

Article

Synthesis of Novel *Sesamol*-Based Hybrids—In Silico Analysis and In Vitro Evaluation of Radical Scavenging Activity

Maria Bachvarova ¹, Yordan Stremski ^{1,*}, Desislava Kirkova ², Stela Statkova-Abeghe ¹ and Margarita Docheva ²

¹ Department of Organic Chemistry, University of Plovdiv “Paisii Hilendarski”, 24 Tsar Asen Str., 4000 Plovdiv, Bulgaria; bachvarova@uni-plovdiv.bg (M.B.); stab@uni-plovdiv.bg (S.S.-A.)

² Agricultural Academy, Tobacco and Tobacco Products Institute, 4108 Plovdiv, Bulgaria; desislavaa894@gmail.com (D.K.); margarita_1980@abv.bg (M.D.)

* Correspondence: stremski@uni-plovdiv.net; Tel.: +359-32-261-346

Abstract

New benzazole–sesamol derivatives **6a–8c** were synthesized via an easily accessible reaction based on the coupling of *Sesamol* with in situ generated electrophilic *N*-alkoxycarbonylbenzazolium ions. This strategy successfully integrated benzothiazole, benzimidazole, and 5,6-dimethylbenzimidazole fragments with the biologically active natural lignan *Sesamol*. The structural integrity and the specific position of the newly formed C–C bond was confirmed by ¹H-, ¹³C{¹H}-, HSQC-NMR, FTIR, and HRMS analyses. The obtained compounds with yields in the range of 71–95% were evaluated for their in vitro radical scavenging activity and subjected to in silico predictions of mutagenicity and toxicity. Radical scavenging activity studies demonstrate that the introduction of a benzothiazoline ring (compounds **6a** and **6b**) enhances radical scavenging activity compared to *Sesamol* in the DPPH assay, outperforming the benzimidazole analogues. In silico analyses identified compounds **7b**, **7c**, **8a**, **8b**, and **8c** as promising molecules due to the absence of mutagenic and irritant effects and their low toxicity profiles. In particular, compounds **7a**, **7b**, and **8a** were found to be significantly safer than *Sesamol*. Compound **7a** exhibited the highest safety profile, characterized by an LD₅₀ value of 3046.92 mg/kg.

Keywords: *Sesamol*; benzazole derivatives; *N*-alkoxycarbonylbenzazolium ions; molecular hybridization; radical scavenging activity; in silico toxicity; mutagenicity

1. Introduction

Within pharmaceutical research [1,2], there is growing interest in the discovery of new and effective anticancer agents derived from natural sources due to their considerable therapeutic potential [3]. The natural lignan *Sesamol* (Figure 1) is a compound of significant biological importance, isolated from the seeds of *Sesamum indicum* [4,5]. *Sesamol* has been shown to possess significant antioxidant [4,6,7], anti-inflammatory [5,8], antimicrobial [9,10], antiemetic activities [11], as well as photoprotective [12], anticancer [13], and antiproliferative properties [4,14]. In addition, it has demonstrated the ability to induce apoptosis in tumour cancer cells [15] and exhibits notable anti-ageing potential [16].

In addition to the biological activities described above, *Sesamol* has been investigated as a tyrosinase inhibitor, suppressing melanin synthesis in human melanoma cells (SK-MEL-2). This property classifies *Sesamol* as a potential anti-melanogenic agent and encourages further research into its safe application in cosmetics or for therapeutic purposes [17,18].



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Accordingly, Khan et al. reported *in silico* predictions indicating low toxicity of *Sesamol* in rodents, with an LD₅₀ value of 580 mg/kg [19]. Other authors, like Koru et al., experimentally demonstrated that at a concentration of 10 µM of *Sesamol* is safe for human umbilical vein endothelial cells (HUVEC, ATCC® CRL-1730™) [8].

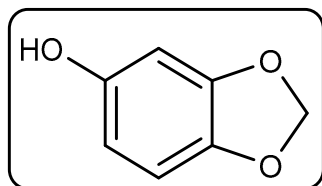


Figure 1. *Sesamol*.

Sesamol exhibits potent antioxidant activity (IC₅₀ < 14.48 µM in the DPPH assay; FRAP = 189.88 ± 17.56 µM) [6,7]. Its antioxidant potential has been extensively investigated and compared with other natural sources, such as carotenoids and polyphenols. Using a series of assays (DPPH, ABTS, FRAP and ORAC), the authors demonstrated a high capacity of *Sesamol* to neutralize free radicals, ranking its efficacy immediately after ellagic acid. The increase in antioxidant activity was established in the following order: ellagic acid > *Sesamol* > olive leaf extract > lutein [7].

As a consequence of its antioxidant activity, *Sesamol* has also been demonstrated to exert neuroprotective, cardioprotective, and hepatoprotective effects, along with improvements in cognitive functions [16,20,21]. Recent studies confirm its high lipophilicity and excellent ability to cross the blood–brain barrier, making it a promising candidate for the treatment of neuroinflammatory disorders [8]. *Sesamol* is also regarded as a promising candidate for anticancer therapy or for the development of drugs containing a natural structural fragment, as it modulates the key signalling pathways involved in carcinogenesis [13,15,22,23].

In recent years, the development of novel hybrid molecules containing two or more pharmacophoric bioactive fragments has emerged as an important synthetic strategy, enabling the generation of new compounds with enhanced biological potential. Several synthetic approaches reported in the literature successfully combine *Sesamol* with other pharmacophoric units [24–27]. In our previous work, *N*-acyliminium reagents, generated *in situ* from benzothiazole and alkyl chloroformates engaged in a Friedel–Crafts reaction with hydroxyarenes, yielding 2-(hydroxyaryl)benzothiazolines with antibacterial properties [28]. A related Friedel–Crafts-type approach has also been employed for *Sesamol* by other authors, who utilized *in situ* generated *N*-Boc imines to achieve regioselective C-6 alkylation under mild aqueous conditions, affording derivatives with potential antioxidant activity [24].

