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Original article

Anti-oxidant, anti-fungal and anti-leishmanial activities of novel 3-[4-(1*H*-imidazol-1-yl) phenyl]prop-2-en-1-ones

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ABSTRACT

A series of new 3-[4-(1*H*-imidazol-1-yl) phenyl]prop-2-en-1-ones were synthesized by the condensation of various acetophenones with 4-(1*H*-imidazol-1-yl) benzaldehyde which was itself prepared by the *N*-arylation of imidazole using hexadecyltrimethylammonium bromide as catalyst for the first time. All the synthesized compounds were subjected to preliminary evaluation for their anti-leishmanial, anti-oxidant and anti-fungal activities. Few of the synthesized compounds showed significant activities.

1. Introduction

Synthesis, reactions and biological properties of substituted imidazoles constitute a significant part of modern heterocyclic chemistry. Compounds possessing imidazoles ring system have been found to exhibit a number of pharmacological properties such anticancer [1], carboxypeptidase [2], anti-aging [3], anti-fungal [4], anti-bacterial [5], anti-diabetic [6] and anti-malarial [7] while others show anti-hypertensive [8], and anti-depressive [9] activities. Among these, few are well known as commercial products such as Metronidazole® (anti-amoebic), Imidazole Salicylate® (anti-inflammatory, anti-pyretic and analgesic), 2-imidazolinone (pesticidal), Nizofenone® (nootropic), Tioconazole® (fungicide) [Fig. 1] and are being sold in the market.

On the other hand, 1,3-diaryl-2-propen-1-ones, also known as chalcones, continue to attract the interest of chemists and microbiologists due to their remarkable biological activities, among which anti-malarial [10], anti-protozoal [11], anti-inflammatory [12], immunomodulatory [13], nitric oxide inhibition [14], tyronase inhibition [15] and cytotoxic [16] activities are the most familiar. Besides, these have a wide range of applications such as in non-linear optical [17] and electro-active fluorescent materials [18] such as fluorescent dyes [19], light-emitting diodes, LEDs, [20] and fluorescent probes [21].

As part of a research program synthesizing various bioactive heterocyclic compounds [22,23], we herein report the synthesis of novel 3-[4-(1*H*-imidazol-1-yl) phenyl]prop-2-en-1-ones with a perception that with the synergism of both the imidazole ring system and chalcone moieties in a single nucleus, the newly synthesized compounds would likely possess significant biological activities.

2. Chemistry

N-Arylation of imidazole was carried out with different aryl halides using hexadecyltrimethylammonium bromide as a catalyst; *para*-fluorobenzaldehyde, *para*-chlorobenzaldehyde and *para*-bromobenzaldehyde were tried as arylating agents among which *para*-fluorobenzaldehyde gave the maximum yield [Table 1] due to the strongest (−) IE of fluoro group among the series and appreciable (−) RE of –CHO group that cumulatively cause electron deficiency at C-4 and thereby, facilitate the nucleophilic attack of imidazole. 4-(1*H*-Imidazol-1-yl) benzaldehyde thus synthesized was then

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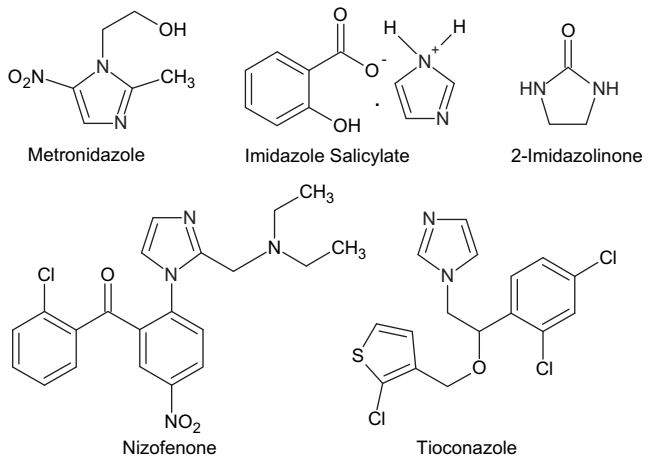


Fig. 1. Structures of some well-known imidazoles containing bioactive molecules.

Table 1
% Yield of *para* substituted benzaldehydes with imidazole.

