



Ultrasound Assisted One Pot Synthesis, Spectral, Antimicrobial and Antioxidant Studies of Novel 4-[1-Oxo-3-(substituted phenyl)-2-propenyl]-3-substituted Phenyl Sydnones

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4-[1-Oxo-3-(substituted aryl)-2-propenyl]-3-substituted phenyl sydnones (**2a-i**, **3a-i**, **4a-i**) are synthesized by ultrasonication method. The synthesis was carried out by reaction of 4-acetyl-3-(substituted phenyl)sydnones (**1a-i**) with various substituted aryl aldehydes (Ar-CHO). The structures of compounds were established by using NMR, IR, MS and elemental analysis. Compounds were evaluated for antibacterial, antifungal and antioxidant activity. Some of the synthesized compounds have shown good to moderate activity against gram negative bacteria whereas compounds **3c**, **4c** and **4f** have shown marked activity against fungal strains. The compounds **2c**, **3c**, **4f** have shown potent antioxidant activity as compared to reference standards. The compound **4f** (IC₅₀ = 3.17 μ M) is the most potent with methyl group as substituent showing good antioxidant activity even at very low concentrations. The ultrasonic method of synthesis was found to be simple, reduces reaction time and gives good yield when compared with traditional methods of synthesis.

Keywords: 1,2,3-Oxadiazol-5-olate, Ultrasonication, Chalcones.

INTRODUCTION

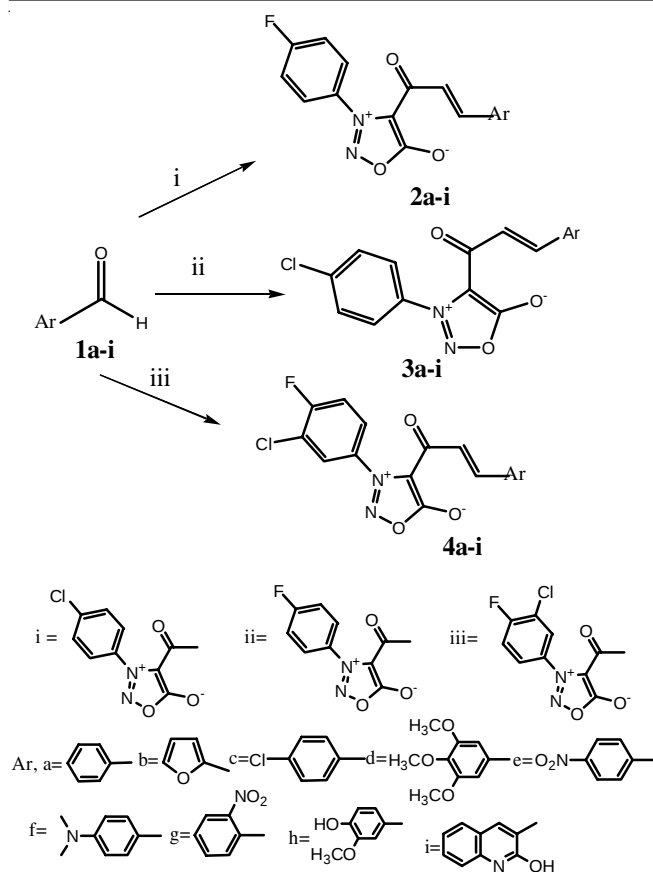
Sydnones form a subclass of mesoionic compounds belong to the category of mesomeric betaines. The characteristics of five membered heterocyclic ring of mesoionic compounds have encouraged study of the chemical, physical and biological properties of sydnones, as well as their potential applications. Sydnones are mesoionic compounds containing the 1,2,3-oxadiazole skeleton with an oxygen atom attached to the fifth position¹. A large number of sydnone derivatives have been synthesized with biological interest and are reported to possess a wide spectrum of biological and pharmacological activities like antioxidant²⁻⁴, anticancer^{5,6}, antihypertensive and anti-anginous⁷, diuretic⁸, antimicrobial⁹⁻¹³, antitubercular¹⁴, analgesic, antiinflammatory and antiarthritic¹⁵⁻¹⁸. Nowadays, the ultrasonic irradiation technique is becoming motivating, as this technique not only decreases reaction times, but also improves yield in a large variety of polyfunctionalized heterocycles. Compared with traditional methods, this method is more convenient and easily controlled¹⁹⁻²¹. In continuation to our interest in the chemical and pharmacological properties of sydnone derivatives, and as sonochemistry is attracting considerable research activity within the synthetic chemistry²², we report herein the ultrasonic promoted synthesis and antimicrobial/

antioxidant activity of a new series of 4-[1-oxo-3-(substituted aryl)-2-propenyl]-3-(substituted phenyl)sydnones.

EXPERIMENTAL

The starting material 4-acetyl-3-(4-chlorophenyl)sydnone (i), 4-acetyl-3-(4-fluorophenyl)sydnone (ii) and 4-acetyl-3-(3-chloro-4-fluorophenyl)sydnone (iii) were synthesized according to the standard procedure. Compounds **2a-i**, **3a-i**, **4a-i** were synthesized under sonication conditions in ethanol by cooling the mixture of 4-acetyl-3-(substituted phenyl)sydnone (i, ii, iii), sodium hydroxide aqueous solution at 5-10 °C and to this, various substituted aryl aldehydes were added under ultrasonication conditions for 15-20 min. The precipitate obtained was filtered, washed with cold water and recrystallized from ethanol and ethyl acetate (1:1) to get the title compounds (**Scheme-I**, Table-1). The structures of all the newly synthesized compounds were confirmed by elemental analysis in addition to the IR, ¹H NMR, ¹³C NMR and mass spectral data.