In this context, the focus of our research group has been the synthesis of new hybrid molecules that combine natural phenolic compounds with a benzazole fragment through α -amidoalkylation reaction, followed by structural elucidation and evaluation of their radical scavenging, antimicrobial, and UV-B filtering activities [28–31]. The present study expands the scope of the α -amidoalkylation reaction by modifying a lignan framework and provides an opportunity to investigate the biological potential of the newly obtained hybrid molecules.

2. Materials and Methods

2.1. Chemistry

2.1.1. General Information

All reagents, such as benzothiazole (BT), benzimidazole (BI), 5,6-dimethylbenzimidazole (5,6-DMBI), *Sesamol*, alkyl chloroformates, etc., and organic solvents were purchased from

commercial suppliers Aldrich (Merck, Sofia, Bulgaria, EAD) and were used without further purification. Melting points were determined on a Boëtius PHMKO5 (Carl Zeiss, Jena, Germany) melting point metr and are uncorrected. IR spectra were measured on VERTEX 70 FT-IR spectrometer (Bruker Optics, Ettlingen, Germany). High-resolution mass spectral measurements were performed on a Bruker MS spectrometer (Bruker, Billerica, MA, USA). NMR spectra were measured on Bruker Avance AV600 spectrometers (Bruker, Billerica, MA, USA) in DMSO- d_6 as solvent at 80 °C. All NMR chemical shifts (δ) are given in parts per million (ppm) with tetramethylsilane (TMS) serving as the reference standard. Coupling constants (J) are presented in hertz (Hz). Thin-layer chromatography (TLC) was conducted on 0.2 mm precoated silica gel 60 plates supplied by Merck. For chromatographic separation and purification, high-grade silica gel 60 (100–200 mesh) from Merck was utilized in column chromatography.

2.1.2. General Procedure for the Synthesis of Benzothiazole–Sesamol Hybrids **6a–c**

A solution of benzothiazole (2 mmol) in dichloromethane (8 mL) was magnetically stirred at room temperature while the corresponding chloroformate (ethyl-, methyl chloroformate or 2,2,2-trichloroethyl chloroformate (Troc-Cl), 2.4 mmol) was added, followed by the *Sesamol*. The reaction was maintained under continuous stirring for the time specified in Table 1, and its progress was monitored by TLC. After completion, the mixture was subjected to purification by column chromatography on silica gel, using petroleum ether/diethyl ether mixtures as the eluent. The desired compounds were isolated as white crystalline products.

Table 1. Optimized reaction conditions and yields of the obtained novel *Sesamol* hybrids **6a–c**, **7a–c** and **8a–c**.

Product	X	R	R ₁	Ratio	Time, h	Yield, %
6a	S	H	CH ₃	2:1	2	90
6b	S	H	CH ₂ CH ₃	2:1	5	78
6c	S	H	CH ₂ CCl ₃	1:1	3	71 (95 *)
7a	N-COOR ₁	H	CH ₃	1:1	24	84
7b	N-COOR ₁	H	CH ₂ CH ₃	1:1	24	86 (93 *)
7c	N-COOR ₁	H	CH ₂ CCl ₃	1:1	24	87
8a	N-COOR ₁	Me	CH ₃	1:1	24	77
8b	N-COOR ₁	Me	CH ₂ CH ₃	1:1	24	94
8c	N-COOR ₁	Me	CH ₂ CCl ₃	1:1	24	92

* ratio of N-alkoxycarbonylabenzazolium ion:*Sesamol* 2:1.

2.1.3. General Procedure for the Synthesis of Sesamol Hybrids **7a–c** or **8a–c** Using Benzimidazole or 5,6-Dimethylbenzimidazole

To a solution of benzimidazole (1 mmol) in dichloromethane (10 mL), triethylamine (Et₃N, 1 mmol) was added as a hydrogen chloride scavenger. Subsequently, the corresponding acid chloride—ethyl chloroformate (2.4 mmol) or Troc-Cl (2.4 mmol), or alternatively methyl chloroformate (2.8 mmol), was slowly added dropwise under stirring. Immediately thereafter, *Sesamol* was added in equimolar amounts. The reaction mixture was stirred using a magnetic stirrer for 30 min at 0 °C and then transferred to room temperature, where it was stirred for an additional 24 h. Then, the organic phase was washed with 30 mL of hydrochloric acid–water solution (1:1, *v/v*), followed by 50 mL of water. The resulting organic layer was dried over anhydrous Na₂SO₄, and the solvent was removed by distillation.

The final products were obtained and isolated as white solids after recrystallization from petroleum ether.

Compound **6a** Methyl 2-(6-hydroxybenzo[d][1,3]dioxol-5-yl)benzo[d]thiazole-3(2H)-carboxylate was isolated and purified by column chromatography on silica gel with mixtures of petroleum/diethyl ether (from 2:1 to 1:1), yield of 90%, m.p. = 162–164 °C, MW = 331.34 g/mol;

¹H-NMR (600 MHz, 80 °C, DMSO-d₆, δ ppm, J Hz): 3.75 (s, 3H, -COOCH₃), 5.81 (d, J = 0.9, 1H, -OCH₂O-), 5.86 (d, J = 1.0, 1H, -OCH₂O-), 6.35 (s, 1H, -CH, *Sesamol*), 6.48 (s, 1H, -CH, *Sesamol*), 6.85 (s, 1H, *CH), 7.03 (t, J = 7.0, 1H, -CH, benzothiazole), 7.15 (t, J = 7.1, 1H, -CH, benzothiazole), 7.18 (d, J = 7.6, 1H, -CH, benzothiazole), 7.79 (d, J = 8.2, 1H, -CH, benzothiazole), 9.55 (brs, 1H, -OH);

¹³C{¹H}-NMR (150 MHz, 80 °C, DMSO-d₆, δ ppm): 53.7(-COOCH₃), 62.4(*CH), 98.6(-CH, *Sesamol*), 101.3(-OCH₂O-), 103.7(-CH, *Sesamol*), 117.4(-C-Ar), 121.1(-C-Ar), 123.0(-C-Ar), 124.9(-C-Ar), 125.6(-C-Ar), 129.0(-C-Ar), 138.5(-C-Ar), 140.4(-C-Ar), 147.9(-C-Ar), 148.5(-C-Ar), 153.2(-C=O);

