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Synthesis, Characterization and Antioxidant Activity of Carvacrol Based Sulfonates

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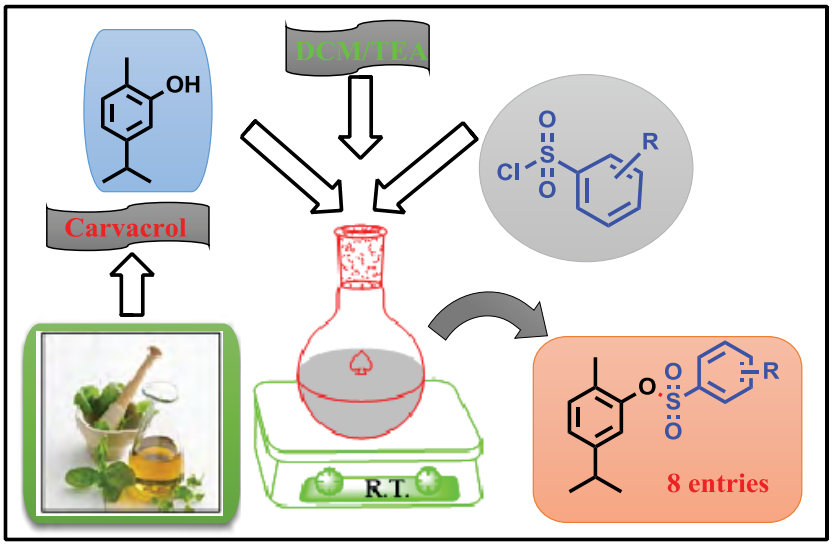
Abstract

In the present investigation, we report eight novel benzenesulfonate derivatives of carvacrol prepared by using sulfonyl chlorides and carvacrol. Their structures were investigated on the basis of modern sophisticated analytical techniques such as ^{1}H and ^{13}C NMR, LC-MS and FT-IR spectroscopy. The synthesized derivatives are screened for their antioxidant test by DPPH radical scavenger assay. Among the tested compounds, **6g** and **6h** have emerged as better antioxidants.



Keywords: Carvacrol; Sulfonyl chloride; Benzenesulfonate; DPPH; Antioxidant activity

Introduction

Nowadays antioxidants have motivated researchers' interest in both medicinal plants and synthetic organic compounds [1]. The implication of free radicals and reactive oxygen species (ROS) has been found to be in the pathogenicity of numerous diseases, including various chronic diseases [2,3]. Antioxidants are recently invented as the drug candidates to counter these diverse diseases, such as carcinogenesis, inflammation, and aging in aerobic organisms [4]. The design of small molecular agents to conflict cellular oxidative stress has become an important therapeutic objective, towards comprehensive damage to cellular macromolecules caused by reactive oxygen species (ROS) [5]. The extensive action of synthetic antioxidants is being ruled out owing to their toxicity and unwanted side effects and there is a growing interest in the use of the natural product as antioxidants and their derivatives for the treatment of oxidative stress-related diseases [6].

The antioxidant activity of phenols has been found depending on the electronic and steric effects of the ring, substituents and the strength of hydrogen-bonding interactions between phenol and solvent [7,8]. Many essential oils exhibit antioxidant and antimicrobial activities [9]. Phenols, such as thymol, carvacrol, eugenol and monocyclic hydrocarbons belong to the most active natural antioxidants found in the essential oils. However, the efficiency of these compounds in treatment is limited due to their poor water solubility and the requirement of high concentrations to reach a therapeutic effect [10,11]. Carvacrol, 5-isopropyl-3-methylphenol (Figure 1 (1)) is a major constituent of organo oil [12-15]. It is a phenolic monoterpenoid that exhibits several interesting biological activities [16-18]. It has anti-inflammatory [19], antibiotic [20], antifungal [21], antioxidant [22], antiviral [23], insecticidal [24], cardioprotective [25] and antidiabetics [26] properties. Josip et al. synthesized 4-(hydroxymethyl)-5-isopropyl-2-methylphenol (Figure 1 (2)) and 4,4′-methylenebis(5-isopropyl-2-methyl)phenol (Figure 1 (3)) and studied their antioxidant activity [27].