All melting points (uncorrected) were determined using a Systonic digital melting/boiling point apparatus. Infrared spectra were recorded in KBr discs using Jasco FTIR 1460 Plus spectrometer. NMR spectra were obtained on a BRUKER AVANCE II 400 NMR spectrometer at 500 MHz for ¹H and



Scheme-I: Synthesis of compounds 2a-i, 3a-i, 4a-i

125 MHz for ^{13}C , the chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane (TMS). Electron impact mass spectra were recorded on WATERS, Q-TOF MICRO-

MASS (LC-MS) instrument. Elemental analysis (C, H, N) were corresponding to the proposed structures within $\pm 0.4\%$ of the theoretical values. The ultrasonic irradiation was performed by using a Biotechnics India TM ultrasonic cleaner bath, model 1510, AC input 115 V, output 50 W, 1.9 liters with a mechanical timer (60 min with continuous hold) and heater switch, 47 KHz. The bacterial strains (*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*), *Candida albicans* and *Aspergillus niger* were obtained from the national collection of industrial micro-organisms (NCIM), branch of national chemical laboratory (NCL) Pune, India. Ampicillin trihydrate, clotrimazole, DPPH, propyl gallate, 2-*tert*-butyl-4-hydroxyanisole were obtained from Sigma-Aldrich, Mumbai, India.

Synthesis of 4-[1-oxo-3-(substituted aryl)-2-propenyl]-3-(substituted) sydnones (2a-g, 3a-g 4a-g): 4-[1-oxo-3-(4-N,N-dimethylaminophenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (**4f**): A mixture of 4-acetyl-3-(3-chloro-4-fluorophenyl)sydnone (iii) (2.6 g, 0.01 mol), aq. NaOH and ethanol (95 %, 20 mL) was cooled at (5-10 $^{\circ}\text{C}$). 4-N,N-dimethylaminobenzaldehyde (2 g, 0.012 mol) was added to this solution under ultra-sonication conditions and allowed to react for 20 min. The precipitate obtained was filtered, washed with cold water and recrystallized from ethanol (95 %) and ethyl acetate (1:1) to give the title compound (86 %). Other compounds were synthesized in same manner using respective aryl aldehydes (Scheme-I).

Spectral data of synthesized compound

4-[1-Oxo-3-(phenyl)-2-propenyl]-3-(4-chlorophenyl)-sydnone (2a): IR (KBr, ν_{max} , cm^{-1}): 1753 (C=O, sydnone), 1662 (C=O, styryl ketone); ^1H NMR δ 6.83 (d, 1H, $J = 15.57$,

TABLE-I
PHYSICO-CHEMICAL DATA OF COMPOUNDS 2a-i, 3a-i, 4a-i

Compound	Ar	m.f.	m.w.	Yield (%)	m.p. ($^{\circ}\text{C}$)
2a	C_6H_5	$\text{C}_{17}\text{H}_{11}\text{N}_2\text{O}_3\text{Cl}$	326.74	83	139-141
2b	2-Furyl	$\text{C}_{15}\text{H}_9\text{N}_2\text{O}_4\text{Cl}$	316.70	87	118-120
2c	4- ClC_6H_4	$\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_3\text{Cl}_2$	361.18	85	112-114
2d	3,4,5-(OCH_3) $_3\text{C}_6\text{H}_2$	$\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_6\text{Cl}$	416.81	80	109-111
2e	4- $\text{NO}_2\text{C}_6\text{H}_4$	$\text{C}_{17}\text{H}_{10}\text{N}_3\text{O}_5\text{Cl}$	371.74	81	117-119
2f	4- $\text{N}(\text{CH}_3)_2\text{C}_6\text{H}_4$	$\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}_3\text{Cl}$	369.74	92	100-102
2g	2- $\text{NO}_2\text{C}_6\text{H}_4$	$\text{C}_{17}\text{H}_{10}\text{N}_3\text{O}_5\text{Cl}$	271.74	83	112-114
2h	3- OCH_3 , 4- OHC_6H_3	$\text{C}_{18}\text{H}_{13}\text{N}_2\text{O}_5\text{Cl}$	372.74	79	135-137
2i	2-OH-3-quinolinyl	$\text{C}_{20}\text{H}_{12}\text{N}_3\text{O}_4\text{Cl}$	393.78	82	189-191
3a	C_6H_5	$\text{C}_{17}\text{H}_{11}\text{N}_2\text{O}_3\text{F}$	310.28	92	135-137
3b	2-Furyl	$\text{C}_{15}\text{H}_9\text{N}_2\text{O}_4\text{F}$	300.24	78	120-122
3c	4- ClC_6H_4	$\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_3\text{ClF}$	344.72	89	115-117
3d	3,4,5-(OCH_3) $_3\text{C}_6\text{H}_2$	$\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_6\text{F}$	400.36	82	106-108
3e	4- $\text{NO}_2\text{C}_6\text{H}_4$	$\text{C}_{17}\text{H}_{10}\text{N}_3\text{O}_5\text{F}$	355.35	84	109-111
3f	4- $\text{N}(\text{CH}_3)_2\text{C}_6\text{H}_4$	$\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}_3\text{F}$	353.28	90	112-114
3g	2- $\text{NO}_2\text{C}_6\text{H}_4$	$\text{C}_{17}\text{H}_{10}\text{N}_3\text{O}_5\text{F}$	355.28	92	96-98
3h	3- OCH_3 , 4- OHC_6H_3	$\text{C}_{18}\text{H}_{13}\text{N}_2\text{O}_5\text{F}$	356.31	95	128-130
3i	2-OH-3-quinolinyl	$\text{C}_{20}\text{H}_{12}\text{N}_3\text{O}_4\text{F}$	377.33	88	194-196
4a	C_6H_5	$\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_3\text{ClF}$	344.72	86	150-152
4b	2-Furyl	$\text{C}_{15}\text{H}_8\text{N}_2\text{O}_4\text{ClF}$	344.72	81	132-134
4c	4- ClC_6H_4	$\text{C}_{17}\text{H}_9\text{N}_2\text{O}_3\text{Cl}_2\text{F}$	379.20	93	133-135
4d	3,4,5-(OCH_3) $_3\text{C}_6\text{H}_2$	$\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_6\text{ClF}$	434.72	95	120-122
4e	4- $\text{NO}_2\text{C}_6\text{H}_4$	$\text{C}_{17}\text{H}_9\text{N}_3\text{O}_5\text{ClF}$	389.72	87	136-138
4f	4- $\text{N}(\text{CH}_3)_2\text{C}_6\text{H}_4$	$\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_3\text{ClF}$	387.72	86	110-112
4g	2- $\text{NO}_2\text{C}_6\text{H}_4$	$\text{C}_{17}\text{H}_9\text{N}_3\text{O}_5\text{ClF}$	389.72	85	106-108
4h	3- OCH_3 , 4- OHC_6H_3	$\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_5\text{ClF}$	390.72	79	157-159
4i	2-OH-3-quinolinyl	$\text{C}_{20}\text{H}_{11}\text{N}_3\text{O}_4\text{ClF}$	411.77	91	205-207