FTIR (KBr, cm⁻¹): 3313, 3081, 2955, 2877, 1677, 1584, 1522, 1474, 1439, 1375, 1263, 1168, 1036, 935, 753;

HRMS *m/z* (ESI): calcd. for C₁₆H₁₃NNaO₅S⁺ [M+Na]⁺ 354.0407; found 354.0409;

Compound **6b** Ethyl 2-(6-hydroxybenzo[d][1,3]dioxol-5-yl)benzo[d]thiazole-3(2H)-carboxylate was isolated and purified by column chromatography on silica gel with mixtures of petroleum/diethyl ether (from 2:1 to 1:1), yield of 78%, m.p. = 179–181 °C, MW = 345.37 g/mol;

¹H-NMR (600 MHz, 80 °C, DMSO-d₆, δ ppm, J Hz): 1.19 (t, J = 7.0, 3H, -COOCH₂CH₃), 4.15–4.25 (m, 2H, -COOCH₂CH₃), 5.81 (d, J = 1.0, 1H, -OCH₂O-), 5.86 (d, J = 1.1, 1H, -OCH₂O-), 6.35 (s, 1H, -CH, *Sesamol*), 6.48 (s, 1H, -CH, *Sesamol*), 6.87 (s, 1H, *CH), 7.02 (t, J = 7.0, 1H, -CH, benzothiazole), 7.15 (t, J = 8.2, 1H, -CH, benzothiazole), 7.18 (d, J = 7.6, 1H, -CH, benzothiazole), 7.80 (d, J = 8.2, 1H, -CH, benzothiazole), 9.52 (s, 1H, -OH);

¹³C{¹H}-NMR (150 MHz, 80 °C, DMSO-d₆, δ ppm): 14.6(-COOCH₂CH₃), 62.3(*CH), 62.6(-COOCH₂CH₃), 98.6(-CH, *Sesamol*), 101.3(-OCH₂O-), 103.7(-CH, *Sesamol*), 117.4(-C-Ar), 121.2(-C-Ar), 122.9(-C-Ar), 124.7(-C-Ar), 125.6(-C-Ar), 129.0(-C-Ar), 138.6(-C-Ar), 140.4(-C-Ar), 147.9(-C-Ar), 148.5(-C-Ar), 152.7(-C=O);

FTIR (KBr, cm⁻¹): 3278, 2987, 2904, 1666, 1581, 1481, 1447, 1329, 1263, 1169, 1036, 933, 752;

HRMS *m/z* (ESI): calcd. for C₁₇H₁₅NNaO₅S⁺ [M+Na]⁺ 368.0563; found 368.0567;

Compound **6c** 2,2,2-trichloroethyl 2-(6-hydroxybenzo[d][1,3]dioxol-5-yl)benzo[d]thiazole-3(2H)-carboxylate was isolated and purified by column chromatography on silica gel with mixtures of petroleum/diethyl ether (from 2:1 to 1:1), yield of 95%, m.p. = 121–123 °C, MW = 448.70 g/mol;

¹H-NMR (600 MHz, 80 °C, DMSO-d₆, δ ppm, J Hz): 4.96 (d, ²J = 12.2, 1H, -COOCH₂CCl₃), 4.99 (d, ²J = 12.2, 1H, -COOCH₂CCl₃), 5.81 (d, J = 1.0, 1H, -OCH₂O-), 5.85 (d, J = 1.0, 1H, -OCH₂O-), 6.37 (s, 1H, -CH, *Sesamol*), 6.47 (s, 1H, -CH, *Sesamol*), 6.96 (s, 1H, *CH), 7.08 (t, J = 7.0, 1H, -CH, benzothiazole), 7.19 (t, J = 8.2, 1H, -CH, benzothiazole), 7.24 (d, J = 7.8 Hz, 1H, -CH, benzothiazole), 7.87 (d, J = 8.2 Hz, 1H, -CH, benzothiazole), 9.56 (s, 1H, -OH);

¹³C{¹H}-NMR (150 MHz, 80 °C, DMSO-d₆, δ ppm): 62.5(*CH), 75.3(-COOCH₂CCl₃), 95.7(-COOCH₂CCl₃), 98.5(-CH, *Sesamol*), 101.3(-OCH₂O-), 103.7(-CH, *Sesamol*), 117.5(-C-Ar), 120.5(-C-Ar), 123.2(-C-Ar), 125.8(-C-Ar), 126.8(-C-Ar), 129.2(-C-Ar), 137.8(-C-Ar), 140.4(-C-Ar), 148.0(-C-Ar), 148.7(-C-Ar), 151.0(-C=O);

FTIR (KBr, cm⁻¹): 3317, 3065, 2926, 1649, 1581, 1469, 1445, 1393, 1231, 1172, 1035, 920, 743;

HRMS *m/z* (ESI): calcd. for C₁₇H₁₂Cl₃NNaO₅S⁺ [M+Na]⁺ 469.9394; 471.9366; found 469.9399; 471.9367;

Compound **7a** Dimethyl 2-(6-hydroxybenzo-[d][1,3]dioxol-5-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate was isolated by recrystallization with petroleum ether, yield of 84%, m.p. = 203–205 °C, MW = 372.33 g/mol;

¹H-NMR (600 MHz, 80 °C, DMSO-d₆, δ ppm, J Hz): 3.69 (s, 6H, 2x-COOCH₃), 5.88 (s, 2H, -OCH₂O-), 6.36 (s, 1H, -CH, *Sesamol*), 6.52 (s, 1H, -CH, *Sesamol*), 6.96 (s, 1H, -NCHN-), 7.01 (dd, J = 3.3, 5.8 Hz, 2H, 2x-CH, benzimidazole), 7.56 (dd, J = 3.4, 5.7 Hz, 2H, 2x-CH, benzimidazole), 9.04 (brs, 1H, -OH);

¹³C{¹H}-NMR (150 MHz, 80 °C, DMSO-d₆, δ ppm): 53.1(2x-COOCH₃), 74.4(-NCHN-), 98.5(-CH, *Sesamol*), 101.4(-OCH₂O-), 107.4(-CH, *Sesamol*), 113.8(2x-CH, benzimidazole), 117.2(-C-Ar), 123.3(2x-CH, benzimidazole), 133.0(-C-Ar), 140.2(-C-Ar), 148.5(-C-Ar), 151.2(-C-Ar), 151.8(2x-C=O);

