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Synthesis, characterization, and antioxidant activity of thymol-based paracetamol analogues

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Abstract

Thymol (2-isopropyl-5-methylphenol) is an important monoterpene phenol occurring in the essential oils isolated from *Thymus vulgaris*, *Thymus zygis*, *Thymus hyemalis*, etc. Thymol and its derivatives show various activities such as antioxidant, antiinflammatory, antibacterial, and antifungal effects. In the present study, a set of new benzamide derivatives (**4a**–**e**), which are structurally similar to paracetamol, were synthesized from thymol using a green synthetic approach and characterized by Fourier-transform infrared (FT-IR) and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopies, liquid chromatography–mass spectrometry (LC–MS), and X-ray single-crystallographic analysis for derivative **4c**. These derivatives were subjected to antioxidant testing by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and antibacterial testing against five microorganisms. Molecular docking studies of all the compounds indicated that they are good inhibitors of heme oxygenase-1. These results extend the development of thymol-based benzamide scaffolds as promising antioxidant agents.

Keywords Benzoylation · Thymol · Antioxidant activity · DPPH · Docking · Oxygenase-1

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Introduction

It has been estimated that the genus *Thymus* includes at least 200 species with many subspecies, varieties, and forms, both endemic and widespread, distributed across Europe, Asia, North Africa, and the Canary Islands [1]. *Thymus* species are used as medicinal and aromatic plants, as well as in cosmetics and perfumery, throughout their range [2]. Most aspects of their medicinal use are related to the essential oils, which contain various levels of thymol and/or carvacrol with strong and wide-spectrum antimicrobial activity [3, 4]. Essential oils including thymol have been found to act as functional antioxidants and as antimicrobials in foods [5]. Essential oils including carvacrol and thymol have been tested for their insecticidal and genotoxic activities against *Drosophila* [6]. Thymol derivatives have also been found to exhibit antioxidant, antitumor, and anticancer activities [7].