olefinic α H), 7.82 (d, 1H, $J = 15.57$, olefinic β H), 7.97, 7.97, 7.97, 7.97 (FC₆H₄-), 7.45, 7.45, 7.43, 7.43, 7.709 (C₆H₅-); ¹³C NMR δ 116.88, 116.88, 124.57, 124.57, 127.33, 127.33, 128.74, 128.74, 128.05, 128.92, 134.71, 136.19, 143.25, 144.45, 168.4, 168.3, 171.3; MS m/z 326.63 (M⁺).

4-[1-Oxo-3-(2-furyl)-2-propenyl]-3-(4-chlorophenyl)-sydnone (2b): IR (KBr, $\nu_{\max}$, cm⁻¹): 1765 (C=O, sydnone), 1676 (C=O, styryl ketone); ¹H NMR δ 6.92 (d, 1H, $J = 15.76$, olefinic α H), 7.03 (t, 1H, $J = 15.76$, furyl-4H), 7.26-7.42 (m, 2H, ArH), 7.73-7.96 (m, 3H, ArH, furyl-3H and olefinic β H), 8.25 (d, 1H, $J = 7.05$, furyl-5H); ¹³C NMR δ 143.25, 154.03, 136.19, 111.36, 129.05, 131.02, 104.83, 124.57, 124.57, 127.28, 142.28, 116.88, 116.88, 129.58, 171.3168.3, 126.08, 126.08, 144.45, 141.39; MS m/z 316.46 (M⁺).

4-[1-Oxo-3-(4-chlorophenyl)-2-propenyl]-3-(4-chlorophenyl)sydnone (2c): IR (KBr, $\nu_{\max}$, cm⁻¹): 1763 (C=O, sydnone), 1671 (C=O, styryl ketone); ¹H NMR δ 6.81 (d, 1H, $J = 15.52$, olefinic α H), 7.28-7.43 (m, 2H, ArH), 7.6 (d, 2H, $J = 15.26$, ArH), 7.73-7.82 (m, 4H, ArH and olefinic β H); ¹³C NMR δ 116.88, 116.88, 124.57, 124.57, 129.05, 129.19, 129.19, 129.54, 129.54, 133.75, 135.68, 136.19, 143.25, 144.45, 168.3, 168.4, 171.3; MS m/z 361.18 (M⁺).

4-[1-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-3-(4-chlorophenyl)sydnone (2d): IR (KBr, $\nu_{\max}$, cm⁻¹): 1752 (C=O, sydnone), 1657 (C=O, styryl ketone); ¹H NMR δ 3.93 (s, 9H, OCH₃), 6.82 (d, 1H, $J = 16.52$, olefinic α H), 6.87 (s, 2H, ArH), 7.21-7.38 (m, 2H, ArH), 7.81 (t, 2H, $J = 16.52$, ArH and olefinic β H); ¹³C NMR δ 56.16, 56.16, 60.90, 111.03, 116.88, 116.88, 124.57, 124.57, 127.05, 127.16, 129.05, 131.02, 136.19, 139.05, 139.75 143.25, 143.60, 144.45, 152.88, 168.3, 168.4, 171.3; MS m/z 416.53 (M⁺).

4-[1-Oxo-3-(4-nitrophenyl)-2-propenyl]-3-(4-chlorophenyl)sydnone (2e): IR (KBr, $\nu_{\max}$, cm⁻¹): 1755 (C=O, sydnone), 1667 (C=O, styryl ketone); ¹H NMR δ 7.38 (d, 1H, $J = 16.56$, olefinic α H), 7.42-7.56 (m, 2H, ArH), 7.76 (m, 1H, ArH), 7.93 (d, 1H, $J = 16.56$, olefinic β H), 8.69 (d, 2H, $J = 5.78$, ArH), 8.93 (d, 2H, $J = 5.78$, ArH); ¹³C NMR δ 116.88, 116.88, 117.29, 117.29, 123.17, 124.57, 124.57, 129.05, 129.10, 129.10, 136.19, 140.47, 143.25, 144.45, 168.4, 168.4, 171.3; MS m/z 371.49 (M⁺).

4-[1-Oxo-3-(4-N,N-dimethylaminophenyl)-2-propenyl]-3-(4-chlorophenyl)sydnone (2f): IR (KBr, $\nu_{\max}$, cm⁻¹): 1755 (C=O, sydnone), 1660 (C=O, styryl ketone); ¹H NMR δ 3.08 (s, 6H, N(CH₃)₂), 6.74-6.77 (m, 3H, ArH and olefinic α H), 7.36-7.49 (m, 2H, ArH), 7.78-7.83 (m, 4H, ArH and olefinic β H); ¹³C NMR δ 40.30, 40.30, 113, 113, 116.88, 116.88, 124.57, 124.57, 127.05, 127.05, 127.05, 127.16, 127.86, 129.05, 131.02, 133.98, 133.98, 136.19, 142.68, 143.25, 143.25, 144.45, 151.43, 168.3, 168.4, 171.3; MS m/z 369.59 (M⁺).