FTIR (KBr, cm⁻¹): 3369, 2954, 2883, 1722, 1695, 1502, 1443, 1382, 1310, 1278, 1081, 1028, 932, 752, 598; 546;

HRMS *m/z* (ESI): calcd. for C₁₈H₁₆N₂NaO₇⁺ [M+Na]⁺ 395.0850; found 395.0855;

Compound **7b** Diethyl 2-(6-hydroxybenzo-[d][1,3]dioxol-5-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate was isolated by recrystallization with petroleum ether, yield of 93%, m.p. = 172–174 °C, MW = 400.39 g/mol;

¹H-NMR (600 MHz, 80 °C, DMSO-d₆, δ ppm, J Hz): 1.16 (t, J = 7.1 Hz, 6H, 2x-COOCH₂CH₃), 4.12 (q, J = 7.0 Hz, 4H, 2x-COOCH₂CH₃), 5.87 (s, 2H, -OCH₂O-), 6.37 (s, 1H, -CH, *Sesamol*), 6.51 (s, 1H, -CH, *Sesamol*), 6.97 (s, 1H, -NCHN-), 7.00 (dd, J = 3.3, 5.8 Hz, 2H, 2x-CH, benzimidazole), 7.59 (dd, J = 3.4, 5.9 Hz, 2H, 2x-CH, benzimidazole), 9.05 (s, 1H, -OH);

¹³C{¹H}-NMR (150 MHz, 80 °C, DMSO-d₆, δ ppm): 14.4(2x-COOCH₂CH₃), 62.0(2x-COOCH₂CH₃), 74.2(-NCHN-), 98.3(-CH, *Sesamol*), 101.4(-OCH₂O-), 107.4(-CH, *Sesamol*), 113.7(2x-CH, benzimidazole), 117.4(-C-Ar), 123.2(2x-CH, benzimidazole), 133.0(-C-Ar), 140.1(-C-Ar), 148.5(-C-Ar), 151.2(-C-Ar), 151.3(2x-C=O);

FTIR (KBr, cm⁻¹): 3383, 2990, 2874, 1694, 1685, 1506, 1421, 1414, 1280, 1228, 1172, 1035, 935, 749, 595, 545;

HRMS *m/z* (ESI): calcd. for C₂₀H₂₀N₂NaO₇⁺ [M+Na]⁺ 423.1163; found 423.1166;

Compound **7c** Bis(2,2,2-trichloroethyl) 2-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate was isolated by recrystallization with petroleum ether, yield of 87%, m.p. = 140–142 °C, MW = 607.04 g/mol;

¹H-NMR (600 MHz, 80 °C, DMSO-d₆, δ ppm, J Hz): 4.94 (d, ²J = 12.4, 2H, -COOCH₂CCl₃), 4.96 (d, ²J = 12.4, 2H, -COOCH₂CCl₃), 5.86 (s, 2H, -OCH₂O-), 6.32 (s, 1H, -CH, *Sesamol*), 6.71 (s, 1H, -CH, *Sesamol*), 7.01 (s, 1H, -NCHN-), 7.09 (dd, J = 5.9, 3.4 Hz, 2H, 2x-CH, benzimidazole), 7.68 (dd, J = 5.9, 3.3 Hz, 2H, 2x-CH, benzimidazole), 9.12 (brs, 1H, -OH);

¹³C{¹H}-NMR (150 MHz, 80 °C, DMSO-d₆, δ ppm): 75.3(2x-COOCH₂CCl₃), 76.3(-NCHN-), 95.7(2x-COOCH₂CCl₃), 98.4(-CH, *Sesamol*), 101.4(-OCH₂O-), 110.0(-CH, *Sesamol*), 114.2(2x-CH, benzimidazole), 115.4(-C-Ar), 124.0(2x-CH, benzimidazole), 132.8(-C-Ar), 139.9(-C-Ar), 148.9(-C-Ar), 149.6(-C-Ar), 151.8(2x-C=O);

FTIR (KBr, cm⁻¹): 3449, 2959, 2922, 1728, 1694, 1504, 1448, 1407, 1285, 1231, 1193, 1040, 940, 861, 742, 575, 434;

HRMS *m/z* (ESI): calcd. for C₂₀H₁₄Cl₆N₂NaO₇⁺ [M+Na]⁺ 628.8795; 630.8765; found 628.8797; 630.8769;

Compound **8a** Dimethyl 2-(6-hydroxybenzo-[d][1,3]dioxol-5-yl)-5,6-dimethyl-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate was isolated by recrystallization with petroleum ether, yield of 77%, m.p. = 193–195 °C, MW = 400.39 g/mol;

¹H-NMR (600 MHz, 80 °C, DMSO-d₆, δ ppm, J Hz): 2.21 (s, 6H, 2x-CH₃, 5,6-dimethylbenzimidazole), 3.67 (s, 6H, 2x-COOCH₃), 5.87 (s, 2H, -OCH₂O-), 6.36 (s, 1H,

-CH, *Sesamol*), 6.48 (s, 1H, -CH, *Sesamol*), 6.94 (s, 1H, -NCHN-), 7.36 (s, 2H, 2x-CH, 5,6-dimethylbenzimidazole), 9.03 (brs, 1H, -OH);

$^{13}\text{C}\{^1\text{H}\}$ -NMR (150 MHz, 80 °C, DMSO- d_6 , δ ppm): 19.8(2xCH₃, 5,6-dimethylbenzimidazole), 53.0(2x-COOCH₃), 74.1(-NCHN-), 98.5(-CH, *Sesamol*), 101.4(-OCH₂O-), 107.0(-CH, *Sesamol*), 115.2(2x-CH, 5,6-dimethylbenzimidazole), 117.4(-C-Ar), 130.6(-C-Ar), 130.8(-C-Ar), 140.3(-C-Ar), 148.5(-C-Ar), 151.0(-C-Ar), 151.7(2x-C=O);

FTIR (KBr, cm^{-1}): 3384, 2956, 2883, 1709, 1696, 1513, 1439, 1384, 1300, 1234, 1177, 1126, 1040, 979, 866, 752, 595, 538;