In this work, we have synthesized carvacrol sulfonate derivatives and characterized them by sophisticated analytical techniques. Antioxidant properties of these compounds have been investigated by *in vitro* systems through the interaction of 2,2-diphenyl-1-picrylhydrazyl

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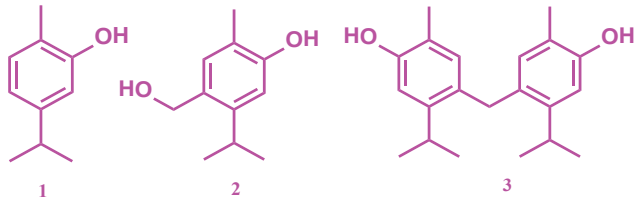


Figure 1: Structures of Carvacrol, 4-hydroxymethyl carvacrol and Dimer of carvacrol.

(DPPH) and scavenging of superoxide radical.

Experimental

Chemicals and instruments

Melting points of all the synthesized compounds were determined by the open capillary method. The confirmation of synthesized compounds was checked by thin layer chromatography on 200 μm thick aluminum sheets having silica gel 60 F_{254} as an adsorbent by developing the TLC plate using hexane: ethyl acetate (4:1) solvent system. Spots were visualized under UV-light. ^{1}H and ^{13}C NMR spectra were scanned at Bruker AC-400 MHz spectrometer FT NMR in $CDCl_3$ using TMS as an internal standard. The chemical shift values are on δ scale. The mass spectra were recorded on LC-MS spectrometer. All chemicals and solvents were locally purchased from Sigma-Aldrich and S. D. Fine chemicals and used without further purification.

General procedure for synthesis of carvacrol benzenesulfonate

Carvacrol **(4)** (1 mL, 0.006 moles) in dichloromethane (5 mL) was charged to the round bottom flask, then triethylamine (1 mL, 0.009 moles) was added drop-wise to it. Substituted benzene sulfonyl chloride (0.006 moles) **(5)** was added to it with constant stirring for 5-6 hours at room temperature. Progress of the reaction was monitored by TLC for every 15th minute. Upon confirmation of completion of reaction, 10% $NaHCO_3$ solution was added and the reaction mixture was further stirred for 30 minutes. The reaction mixture was extracted by using separating funnel and the organic layer evaporated at room temperature [28,29]. The remaining solid/liquid was collected and recrystallized with suitable solvent. Melting / Boiling point and practical yield were recorded. A detailed description of the spectral data for compounds is provided in the Supporting Information.

5-isopropyl-2-methylphenyl 2-fluorobenzenesulfonate (6a): ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.09-1.11 (6H, d, J=6.87 Hz), 2.22 (3H, s), 2.73-2.88 (1H, m), 6.76 (1H, s), 7.25 (1H, d, J=7.9 Hz), 7.12 (1H, d, J=7.9 Hz), 7.26 (1H, t, J=7.9 Hz), 7.32 (1H, d, J=7.9 Hz), 7.66 (1H, t, J=7.9 Hz), 7.85 (1H, d, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.81, 23.11, 33.38, 17.01, 117.43-117.64, 119.74, 124.44-125.43, 128.66, 131.38-131.52, 136.63-136.72, 148.01-148.18, 158.25, 161.14 FT-IR (KBr, cm^{-1}) 3090 (Aromatic C-H Stretch), 1575 (Aromatic C=C Bending), 1489 (C-F Stretching), 1386 and 1266 (SO_2 Stretching), 1067 (C-O Stretching), 815 and 775 (Aromatic C-H Bending), LC-MS m/z calculated $C_{16}H_{17}FO_3S$: 308.37 found: $[M+Na]^+$ 331.26.

5-isopropyl-2-methylphenyl 4-fluorobenzenesulfonate (6b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (6H, d, J=6.87 Hz), 2.02 (3H, s), 2.75-2.81 (1H, m), 6.64 (1H, s), 6.99 (1H, d, J=7.9 Hz), 7.16 (1H, d, J=7.9 Hz), 7.19 (2H, d, J=7.9 Hz), 7.81 (2H, d, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.93, 23.15, 33.41, 76.06-77.49, 116.43-116.65, 128.11, 131.35-132.19, 148.16-148.21, 164.15, 167.34, FT-IR (KBr, cm^{-1}) 3061 and 2964 (Aromatic C-H Stretch), 1589 (Aromatic C=C Bending), 1499 (C-F Stretching), 1319 and 1192 (-SO_2 Stretching), 1079 (C-O Stretching), 796 (Aromatic C-H Bending), LC-MS m/z calculated $C_{16}H_{17}FO_3S$: 308.37 found: $[M+Na]^+$ 331.27.

