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Step-by-step synthetic route to access eugenol-1,2,3-triazole-chalcone hybrid ☆,☆☆

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Synthesis of chalcone containing an eugenol-1,2,3-triazole scaffold by aldol condensation and cycloaddition reactions

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ABSTRACT

Molecular hybridization represents a strategic approach in drug design, where two or more pharmacophoric elements from distinct bioactive molecules are integrated into a single hybrid compound. In this study, we synthesized hybrid compounds of chalcone, triazole, and eugenol through straightforward reactions using 4-hydroxyacetophenone as the starting material. Initially, 4-hydroxyacetophenone (**1**) underwent alkylation with 1,4-dibromobutane to produce compound **2** with an 84 % yield. Compound **2** was then subjected to azidation, resulting in azidobutoxyacetophenone **3** with a 71 % yield. Subsequently, compound **3** was reacted with either benzaldehyde or 4-methoxybenzaldehyde via base-catalyzed aldol condensation, yielding azidobutoxychalcones **4a** (69 %) and **4b** (84 %). Finally, azide-alkyne [3+2] cycloaddition between **4a**/**4b** and propargylated eugenol afforded chalcone derivatives bearing eugenol-1,2,3-triazole hybrids 5a and 5b, each with a 90 % yield.

- Synthesized chalcones featuring an eugenol-1,2,3-triazole scaffold using 4-hydroxyacetophenone as the starting material.
- Synthesis was accomplished through a four-step reaction sequence.
- Products were obtained in good yield.

Specifications table

Subject area:	Chemistry
More specific subject area:	*Organic Chemistry*
Name of your method:	Synthesis of chalcone containing an eugenol-1,2,3-triazole scaffold by aldol condensation and cycloaddition reactions
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☆ **Related research article:** Yes, we have related article below.
☆☆ **For a published article:** B. Ardiansah, A. Farhan, A. Firdaus, T. Ariyani, M.A.F. Nasution, A. Fadlan, A.H. Cahyana, E.E. Prabandari, J.C. Mené ndez, Eugenol derivatives containing 1,2,3-triazole hybrids for shikimate kinase inhibition, J. Saudi Chem. Soc. 28 (2024) 101,826. https://doi.org/10.1016/j.jscs.2024.101826

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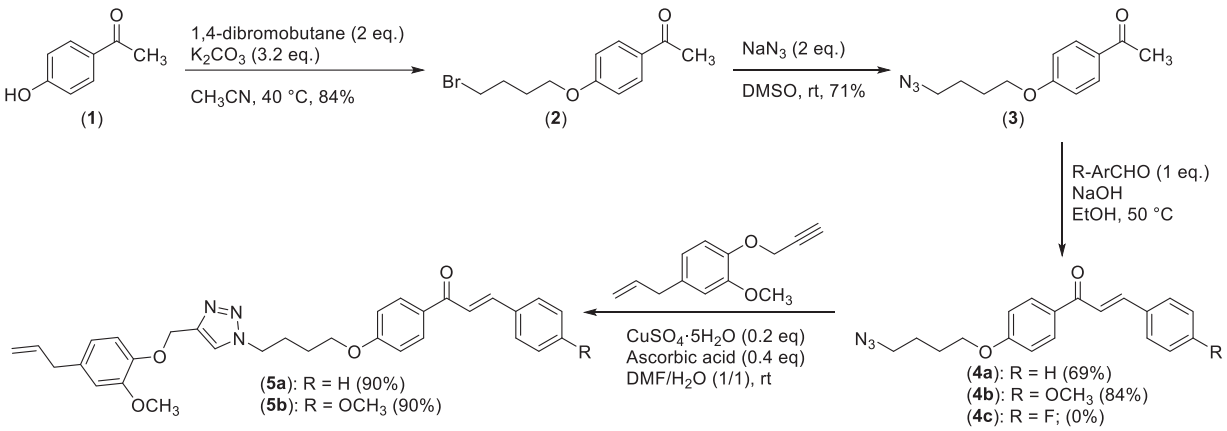

Scheme 1. Synthetic route to produce eugenol-1,2,3-triazole-chalcones.

