demonstrated that modified synthetic derivatives of tyrosine have strong anti-tyrosinase action [29]. There is proof that the two ortho ring carbons (carbons 2 and 6) and compounds **68b**, **68c**, and **68e** have the hydrazine motif. The two meta-ring carbons (carbons 3 and 5 in compounds **68b**, **68c**, and **68e**) produce distinct ^{13}C single peaks and are magnetically inequivalent. Similar results with hydrazine linkers were documented in earlier research [24]. The analysis of compounds **68f**, **68j**, and **68k** that were substituted with nitro showed that adding the nitro group improved the inhibitory activity. These analogue activities shift in the following order: para > ortho > meta. Furthermore, it was shown that chemicals containing a strong substituent that draws electrons were highly potent in inhibiting the tyrosinase enzyme. (Figure **6**).



54 R=H
55-60 R=CH_3
61 R=OCH_3
62 R=Cl
63 R=$COOCH_3$
64 R=CF_3

Figure 5. Photocatalytic homo-coupling of various benzylic chlorides to the corresponding bibenzyls using Cu/ZnO photocatalyst.

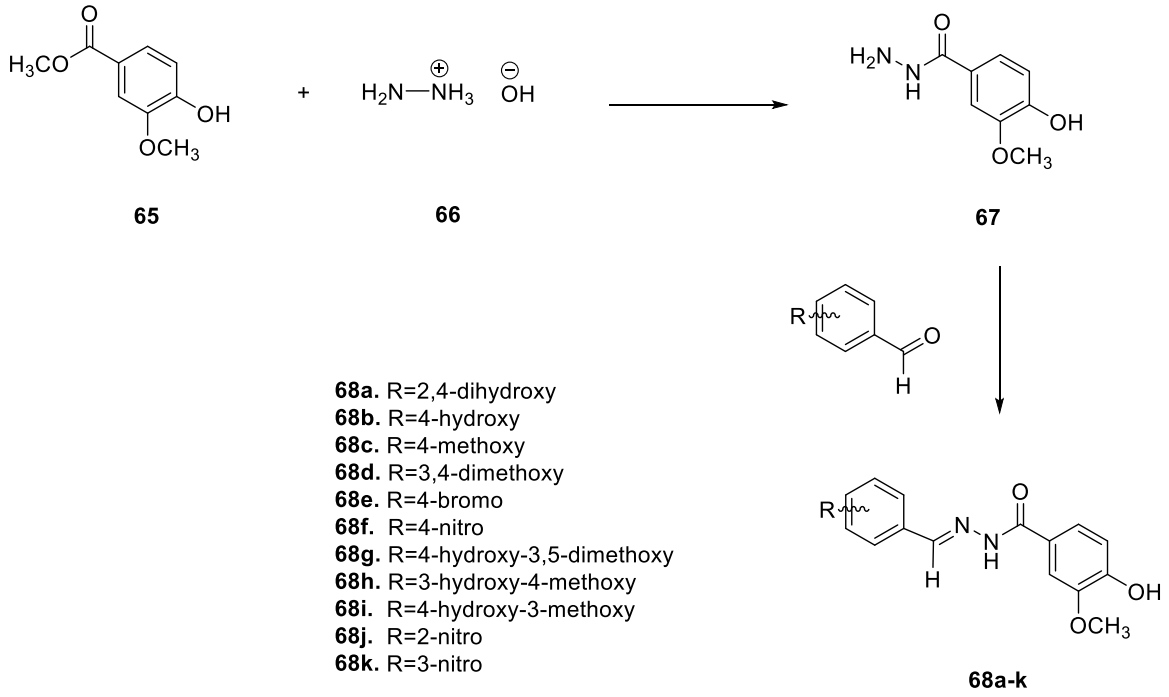


Figure 6. Synthesis of (E)-N′-benzylidene-4-hydroxy-3-methoxybenzohydrazide derivatives **4a–k**.

