Bioorganic & Medicinal Chemistry Letters 26 (2016) 3621–3625

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of lignan conjugates via cyclopropanation: Antimicrobial and antioxidant studies

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ARTICLE INFO

Article history:
Received 19 March 2016
Revised 23 May 2016
Accepted 3 June 2016
Available online 4 June 2016

Keywords:
Antimicrobial
Antioxidant
Lignans
MIC
Molecular docking

ABSTRACT

Ethyl 2-(4-methoxyphenyl)-3-(thiophene-2-carbonyl)cyclopropanecarboxylates **2**(**a**–**f**) and ethyl 4-aryl-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-carboxylates **4**(**a**–**f**) were synthesized by simple procedure. The synthesized new compounds were screened in vitro for their antimicrobial and antioxidant activities. The compounds **2b** and **4f** showed excellent antibacterial activity; while **2b** and **4f** showed remarkable antifungal properties. The results of antioxidant activity studies revealed that compounds **4b** and **4f** manifested profound antioxidant potential. The docking studies were done for the final compounds. The ADME result indicates that all these molecules possess pharmaceutical properties in the range of 95% of drugs.

In recent years cyclopropane derivatives have attracted a lot of interest because of their biological and pharmaceutical applications. Cyclopropane ring systems are ubiquitous in nature and are found in a large number of natural products, insecticides, and pharmaceutical drug candidates. Designing small molecules that bind to therapeutically important biological targets with high affinity and selectivity is a major goal in contemporary bioorganic and medicinal chemistry. The reactivity of cyclopropanes allows them to be utilized as versatile intermediates in the organic synthesis of complex molecules and, thus, is frequently employed for the above purposes.

The synthesis and application of multi-substituted cyclopropanes has been a subject of great interest due to their roles as the basic structural elements in a wide range of biologically active compounds and important intermediates in organic synthesis with diverse applications in synthetic, agricultural, and medicinal chemistry as well as in material science.[1] Thienyl- and furylpropenones are treated as useful intermediates in organic synthesis. These α,β-unsaturated ketones reacts with activated methylene compounds such as malonates, cyanoacetates, and malononitrile to give addition products which were cyclized to heteroaryl substituted dihydropyranes, cyclohexanols, and piperidones.[2] Cyclopropane analogues have been found to exhibit diverse biological applications such as antibacterial, antifungal, antiviral, anti-HIV, anticancer, antitumor, antimicobacterial, antiestrogenic, agonist and COX-II inhibitor properties.[3]

The lignans are a group of secondary metabolites found in plants, which are produced by oxidative dimerization of two phenylpropanoid units and show bioactive diversity in their chemical assembly. An efficient transformation of thienylpropenones to heteroaryl substituted cyclopropyl ketones by reactions with $Me_3SO^+I^-$, and then to dihydrobenzo[*b*]thiophenones was reported.[2] Synthesis of several types of lignans such as dibenzylbutanediols, dibenzylbutanes, substituted tetrahydrofurans by an accessible approach was developed.[4] Selectively functionalized 1,4-diarylbutane-1,4-diols undergo a number of different reactions upon treatment with methanesulfonyl chloride and triethylamine leading to (4*R*,5*S*)-4-(4-methoxyphenyl)-5.6-dimethyl-4,5-dihydrobenzo(*c*)thiophene lignans.[5] Lignans possesses broad range of structures and biological activities. These were known to have anti-tumor, antimitotic and antiviral activity and to specifically inhibit certain enzymes.[6] Novel lignans continue to be described by natural products chemists at a steady rate and knowledge of their variety, as well as their range of occurrence in the plant kingdom, is continually expanding.[7]

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http://dx.doi.org/10.1016/j.bmcl.2016.06.005
0960-894X/

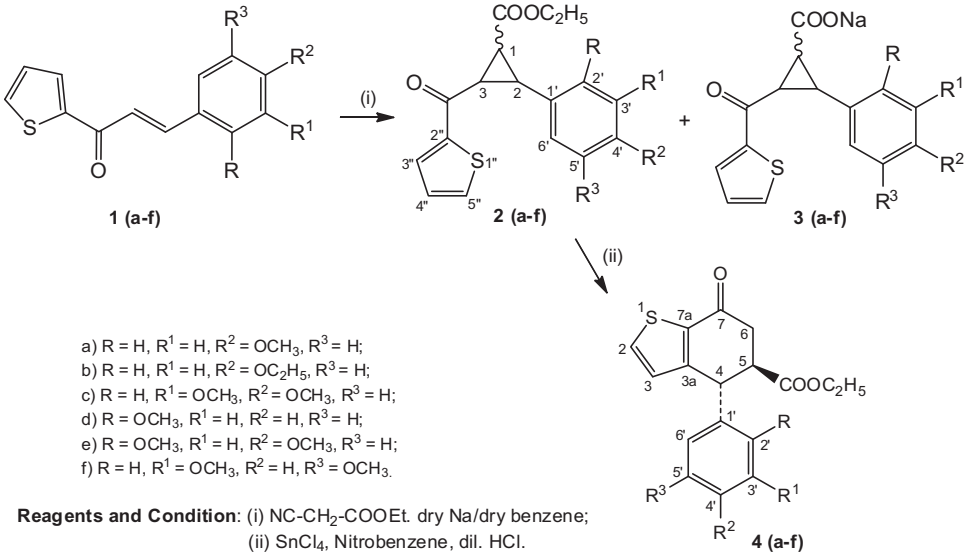
In view of enormous biological applications associated with lignans, and to explore further possibilities of using thiophenylpropenones in drug synthesis, we herein report about the reactions of thiophenylpropenones with activated methylene compound ethyl cyanoacetate into cyclopropyl esters, and about their transformations into lignan conjugates of more biological potency.