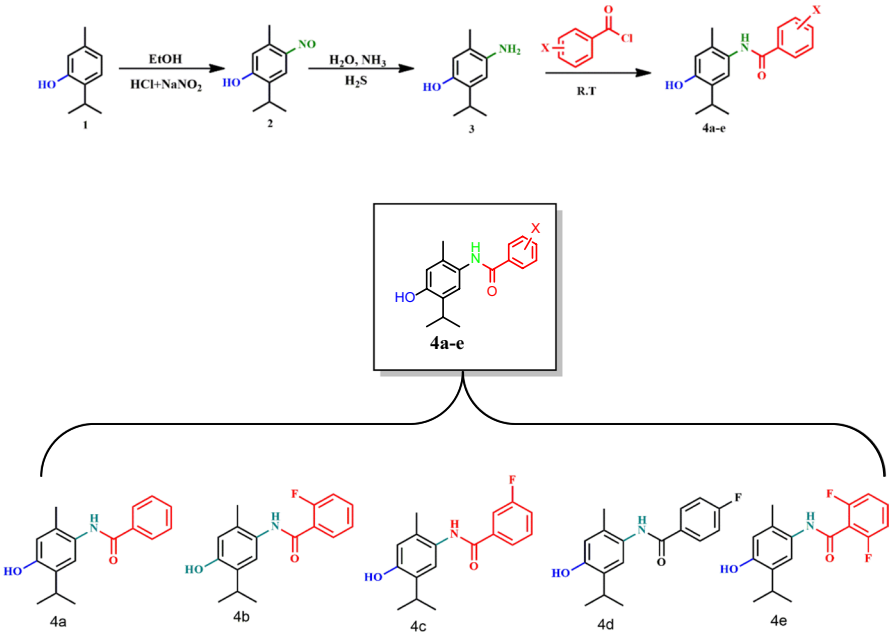
Thymol, a compound derived from *p*-cymene, is widely used in medicine for its antimicrobial, antiseptic, disinfectant, and wound healing properties. Thymol derivatives such as 1,3,4-oxadiazoles have been synthesized and their antimicrobial activity screened [8]. Lupo et al. [9] showed that modified thymol derivatives, viz. 2-(allyloxy)-1-isopropyl-4-methylbenzene, 4-allyl-2-isopropyl-5-methylphenol, and 2-isopropyl-5-methyl-4-propylphenol, exhibit good antibacterial activity against *Streptococcus aureus* 6538 and *Escherichia coli* 11229. Compounds derived from 4-nitrosothymol showed moderate to good antimicrobial and antituberculostatic activities [10, 11]. Liang et al. [12] reported the antibacterial activity of seven structurally characterized thymol derivatives isolated from *Centipeda minima*. The potent antioxidant activity of isoespintanol may be because of the high stability of radicals [13]. Schiff bases derived from 4-aminothymol were synthesized and screened for their antioxidant activities [14]. The essential oil composition, total phenolic and flavonoid contents, and antioxidant activity of *Thymus* species collected from different regions of Iran were also reported [15]. Thymol nanoemulsion exhibits potential antibacterial activity against bacterial pustule disease and a promotory effect on the growth of soybean [16]. Various derivatives of thymol have been synthesized and their different activities (antimicrobial, antifungal, etc.) studied, confirming the biological importance of such compounds [17, 18]. Thymol is a well-known natural phenolic monoterpenoid present as a functional ingredient in numerous products [19]. Paracetamol is a medicine commonly used to treat pain and reduce high body temperature (fever). It is typically used to relieve mild pain such as headache, toothache, etc. It is safe to take, and side effects are rare in most people. It is also observed to exhibit antioxidant activity. Biochemical studies have suggested a direct relationship between its radical scavenging activity and antipyretic and analgesic action. Alisi et al. [20] studied the antioxidant activity of various derivatives of paracetamol. The DPPH assay revealed that all the paracetamol derivatives exhibited significantly higher efficiency than the parent compound and that their radical scavenging activity could be increased by introducing a substituent such as an indazole ring or the ionic *N*-methyl morpholinium group on acyl moiety.

The aim of the work presented herein is to synthesize paracetamol analogues from thymol. These derivatives were synthesized in solvent-free condition,

resulting in good-quality products in short time. All synthesized derivatives were characterized by spectroscopic techniques such as FT-IR and ^{1}H and ^{13}C NMR as well as LC–MS and single-crystal X-ray analysis. All the derivatives were subjected to antioxidant testing using the DPPH assay and antibacterial testing against five microorganisms. Docking studies against the active site of human heme oxygenase-1 indicated that the interaction with many amino acid residues of human heme oxygenase-1 is vital for their antioxidant activity.

Results and discussion

The synthesized benzamides are structurally similar to paracetamol based on the hydroxyl group *para* to –NH – (core moiety of paracetamol) functionality. Paracetamol is a widely used drug exhibiting antipyretic, analgesic, antioxidant, and antiinflammatory activities. Antioxidants are molecules that inhibit or quench free radical reactions and delay or inhibit cellular damage. The title compounds were synthesized in three steps as shown in Scheme 1. In the first step, thymol (**1**) was treated with sodium nitrite and conc. HCl at 0 °C to obtain intermediate 4-nitrosothymol (**2**), which was further treated with ammonia and hydrogen sulfide at room temperature to obtain intermediate 4-aminothymol (**3**), which was further treated with various benzoyl chlorides in neat phase at room temperature to obtain the final products **4a**–**e**, which were crystallized from ethanol.