4-[1-Oxo-3-(2-nitrophenyl)-2-propenyl]-3-(4-chlorophenyl)sydnone (2g): IR (KBr, $\nu_{\max}$, cm⁻¹): 1759 (C=O, sydnone), 1662 (C=O, styryl ketone); ¹H NMR δ 6.98 (d, 1H, $J = 16.56$, olefinic δ H), 7.32-7.48 (m, 2H, ArH), 7.78-8.21 (m, 4H, ArH), 8.30-8.33 (m, 2H, ArH and olefinic β H); ¹³C NMR δ 116.88, 116.88, 121.77, 122.2, 124.57, 124.57, 127.6, 128.55, 129.39, 129.5, 133.41, 136.19, 143.23, 148.37, 168.3, 168.4, 171.3; MS m/z 271.52 (M⁺).

4-[1-Oxo-3-(phenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3a): IR (KBr, $\nu_{\max}$, cm⁻¹): 1753 (C=O, sydnone),

1662 (C=O, styryl ketone); ¹H NMR δ 6.818 (d, 1H, $J = 15.57$, olefinic α H), 7.816 (d, 1H, $J = 15.57$, olefinic β H), 7.57, 7.95, 7.85 (FCIC₆H₃-), 7.45, 7.45, 7.43, 7.43, 7.64 (C₆H₅-); ¹³C NMR δ 126.88, 126.88, 124.57, 124.57, 127.33, 127.33, 128.74, 128.74, 128.05, 128.92, 134.71, 136.19, 141.39, 143.25, 144.45, 168.3, 171.3; MS m/z 310.63 (M⁺).

4-[1-Oxo-3-(2-furyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3b): IR (KBr, $\nu_{\max}$, cm⁻¹): 1765 (C=O, sydnone), 1676 (C=O, styryl ketone); ¹H NMR δ 6.92 (d, 1H, $J = 16.85$, olefinic α H), 7.03 (t, 1H, $J = 16.76$, furyl-4H), 7.26-7.42 (m, 2H, ArH), 7.73-7.96 (m, 3H, ArH, furyl-3H and olefinic β H), 8.25 (d, 1H, $J = 15.11$, furyl-5H); ¹³C NMR δ 143.25, 154.03, 136.19, 111.36, 129.05, 131.02, 104.83, 124.57, 124.57, 127.28, 142.28, 126.77, 116.88, 129.58, 171.3168.3, 126.08, 126.08, 144.45, 141.39; MS m/z 300.46 (M⁺).

4-[1-Oxo-3-(4-chlorophenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3c): IR (KBr, $\nu_{\max}$, cm⁻¹): 1763 (C=O, sydnone), 1671 (C=O, styryl ketone); ¹H NMR δ 6.81 (d, 1H, $J = 10.73$, olefinic α H), 7.28-7.43 (m, 2H, ArH), 7.6 (d, 2H, $J = 5.35$, ArH), 7.73-7.82 (m, 4H, ArH and olefinic β H); ¹³C NMR δ 126.77, 126.77, 124.57, 124.57, 129.05, 129.19, 129.19, 129.54, 129.54, 133.75, 135.68, 136.19, 143.25, 144.45, 168.3, 141.39, 171.3; MS m/z 344.18 (M⁺).

4-[1-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3d): IR (KBr, $\nu_{\max}$, cm⁻¹): 1752 (C=O, sydnone), 1657 (C=O, styryl ketone); ¹H NMR δ 3.93 (s, 9H, OCH₃), 6.82 (d, 1H, $J = 10.52$, olefinic α H), 6.87 (s, 2H, ArH), 7.21-7.38 (m, 2H, ArH), 7.81 (t, 2H, $J = 10.49$, ArH and olefinic β H); ¹³C NMR δ 56.16, 56.16, 60.90, 111.03, 126.88, 122.66, 124.57, 124.57, 127.05, 127.16, 129.05, 131.02, 136.19, 139.05, 139.75 143.25, 143.60, 144.45, 152.88, 168.3, 141.4, 171.3; MS m/z 400.53 (M⁺).

4-[1-Oxo-3-(4-nitrophenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3e): IR (KBr, $\nu_{\max}$, cm⁻¹): 1755 (C=O, sydnone), 1667 (C=O, styryl ketone); ¹H NMR δ 7.38 (d, 1H, $J = 16.23$, olefinic α H), 7.42-7.56 (m, 2H, ArH), 7.76 (m, 1H, ArH), 7.93 (d, 1H, $J = 16.56$, olefinic β H), 8.69 (d, 2H, $J = 5.65$, ArH), 8.87 (d, 2H, $J = 5.78$, ArH); ¹³C NMR δ 117.29, 117.29, 123.17, 124.57, 124.57, 126.77, 126.77, 129.05, 129.10, 129.10, 136.19, 140.47, 141.39, 143.25, 144.45, 168.4, 171.3; MS m/z 355.49 (M⁺).

4-[1-Oxo-3-(4-N,N-dimethylaminophenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3f): IR (KBr, $\nu_{\max}$, cm⁻¹): 1755 (C=O, sydnone), 1660 (C=O, styryl ketone); ¹H NMR δ 3.08 (s, 6H, N(CH₃)₂), 6.74-6.77 (m, 3H, ArH and olefinic α H), 7.36-7.49 (m, 2H, ArH), 7.78-7.83 (m, 4H, ArH and olefinic β H); ¹³C NMR δ 40.30, 40.30, 113, 113, 126.77, 126.77, 124.57, 124.57, 127.05, 127.05, 127.05, 127.16, 127.86, 129.05, 131.02, 133.98, 133.98, 136.19, 142.68, 143.25, 143.25, 144.45, 151.43, 168.3, 141.39, 171.3 ; MS m/z 353.59 (M⁺).