HRMS m/z (ESI): calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{NaO}_7^+$ $[\text{M}+\text{Na}]^+$ 423.1163; found 423.1164;

Compound **8b** Diethyl 2-(6-hydroxybenzo-[*d*][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole-1,3(2*H*)-dicarboxylate was isolated by recrystallization with petroleum ether, yield of 94%, m.p. = 195–197 °C, MW = 428.44 g/mol;

^1H -NMR (600 MHz, 80 °C, DMSO- d_6 , δ ppm, J Hz): 1.15 (t, J = 7.0 Hz, 6H, 2x-COOCH₂CH₃), 2.21 (s, 6H, 2x-CH₃, 5,6-dimethylbenzimidazole), 4.10 (q, J = 7.0 Hz, 4H, 2x-COOCH₂CH₃), 5.86 (s, 2H, -OCH₂O-), 6.37 (s, 1H, -CH, *Sesamol*), 6.46 (s, 1H, -CH, *Sesamol*), 6.94 (s, 1H, -NCHN-), 7.39 (s, 2H, 2x-CH, 5,6-dimethylbenzimidazole), 8.85 (brs, 1H, -OH);

$^{13}\text{C}\{^1\text{H}\}$ -NMR (150 MHz, 80 °C, DMSO- d_6 , δ ppm): 14.4(2x-COOCH₂CH₃), 19.8(2xCH₃, 5,6-dimethylbenzimidazole), 61.8(2x-COOCH₂CH₃), 73.9(-NCHN-), 98.2(-CH, *Sesamol*), 101.4(-OCH₂O-), 106.9(-CH, *Sesamol*), 115.1(2x-CH, 5,6-dimethylbenzimidazole), 117.6(-C-Ar), 130.5(-C-Ar), 130.9(-C-Ar), 140.2(-C-Ar), 148.4(-C-Ar), 151.1(-C-Ar), 151.2(2x-C=O);

FTIR (KBr, cm^{-1}): 3422, 2982, 2915, 1720, 1673, 1514, 1445, 1411, 1294, 1230, 1175, 1040, 937, 757, 597, 432;

HRMS m/z (ESI): calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{NaO}_7^+$ $[\text{M}+\text{Na}]^+$ 451.1476; found 451.1479;

Compound **8c** bis(2,2,2-trichloroethyl) 2-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole-1,3(2*H*)-dicarboxylate was isolated by recrystallization with petroleum ether, yield of 92%, m.p. = 176–177 °C, MW = 635.09 g/mol;

^1H -NMR (600 MHz, 80 °C, DMSO- d_6 , δ ppm, J Hz): 2.23 (s, 6H, 2x-CH₃, 5,6-dimethylbenzimidazole), 4.92 (d, ^2J = 12.4, 2H, -COOCH₂CCl₃), 4.95 (d, ^2J = 12.4, 2H, -COOCH₂CCl₃), 5.86 (s, 2H, -OCH₂O-), 6.30 (s, 1H, -CH, *Sesamol*), 6.66 (s, 1H, -CH, *Sesamol*), 6.99 (s, 1H, -NCHN-), 7.50 (s, 2H, 2x-CH, 5,6-dimethylbenzimidazole), 9.10 (brs, 1H, -OH);

$^{13}\text{C}\{^1\text{H}\}$ -NMR (150 MHz, 80 °C, DMSO- d_6 , δ ppm): 19.8(2xCH₃, 5,6-dimethylbenzimidazole), 75.2(2x-COOCH₂CCl₃), 76.0(-NCHN-), 95.8(2x-COOCH₂CCl₃), 98.4(-CH, *Sesamol*), 101.4(-OCH₂O-), 109.4(-CH, *Sesamol*), 115.5(2x-CH, 5,6-dimethylbenzimidazole), 115.7(-C-Ar), 130.8(-C-Ar), 131.4(-C-Ar), 140.0(-C-Ar), 148.8(-C-Ar), 149.5(-C-Ar), 151.7(2x-C=O);

FTIR (KBr, cm^{-1}): 3436, 2956, 2921, 2856, 1720, 1686, 1512, 1415, 1303, 1134, 1043, 942, 751, 717, 575;

HRMS m/z (ESI): calcd. for $\text{C}_{22}\text{H}_{18}\text{Cl}_6\text{N}_2\text{NaO}_7^+$ $[\text{M}+\text{Na}]^+$ 656.9108; 658.9078; found 656.9111; 658.9083;

2.1.4. Radical Scavenging Activity Assays

The stock solution of all compounds was prepared in a concentration of 1 mg/mL. The working solutions were prepared by dissolving aliquot parts of the stock solution with methanol. The final concentration of IC₅₀ was calculated according to the dilution factor [30]. The radical scavenging activity of the tested compounds was evaluated over a concentration range of 1–250 ppm using a series of two-fold dilutions. The linear range of each compound differed but, in all cases, it fell within the tested concentration interval.

Method for DPPH Free Radical Scavenging Evaluation

The DPPH free radical scavenging capabilities were assessed as previously described by Docheva et al. [32], with 0.12 mM DPPH dissolved in methanol. The absorbance variation was quantified at 515 nm using a UV-Vis spectrophotometer. The total DPPH radical scavenging activity was assessed in triplicate during 30 min in darkness. The IC₅₀ was calculated indicating the concentration at which 50% of DPPH radicals are neutralized [30].

Method for ABTS Free Radical Scavenging Evaluation

The ABTS free radical was prepared following Re et al. [33], with several modifications. ABTS^{•+} was generated by dissolving 7 mM ABTS and 2.45 mM K₂S₂O₈ in deionised H₂O, with the mixture incubated in the dark at room temperature for 12–16 h before to use. A 1:1 (v/v) mixture of the reagents was diluted with methanol to achieve an absorbance of 0.70 ± 0.02 at 734 nm for the ABTS^{•+} solution. The ABTS radical scavenging activity was assessed in triplicate in the absence of light at room temperature during a 10-min period. The percentage inhibition (%) of radical scavenging activity was computed in accordance with the relevant equation of the approach [30].