Scheme 1 Synthesis of thymol-based benzamide derivatives

Biological evaluation

The antioxidant activity of compounds is related to their electron or hydrogen radical releasing abilities with DPPH [21]. The mechanism of generation and the stabilization of free radicals of the newly synthesized benzamides during the antioxidant reaction are shown in Fig. 1. The DPPH radical scavenging activity of all the compounds was found to be good to moderate. The presence of free phenolic –OH and –NH–C=O groups in the benzamide might be the cause of such antioxidant activity [22]. Compared with **4a**, **c**, **e**, the percentage inhibition of compounds **4b** and **4d** was closer to that of butylated hydroxytoluene (BHT) standard at all concentrations. This may be due to the presence of *ortho* and *para* substituent on the phenyl ring, which influences the antioxidant potency of the molecule, while compounds **4a**, **c**, **e** exhibited inferior antioxidant activities (Fig. 2; Table 1).

The results for the antibacterial activity revealed that all the synthesized compounds showed less antibacterial activity compared with chloramphenicol against only *Staphylococcus aureus* (Gram +ve bacteria), while the remaining compounds did not show any antibacterial activity (Fig. 3).

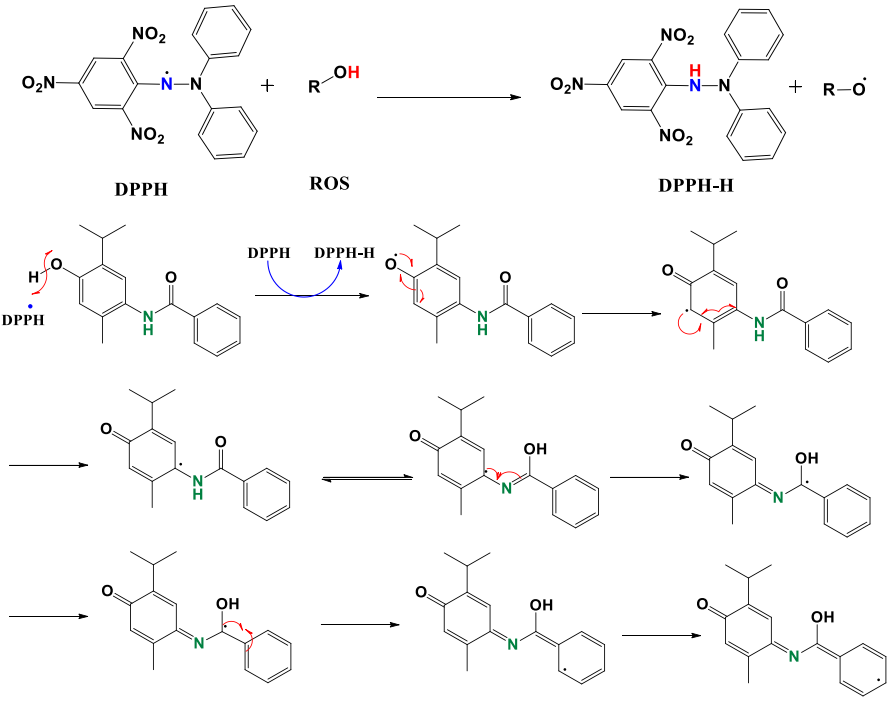


Fig. 1 Proposed mechanism of formation and stabilization of free radical in benzamides