4-[1-Oxo-3-(2-nitrophenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3g): IR (KBr, $\nu_{\max}$, cm⁻¹): 1759 (C=O, sydnone), 1662 (C=O, styryl ketone); ¹H NMR δ 6.98 (d, 1H, $J = 16.49$, olefinic α H), 7.32-7.48 (m, 2H, ArH), 7.78-8.21 (m, 4H, ArH), 8.30-8.33 (m, 2H, ArH and olefinic β H); ¹³C NMR δ 126, 126, 121.77, 122.2, 124.57, 124.57, 127.6, 128.55, 129.39, 129.5, 133.41, 136.19, 143.23, 148.37, 168.3, 141.4, 171.3; MS m/z 358.52 (M⁺).

4-[1-Oxo-3-(phenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4a): IR (KBr, $\nu_{\max}$, cm^{-1}): 1753 (C=O, sydnone), 1662 (C=O, styryl ketone); ^1H NMR δ 6.81 (d, 1H, $J = 16.36$, olefinic αH), 7.83 (d, 1H, $J = 16.36$, olefinic βH), 7.59, 7.59, 7.97, 7.97, 7.50 (C_6H_4 -), 7.45, 7.45, 7.43, 7.43, 7.64, 7.709 (C_6H_5 -); ^{13}C NMR δ 117.23, 122.66, 124.57, 125.16, 127.33, 127.33, 128.74, 128.74, 128.05, 128.92, 134.71, 136.19, 143.25, 144.45, 162, 168.3, 171.3; MS m/z 344.63 (M^+).

4-[1-Oxo-3-(2-furyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4b): IR (KBr, $\nu_{\max}$, cm^{-1}): 1765 (C=O, sydnone), 1676 (C=O, styryl ketone); ^1H NMR δ 6.92 (d, 1H, $J = 16.54$, olefinic αH), 7.03 (t, 1H, $J = 16.73$, furyl-4H), 7.26-7.42 (m, 2H, ArH), 7.73-7.96 (m, 3H, ArH, furyl-3H, and olefinic βH), 8.25 (d, 1H, $J = 7.05$, furyl-5H); ^{13}C NMR δ 143.25, 154.03, 136.19, 111.36, 129.05, 131.02, 104.83, 124.57, 124.57, 127.28, 142.28, 117.23, 122.66, 129.58, 171.3168.3, 126.08, 126.08, 144.45, 162; MS m/z 334.46 (M^+).

4-[1-Oxo-3-(4-chlorophenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4c): IR (KBr, $\nu_{\max}$, cm^{-1}): 1763 (C=O, sydnone), 1671 (C=O, styryl ketone); ^1H NMR δ 6.81 (d, 1H, $J = 15.69$, olefinic αH), 7.28-7.43 (m, 2H, ArH), 7.6 (d, 2H, $J = 15.45$, ArH), 7.73-7.82 (m, 4H, ArH and olefinic βH); ^{13}C NMR δ 117.23, 116.88, 124.57, 124.57, 129.05, 129.19, 129.19, 129.54, 129.54, 133.75, 135.68, 136.19, 143.25, 144.45, 168.3, 162, 171.3; MS m/z 379.18 (M^+).

4-[1-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4d): IR (KBr, $\nu_{\max}$, cm^{-1}): 1752 (C=O, sydnone), 1657 (C=O, styryl ketone); ^1H NMR δ 3.93 (s, 9H, OCH_3), 6.82 (d, 1H, $J = 15.66$, olefinic αH), 6.87 (s, 2H, ArH), 7.21-7.38 (m, 2H, ArH), 7.81 (t, 2H, $J = 15.53$, ArH and olefinic βH); ^{13}C NMR δ 56.16, 56.16, 60.90, 111.03, 127.23, 122.66, 124.57, 124.57, 127.05, 127.16, 129.05, 131.02, 136.19, 139.05, 139.75, 143.25, 143.60, 144.45, 152.88, 168.3, 162, 171.3; MS m/z 434.53 (M^+).

4-[1-Oxo-3-(4-nitrophenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4e): IR (KBr, $\nu_{\max}$, cm^{-1}): 1755 (C=O, sydnone), 1667 (C=O, styryl ketone); ^1H NMR δ 7.38 (d, 1H, $J = 16.49$, olefinic αH), 7.42-7.56 (m, 2H, ArH), 7.76 (m, 1H, ArH), 7.93 (d, 1H, $J = 16.42$, olefinic βH), 8.69 (d, 2H, $J = 5.66$, ArH), 8.93 (d, 2H, $J = 5.72$, ArH); ^{13}C NMR δ 117.23, 117.29, 117.29, 122.66, 123.17, 124.57, 125.16, 129.05, 129.10, 129.10, 136.19, 140.47, 143.25, 144.45, 168.4, 162, 171.3; MS m/z 389.49 (M^+).

4-[1-Oxo-3-(4-N,N-dimethylaminophenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4f): m.p. 110-112 $^\circ\text{C}$; IR (KBr, $\nu_{\max}$, cm^{-1}): 1755 (C=O, sydnone), 1660 (C=O, styryl ketone); ^1H NMR δ 3.08 (s, 6H, $\text{N}(\text{CH}_3)_2$), 6.74-6.77 (m, 3H, ArH and olefinic αH), 7.36-7.49 (m, 2H, ArH), 7.78-7.83 (m, 4H, ArH and olefinic βH); ^{13}C NMR δ 40.30, 40.30, 113, 113, 117.23, 122.86, 124.57, 125.16, 127.05, 127.05, 127.05, 127.16, 127.86, 129.05, 131.02, 133.98, 133.98, 136.19, 142.68, 143.25, 143.25, 144.45, 151.43, 168.3, 162, 171.3; MS m/z 387.59 (M^+).

