Bioorganic & Medicinal Chemistry Letters xxx (2016) xxx–xxx

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

Kanchipura Ramachandrappa Raghavendra [a], Nagamallu Renuka [b], Vivek H. Kameshwar [c], Bharath Srinivasan [d], Kariyappa Ajay Kumar [b,*], Sheena Shashikanth [a,*]

[a] Department of Studies in Chemistry, University of Mysore, Manasagangothri, Mysore, India
[b] Department of Chemistry, Yuvaraja College, University of Mysore, India
[c] Central Research Laboratory, Adichunchanagiri Institute of Medical Sciences, B.G. Nagara, India
[d] Center for the Study of Systems Biology, School of Biology, Georgia Institute of Technology, Atlanta, GA 30332, USA

ARTICLE INFO

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

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]

* Corresponding authors.
E-mail addresses: padduammu2016@gmail.com (S. Shashikanth), ajaykumar@ycm.uni-mysore.ac.in (K. Ajay Kumar).

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

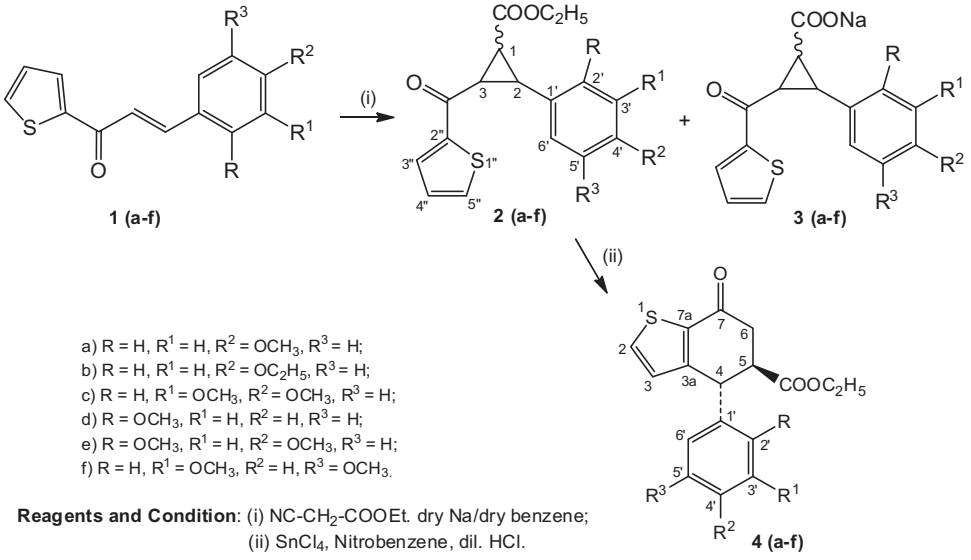
In view of enormous biological applications associated with lignans, and to explore further possibilities of using thiophenylpropenones in drug synthesis, we herein report about the reactions of thiophenylpropenones with activated methylene compound ethyl cyanoacetate into cyclopropyl esters, and about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

resonate at 3.55–3.38 as dd (J = 14.0–12.5 Hz and 4.6–3.4 Hz). These chemical shifts and coupling patterns suggested that C_6-H_{ax} protons coupled with C_6-H_{eq} and C_5-H; and C_6-H_{eq} protons coupled with C_6-H_{ax} and C_5-H and making C_6-H_{ax} and C_6-H_{eq} protons diastereotopic.

In ^{13}C NMR spectra, **4**(**a**–**f**) showed the signals at δ 14.12–14.90 and 61.30–63.71 ppm for CH_3 and OCH_2 carbons. The signals appearing at δ 171.06–171.60 and δ 189.38–191.68 ppm were assigned to COO and C=O carbons, confirming the formation of the products. All the new compounds showed M^+ ion peaks at 32–68% abundance and a base peak at (M^+-72). The satisfactorily elemental analysis proves the structures of the synthesized compounds.

Minimum inhibitory concentrations (MIC's) of the compounds **2** (**a**–**f**) and **4**(**a**–**f**) were determined by broth dilution technique.[15,16] The tests were conducted against bacterial pathogens *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli* and against fungal strains *Cryptococcus neoformans*, *Aspergillus niger*, *Aspergillus flavus*. The antibiotics ciprofloxacin and nystatin were used as positive controls against bacterial and fungal stains, respectively. Dimethyl sulfoxide was used as solvent control. The experiments were carried out in triplicate; the results were taken as a mean ± standard deviation (SD) and are summarized in Table 1.