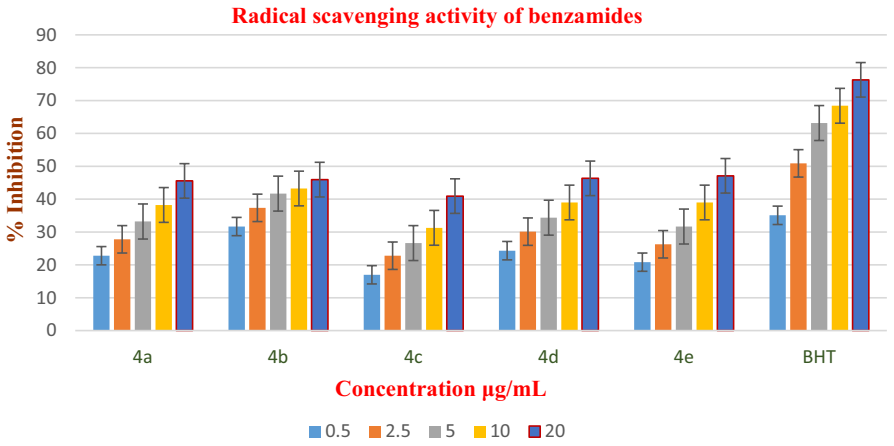


Fig. 2 Percentage radical scavenging at different concentrations

Table 1 Antioxidant activity of benzamide series

Compound	Concentration (µg/mL)				
	0.5	2.5	5	10	20
4a	0.02 ± 0.001	0.0187 ± 0.0003	0.0173 ± 0.0004	0.016 ± 0.0003	0.0141 ± 0.0003
Inhibition (%)	22.77 ± 0.01	27.79 ± 0.015	33.20 ± 0.03	38.22 ± 0.015	45.55 ± 0.01
4b	0.0177 ± 0.0003	0.0162 ± 0.0002	0.0151 ± 0.003	0.0147 ± 0.0003	0.014 ± 0.0002
Inhibition (%)	31.66 ± 0.015	37.33 ± 0.02	41.69 ± 0.01	43.24 ± 0.01	45.94 ± 0.015
4c	0.0212 ± 0.00073	0.02 ± 0.001	0.019 ± 0.001	0.0178 ± 0.0004	0.0153 ± 0.0002
Inhibition (%)	16.98 ± 0.01	22.77 ± 0.01	26.64 ± 0.02	31.27 ± 0.015	40.92 ± 0.02
4d	0.0196 ± 0.00015	0.0181 ± 0.004	0.017 ± 0.001	0.0158 ± 0.0003	0.0139 ± 0.0001
Inhibition (%)	24.32 ± 0.01	30.11 ± 0.015	34.36 ± 0.020	38.99 ± 0.020	46.33 ± 0.03
4e	0.0205 ± 0.010	0.0191 ± 0.003	0.0177 ± 0.0001	0.0158 ± 0.001	0.0139 ± 0.0001
Inhibition (%)	20.84 ± 0.01	26.25 ± 0.015	31.66 ± .02	38.99 ± 0.015	47.10 ± 0.02
BHT	0.0074 ± 0.00025	0.0056 ± 0.0019	0.0042 ± 0.0002	0.0036 ± 0.0002	0.0027 ± 0.00023
Inhibition (%)	35.08 ± 0.020	50.87 ± 0.015	63.15 ± 0.03	68.42 ± 0.02	76.3 ± 0.015

X-ray Single-crystal diffraction studies

Crystal of suitable size was mounted on Bruker APEX-II CCD diffractometer equipped with graphite-monochromated Mo K_α radiation with wavelength of 0.71073 Å. The crystallographic parameters, data collection, and refinement are summarized in the Electronic Supplementary Material. The single crystal of benzamide demonstrated the monoclinic system in space group *P21*. The ORTEP diagram with numbering is shown in Fig. 4, supporting the formation of the expected benzamide [23, 24].

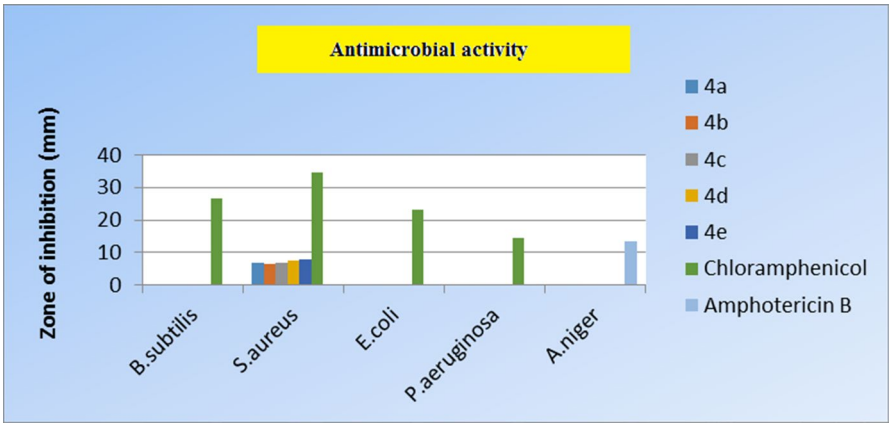


Fig. 3 Antimicrobial susceptibility testing of synthesized compounds **4a–e** against different bacterial and fungal species