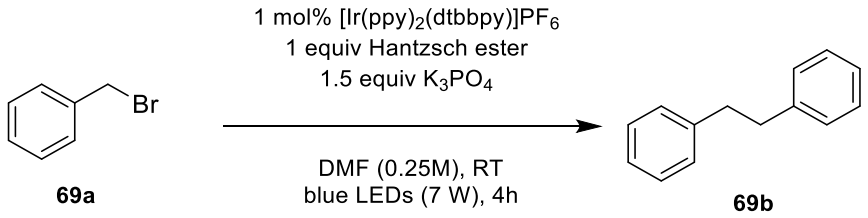


Figure 7. [a] Reaction scale: 1 a (0.1 mmol). [b] Yields were determined by performing gas chromatography with dodecane as the internal standard. [c] Ammonium salts were formed.

According to a paper reported by Park et al. [30], innovative techniques pertaining to the Csp3-Csp3 coupling of halomethyl arenes were created. This includes incorporating the use of excessive reducing agents such as Li, Mg, Mn, Fe, Ni, and Zn [21]. Various reaction conditions resulted in the yield of the targeted bibenzyl product between 63 and 89% when the IrIII and PtI complexes were used. However, because of the negative driving force for the reductive quenching of the excited-state species by HEH, the Ru complexes utilized do not yield bibenzyls. The Ir complex, $[Ir(ppy)_2(dtbbpy)]PF_6$ is the most promising photo redox catalyst in regard to yield and solubility. The presence of K_3PO_4 has a crucial effect on improving reaction yield while nullifying byproduct formation. Compound **69a** produced a 96% yield when K_3PO_4 was used in 1.5 equiv. However, the yield did not increase when using 2.0 equiv. (Figure **7**).

BIOLOGICAL ACTIVITY

Cytotoxic Activity

Oka et al. [13] stated that the capability of **1** to cause apoptosis in five cancer cells (HCT116, Hela, HL-60, Jurkat, and BALL-1 cells) was assessed via the WST-8 method after treatment with test compounds for 48 h [31]. SN-38, the active metabolite of irinotecan, was used as a positive control in this study. The IC_{50} data for cell viability of **1** showed cytotoxic activity against HCT116, Hela, and HL-60 cells with IC_{50} values below 100 μM. Furthermore, this compound did not affect the proliferation of Jurkat and BALL-1 cells. The antibacterial activity of **1** against Gram-positive B. subtilis and Gram-negative E. coli was evaluated by a broth microdilution assay [32]. However, compound

1 did not show antibacterial activity against B. subtilis and E. coli at concentrations below 128 μg/mL.

Antimicrobial Activity

Oka et al. [13] continued that the broth microdilution method was used to determine the minimum inhibitory concentration (MIC) of the compounds against Escherichia coli (NBRC 3301) and Bacillus subtilis (NBRC 3134) (CLSI, 2012). The final concentration of bacteria in the assay was 5 × 105 CFU/mL, and that of DMSO was 1.28% v/v. The plates were incubated at 37 °C for 18 h. After incubation, the MIC was determined as the lowest concentration at which no growth was observed in triplicate wells, both visually and by measuring OD550. Ampicillin (Nacalai tesque, Kyoto, Japan) was used as a positive control.

Enzyme Assays

Boddington et al. [14] reported that a 4CL enzyme assay produced results by using 5 μg of purified recombinant protein (0.8 μM), 1 mM substrate, 1 mM CoA, and 5 mM ATP in 100 mM Tris-HCl, 5 mM MgCl2, pH 7.8, for 30 min. The eluted products were detected by absorption at 311 nm for cinnamoyl-CoA, 333 nm for p-coumaroyl-CoA, 346 nm for caffeoyl-CoA, feruloyl-CoA, and sinapoyl-CoA, and 260 nm for dihydro-pcoumaroyl-CoA and dihydrocaffeoyl-CoA. As for the DBR assays, double-bond reductase enzyme activity was performed using 15 lg of purified recombinant DBR (4 μM), 0.5 mM substrate, and 2 mM NADPH in 100 mM Tris-HCl, pH 7.5. The enzymatic reactions were incubated for 60 min for the determination of relative activity and 120 min to produce representative chromatograms. Commercial standards were available for dihydro-pcoumaroyl-CoA only, and therefore all products were quantified relative to this standard curve at 260 nm.