All the synthesized compounds **2**(**a**–**f**) and **4**(**a**–**f**) exerted a wide range of modest in vitro antibacterial activity against all the tested organisms. However, compound **2b** having an ethoxy and **4f** having a methoxy substituent exhibited excellent antibacterial activity against all the tested organisms compared to standard. The sole exception was compound **2b**, the action of which against *E. coli* was comparable to that shown by the standard. Compound **2e** and **4a** were active with *S. pyogenes*, while compound **2c** inhibited the growth of the organisms similar to that shown by standard. The remaining compounds showed less activity compared to the standard.

Synthesized compounds **2**(**a**–**f**) and **4**(**a**–**f**) exerted modest antifungal activity having minimum inhibitory concentration value (MIC) 12.5–100 μg/mL. In the series **2**(**a**–**f**), compound **2b** having an ethoxy substitution showed greater extent of inhibition against the organisms tested. Compound **2c** was active with *A. niger*, while compound **2d** showed higher inhibition of *A. flavus*. Remaining compounds also showed modest inhibitory effect against the organisms tested, albeit lesser than that shown by the standard.

In the series **4**(**a**–**f**), compound **4f** demonstrated excellent activity against the tested organisms when compared to standard. However compound **4a**, **4c** and **4d** displayed higher potency against *A. niger*. Remaining compounds **4b** and **4e** showed less potency of inhibition against the fungal strains as compared to the standard.

Further, various assays were performed to assess the antioxidant activities of the compounds. Radical scavenging potency of all the compounds **4**(**a**–**f**) was assessed in vitro by the DPPH[17] and hydroxyl radical scavenging assay.[18,19] The experiments were performed in triplicate at five different concentrations; the results were taken as a mean ± standard deviation (SD) and are presented in Tables 2 and 3.

A freshly prepared DPPH solution shows a deep purple color with an absorption maximum at 517 nm. When the purple color changes to yellow, it leads to decreased absorbance. This is because of the antioxidant molecule reducing the DPPH free radical through donation of hydrogen atom. Instantaneous or concomitant decrease in absorbance would be indicative of potent antioxidant activity by the compound. Based on the experimental results, compound **4b** and **4f** having ethoxy and methoxy substituent showed stronger DPPH scavenging activity than others. Compounds **4a** and **4c** having a methoxy substitution showed antioxidant properties similar to that displayed by the standard. Remaining compounds **4d** and **4e** showed less activity compared with the standard ascorbic acid.

The hydroxyl radical is a highly reactive free radical formed in biological systems and it is capable of damaging biomolecule found in living cells. The hydroxyl radical has the ability to break DNA and cause strand breakage, which contributes to carcinogenesis, mutagenesis and cytotoxicity. In this method, compound **4**(**a**–**f**) displayed a range of hydroxyl radical scavenging activity ranging from highly potent to weak. Among the compounds studied, compounds **4b** and **4f** exhibited remarkable capacity for scavenging hydroxyl radical, significantly higher than that of the standard BHA, whereas compound **4a** showed moderate scavenging activity. However the remaining compounds **4c**, **4d** and **4e** exhibited weak radical scavenging activity.

Molecular docking has emerged as an important tool in drug design and discovery of novel potential ligands.[20] In order to understand possible mechanisms by which the synthesized compounds exerted their antibacterial activity; they were docked onto a protein critical for bacterial cell wall synthesis. Peptidoglycan biosynthesis begins with the action of two enzymes viz., MurA and MurB, with MurB catalyzing the second step in the formation of muramyl sugar. MurB is a known target for antibacterial chemotherapy.[21] The small molecules were systematically docked onto the structure of MurB (PDB ID: 1MBT). The docking studies

Table 1
Minimum inhibitory concentrations (MIC) (in μg/mL*) of the synthesized compounds **2**(**a**–**f**) and **4**(**a**–**f**) against bacterial and fungal species