5-isopropyl-2-methylphenyl 2-chlorobenzenesulfonate (6c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09-1.12 (6H, d, J=6.87 Hz), 2.22 (3H, s), 2.71-2.81 (1H, m), 6.99 (1H, s), 7.28 (1H, d, J=7.9 Hz), 7.66 (1H, d, J=7.9 Hz), 7.68 (1H, t, J=7.9 Hz), 7.71 (1H, d, J=7.9 Hz), 7.82 (1H, t, J=7.9 Hz), 7.86 (1H, d, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.42, 22.88-23.12, 38.83-40.08, 64.50, 109.37, 123.33, 128.00-129.55, 131.47, 132.98, 142.42, 153.71, FT-IR (KBr, cm^{-1}) 3066 and 2958 (Aromatic C-H Stretch), 1535 (Aromatic C=C Bending), 1425 (C-F Stretching), 1282 and 1190 (-SO_2 Stretching), 1008 (C-O Stretching), 867 (Aromatic C-H Bending), LC-MS m/z calculated $C_{16}H_{17}ClO_3S$: 324.82 found: $[M+H]^+$ 325.24.

5-isopropyl-2-methylphenyl 4-chlorobenzenesulfonate (6d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.14 (6H, d, J=6.87 Hz), 2.01 (3H, s), 2.15-2.82 (1H, m), 6.73 (1H, s), 7.02 (1H, d, J=7.9 Hz), 7.2 (1H, d, J=7.9 Hz), 7.82 (2H, d, J=7.9 Hz), 9.02 (2H, d, J=7.9 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.95, 23.15, 33.41, 76.11, 77.46, 116.41-116.63, 120.88, 125.48, 128.68, 131.34-132.19, 148.14-148.21, 164.14, FT-IR (KBr, cm^{-1}) 3273 and 2972 (Aromatic C-H Stretch), 1517 (Aromatic C=C Bending), 1427 (C-F Stretching), 1394and 1276 (-SO_2 Stretching), 1020 (C-O Stretching), 879 (Aromatic C-H Bending), LC-MS m/z calculated $C_{16}H_{17}ClO_3S$: 324.82 found: $[M+H]^+$ 325.03.

5-isopropyl-2-methylphenyl 2-bromobenzenesulfonate (6e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.14 (6H, d, J=6.87 Hz), 2.01 (3H, s), 2.76-2.92 (1H, m), 6.73 (1H, s), 7.11 (1H, d, J=7.9 Hz), 7.21 (1H, d, J=7.9 Hz), 7.25 (1H, t, J=7.9 Hz), 7.75 (1H, d), 7.81 (1H, t, J=7.9 Hz), 7.91 (1H, d, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.94, 23.15, 33.41, 77.88, 116.43-116.65, 128.11, 131.35-132.19, 148.14-148.21, 167.29, FT-IR (KBr, cm^{-1}) 3253 and 2972 (Aromatic C-H Stretch), 1527 (Aromatic C=C Bending), 1423 (C-F Stretching), 1278 and 1201 (-SO_2 Stretching), 1024 (C-O Stretching), 721 (Aromatic C-H Bending), LC-MS m/z calculated $C_{16}H_{17}BrO_3S$: 369.27 found: $[M+Na]^+$ 393.40.

5-isopropyl-2-methylphenyl 4-bromobenzenesulfonate (6f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.14 (6H, d, J=6.87 Hz), 2.01 (3H, s), 2.76-2.92 (1H, m), 6.73 (1H, s), 7.02 (1H, d, J=7.9 Hz), 7.21 (1H, d, J=7.9 Hz), 7.46 (2H, d, J=7.9 Hz), 7.91 (2H, d, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.93, 23.15, 33.41, 76.06-77.49, 116.43-116.65, 128.11, 131.35-132.19, 148.16-148.21, 164.14, FT-IR (KBr, cm^{-1}) 2964 (Aromatic C-H Stretch), 1562 (Aromatic C=C Bending), 1479 (C-F Stretching), 1377 and 1282 (-SO_2 Stretching), 1083 (C-O Stretching), 806 (Aromatic C-H Bending), LC-MS m/z calculated $C_{16}H_{17}BrO_3S$: 369.27 found: $[M+Na]^+$ 393.40.