2.1.5. In Silico Prediction of Toxicological Profiles Using QSAR Models

The application of specialized QSAR models supports the design, synthesis, and safety assessment of new synthetic compounds, including those with potential applications in the cosmetic industry [34–36]. This approach enables the evaluation of toxicological, ecotoxicological, and physicochemical risks associated with newly developed chemical substances. A widely used tool for such purposes is VEGA (version 1.2.3, Mario Negri Institute for Pharmacological Research, Milano (MI), Italy), a software platform for in silico analyses [34–36].

In the present study, the VEGA system was employed to assess potential risks such as mutagenicity, skin irritation, acute toxicity (LD₅₀), and reproductive toxicity for compounds **6a–8c** using various QSAR models. Mutagenicity was evaluated using the Mutagenicity model (CAESAR, version 2.1.14) and the Mutagenicity (Ames test) model (ISS, version 1.0.3). Skin irritation was assessed using the Skin Irritation models CONCERT/Coral (version 1.0.0) and CONCERT/SarPy (version 1.0.0).

The effects on the thyroid hormone receptor alpha (TR α) were analyzed using the Thyroid Receptor Alpha Effect model (NRMEA, version 1.0.1), while the Thyroid Receptor Beta Effect model (NRMEA, version 1.0.1) was applied for the β -receptor (THR β). Acute toxicity (LD₅₀) was predicted using the Acute Toxicity model (KNN, version 1.0.0), and reproductive toxicity was evaluated using the Developmental/Reproductive Toxicity library (PG, version 1.1.2).

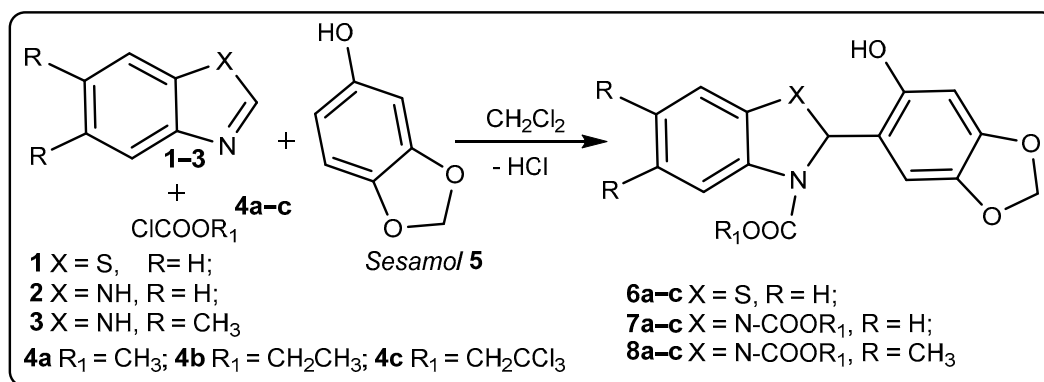
2.1.6. Statistics

The data obtained were expressed as the mean ± standard error of the mean (SEM). All statistical analyses were performed using the specialized software—SPSS (version 16.0 SPSS Inc., Chicago, IL, USA).

3. Results and Discussion

3.1. Molecular Hybridization by α -Amidoalkylation of Sesamol

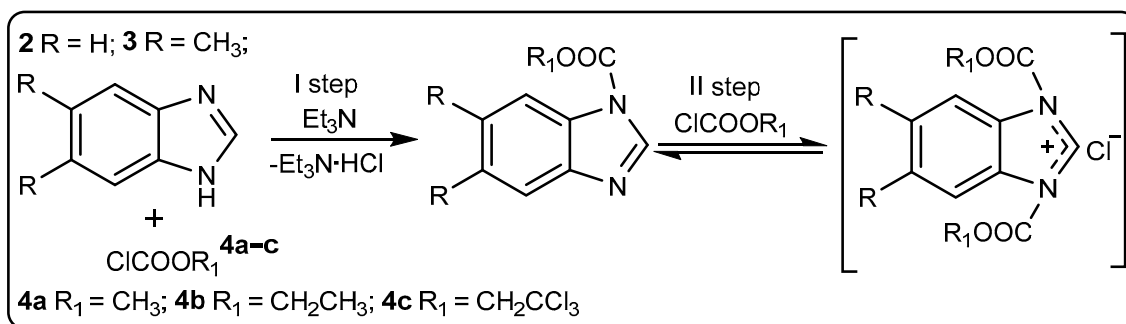
Molecular hybridization of *Sesamol* was successfully accomplished using *N*-acyliminium reagents generated from heterocyclic precursors, such as benzothiazole **1**, benzimidazole **2**, and 5,6-dimethylbenzimidazole **3**, in the presence of acid chlorides—methyl chloroformate, ethyl chloroformate, and Troc-Cl (**4a–c**, Scheme 1).



Scheme 1. Modification of *Sesamol* via reactions of α -amidoalkylation.

For the α -amidoalkylation of *Sesamol*, the optimal reaction conditions previously established by our group for the synthesis of monoterpenoid–benzothiazole hybrids were successfully applied [30]. A reactant ratio of *N*-acyliminium reagent to *Sesamol* 2:1 was required when benzothiazole **1** was employed. Under these conditions, the reaction proceeded significantly faster, with reaction times ranging from 2 h for compound **6a** to 5 h for compound (**6b**, Table 1). A pronounced dependence of the amidoalkylation rate leading to the formation of hybrid compounds **6a–c** (see Sections 2 and 2.1.2) on the structure of the used alkyl chloroformate was observed.

In the amidoalkylation involving *N*-acyliminium reagents derived from benzimidazole **2** and 5,6-dimethylbenzimidazole **3**, the reactions were found to proceed successfully with an equimolar ratio of the starting reactants. However, the reaction rate was significantly slower, requiring 24 h for completion (monitored by TLC). In this case, triethylamine was used as a hydrogen chloride scavenger in the initial *N*-acylation step (Scheme 2), analogous to the previous reactions with resorcinol [37].



Scheme 2. In situ generated electrophilic *N*-alkoxycarbonylbenzazolum ions in the α -amidoalkylation reaction for the synthesis of *Sesamol* hybrids **7a–c**, **8a–c**.