Compounds	*S. aureus*	*S. pyogenes*	*E. coli*	*C. neoformans*	*A. niger*	*A. flavus*
2a	50.0 ± 0.45	50.0 ± 0.42	50.0 ± 0.76	500.±0.66	100 ± 0.51	100 ± 0.65
2b	12.5 ± 0.06	25.0 ± 0.56	25.0 ± 0.65	12.5 ± 0.76	12.5 ± 0.32	25.0 ± 0.43
2c	25.0 ± 0.87	50.0 ± 0.54	25.0 ± 0.76	25.0 ± 0.66	25.0 ± 0.32	50.0 ± 0.75
2d	50.0 ± 0.32	100 ± 0.53	75.0 ± 0.21	75.0 ± 0.54	75.0 ± 0.64	25.0 ± 0.33
2e	25.0 ± 1.03	25.0 ± 0.97	25.0 ± 0.43	25.0 ± 0.66	50.0 ± 0.98	50.0 ± 1.05
2f	50.0 ± 0.65	75.0 ± 0.76	75.0 ± 0.32	50.0 ± 1.34	50.0 ± 0.61	75.0 ± 0.43
4a	50.0 ± 0.77	25.0 ± 0.76	50.0 ± 0.32	50.0 ± 0.55	25.0 ± 0.76	50.0 ± 0.43
4b	75.0 ± 0.76	50.0 ± 0.81	50.0 ± 0.21	25.0 ± 0.87	75.0 ± 0.21	100 ± 0.65
4c	50.0 ± 0.54	50.0 ± 0.22	25.0 ± 0.17	25.0 ± 0.53	25.0 ± 0.32	50.0 ± 0.21
4d	25.0 ± 0.55	50.0 ± 0.42	50.0 ± 0.65	25.0 ± 0.65	25.0 ± 0.76	50.0 ± 0.87
4e	50.0 ± 0.21	50.0 ± 0.55	75.0 ± 0.63	50.0 ± 0.42	100 ± 1.08	75.0 ± 0.65
4f	12.5 ± 0.21	25.0 ± 0.93	12.5 ± 1.05	12.5 ± 0.76	25.0 ± 0.65	25.0 ± 0.87
Cipro[a]	25.0 ± 0.54	50.0 ± 0.21	25.0 ± 0.66	—	—	—
Nyst[b]	—	—	—	25.0 ± 1.04	50.0 ± 0.54	50.0 ± 0.23

* Values are mean ± SD of three replicates.
[a] Ciprofloxacin was used as a positive control against bacteria species.
[b] Nystatin was used as a positive control against fungal species.

Please cite this article in press as: Raghavendra, K. R.; et al. *Bioorg. Med. Chem. Lett.* (2016), http://dx.doi.org/10.1016/j.bmcl.2016.06.005

Table 2
Antioxidant activity of the compounds **4**(**a**–**f**) by DPPH radical scavenging method

Compounds	% Radical scavenging activity*				
	20 (μg/mL)	40 (μg/mL)	60 (μg/mL)	80 (μg/mL)	100 (μg/mL)
4a	15.02 ± 0.43	16.71 ± 0.32	20.31 ± 0.32	23.92 ± 0.41	26.22 ± 0.44
4b	17.08 ± 0.32	18.54 ± 0.32	22.87 ± 0.32	25.43 ± 0.32	28.96 ± 0.43
4c	14.65 ± 0.65	14.76 ± 0.87	20.93 ± 0.65	22.87 ± 0.65	25.54 ± 0.27
4d	10.76 ± 0.54	13.54 ± 0.41	17.76 ± 0.32	19.65 ± 0.41	21.65 ± 0.76
4e	9.76 ± 0.41	11.76 ± 0.98	14.98 ± 0.54	18.64 ± 0.87	20.76 ± 0.87
4f	18.56 ± 0.41	19.97 ± 0.54	24.76 ± 0.10	27.43 ± 0.65	31.54 ± 1.32
AA[a]	15.08 ± 0.89	16.87 ± 0.89	21.98 ± 0.31	24.25 ± 0.22	28.65 ± 0.98

* Values are mean ± SD of three replicates.
[a] Ascorbic acid was used as a standard antioxidant.