In the synthesized compounds, thiophene was embedded as the aromatic component of ligans for several reasons that are delineated below. Thiophenes are flat five-membered aromatic heterocyclic rings containing sulfur. This chemical class is important in the development of pharmaceutical agents because of its ready availability, ease of functionalization and high stability. The aromaticity of the ring makes this structure highly amenable to either electrophilic or nucleophilic substitution reactions potentially enabling the medicinal chemist to generate greater number of modifications and synthesize novel structural congeners and bioisosteres for improved bioavailability, reduced toxicity, and greater half-life and for improving its activity against the intended target. Further, since the aromaticity is lesser than that for benzene, it has slightly better solubility properties as compared to benzene. Further, unlike thioethers, thiophenes show resistance to degradation by alkylation and oxidation, yet are amenable to oxidation-induced metabolic activation within biological systems. The highly reactive carbon centers flanking the sulfur makes halogen substitution on thiophenes an order of magnitude better than on benzenes. Thus, use of thiophenes affords the dual advantage of retaining rigidity (by virtue of its aromaticity) yet acting as synthons for substitution of non-aromatic structural moieties.[8] Considering all the above-mentioned favorable aspects and wanting to develop a scaffold that is amenable to modifications for improving drug-like properties, thiophenes were embedded as the aromatic component of lignans. Further, selective organic chemistry efforts have demonstrated the incorporation of thiophenes into lignans as a successful precedent to our current work.[2,9–13]

3-Aryl-1-(thiophen-2-yl)prop-2-en-1-ones, **1**(**a**–**f**) were converted to a mixture of ethyl 2-aryl-3-(thiophene-2-carbonyl) cyclopropanecarboxylates **2**(**a**–**f**) in 68–78% yield, and sodium 2-aryl-3-(thiophene-2-carbonyl)cyclopropanecarboxylates **3**(**a**–**f**) in 07–14% yield by the reaction of ethyl cyanoacetate and dried sodium metal in dry benzene at room temperature. Compounds **2**(**a**–**f**) on cyclization reaction with $SnCl_2$ and nitrobenzene under reflux conditions produced (4*R*,5*R*)-ethyl 4-aryl-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-carboxylates **4**(**a**–**f**) in 72–86% yields (Scheme 1). The intermediates 3-aryl-1-(thiophen-2-yl)prop-2-en-1-ones **1**(**a**–**f**) were prepared by the condensation of 2-acetylthiophene with aromatic aldehydes in the presence of sodium hydroxide in methanol.

The structural analysis of the ethyl 2-(aryl)-3-(thiophene-2-carbonyl)cyclopropanecarboxylate, **2**(**a**–**f**) was made by ^{1}H NMR and ^{13}C NMR spectral studies and elemental analysis. In ^{1}H NMR spectra, triplets for one proton each at δ 1.64–1.66, 2.10–2.13 ppm and δ 2.32–2.37 ppm was observed for C_1-H, C_3-H and C_2-H protons, respectively. Signals appearing as quartet for two protons at δ 4.12–4.21 ppm and triplet for three protons at δ 1.28–1.31 ppm were assigned to ester CH_3 and OCH_2 protons respectively. Array of signals appearing as multiplet in the region δ 6.96–7.75 ppm were due to aromatic and five membered ring protons. In ^{13}C NMR spectra, the signals at δ 14.16–14.44 and δ 61.17–61.90 ppm were due to ester CH_3 and OCH_2 carbons, respectively. The signals due to carbons of newly formed cyclopropyl ring were observed at δ 24.06–24.60, 28.95–32.80 ppm and δ 39.10–39.77 ppm for C-1, C-2 and C-3 atoms, respectively. The carbonyl carbon showed the signal in the downfield at δ 191.56–192.96 ppm while ester carbonyl carbon absorbed at δ 171.10–171.80 ppm. These ^{13}C NMR spectral data supports the cyclopropyl system formation. All the synthesized compounds **2**(**a**–**f**) showed molecular ion peaks as their base peaks in their mass spectra and were supported by satisfactory elemental analysis. Thus, all these spectral and elemental analysis data confirms the structures of synthesized compounds **2**(**a**–**f**).

Compounds **2**(**a**–**f**) was taken in nitrobenzene, anhydrous stannic chloride was added drop wise with stirring at 0 °C and the cooled reaction mass was stirred for 8 h at room temperature deliver the expected final compound **4**(**a**–**f**) in 72–86% yields. In ^{1}H NMR spectra, **4**(**a**–**f**) showed triplet for three proton at δ 1.21–1.30 ppm and quartet for two protons at δ 4.11–4.21 ppm were due to ester CH_3 and OCH_2 protons, respectively. The absolute stereochemistry (configuration) of the two stereogenic centers at C-4 and C-5 was determined on the basis of NMR studies.[14] The coupling constants in the spectra of the compounds **4**(**a**–**f**) for C_4-H as d (J = 11.9–10.3 Hz) and for C_5-H dd (J = 13.8–12.3 and 11.9–10.3 Hz) suggests that the two hydrogen atoms at C-4 and C-5 stereogenic centers are axially oriented, while the phenyl, carboxylic ester substitutions are equatorially oriented. Based on these observation the compounds **4**(**a**–**f**) have assigned (4*R*,5*R*)-configuration. The C_6-H_{ax} protons resonate at 3.20–3.10 as dd (J = 14.0–12.8 Hz and 11.5–10.2 Hz) and the 6-H_{eq} protons



Scheme 1. Schematic diagram for the synthesis of lignan conjugates, **4**(**a**–**f**).