The obtained benzimidazoline–*Sesamol* hybrid molecules **7a–c** and **8a–c** (see Sections 2 and 2.1.3) were isolated by recrystallization in yields ranging from 77% **8a** to 94% **8b** (Table 1). To enhance the yield of product **7b** with *N*-acyliminium reagents generated from benzimidazole and ethyl chloroformate, the reactant ratio was adjusted to 2:1, affording 93% yield of **7b**.

Synthetic modification of the natural lignan *Sesamol* afforded nine novel compounds by reaction of α -amidoalkylation. Spectral analyses of all newly synthesized compounds indicated substitution at the less hindered “ortho” position 6th in the *Sesamol* ring, clearly corresponding to already published synthetic procedures and analogues [24,27].

The structure of the synthesized novel benzazole–*Sesamol* hybrids **6a–8c** was fully characterized spectrally using ¹H-, ¹³C{¹H}-, HSQC-NMR, FTIR, and HRMS data (original

spectra are available in Supporting Information). Recording the NMR-spectra at room temperature or CDCl_3 as a solvent, previously resulted in the registration of strongly broadened or doubled signals, which made their correct interpretation impossible [28,29]. Thus, to average out the rotamers reaching adequate assignment of peaks and structure determination, the spectra were measured under heating at 80 °C. Under optimized conditions, clear signals were registered, corresponding to the chemical shifts and multiplicity for the expected structural fragments of the obtained products **6a–8c**.

The 2D HSQC-NMR technique clearly visualized the position of the distinctive signals for the obtained compounds (see all reported signals in Section 2 and Supporting Information Section). For example, in ^1H -NMR spectrum of compound **7b**, the triplet at 1.16 ppm corresponds to the methyl protons of the ethoxycarbonyl fragments, while the quartet at 4.12 ppm is assigned to the methylene protons. The singlet at 5.87 ppm is attributed to the two protons of the methylenedioxy fragment in the *Sesamol* moiety. Singlets observed at 6.37 ppm and 6.51 ppm correspond to the aromatic protons of the *Sesamol*, indicating substitution at 6th position.

The characteristic singlet in the range of $\delta = 6.85\text{--}7.01$ ppm is assigned to the proton at the asymmetric C-2 carbon of the benzazoline ring. Also, the broad singlet in the range of $\delta = 8.85\text{--}9.56$ ppm corresponds to the proton of hydroxyl group. The signals found in of $^{13}\text{C}\{^1\text{H}\}$ -NMR spectra comply with all carbon atoms from the expected structures. The FTIR and HRMS spectra match precisely to those anticipated for the synthesized compounds **6a–c**, **7a–c** and **8a–c** (see Supplementary Information Section).

3.2. In Vitro Radical Scavenging Assay

The aim of the present study was to evaluate the radical scavenging activity of the newly synthesized *Sesamol* hybrids (**6a–8b**, Table 2). For this purpose, previously reported data from our studies on the natural compounds *Quercetin*, *Rutin*, *Thymol*, *Carvacrol*, and *Sesamol* were selected. In addition to their antioxidant properties, these natural compounds exhibit a range of well-established biological activities and broad therapeutic potential [29,30,32]. *Quercetin* and *Rutin* are distinguished as potent antioxidants with pronounced anti-inflammatory properties [29,32], whereas *Thymol* and *Carvacrol* possess antimicrobial and antiseptic activities [30]. In this context, *Sesamol* complements the group of natural compounds with its radical scavenging capacity [4,6,7], antitumor effect [13], and other biological activities [4]. The radical scavenging activity of the synthesized *Sesamol* hybrids was evaluated using DPPH and ABTS assays.

Table 2. IC_{50} values (μM) of the investigated natural and synthetic phenolic compounds determined by the DPPH and ABTS assays.

Compound	MW	DPPH	ABTS
<i>Quercetin</i> [29,32]	302.24	4.60 ± 0.3	48.0 ± 4.4
<i>Rutin</i> [29,32]	610.52	5.02 ± 0.4	95.3 ± 4.5
<i>Thymol</i> [30]	150.22	506 ± 15	92.5 ± 10
<i>Carvacrol</i> [30]	150.22	456 ± 15	52.6 ± 5.0
<i>Sesamol</i>	138.12	11.60 ± 1.5	46.3 ± 5.0
6a	331.34	9.20 ± 1.0	85.7 ± 7.5
6b	345.37	11.0 ± 1.0	96.7 ± 7.5
7a	372.33	94.5 ± 7.5	151.7 ± 9.5
7b	400.39	84.8 ± 7.5	133.3 ± 9.5
8a	400.39	ND *	112.9 ± 9.5
8b	428.44	ND *	105.3 ± 9.5

* ND-not determined.

Comparative analysis of the DPPH assay results indicated that the flavonoids (*Quercetin* and *Rutin*) are the most potent antioxidants [29,32]. In contrast, when evaluated by the ABTS assay, *Sesamol* **5** exhibited an antioxidant potential ($IC_{50} = 46.3 \pm 5.0 \mu M$) comparable to that of *Quercetin* ($IC_{50} = 48.0 \pm 4.4 \mu M$) [29]. The antioxidant efficiency of the selected natural compounds is directly dependent on the number and spatial arrangement of their hydroxyl groups or other substituents on the aryl fragment, which determine their ability to neutralize free radicals [38]. The calculated IC_{50} values (μM) obtained by the two radical scavenging methods are presented in Table 2.

Comparative evaluation of the antioxidant activity of the synthetic compounds showed that, in the DPPH assay, the *N*-acylbenzothiazoline-*Sesamol* hybrids **6a** ($9.2 \pm 1.0 \mu M$) and **6b** ($11.0 \pm 1.0 \mu M$) exhibited a similar radical-scavenging activity to the natural lignan *Sesamol* ($11.6 \pm 1.5 \mu M$). These results indicate that structural modification with a benzothiazoline moiety and an alkoxycarbonyl group do not adversely affect antioxidant efficiency comparing to *Sesamol* in the DPPH assay. In contrast, the benzimidazoline hybrid compounds **7a** ($94.5 \pm 7.5 \mu M$) and **7b** ($84.8 \pm 7.5 \mu M$) displayed lower activity.