4-[1-Oxo-3-(2-nitrophenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4g): IR (KBr, $\nu_{\max}$, cm^{-1}): 1759 (C=O, sydnone), 1662 (C=O, styryl ketone); ^1H NMR δ 6.98 (d, 1H, $J = 16.56$, olefinic αH), 7.32-7.48 (m, 2H, ArH), 7.78-8.21 (m, 4H, ArH), 8.30-8.33 (m, 2H, ArH and olefinic βH); ^{13}C

NMR δ 116.88, 122.66, 121.77, 122.2, 124.57, 124.57, 127.6, 128.55, 129.39, 129.5, 133.41, 136.19, 143.23, 148.37, 168.3, 162, 171.3; MS m/z 389.52 (M^+).

General procedure for synthesis of 4-[1-oxo-3-(substituted aryl)-2-propenyl]-3-(substituted phenyl)sydones (2h, 2i, 3h, 3i, 4h, 4i).

4-[1-Oxo-3-(4-hydroxy-3-methoxyphenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4h): Dry hydrogen chloride gas was passed through the suspension of compound iii (2.6 g, 0.01 mol) and vanillin (1.8 g, 0.012 mol) in 20 mL ethanol (95 %), for 0.5 h under cooling (5-10 $^\circ\text{C}$). The reaction mixture was left overnight at room temperature and poured into cold water. The separated precipitate was filtered, washed, dried in air and re-crystallised from ethanol (95 %) to give 4 h (79.10 %): Other compounds were synthesized similarly using respective aryl aldehydes.

4-[1-Oxo-3-(4-hydroxy-3-methoxyphenyl)-2-propenyl]-3-(4-chlorophenyl)sydnone (2h): IR (KBr, $\nu_{\max}$, cm^{-1}): 1758 (C=O, sydnone), 1660 (C=O, styryl ketone); ^1H NMR δ 3.97 (s, 3H, OCH_3), 5.98 (s, br, 1H, OH), 6.79-6.88 (m, 2H, ArH and olefinic αH), 7.32-7.68 (m, 4H, Ar-H), 7.76-7.78 (m, 2H, ArH and olefinic βH); ^{13}C NMR δ 55.93, 105.73, 112.08, 117.32, 120.96, 121.48, 123.31, 125.83, 128.36, 131.89, 136.15, 146.10, 148.63, 149.76, 159.38, 166.48, 188.56; MS m/z 272 (M^+).

4-[1-Oxo-3-(2-hydroxy-3-quinolinyl)-2-propenyl]-3-(4-chlorophenyl)sydnone (2i): IR (KBr, $\nu_{\max}$, cm^{-1}): 1757 (C=O, sydnone), 1672 (C=O, styryl ketone); ^1H NMR δ 6.76 (d, 1H, $J = 16.29$, olefinic αH), 7.27-7.39 (m, 2H, ArH), 7.57-7.8 (m, 2H, ArH and olefinic βH), 7.81-8.14 (m, 4H ArH), 8.42 (s, 1H, ArH), 11.47 (s, br, 1H, OH); ^{13}C NMR δ 106.18, 117.61, 121.13, 122.24, 124.30, 125.26, 125.60, 127.31, 127.86, 128.63, 130.75, 131.89, 136.12, 136.65, 145.74, 146.58, 159.38, 166.37, 174.92, 187.64; MS m/z 393.48 (M^+).

4-[1-Oxo-3-(4-hydroxy-3-methoxy phenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3h): m.p. 128-130 $^\circ\text{C}$; IR (KBr, $\nu_{\max}$, cm^{-1}): 1758 (C=O, sydnone), 1660 (C=O, styryl ketone); ^1H NMR δ 3.97 (s, 3H, OCH_3), 5.98 (s, br, 1H, OH), 6.79-6.88 (m, 2H, ArH and olefinic αH), 7.32-7.68 (m, 4H, Ar-H), 7.76-7.78 (m, 2H, ArH and olefinic βH); ^{13}C NMR δ 55.93, 105.73, 112.08, 117.32, 120.96, 121.48, 123.31, 125.83, 128.36, 131.89, 136.15, 146.10, 148.63, 149.76, 159.38, 166.48, 188.56; MS m/z 356.50 (M^+).

4-[1-Oxo-3-(2-hydroxy-3-quinolinyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (3i): IR (KBr, $\nu_{\max}$, cm^{-1}): 1757 (C=O, sydnone), 1672 (C=O, styryl ketone); ^1H NMR δ 6.76 (d, 1H, $J = 16.30$, olefinic αH), 7.27-7.39 (m, 2H, ArH), 7.57-7.8 (m, 2H, ArH and olefinic βH), 7.81-8.14 (m, 4H ArH), 8.42 (s, 1H, ArH), 11.47 (s, br, 1H, OH); ^{13}C NMR δ 106.18, 117.61, 121.13, 122.24, 124.30, 125.26, 125.60, 127.31, 127.86, 128.63, 130.75, 131.89, 136.12, 136.65, 145.74, 146.58, 159.38, 166.37, 174.92, 187.64; MS m/z 377.48 (M^+).

4-[1-Oxo-3-(4-hydroxy-3-methoxy phenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4h): m.p. 157-159 $^\circ\text{C}$; IR (KBr, $\nu_{\max}$, cm^{-1}): 1758 (C=O, sydnone), 1660 (C=O, styryl ketone); ^1H NMR δ 3.97 (s, 3H, OCH_3), 5.98 (s, br, 1H, OH), 6.79-6.88 (m, 2H, ArH and olefinic αH), 7.32-7.68 (m, 4H, Ar-H), 7.76-7.78 (m, 2H, ArH and olefinic βH); ^{13}C NMR δ 55.93, 105.73, 112.08, 117.32, 120.96, 121.48, 123.31, 125.83,

128.36, 131.89, 136.15, 146.10, 148.63, 149.76, 159.38, 166.48, 188.56; MS m/z 390.50 (M^+).