Background

Molecular hybridization in drug design has led to the combination of pharmacophoric scaffolds, creating new hybrid compounds with enhanced stability and bioactivity [1]. Eugenol, a major constituent in clove oil, offers plentiful health benefits because of its potent biological properties [2,3]. Due to its known antiviral, anticancer, antibacterial, antioxidant and anti-inflammatory properties, it has long been used in various area [4]. 1,4-Disubstituted-1,2,3-triazole are of significant interest in medicinal chemistry because of their diverse biological activities and robust chemical properties [5]. These compounds demonstrate significant antioxidant, antiproliferative, antitubercular, antimicrobial, and anticonvulsant activities, highlighting their potential value in the development of treatments for a range of diseases [6,7]. Their stable structure and ease of synthesis via the copper(I) alkyne-azide cycloaddition (CuAAC) reaction make them highly attractive appeal as versatile scaffolds in drug design [8]. Concurrently, chalcones, recognized for their distinctive structure and biological properties, exhibit wide range of pharmacological effects such as analgesic, anti-inflammatory, antibacterial, antiviral, and anticancer actions [9,10]. In this study, two novel eugenol-1,2,3-triazole-chalcones were synthesized via a step-by-step synthesis starting from the simple compound 4-hydroxyacetophenone (Scheme 1).

Method details

To accomplish our objective, we began the synthesis with the alkylation of 4-hydroxyacetophenone (**1**). Experimentally, the mixture of compound **1** (1.67 g, 12.3 mmol), potassium carbonate (5.4 g, 39.1 mmol), and 1,4-dibromobutane (2.83 mL, 24.2 mmol) was dissolved in acetonitrile (15 mL) and stirred at 40 °C for 17 h. The reaction mixture was extracted with ethyl acetate and subsequently washed with saturated aqueous sodium bicarbonate solution, water, and brine. The organic layer was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using *n*-hexane/ethyl acetate (10:1 v/v) to afford 1-(4-(4-bromobutoxy)phenyl)ethan-1-one (**2**) (2.80 g, 84 %) as a colorless liquid. Compound **2** (1.63 g, 6 mmol) was subjected to a nucleophilic substitution reaction by stirring with sodium azide (0.78 g, 12 mmol) in DMSO (12 mL) at room temperature for 23 h. The mixture was extracted with ethyl acetate, washed with water and brine, and the organic layer was dried over anhydrous sodium sulfate before the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 10/1 v/v) to obtain compound **3**, 1-(4-(4-azidobutoxy)phenyl)ethan-1-one (994 mg, 71 %) as a colorless liquid.

Chalcone skeleton was synthesized by reacting compound **3** with benzaldehyde, 4-methoxybenzaldehyde, or 4-fluorobenzaldehyde through a base-catalyzed aldol condensation. The mixture containing compound **3** (0.466 g, 2 mmol) and benzaldehyde (2 mmol) in 4 mL of EtOH was initially stirred at room temperature for 15 min. Subsequently, NaOH solution (1.2 g in 4 mL of EtOH) was added dropwise, and the reaction was stirred at 50 °C for 29 h. The reaction mixture was neutralized with a 10 % v/v HCl solution and then placed in an ice-filled beaker for 15 min. The resulting solid was filtered, washed with water, and dried. The crude product was purified by silica gel column chromatography (*n*-hexane/ ethyl acetate = 20/1 v/v to 8/1 v/v) to obtained compound **4a**, (*E*)−1-(4-(4-azidobutoxy)phenyl)−3-phenylprop-2-en-1-one, as a white solid (444 mg, 69 %). Compound **4b**, (*E*)−1-(4-(4-azidobutoxy)phenyl)−3-(4-methoxyphenyl)prop-2-en-1-one was obtained in 84 % yield (592 mg) as a yellow solid by using 4-methoxybenzaldehyde instead of benzaldehyde at the same reaction condition for 20 h reaction time. However, preparation of compound **4c** from 4-fluorobenzaldehyde was unsuccessful, even optimizing some parameters such as temperature, solvent, catalyst.

The final step in constructing chalcone derivatives with an eugenol-1,2,3-triazole scaffold involves azide-alkyne cycloaddition. In this process, a mixture of **4a** (64 mg, 0.20 mmol), propargylated eugenol (40 mg, 0.20 mmol), copper sulfate pentahydrate (10 mg, 0.04 mmol), and ascorbic acid (14 mg, 0.08 mmol) in DMF/H_2O (2 ml, 1:1 v/v) was stirred at room temperature for 42 h. The mixture was poured into cold water, and the resulting precipitate was filtered and dried to obtain compound **5a**, (*E*)−1-(4-(4-(4-((4-allyl-2-methoxyphenoxy)methyl)−1*H*-1,2,3-triazol-1-yl)butoxy)phenyl)−3-phenylprop-2-en-1-one (94 mg, 90 %) as a yel-