Entry	Aryl halide	Yield, %
1	4-Fluorobenzaldehyde	78.3
2	4-Chlorobenzaldehyde	16.1
3	4-Bromobenzaldehyde	5.2

reacted with a number of substituted aromatic acetophenones in the presence of 10% methanolic sodium hydroxide to get the title compounds in good overall yields (Scheme 1).

3. Results and discussion

The synthesis of *N*-arylimidazoles and other aryl amines has attracted significant interest because of the frequent occurrence of these structural units in biologically active inhibitors [24]. The development of mild and cost effective catalytic procedures for *N*-arylation of imidazoles still remains an active research area [25]. Herein, hexadecyltrimethylammonium bromide has been used as a catalyst for the purpose for the first time. Different *para* substituted benzaldehydes were condensed to check the structure–activity relationship and was found that 4-fluorobenzaldehyde is the most reactive than the corresponding bromo and chloro analogues [Table 1]. 4-(1*H*-Imidazol-1-yl) benzaldehyde (**3**) thus synthesized, is further reacted with twenty different substituted acetophenones to get a series of novel biologically active 3-[4-(1*H*-imidazol-1-yl) phenyl]prop-2-en-1-ones.

All of the newly synthesized compounds were characterized through spectroscopic techniques along with their elemental analyses which were found in accordance with the calculated values [Table 2]. Configuration of the title compounds across the double bond (C-8–C9) is proposed as *E* on the basis of single crystal X-ray crystallography of two of the representative chalcones (**4c**, **4j**) and is discussed in the following section in detail.

4. Single crystal X-ray crystallography

Single crystals of the compounds **4c** and **4j** were grown in methanol and studied In order to determine the stereochemistry (*E* or *Z* configuration) of the compounds under investigation, single crystals of the products (**4c** and **4j**) were grown by dissolving the compound in absolute methanol and studied by X-ray crystallography. The crystal structures indicate that both the compounds crystallize with $Z = 4$ (in space group $P21/n$; monoclinic).

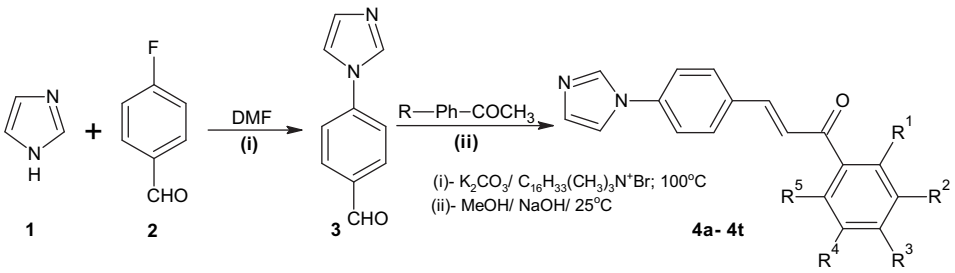
The molecular structure of **4c** is presented in Fig. 1 and is not planar. The crystallographic parameters (Table 3) and selected bond length and bond angles (Table 4) indicate that the phenyl-prop-en-one moiety [O(1)/C(7)–C(15)] forms a plane (plane 1) wherein C(8) lies out of the plane. The mean-plane of the chlorophenyl ring [Cl(1)/C(1)–C(6)] is oriented at 25.55(6)° with respect to the plane 1. The mean-plane of imidazole ring [N(1)/N(2)/C(16)–C(18)] forms an angle 30.22(6)° with the plane 1. The structure is devoid of any classical hydrogen bonds but non-classical hydrogen bonding interactions are present (CCDC No. 718262).

As evident from Fig. 2, phenyl-prop-en-one moiety in the compound **4j** is also not planar like **4c** In this case, the mean-planes formed by the phenyl ring [C(10)–C(15)] and the propenone group atoms [O(1)/C(7)–C(9)] are inclined at 26.53(8)° with respect to each other. Moreover, the mean-planes of the phenyl ring [C(10)–C(15)] and the imidazole ring [N(1)/N(2)/C(16)–C(18)] form an angle 30.72(8)°. The mean-plane of the fluorophenyl ring [F(1)/C(1)–C(6)] is twisted by 56.41(5)° with respect to the plane of the other phenyl ring. The structure of **4j** is also devoid of any classical hydrogen bonds and is stabilized by non-classical hydrogen bonding interactions, C(8)–H(8)···O(1), C(17)–H(17)···F(1) and C(18)–H(18)···N(2) which link the molecules into a three-dimensional network (CCDC No. 718263).