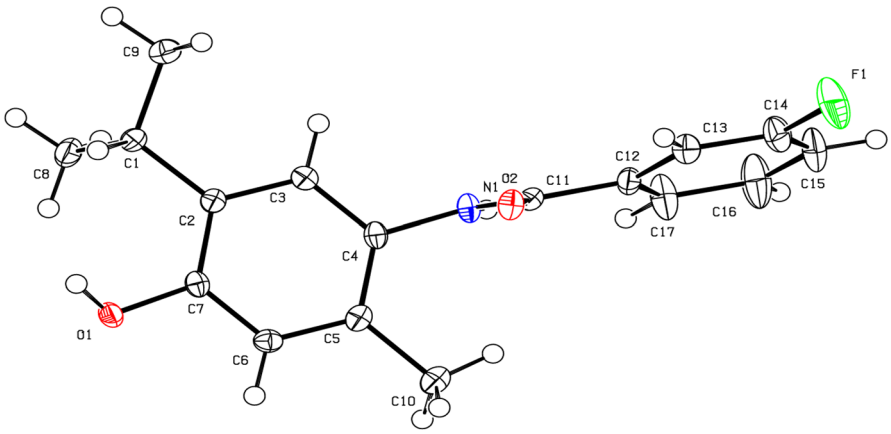


Fig. 4 Crystal structure (ORTEP plot) of 3-fluoro-*N*-(4-hydroxy-5-isopropyl-2-methylphenyl)benzamide (**4c**), showing that benzene ring of the thymol moiety and that of benzamide portion are almost perpendicular to each other

Molecular docking results

The docking of ligand molecules with human heme oxygenase-1 (3CZY) indicated that all the derivatives exhibited bonding with one amino acid in the active pocket (Fig. 5), thus being considered as good inhibitors of heme oxygenase-1 (3CZY). The benzamide scaffolds attached to the key residues GLY139, ASP140, and ARG136. The docking score, model, and binding energy are recorded for analysis of the results (Table 2). The theoretical outcomes highlight that the minimum binding energy of all the molecules with the targeted enzyme is lower than biliverdin, suggesting that the synthesized benzamides are good inhibitors of heme oxygenase-1 (3CZY).

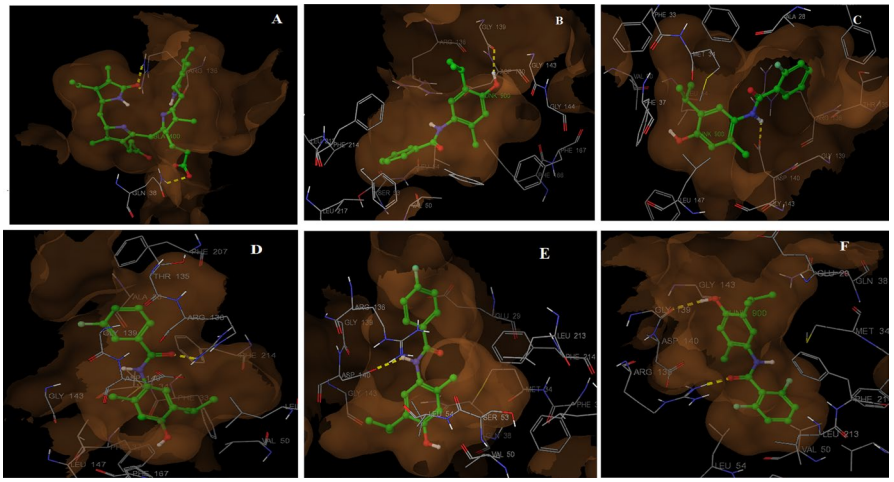


Fig. 5 **A** Biliverdin in complex with heme oxygenase-1 (hydrogen bond interaction with Arg 136 and Gln 138); **B** compound **4a** interacting with Gly 139; **C** compound **4b** interacting with Asp 140; **D** compound **4c** interacting with Arg 136; **E** compound **4d** interacting with Arg 136; **F** compound **4e** interacting with Arg 136 and Gly 139