Oozeki et al. [15] reported that derivative **15-18** shows promising tyrosinase inhibitory activity. It is stated that **15** has an IC_{50} value of 1.6 μM, which is proven to be five times more potent as compared to that of kojic acid. As compared to other derivatives, derivative **16** has the lowest IC_{50} value of 0.43 μM. The characteristic difference between **15** and **16** is the functional group on the bibenzyl structure. Derivative **15** has a -Xyl functional group on R1 and a -H on R2, while derivative **16** is just in the opposite position, with a -H on R1 and a -Xyl functional group on R2. It can be said that the IC_{50} value is lower as the -Xyl functional group is in a para-substituted position as compared to an ortho-substituted position.

Based on an analysis of the IC_{50} values against the tyrosinase enzyme, it was found that every drug had noteworthy inhibitory activity at micro-molar levels, with IC_{50} values varying between 1.58 and 37.09 μM. To determine how the type of aryl ring substitution affects a compound's potency, structure-activity investigations are used. Compounds **68i** and **68e** outperformed the positive control kojic acid (IC_{50} = 9.3 μM) in enzyme assays, showing the greatest activity against the tyrosinase enzyme (IC_{50} values of 1.58 and 1.95 μM, respectively). Moderate inhibitory action was seen in compounds with only an OH group on the benzene ring. In this regard, compounds **68a** and **68b** having 2- and 4-OH substitutions on the benzene ring (IC_{50} = 37.09 ± 1.02 μM and 15.21 ± 1.34 μM, respectively) showed considerable potencies. It is surprising to see that the inhibitory activity can be greatly increased by adding an additional methoxy group with electron-donating capabilities to the benzene ring. For example, **68g** has an IC_{50} of 4.58 μM and **68h** has an IC_{50} of 10.00 μM.

Acetylcholinesterase and Butyrylcholinesterase Inhibition

Wang et al. [16] reported that acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are performed using rat AChE that was conditioned from the rat brain and human BuChE that was obtained from human serum. The biological evaluation performed showed that most biphenyl derivatives are potent AChE and BuChE inhibitors. Compound **32** showed one of the lowest values of IC_{50} in inhibiting BuChE at (IC_{50} = 0.74 μM) while showing a mild value of (IC_{50} = 1.18 μM) for AChE inhibition. However, compound **37** has the lowest value for BuChE inhibition (IC_{50} = 0.72 μM). Compound **36** has the lowest value (IC_{50} = 0.096 μM) for AChE inhibition, which makes compound **36** a potent inhibitor. This shows that inhibitory activities decrease as the length of the carbon linker increases from one carbon atom to three or four carbon atoms. Compound **41**, a four-carbon linker with an IC_{50} of 0.82 μM, is slightly less potent than compound **36**, a two-carbon linker with an IC_{50} of 0.096 μM. This would imply that for molecules with a biphenyl moiety to exhibit inhibitory actions, a linker length of two carbon atoms is optimal.

CONCLUSION

In conclusion, recent investigations regarding the bibenzyl scaffold and its biological activity holds enormous potential in terms of medical contribution and research materials. The synthesis methods reported greatly contributed to the understanding of synthesizing bibenzyls effectively including optimizations which increases yield percentage. The various biological activities performed proves that bibenzyl core structure are essential in providing the biological activity capability. Bibenzyls show promising effects towards antimicrobial, cytotoxic activity and both acetylcholinesterase and butyrylcholinesterase. This paves the way for future researchers to provide insight into growing the benefits of bibenzyls for more than what they are now. As some of the biological activity data could be used in developing a cure for Alzheimer's disease. In the end, this would prove beneficial to the field

of medicine and develop cures for incurable diseases in the future.

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