Table 3
Antioxidant activity of the compounds **4** (**a**–**f**) by hydroxyl radical scavenging method

Compounds	% Radical scavenging activity*				
	20 (μg/mL)	40 (μg/mL)	60 (μg/mL)	80 (μg/mL)	100 (μg/mL)
4a	13.03 ± 0.53	17.98 ± 1.21	24.76 ± 0.45	30.98 ± 0.54	34.09 ± 0.76
4b	15.43 ± 0.54	19.76 ± 1.32	26.98 ± 1.06	34.13 ± 0.65	37.99 ± 0.76
4c	12.23 ± 0.50	16.64 ± 0.87	24.07 ± 0.56	30.37 ± 0.65	34.02 ± 0.98
4d	11.87 ± 0.24	15.98 ± 0.43	22.76 ± 1.06	29.77 ± 0.21	31.56 ± 0.74
4e	10.05 ± 0.76	12.76 ± 0.65	19.87 ± 0.66	23.87 ± 0.32	26.82 ± 0.51
4f	16.76 ± 0.12	20.65 ± 0.32	29.65 ± 0.43	36.32 ± 0.41	41.50 ± 0.32
BHA[b]	13.87 ± 0.10	17.95 ± 0.12	25.58 ± 0.20	32.03 ± 0.32	36.87 ± 0.76

* Values are mean ± SD of three replicates.
[b] Butylated hydroxyanisole was used as a positive control.

revealed that, all the twelve novel compounds exhibited excellent docking and binding energies toward the receptor active site pocket ranging from −4.64 to −6.94 kcal mol^{-1} (Table 4). A total of twelve validated potential leads are suggested from the in vitro studies among which, compounds **4b** and **4f** satisfy both the docking and ADME drug-like criteria when compared with that of the reported standards. Derivatives (compounds **4b** and **4f**) of parental nucleus imparted a specific geometrical space around the active site of MurB and considered as the best docking poses. Compound **4b** formed a hydrogen bond with the backbone amino group of Ile173 (Data not shown), whereas compound **4f** formed an additional cation–π interaction with Arg 327 apart from a hydrogen bond with the backbone amino group of Ile173 (Fig. 1). Hence, it can be reasonably speculated that compounds **4b** and **4f** inhibits the bacterial peptidoglycan bio-synthesis by restricting the vital MurB enzyme from carrying out its function.[21–23] Having performed this exercise, we fully understand the limitation of blind docking studies in assigning a target receptor for a particular small-molecule and that it is highly likely that the small-molecules may interact with additional targets in the bacterial and fungal organisms tested to bring about their inhibition. However, by demonstrating it in the case of MurB, a critical enzyme involved in bacterial cell wall synthesis, we have established one plausible target for the synthesized molecules. Future studies in the lab would explore additional targets for the newly synthesized molecules.

Table 4
Docking scores of synthesized compounds **2**(**a**–**f**) and **4**(**a**–**f**) against MurB from *E. coli* (PDB id: 1MBT)

Compound	RMS Derivative OPLS-2005	Docking score (kcal/mol)	Glide energy (kcal/mol)
2a	0.038	−6.25	−40.91
2b	0.018	−6.55	−45.44
2c	0.047	−6.64	−50.21
2d	0.037	−6.66	−49.67
2e	0.005	−6.50	−47.54
2f	0.049	−6.45	−50.38
4a	0.026	−6.31	−33.78
4b	0.009	−6.55	−37.13
4c	0.026	−4.94	−44.65
4d	0.024	−6.32	−41.82
4e	0.022	−4.64	−34.96
4f	0.012	−6.80	−46.65
Ascorbic acid	0.050	−6.94	−34.56
BHA	0.001	−4.79	−24.35

QikProp, the prediction program was used to calculate pharmacokinetic ADME (absorption, distribution, metabolism and excretion) properties consisting of principal descriptors and physiochemical properties. Qikprop modules predict the range of molecular properties for the newly synthesized compounds to compare them with those of 95% of known drugs.[20] All the ligands obey the Lipinski's rules: molecular weight below 500 Da, hydrogen bond donor (less than five) and acceptor (less than ten). QPlogPo/w (octanol/water partition coefficient) for all the ligands is less than five.[23] Further, all the ligands satisfy the values of partition coefficient of octanol/gas (QPlogPoct), water/gas (QPlogPw) and brain/blood (QPlogBB) permeability, Skin permeability (QPlogKp), aqueous solubility (QPlogS) and the predicted values are within the permissible range (Data not shown). Qualitative Model for Human Oral Absorption was predicted and all the twelve synthesized compounds **2**(**a**–**f**) and **4**(**a**–**f**) showed high oral absorption (Table 5).