Table 2 Docking results for benzamides

Sr. no.	Compound	Docking score	Binding energy
01	**4a**	– 6.2345	– 45.1234
02	**4b**	– 8.9573	– 63.6753
03	**4c**	– 7.8224	– 61.3456
04	**4d**	– 9.2345	– 66.4573
05	**4e**	– 9.5643	– 68.3456
06	Biliverdin	– 11.23	– 82.4532

Therefore, it is noteworthy that these docking simulation results extend the scope of development of thymol-based benzamide scaffolds as promising antioxidant agents.

Materials and methods

Reagents and chemicals

All chemicals and reagents were procured from Sigma-Aldrich and Fisher Scientific with purity of 98% and used without further purification. The synthesized compounds were characterized by using ^{1}H, ^{13}C NMR, IR spectra, and LC–MS. IR spectra were recorded on an FTIR-8400 Shimadzu spectrophotometer. NMR spectra ($CDCl_3$) were recorded on a Bruker AC spectrophotometer (400 MHz for ^{1}H NMR,

100 MHz for ^{13}C NMR) with tetramethylsilane (TMS) as internal standard. The crystal structure was examined using a Bruker APEX-II CCD diffractometer.

General procedure for synthesis of 2-isopropyl-5-methyl-4-nitrosophenol (2)

Synthesis of 2-isopropyl-5-methyl-4-nitrosophenol (**2**) was carried out using a previously reported method [25].

General procedure for synthesis of 4-amino-2-isopropyl-5-methylphenol (3)

Synthesis of 4-amino 2-isopropyl-5-methylphenol (**3**) was carried out using a previously reported method [26].

General procedure for synthesis of benzamides 4a–e [27]

Benzamides were prepared by reacting equimolar quantities of 4-amino-2-isopropyl-5-methylphenol (**3**) and substituted benzoyl chlorides in neat phase. The reaction mixture was stirred for some time. Instantaneously it became hot with evolution of HCl gas and became a solid mass or paste. Crushed ice was then added to the contents of the beaker and stirred well with a glass rod. The thick reaction mixture gradually became soft, and product began to deposit on the walls of the beaker by dissolution of any hydrochloride adhered with the product or by gradual dispersion of traces of benzoyl chloride in aqueous phase during stirring, and finally the supernatant aqueous layer became clear when precipitation of the product was complete as a crystalline product. The reaction time usually ranged on average from 3–5 min. The product was filtered and washed with water to free it from any adhering amine hydrochloride, and further crystallized from ethanol to obtain the pure product.

N-(4-Hydroxy-5-isopropyl-2-methylphenyl)benzamide (4a) Molecular formula: $C_{17}H_{19}O_2N$, molecular weight: 269, physical nature: white solid, melting point: 174–176 °C, yield: 86 (%); LC–MS *m/z*, found: 270 [M + 1]. IR (cm^{-1}): 3493 (O–H), 3290 (N–H), 2962 (C–H), 1643 (C=O), 1521, 1282. ^1H NMR ($CDCl_3$): δ 1.18 (6H, d, $J = 6.8$ Hz), 2.15(3H, s), 3.23 (1H, m) 6.68 (1H, s), 7.05 (1H, s), 7.48 (3H, m), 7.98 (2H, d, $J = 7.2$ Hz), 8.80(1H, s), 9.40 (1H, s). ^{13}C NMR ($CDCl_3$): δ 17.33, 22.28, 26.10, 116.33, 124.17, 127.16, 127.87, 130.79, 131.61, 132.11, 134.56, 152.37, 165.76.