When evaluated by the ABTS assay, *Sesamol* ($46.3 \pm 5.0 \mu M$) was confirmed as the most potent antioxidant among the tested natural compounds and all synthetic molecules (Table 2). The closest activities to the reference compound were again observed for compounds **6a** ($85.7 \pm 7.5 \mu M$) and **6b** ($96.7 \pm 7.5 \mu M$), followed by analogues **8b** ($105.3 \pm 9.5 \mu M$) and **8a** ($112.9 \pm 9.5 \mu M$), whereas hybrid compounds **7a** and **7b** exhibited the lowest antioxidant activity ($IC_{50} = 151.7 \pm 9.5 \mu M$ and $133.3 \pm 9.5 \mu M$, respectively).

In summary, the antioxidant activity of the synthesized compounds was examined using the DPPH and ABTS assays. As the ABTS assay gives a more precise evaluation of structure–activity relationships, the antioxidant potential of hybrid compounds **8a** and **8b** was preferentially investigated by this method (Table 2).

3.3. In Silico Predictions of Sesamol Hybrids Toxicity

The VEGA platform [34–36] was utilized to generate in silico predictions of mutagenicity, acute toxicity (LD_{50}), skin irritation, interactions with thyroid hormone receptors α and β ($TR\alpha/THR\beta$), and reproductive toxicity for the newly synthesized compounds (**6a–8c**) as well as for the reference compound *Sesamol*. The VEGA platform was selected as the primary tool in the present study because it provides well-validated QSAR models for the prediction of a wide range of toxicological, ecotoxicological, and physicochemical properties of novel chemical substances. The use of such in silico approaches is essential for early-stage safety assessment in the development of new synthetic substances or cosmetic products. This concept is in accordance with the 3R principles formulated by Russell and Burch aimed at reducing animal experimentation [34–36,39,40].

It should be noted that the acute toxicity (LD_{50}) prediction models were not applicable to all compounds listed in Table 3. Thus, the discussion focuses on the predicted results obtained for selected structures (**7a**, **7b**, and **8a**), which were directly compared with the reference compound *Sesamol*. The predicted LD_{50} values indicate that compounds **7a** (3046.92 mg/kg), **8a** (1873.06 mg/kg), and **7b** (1388.57 mg/kg) exhibit low acute toxicity and are considerably less toxic than *Sesamol* (808.82 mg/kg).

According to mutagenicity predictions, compounds **7b**, **7c**, and the series **8a–8c** were classified as non-mutagenic based on the CAESAR and ISS models. With respect to the remaining safety endpoints, all evaluated molecules **6a–8c** were predicted to be non-irritant to the skin, inactive toward thyroid hormone receptors, and devoid of reproductive toxicity.

The presented data identify the newly synthesized structures (**7a**, **7b**, and **8a**) as promising hit molecules for future multifunctional applications.

Table 3. Prediction results for the mutagenicity, skin irritation, thyroid receptor alpha effect (TR α) and beta effect (THR β), and reproductive toxicity with the VEGA tool on compounds (**6a–8c** and *Sesamol* **5**).

Compound	Mutagenicity Model (CAESAR) 2.1.14	Mutagenicity Model (ISS) 1.0.3	Skin Irritation	Thyroid Receptor Alpha Effect (TR α) and Beta Effect (THR β)	Reproductive Toxicity
6a	Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
6b	Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
6c	Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
7a	Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
7b	NON-Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
7c	NON-Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
8a	NON-Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
8b	NON-Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
8c	NON-Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant
<i>Sesamol</i>	NON-Mutagenic	NON-Mutagenic	NON-Sensitizer	Inactive	NON-Toxicant

The predicted non mutagenic is indicated in bold.

4. Conclusions

In the present work, the synthesis of a series of novel hybrid compounds **6a–8c** in high yields was successfully accomplished by combining the biologically active lignan *Sesamol* with benzothiazole **1**, benzimidazole **2**, and 5,6-dimethylbenzimidazole **3**. The applied synthetic approach represents a logical continuation of our previous studies on naturally occurring phenolic compounds and monoterpenoids [28–30].

Incorporation of a benzothiazoline moiety into hybrid compounds **6a** and **6b** showed comparable radical scavenging activity in the DPPH assay relative to *Sesamol*, whereas the ABTS assay confirmed the high radical scavenging capacity of the natural compound. Overall, the benzothiazoline-based hybrid compounds were established as more potent antioxidant agents than their benzimidazoline and 5,6-dimethylbenzimidazoline analogues.

In silico tools implemented within the VEGA software platform [34–36] identified compounds **7b**, **7c**, and **8a–8c** as non-mutagenic and non-irritant to the skin. QSAR models for acute toxicity were applicable only to three of the newly synthesized hybrid compounds **7a**, **7b**, and **8a**. These compounds were predicted to exhibit a substantially improved safety profile compared with *Sesamol* (LD₅₀ = 808.82 mg/kg), *Thymol* (LD₅₀ = 970.11 mg/kg), and *Carvacrol* (LD₅₀ = 806.9 mg/kg). The predicted safety profile of compound **7a** (LD₅₀ = 3046.92 mg/kg) is nearly identical to that of the previously synthesized aromatic analogues 4-(benzo[d]thiazol-2-yl)-2-isopropyl-5-methylphenol (LD₅₀ = 3192.7 mg/kg) and 4-(benzo[d]thiazol-2-yl)-5-isopropyl-2-methylphenol (LD₅₀ = 3191.84 mg/kg) [30]. Moreover, the predicted LD₅₀ values for compounds **8a** (1873.06 mg/kg) and **7b** (1388.57 mg/kg) significantly exceed that of *Sesamol* and closely approach the predicted value for the commercial UVB filter 2-phenylbenzimidazole-5-sulfonic acid (PBSA, LD₅₀ = 1465.52 mg/kg) [30].

Supplementary Materials: The following Supplementary Materials can be downloaded at: <https://www.mdpi.com/article/10.3390/appliedchem6020021/s1>, S1.PDF—processed original ¹H-, ¹³C{¹H}-, HSQC-NMR, FTIR and HRMS spectra of the novel compounds **6a–c**, **7a–c** and **8a–c**.

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