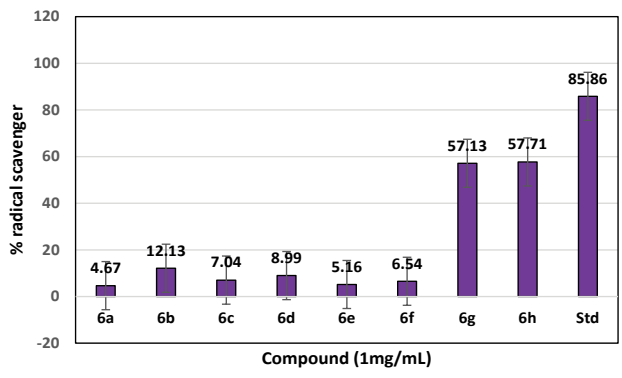
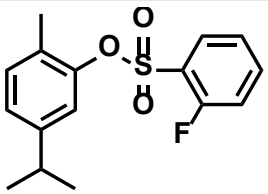
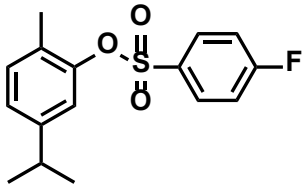
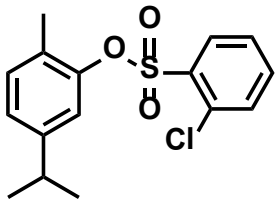
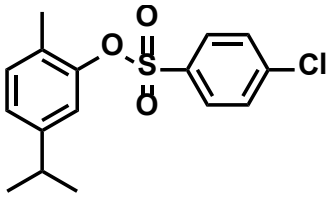
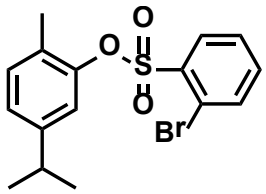
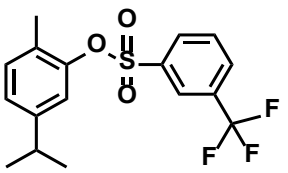
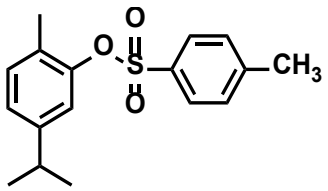
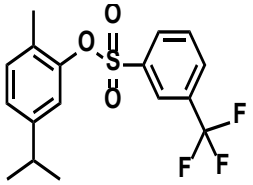


Figure 2: DPPH radical scavenging assay of synthesized compounds (6 a-h) and ascorbic acid.

Entry	Chemical Structure	M.P/B.P* (°C)	Yield[b] (%)	(%) Radical scavenger
1		56-58*	91.13	4.67
2		86-88	78.59	12.13
3		104-106	85.45	7.04
4		98-100*	72.00	8.99
5		114-116	83.26	5.16
6		64-68	89.16	6.54
7		92-94*	82.95	57.13
8		76-78*	84.49	57.71

[a]Reaction conditions: Carvacrol (0.006 moles) and benzenesulfonylchlorides (0.006 moles), Triethylamine (0.009 moles); [b]Isolated Yield; *BP

Table. 1: Synthesis of benzenesulfonate derivatives using Carvacrol and benzenesulfonylchlorides[a].

5-isopropyl-4-methylphenylbenzenesulfonate (6g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.12 (6H, d, J=6.87 Hz), 2.14 (3H, s), 2.41 (3H, s), 2.75-2.77 (1H, m), 6.67 (1H, s), 6.71 (1H, d, J=7.9 Hz), 7.95 (1H, d, J=7.9 Hz), 7.25 (2H, d, J=7.9 Hz), 7.75 (2H, d, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.45, 15.99, 21.71, 23.74, 24.05, 33.41, 33.70, 76.82-77.46, 113.09, 118.46, 120.19, 120.06, 125.22, 128.56-128.74, 129.78, 130.77, 131.35, 133.13, 145.37, 148.04-148.30, 153.97, FT-IR (KBr, cm^{-1}): 2964 (Aromatic C-H Stretch), 1590 (Aromatic C=C Bending), 1436 (C-F Stretching), 1363 and 1288 (-SO_2 Stretching), 1091 (C-O Stretching), 808 (Aromatic C-H Bending), LC-MS m/z calculated $C_{17}H_{20}O_3S$: 304.40 found: $[M+Na]^+$ 327.28.