2-Fluoro-N-(4-hydroxy-5-isopropyl-2-methylphenyl)benzamide (4b) Molecular formula: $C_{17}H_{18}O_2NF$, molecular weight: 287, physical nature: white solid, melting point: 114–116 °C, yield: 90 (%); LC–MS *m/z* found: 288 [M + 1]. IR (cm^{-1}): 3400 (O–H), 3307 (N–H), 2945, 1614 (C=O), 1546-1413, 1209. ^1H NMR ($CDCl_3$): δ 1.21 (6H, d, $J = 8$ Hz); 2.17 (3H, s), 3.16 (1H, m), 6.39 (1H, s), 6.51 (1H, s), 7.19 (1H, m), 7.25 (1H, m), 7.33 (1H, s), 7.55 (1H, m), 8.21 (2H, m). ^{13}C NMR ($CDCl_3$):

δ17.49, 22.56, 26.78, 116.02, 117.48, 121.12, 123.12, 125.11, 127.45, 130.30, 132.42, 133.69, 151.81, 159.47, 161.92 (J_{CF}=245 Hz), 162.41.

3-Fluoro-N-(4-hydroxy-5-isopropyl-2-methylphenyl)benzamide (4c) Molecular formula: $C_{17}H_{18}O_2NF$, molecular weight: 287, physical nature: white solid, melting point: 170–172 °C, yield: 60 (%); LC–MS *m/z* found: 288 [M + 1]. IR (cm^{-1}): 3294 (O–H), 3196 (N–H), 3076, 1643 (C=O), 1585, 1282-1228, 1188. ^{1}H NMR($CDCl_3$): δ 1.18 (6H, d, J=8 Hz),2.14 (3H, s), 3.22 (1H, m), 6.68 (1H, s),7.01 (1H, s), 7.24 (1H, m), 7.45 (1H, m), 7.75 (1H, dd, J=11 and 4 Hz), 7.83 (1H, t, J=8 Hz), 8.81 (1H, s), 9.56 (1H, s). ^{13}C NMR ($CDCl_3$): δ 17.37, 22.31, 26.08, 114.24, 117.75, 123.15 124.39, 126.89, 129.69, 131.94, 136.82, 152.60, 160.76 (J_{CF}=245 Hz), 163.20, 164.29.

4-Fluoro-N-(4-hydroxy-5-isopropyl-2-methylphenyl)benzamide (4d) Molecular formula: $C_{17}H_{18}O_2NF$, molecular weight: 287, physical nature: white solid, melting point: 176–178 °C, yield: 99 (%); LC–MS: *m/z* found 288[M + 1]. IR (cm^{-1}): 3400 (O–H), 3236 (N–H), 2964 (C–H), 1643 (C=O), 1600-1477, 1290, 1240, 1097. ^{1}H NMR ($CDCl_3$): δ 1.19 (6H, d, J=8 Hz), 2.15 (3H, s), 3.23 (1H, m), 6.69 (1H, s), 7.10 (3H, m), 8.03 (2H, dt, J=11 and 4 Hz), 8.63 (1H, s), 9.21 (1H, s). ^{13}C NMR ($CDCl_3$): δ 17.28, 22.24, 26.08, 114.80, 116.36, 124.23, 126.94, 129.56, 130.70, 131.74, 132.18, 152.43, 162.74 (J_{CF}=245 Hz), 163.68, 164.71, 165.23.