In summary, in order to develop antimicrobial and antioxidant molecules, we have synthesized new bioactive lignans via cyclopropyl esters. This is done by developing new methodologies that increases the structural complexity of new lignans, while decreasing the number of synthetic steps required. These compounds were evaluated for antimicrobial and antioxidant activities. Compound **4f** exhibited potent antimicrobial and antioxidant activity among the series. In silico ADME predictions indicate that all these molecules possess pharmaceutical properties in the range of 95% of drugs. It may be concluded from ADME studies that compound **4f** might act as a good antimicrobial compound with satisfactory ADME properties. Further, docking studies point out to efforts at

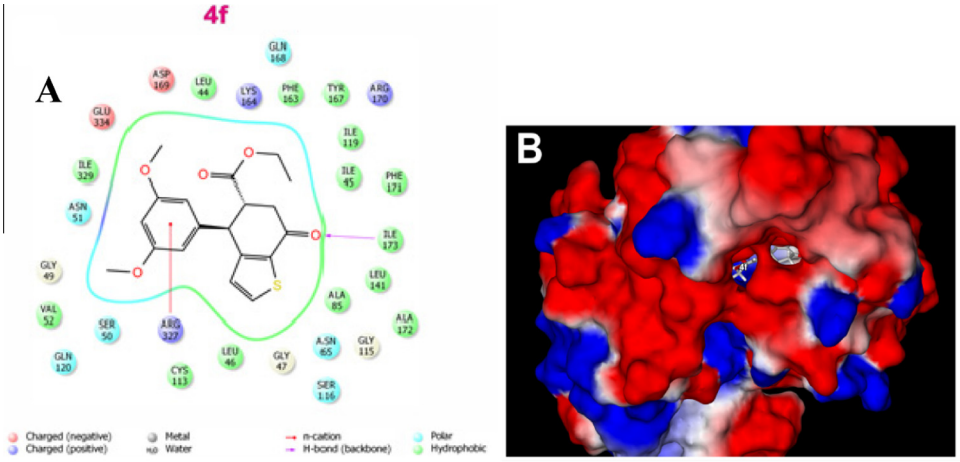


Figure 1. (A) Molecular interaction of MurB (PDB ID: 1MBT) with compound **4f** showing the hydrogen bond with the backbone amino group of Ile173 and the n-cation interaction with Arg 327. (B) Electrostatic surface representation of the protein depicting the best docked pose for compound **4b** in the active site of MurB.

Table 5
Computer aided ADME screening of the synthesized compounds

Ligand	Mol MW	QPlogHERG	QPPCaco	QPlogBB	QPlogKp	a*	b*	c*	d*
2a	330.4	−5.41	1856.56	−0.40	−1.57	0.22	100	1376.5	0
2b	344.4	−5.81	1856.58	−0.51	−1.48	0.39	100	1376.3	0
2c	360.4	−5.42	1857.56	−0.49	−1.61	0.21	100	1370.5	0
2d	330.4	−5.62	1838.42	−0.44	−1.51	0.25	100	1257.2	0
2e	360.4	−5.54	1837.03	−0.52	−1.61	0.23	100	1255.9	0
2f	360.4	−5.35	1853.70	−0.48	−1.63	0.20	100	1372.9	0
4a	330.4	−5.20	1591.10	−0.32	−2.11	0.28	100	1477.5	0
4b	344.4	−5.60	1591.07	−0.43	−2.02	0.45	100	1477.5	0
4c	360.4	−5.25	1592.67	−0.41	−2.16	0.27	100	1479.1	0
4d	330.4	−4.90	1665.84	−0.26	−2.04	0.24	100	1505.3	0
4e	360.4	−5.07	1713.77	−0.35	−2.09	0.26	100	1550.6	0
4f	360.4	−5.03	1616.09	−0.38	−2.19	0.25	100	1494.8	0
BHA	180.2	−3.56	3008.64	−0.06	−1.91	0.08	100	1627.0	0
Ascorbic acid	176.1	−2.68	48.59	−1.66	−5.37	−0.94	48.13	18.82	0
Range 95% of Drugs	130.0 to 725.0	<−5	<25 poor, >500 great	−3.0 to 1.2	−8.0 to −1.0	−1.5 to 1.5	>80% is high	<25 poor,>500 great	0–4

a*—QPlogKhsa, b*—% human oral absorption, c*—QPPMDCK, d*—Volition of Lipinski's rule.