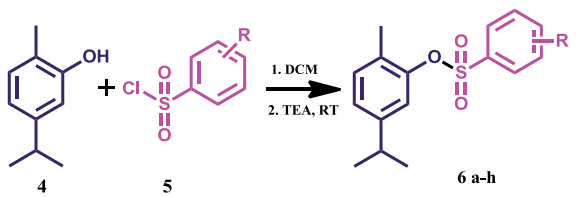
5-isopropyl-2-methylphenyl 3(trifluoromethyl)benzenesulfonate (6h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (6H, d, J=6.87 Hz), 2.09 (3H, s), 2.72-2.81 (1H, m), 6.65 (1H, s), 6.71 (1H, d, J=7.9 Hz), 7.03 (1H, d, J=7.9 Hz), 7.64 (1H, d, J=7.9 Hz), 7.25 (1H, d, J=7.9 Hz), 7.92 (1H, d, J=7.9 Hz), 8.12 (1H, d, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.63, 15.52, 23.67, 36.40, 46.45, 76.63-77.46, 117.97, 119.25, 125.66, 128.52, 129.08, 129.40, 130.20, 130.81, 130.88, 131.69, 132.29, 145.02, 148.05, 148.18, 148.45, 154.32, FT-IR (KBr, cm^{-1}) 3051 and 2801 (Aromatic C-H Stretch), 1521 (Aromatic C=C Bending), 1379 (C-F Stretching), 1269 and 1199 (-SO_2 Stretching), 1055 (C-O Stretching), 877 (Aromatic C-H Bending), LC-MS m/z calculated $C_{17}H_{17}F_3O_3S$: 358.38 found: $[M+3]^+$ 361.25.

Results and Discussion

In order to obtain carvacrol-phenylsulfonyl derivatives, carvacrol was treated with substituted phenylsulfonyl chlorides to get desired compounds as indicated in Scheme 1. Synthesized derivatives were obtained in good yields. Purification of these derivatives was carried out by simple recrystallization.

In vitro antioxidant activity

The antioxidant activity of the synthesized compounds was evaluated by 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging method [30,31]. The decreasing capacity of DPPH radicals was determined by a decline in their absorbance at 517 nm prompted by antioxidants. The inhibitory effects of the synthesized compounds **6a-h** on DPPH radical are presented as the value of % inhibition (Figure 2). All the synthesized carvacrol derivatives were dissolved to prepare a stock solution of 1 mg/mL using DMSO. Fifty microliter solutions of compounds were added to 1 mL of a 0.1 mM solution of DPPH in methanol. After 2 h, absorbance values were measured at 517 nm. Ascorbic acid was used as a standard. The decrease in absorbance of DPPH radical was caused by antioxidants because of the reaction between antioxidant molecules and radical, which resulted in the scavenging of the DPPH radicals. DPPH radical scavenging activity of the synthesized compounds was distinguished to be good to moderate as compared with the standard ascorbic acid. The value of % inhibition of the compounds **6g** (57.13%) and **6h** (57.71%) has been found to be greater as compared to standard ascorbic acid (85.86%) at the same concentration. While it appears that compounds **6a, 6b, 6c, 6d, 6e,** and **6f** are a poor scavenger of the DPPH radical (4.67%, 12.13%, 7.04%, 8.99%, 5.16%, and 6.54%) as compared to ascorbic acid (85.86).



R= a) 2-F, b) 4-F, c) 2-Cl, d) 4-Cl, e) 2-Br, f) 4-Br, g) 4-me, h) Triflurometh

Scheme 1: Synthesis of Carvacrol-phenylsulfonyl derivatives.

Conclusion

We have synthesized eight new carvacrol benzenesulfonate derivatives **(6a-h)** by simple and convenient methodology and characterized them by IR, ^{1}H and ^{13}C NMR and LC-MS spectroscopy. The comparison of the antioxidant activities of **6a-h** derivatives has revealed that the halo-substituted carvacrol benzenesulfonate derivatives have less antioxidant activity than the methyl and trifluoromethyl carvacrol benzenesulfonate derivatives. Amongst the series compounds, **6g** and **6h** exhibited remarkable antioxidant activity by DPPH radical scavenging assay (Table 1).

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