2,6-Difluoro-N-(4-hydroxy-5-isopropyl-2-methylphenyl)benzamide (4e) Molecular formula: $C_{17}H_{17}O_2NF_2$, molecular weight: 305, physical nature: white solid, melting point: 168–170 °C, yield: 92 (%); LC–MS *m/z* found: 306 [M + 1]. IR (cm^{-1}): 3263 (O–H), 3194 (N–H), 3034, 2962, 1639(C=O), 1529-1346, 1220, 1197. ^{1}H NMR ($CDCl_3$): δ 1.18 (6H, d, J=8 Hz), 2.17 (3H, s), 3.20 (1H, m), 7.04 (2H, t, J=7.6 Hz), 7.44 (1H, m), 8.92 (1H, s), 9.74 (1H, s). ^{13}C NMR ($CDCl_3$): δ 17.34, 22.00, 25.30, 111.43, 115.66, 116.36, 123.87, 126.31, 130.81, 131.33, 132.00, 152.69, 157.89, 158.63, 160.38 (J_{CF}=245 Hz), 162.68.

Bioassay

Antioxidant activity

The in vitro antioxidant properties of the newly synthesized compounds **4a**–**e** at different concentrations were examined by a well-documented reported assay, viz. DPPH free radical scavenging assay. The synthesized compounds and standard (butylated hydroxytoluene) were assessed based on their radical scavenging effect of the stable DPPH free radical. The absorbance of each solution was determined at 519 nm using spectrophotometer. DPPH solution (100 ppm) in methanol was prepared, and 1.0 mL was added to solutions of compound at different concentrations. Thirty minutes later, the absorbance was determined. The antioxidant

activities of the compounds are related to their electron or hydrogen radical releasing abilities for DPPH [28]. All determinations were carried out in triplicate. The radical scavenging activity was expressed as % inhibition of DPPH.

DPPH radical scavenging activity (%) = $[Abs_{(control)} - Abs_{(sample)}] \times 100/Abs_{(control)}$, where $Abs_{(control)}$ is the absorbance of DPPH radical + methanol and $Abs_{(sample)}$ is the absorbance of DPPH radical + extract/standard.

Antimicrobial activity

The agar well diffusion method [29] was used for determination of antimicrobial activity of compounds **4a**–**e** against four bacterial and one fungal strain, viz. *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Aspergillus niger*. Stock solution of 1000 micrograms per milliliter of each compound in dimethylsulfoxide (DMSO) was taken, and the assay carried out by taking 100 micrograms per disk. HiMedia antibiotic disk containing chloramphenicol (10 µg/disk) and amphotericin B (100 units/disk) was moistened with water and used as standard. All bacterial and fungal strains were incubated at 28 °C. The average diameter of inhibition zone surrounding the wells was measured in mm [30].

Molecular docking

Docking study was performed under the Windows XP operating system, using Glide and QuickPro module (Schrodinger, LLC, New York, USA, 2008). An earlier reported protein structure of keap1 (PDB ID: 1s8c) was used for grid generation. Benzamides were optimized using LigPrep 2.2, and conformers were generated using a "rapid torsion angle" search approach, followed by minimization of each generated structure using the Merck Molecular Force Field (MMFF). The crystal structure of the heme oxygenase-1 complex [PDB: 1s8c] was obtained from the Protein Data Bank (PDB). The protein structure of heme oxygenase-1 complex consists of four chains. Protein preparation was carried out using the protein preparation wizard in Maestro 8.0 in two steps: preparation and refinement. After ensuring chemical correctness, water molecules in the crystal structures were deleted, and hydrogens were added, wherever necessary. Using the OPLS 2005 force field, the energy of the crystal structure was minimized. To study the interaction of the compounds with heme oxygenase-1, the molecules were selectively docked on a chain representing where biliverdin is bound, using the extra precision (XP) docking mode. The final evaluation was done based on the glide score (docking score), and the single best pose was generated as the output for a particular ligand [31–34].

Conclusions

Novel benzamides were synthesized from thymol using a three-step pathway with good practical yield and screened for their in vitro antioxidant and antibacterial activities. The results revealed that all the synthesized compounds exhibited notable antioxidant activity and antibacterial activity against *Staphylococcus aureus*

(Gram +ve bacteria). Thus, hybrids prepared using these structural motifs could also lead to potent biologically active agents; such compounds would represent a profitable matrix for development of a new class of antioxidant agents from phenolic monoterpenes.

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