assigning a tentative receptor that is targeted by these compounds to bring about their antimicrobial activity. Furthermore, this study provides suitable candidates as potential lead compounds that can be employed in ameliorating various diseased conditions caused by microbes, fungi and free radicals.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.06.005.

References and notes

1. Cao, W.; Zhang, H.; Chen, J.; Deng, H.; Shao, M.; Lei, L.; Qian, J.; Zhu, Y. *Tetrahedron* **2008**, *64*, 6670.
2. Greiner-Bechert, L.; Sprang, T.; Otto, H.-H. *Monatsh. Chem.* **2005**, *136*, 635.
3. Ajay Kumar, K. *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 467.
4. Wang, Q.; Yang, Y.; Li, Y.; Yu, W.; Hou, Z. J. *Tetrahedron* **2006**, *62*, 6107.
5. Davidson, S. J.; Barker, D. *Tetrahedron Lett.* **2015**, *56*, 4549.
6. Raghavendra, K. R.; Shashikanth, S.; Ajay Kumar, K. *Int. J. Pharm. Pharm. Sci.* **2015**, *7*, 190.
7. Donald Macrae, W.; Neil Towers, G. H. *Phytochemistry* **1984**, *23*, 1207.
8. Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Disc. Dev.* **2005**, *8*, 723.
9. Ramos, A. C.; Pelaze, R.; Lopez, J. L.; Caballero, E.; Medarde, M.; Feliciano, A. S. *Tetrahedron* **2001**, *57*, 3963.
10. Medarde, M.; Ramos, A. C.; Caballero, E.; Lopez, J. L. *Tetrahedron Lett.* **1998**, *39*, 2001.
11. Medarde, M.; Pelaze, R.; De Clairac, L.; Tome, F.; Lopez, J. L.; Feliciano, A. S. *Arch. Pharm.* **1994**, *327*, 91.
12. Medarde, M.; Pelaze, R.; De Clairac, L.; Tome, F.; Lopez, J. L.; Feliciano, A. S.; Gravalos, D. G. *Arch. Pharm.* **1995**, *328*, 403.
13. Amaral, M. F. Z. J.; Callejon, D. R.; Riul, T. B.; Baruffi, M. D.; Toledo, F. T.; Lopes, N. P.; Clososki, G. C. *J. Braz. Chem. Soc.* **2014**, *25*, 1907.
14. Magoulas, G. E.; Rigopoulos, A.; Piperigkou, Z.; Gialelio, C.; Karamanos, N. K.; Takis, P. G.; Troganis, A. N.; Chrissanthopoulos, A.; Maroulis, G.; Papaioannou, D. *Bioorg. Chem.* **2006**, *66*, 132.
15. El-Amraoui, B.; Biard, J. F.; Uriz, M. J.; Rifai, S.; Fassouane, A. *J. Med. Mycol.* **2010**, *20*, 70.
16. Nagamallu, R.; Kariyappa, A. K. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6406.
17. Marsden, S. *Blois. Nat.* **1958**, *181*, 1199.
18. Jayaraman, J.; Venugopal, T.; Nagarajan, R.; Kanagarathinam, S.; Marimuthu, V. P. *Med. Chem. Res.* **2012**, *21*, 1850.
19. Nagamallu, R.; Srinivasan, B.; Ningappa, M. B.; Kariyappa, A. K. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 690.
20. Hochestein, P.; Atallah, A. S. *Mutat. Res.* **1988**, *202*, 363.
21. Bugg, T. D. H.; Braddick, D.; Dowson, C. G.; Roper, D. I. *Trends Biotechnol.* **2011**, *29*, 167.
22. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **2001**, *46*, 3.
23. Ramesh, G.; Janardhan, B.; Ranjith Kumar, T.; Althaf Hussain, S. K.; Rajitha, B. *RSC Adv.* **2015**, *5*, 33562.