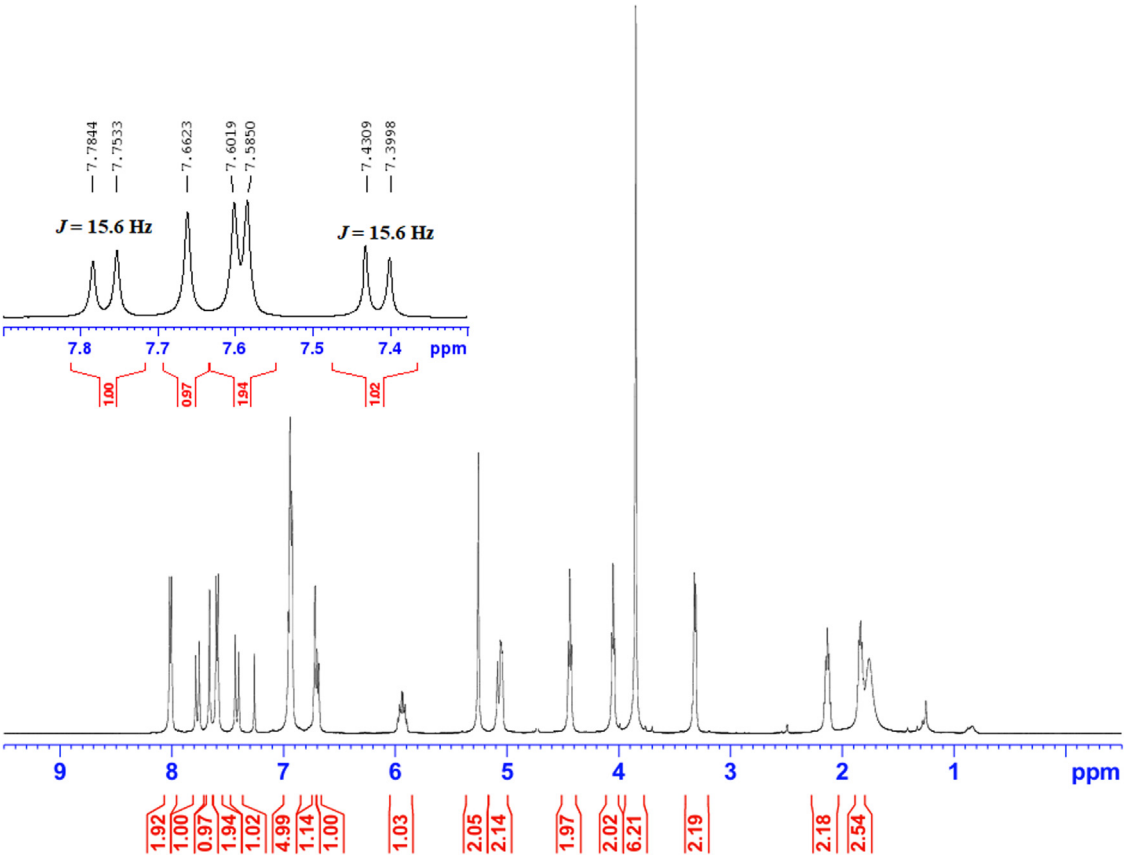

Fig. 1. ^{1}H NMR spectrum of **5b**.

low solid. Meanwhile, compound **5b**, (*E*)−1-(4-(4-(4-((4-allyl-2-methoxyphenoxy)methyl)−1*H*-1,2,3-triazol-1-yl)butoxy)phenyl)−3-(4-methoxyphenyl)prop-2-en-1-one was obtained from **4b** under the same reaction conditions in 90 % yield (100 mg) as a yellow solid after 19 h.

Method validation

The structures of the products were confirmed by IR, ^{1}H and ^{13}C NMR, and HRMS (See Supplementary Material). For instance, ^{1}H NMR spectrum of compound **5b** is depicted in Fig. 1, which clearly showed olefinic hydrogens of *trans*-chalcone at δ 7.4–7.8 ppm and olefinic hydrogens of eugenol moiety at δ 5–6 ppm region. In conclusion, two chalcone derivatives featuring eugenol-1,2,3-triazole functionality were successfully synthesized from 4-hydroxyacetophenone through a series of reactions including bromoalkylation, azidation, base-catalyzed aldol condensation, and azide-alkyne [3+2] cycloaddition. All steps produced compounds in good yields, and characterized well with IR, HRMS, and NMR.

Limitations

We found that reaction of compound **3** with 4-fluorobenzaldehyde did not afford the desired product even modifying catalyst, reaction time, and temperature.

Ethics statements

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Atta Ullah: Investigation, Visualization. **Bayu Ardiansah:** Conceptualization, Methodology, Validation, Resources, Writing – original draft, Supervision, Funding acquisition. **Antonius Herry Cahyana:** Resources, Supervision, Writing – review & editing. **Abad Ali:** Validation, Writing – review & editing, Supervision.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mex.2024.102956.

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