4-[1-Oxo-3-(2-hydroxy-3-quinolinyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (4i): IR (KBr, $\nu_{\max}$, cm^{-1}) 1757 (C=O, sydnone), 1672 (C=O, styryl ketone); ^1H NMR δ 6.76 (d, 1H, $J = 16.35$, olefinic αH) 7.27-7.39 (m, 2H, ArH), 7.57-7.8 (m, 2H, ArH and olefinic βH), 7.81-8.14 (m, 4H ArH), 8.42 (s, 1H, ArH), 11.47 (s, br, 1H, OH); ^{13}C NMR δ 106.18, 117.61, 121.13, 122.24, 124.30, 125.26, 125.60, 127.31, 127.86, 128.63, 130.75, 131.89, 136.12, 136.65, 145.74, 146.58, 159.38, 166.37, 174.92, 187.64; MS m/z 411.48 (M^+).

in-vitro Antimicrobial activity: The synthesized compounds were tested for their *in vitro* antimicrobial activity against a panel of standard strains of the Gram-positive bacteria (*Staphylococcus aureus* ATCC NO 25923 and *Bacillus subtilis* ATCC NO 6051), the Gram-negative bacteria (*Escherichia coli* ATCC NO 25922 and *Pseudomonas aeruginosa* ATCC NO 9721) and the yeast-like pathogenic fungus, *Candida albicans* ATCC NO 2091 and *Aspergillus niger* ATCC NO 10594. The primary screening was carried out using the agar disc-diffusion method using Mullere Hinton agar medium and further MIC was determined.

Antioxidant assay: The free radical scavenging capacity of the compound was measured by 1,1-diphenyl-2-picrylhydrazyl (DPPH) methods described by Chaudhary *et al.*²³. The

assay involved the reaction of the test compounds with 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical. The reaction was decrease in absorbance and it was measured at 515 nm using micro plate reader (India). The radical scavenging activity (%) was determined for the sample using DMSO treated control group in comparison. The following equation was used for calculation of radical scavenging activity.

$$\text{Radical scavenging activity (\%)} = 100 - \left(\frac{\text{OD test well}}{\text{OD control}} \right) \times 100$$

RESULTS AND DISCUSSION

The ultrasound assisted synthesized compounds were identified by spectral data and evaluated for their antimicrobial and antioxidant activity. Compound 4-[1-oxo-3-(2-furyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (**3b**), 4-[1-oxo-3-(2-furyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (**4b**) and 4-[1-oxo-3-(2-hydroxy-3-quinolinyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (**4i**) were found to possess good antibacterial activity whereas 4-[1-oxo-3-(4-chlorophenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (**3c**), 4-[1-oxo-3-(4-chlorophenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (**4c**) and 4-[1-oxo-3-(4-N,N-dimethylaminophenyl)-2-propenyl]-3-(3-chloro-4-fluorophenyl)sydnone (**4f**) were found to possess good antifungal activity. Compounds showed

TABLE-2
ANTIMICROBIAL ACTIVITIES AND MINIMUM INHIBITORY CONCENTRATION (MIC, $\mu\text{g/mL}$) OF
4-[1-OXO-3-(SUBSTITUTEDARYL)-2-PROPENYL]-3-SUBSTITUTED PHENYL SYDNONES

Compound	Diameter of growth inhibition zone (mm)						Compound	Minimum inhibitory concentration (MIC, $\mu\text{g/mL}$)					
	SA	BS	EC	PA	CA	AN		SA	BS	EC	PA	CA	AN
2a	-	-	10	09	-	-	2b	8	8	8	8	ND	ND
2b	13	12	13	15	-	-	2c	ND	ND	ND	ND	8	8
2c	10	11	11	12	17	16	2d	8	4	8	8	8	8
2d	14	14	14	14	14	14	2f	ND	ND	ND	ND	8	8
2e	11	12	12	13	-	-	2h	ND	ND	ND	ND	16	16
2f	11	10	12	12	17	16	2i	8	8	8	4	ND	ND
2g	09	10	-	-	11	12	3b	8	4	4	4	ND	ND
2h	-	-	-	-	17	14	3c	ND	ND	ND	ND	4	8
2i	13	13	14	15	-	-	3d	8	8	4	8	8	8
3a	-	-	10	-	-	-	3f	ND	ND	ND	ND	8	8
3b	14	14	14	15	-	-	3h	ND	ND	ND	ND	16	16
3c	11	12	12	13	18	17	3i	16	8	8	8	ND	ND
3d	13	13	15	14	17	17	4b	8	4	8	4	ND	ND
3e	12	12	13	13	-	-	4c	16	8	16	8	4	4
3f	10	11	12	12	14	13	4d	8	8	4	8	8	8
3g	-	-	-	-	12	12	4e	8	8	16	16	ND	ND
3h	-	-	-	-	12	13	4f	8	8	8	8	4	4
3i	13	13	14	14	-	-	4g	8	8	8	8	ND	ND
4a	10	-	11	12	-	-	4h	ND	ND	ND	ND	8	8
4b	14	14	14	15	-	-	4i	8	4	4	4	ND	ND
4c	11	13	12	13	18	17	Ampicillin	1	0.5	2	2	ND	ND
4d	14	13	15	13	17	16	Clotrimazole	ND	ND	ND	ND	2	2
4e	13	12	12	12	-	-							
4f	13	12	13	12	17	17							
4g	10	-	-	-	13	12							
4h	10	-	-	-	17	14							
4i	14	14	15	15	-	-							
Ampicillin	19	18	16	15	NT	NT							
Clotrimazole	NT	NT	NT	NT	21	20							

Inactive (inhibition zone < 9 mm). NT: not tested; ND = not detected;