5. Biological activity

5.1. Anti-oxidant activity

Generation of reactive oxygen species (ROS) and free radicals *in vivo* is involved in a wide range of human diseases [26]. ROS, including superoxide anion, hydrogen peroxide and hydroxyl radical are byproducts of a variety of pathways of aerobic metabolism [27]. These are unstable and react readily with a wide range of biological substrates, such as lipids, DNA and protein molecules,



Scheme 1. Conversion of imidazole to 3-[4-(1*H*-imidazol-1-yl) phenyl]prop-2-en-1-ones.

Table 2
Characterization of 3-[4-(1*H*-imidazol-1-yl) phenyl]prop-2-en-1-ones.

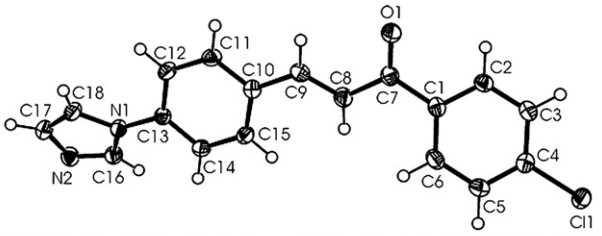
Compound	R_1	R_2	R_3	R_4	R_5	Molecular formula	Yield, %	mp, °C	Analysis, %		
									Calculated (Found)		
									C	H	N
4a	H	H	H	H	H	$C_{18}H_{14}N_2O$	83	150–151	78.81 (78.80)	5.14 (5.14)	10.21 (10.22)
4b	Cl	H	H	H	H	$C_{18}H_{13}ClN_2O$	58	116–117	70.02 (70.01)	4.24 (4.23)	9.07 (9.09)
4c	H	H	Cl	H	H	$C_{18}H_{13}ClN_2O$	76	163–164	70.02 (70.02)	4.24 (4.25)	9.07 (9.07)
4d	Cl	H	Cl	H	H	$C_{18}H_{12}Cl_2N_2O$	75	124–125	62.99 (62.98)	3.52 (3.51)	8.16 (8.18)
4e	H	Cl	Cl	H	H	$C_{18}H_{12}Cl_2N_2O$	65	168–170	62.99 (62.99)	3.52 (3.53)	8.16 (8.15)
4f	Cl	H	H	Cl	H	$C_{18}H_{12}Cl_2N_2O$	95	166–167	62.99 (63.01)	3.52 (3.53)	8.16 (8.15)
4g	Cl	H	H	H	Cl	$C_{18}H_{12}Cl_2N_2O$	93	150–152	62.99 (63.00)	3.52 (3.51)	8.16 (8.16)
4h	Cl	Cl	Cl	H	H	$C_{18}H_{11}Cl_3N_2O$	93	168	57.25 (57.26)	2.94 (2.94)	7.42 (7.43)
4i	F	H	H	H	H	$C_{18}H_{13}FN_2O$	54	120–122	73.96 (73.95)	4.48 (4.49)	9.58 (9.58)
4j	H	H	F	H	H	$C_{18}H_{13}FN_2O$	72	142–143	73.96 (73.95)	4.48 (4.48)	9.58 (9.60)
4k	F	F	H	H	H	$C_{18}H_{12}F_2N_2O$	68	124–126	69.67 (69.69)	3.90 (3.89)	9.03 (9.02)
4l	H	F	F	H	H	$C_{18}H_{12}F_2N_2O$	65	176–178	69.67 (69.67)	3.90 (3.91)	9.03 (9.02)
4m	F	H	H	H	F	$C_{18}H_{12}F_2N_2O$	59	142–143	69.67 (69.68)	3.90 (3.91)	9.03 (9.03)
4n	Br	H	H	H	H	$C_{18}H_{13}BrN_2O$	97	118	61.21 (61.22)	3.71 (3.70)	7.93 (7.92)
4o	H	H	Br	H	H	$C_{18}H_{13}BrN_2O$	79	163–164	61.21 (61.21)	3.71 (3.73)	7.93 (7.93)
4p	H	H	I	H	H	$C_{18}H_{13}IN_2O$	80	192–194	54.02 (54.01)	3.27 (3.25)	7.00 (7.01)
4q	H	OCH_3	H	H	H	$C_{19}H_{16}N_2O_2$	72	120	74.98 (75.00)	5.30 (5.31)	9.20 (9.19)
4r	H	H	OCH_3	H	H	$C_{19}H_{16}N_2O$	58	148–150	74.98 (74.99)	5.30 (5.29)	9.20 (9.22)
4s	H	OCH_3	OCH_3	H	H	$C_{20}H_{18}N_2O_3$	93	134–135	71.84 (71.83)	5.43 (5.44)	8.38 (8.40)
4t	H	OH	H	H	H	$C_{18}H_{14}N_2O_2$	65	238–239	74.47 (74.45)	4.86 (4.87)	9.65 (9.67)