The broad spectrum antibacterial drug ampicillin and the antifungal drug clotrimazole against *Staphylococcus aureus* ATCC NO 25923 (SA), *Bacillus subtilis* ATCC NO 6051 (BS), *Escherichia coli* ATCC NO 25922 (EC), *Pseudomonas aeruginosa* ATCC NO 9721 (PA), *Candida albicans* ATCC NO 2091 (CA) and *Aspergillus niger* ATCC NO 10594 (AN)

significant to moderate activity for *in vitro* antimicrobial activity (Table-2). This report proposed its potential application as a lead compounds for designing and development of potent antimicrobial agent. In general, the antibacterial activity to be dependent on the nature of substituents rather than basic skeleton of the molecules. Within the 1,2,3-oxadiazol-5-olate series **2a-i**, **3a-i**, **4a-i**, it was noticed that the substituents at both position 3-substituted phenyl and 4-substituted aryl have great influence on the antifungal activity, the highest antifungal activity was observed with the 4-substituted aryl, 4-ClC₆H₄ (**2c**, **3c**, **4c**), 3,4,5-(OCH₃)₃C₆H₂ (**2d**, **3d**, **4d**), 4-N(CH₃)₂C₆H₄ (**2f**, **3f**, **4f**) and 3-OCH₃, 4-OHC₆H₃ (**4h**). Similarly the substituents at both position 3-substituted phenyl and 4-substituted aryl also have great influence on the antibacterial activity, the highest antibacterial activity was observed with the 4-substituted aryl, 2-furyl (**2b**, **3b**, **4b**), 3,4,5-(OCH₃)₃C₆H₂ (**2d**, **3d**, **4d**), 2-OH-3-quinolinyl (**2i**, **3i**, **4i**) and 4-NO₂C₆H₄ (**4e**). In series, it seems that the presence of 4-Cl (in series **2**), 4-F (in series **3**), 4-F, 3-Cl (in series **4**) at 3-substituted phenyl along with only electron donating functional groups at 4-substituted aryl (such as 3,4,5-(OCH₃)₃C₆H₂, 4-N(CH₃)₂C₆H₄, 3-OCH₃, 4-OHC₆H₃ might be responsible for highest antifungal activity,

while both electron donating groups (such as -OCH₃, -OH) and electron withdrawing groups (such as -Cl, -NO₂) might be responsible for highest antibacterial activity. Compounds **2b**, **2c**, **2f**, **3b**, **3c**, **3f**, **3b**, **4b**, **4c**, **4f** showed good antioxidant activity with IC₅₀ values 5.18, 4.18, 5.12, 6.18, 4.26, 4.15, 5.32, 3.34 and 3.172 µM, respectively compared with reference standards Propyl gallate and 2-*tert*-butyl-4-hydroxyanisole (Table-3). Some of the tested compounds (**2c**, **3c** and **4f**) are found to be more potent antioxidants as compared to reference standards. The compound **4f** (IC₅₀ = 3.17 µM) was the most potent compound with methyl group as substituent showing good antioxidant activity even at very low concentrations. The results proved the necessity for further investigations to design molecules such as cyclization of sydnone with phenyl hydrazine, hydrazine and hydroxylamine for development of imminent potent antimicrobial, antioxidant and antitumor molecules.

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TABLE-3

ULTRASOUND IRRADIATED SYNTHESIZED
4-[1-OXO-3-(SUBSTITUTED ARYL)-2-PROPENYL]-3-
SUBSTITUTED PHENYL SYDNONES UNDER AMBIENT
CONDITIONS (5-10 °C), TIME REQUIRED FOR SYNTHESIS
AND THEIR ANTIOXIDANT ACTIVITY

Compd.	Ar	Time reaction (min)	Antioxidant IC ₅₀ (µM) ± SEM
2a	C ₆ H ₅	15	6.13 ± 0.01
2b	2-Furyl	20	5.18 ± 0.27
2c	4-ClC ₆ H ₄	20	4.18 ± 0.56
2d	3,4,5-(OCH ₃) ₃ C ₆ H ₂	15	29.7 ± 1.06
2e	4-NO ₂ C ₆ H ₄	20	12.09 ± 1.02
2f	4-N(CH ₃) ₂ C ₆ H ₄	20	05.12 ± 1.12
2g	2-NO ₂ C ₆ H ₄	20	13.04 ± 0.32
2h	3-OCH ₃ , 4-OHC ₆ H ₃	15	25.34 ± 0.41
2i	2-OH-3-quinolinyl	15	8.23 ± 2.43
3a	C ₆ H ₅	15	7.43 ± 0.23
3b	2-Furyl	20	6.18 ± 1.02
3c	4-ClC ₆ H ₄	20	4.26 ± 0.45
3d	3,4,5-(OCH ₃) ₃ C ₆ H ₂	15	24.11 ± 0.18
3e	4-NO ₂ C ₆ H ₄	20	10.12 ± 0.26
3f	4-N(CH ₃) ₂ C ₆ H ₄	20	04.15 ± 1.82
3g	2-NO ₂ C ₆ H ₄	20	11.04 ± 1.33
3h	3-OCH ₃ , 4-OHC ₆ H ₃	15	19.45 ± 1.56
3i	2-OH-3-quinolinyl	15	13.65 ± 0.06
4a	C ₆ H ₅	15	9.23 ± 1.78
4b	2-furyl	20	5.32 ± 0.27
4c	4- ClC ₆ H ₄	20	3.34 ± 0.56
4d	3,4,5-(OCH ₃) ₃ C ₆ H ₂	20	29.7 ± 1.06
4e	4-NO ₂ C ₆ H ₄	20	12.09 ± 1.02
4f	4-N(CH ₃) ₂ C ₆ H ₄	20	03.17 ± 0.42
4g	2-NO ₂ C ₆ H ₄	20	13.04 ± 0.32
4h	3-OCH ₃ , 4-OHC ₆ H ₃	15	21.34 ± 0.41
4i	2-OH-3-quinolinyl	20	11.12 ± 0.45
Pg			23.8 ± 5
Tb			26.6 ± 3

Pg, Propyl gallate Tb, 2-*tert*-butyl-4-hydroxyanisole