Table 3
Crystal data and structure refinement for (**4c**) and (**4j**).

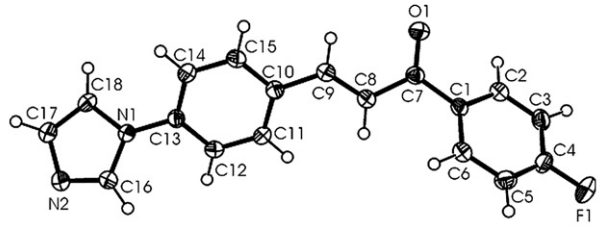
Parameter	**4c**	**4j**
Structural formula	$C_{18}H_{13}ClN_2O$	$C_{18}H_{13}FN_2O$
Formula weight	308.75	292.30
Crystal system	Monoclinic	Monoclinic
Space group	*P*21/*n*	*P*21/*n*
T, K	173(2)	173(2)
a, Å	6.987(6)	14.923(3)
b, Å	22.490(9)	10.876(5)
c, Å	9.270(3)	8.512(4)
Cell volume, Å^3	1430.1(8)	1373.8(9)
Z	4	4
Calculated density, mg/m^3	1.434	1.413
Crystal size, mm^3	0.16 × 0.08 × 0.07	0.20 × 0.16 × 0.04
Reflections collected	4934	5701
σ min; σ max	2.7–27.5°	3.0–27.5°
Goodness-of-fit on F^2	1.04	1.04
F(000)	640	608

Table 4
Selected bond lengths [Å] and angles [°] for (**4c**) and (**4j**).

Bond length	**4c**	**4j**
Cl/F(1)–C(4)	1.747(2)	1.359(2)
O(1)–C(7)	1.227(2)	1.225(2)
N(1)–C(16)	1.366(2)	1.365(2)
N(1)–C(13)	1.428(2)	1.423(2)
N(2)–C(16)	1.317(2)	1.313(2)
N(2)–C(17)	1.380(2)	1.382(2)
C(16)–N(1)–C(18)	106.15(15)	106.48(14)
C(16)–N(1)–C(13)	127.39(15)	127.05(14)
C(18)–N(1)–C(13)	126.27(15)	126.38(15)
C(16)–N(2)–C(17)	104.73(16)	104.38(14)



ORTEP-3 drawing of (**4c**) with displacement ellipsoids plotted at 50% Probability level.



ORTEP-3 drawing of (**4j**) with displacement ellipsoids plotted at 50% Probability level.

Fig. 2.

Table 5
% Age superoxide anion radical scavenging activity at 0.5 mM conc.

Compound	% RSA	Compound	% RSA
4a	81.94	**4l**	8.30
4b	70.40	**4m**	69.47
4c	90.06	**4n**	76.02
4d	3.30	**4o**	42.10
4e	0.40	**4p**	40.43
4f	18.80	**4q**	83.90
4g	47.70	**4r**	66.02
4h	2.40	**4s**	50.95
4i	79.25	**4t**	8.65
4j	64.50	*N*-Propyl gallate	91.3
4k	16.70		

consequently resulting in the cell damage [28,16]. All the synthesized compounds were assessed for their superoxide anion radical scavenging activity. All the synthesized compounds were subjected to anti-oxidant studies.

The synthesized compounds were assessed for their superoxide anion radical scavenging activity. The compounds **4a**–**4c**, **4i**, **4n** and **4q** showed potent activity. From the results (Table 5), it is evident that substitution of Cl at *para* position in benzene ring belonging to acetophenone moiety has maximum activity, almost equal to the standard (*n*-propyl gallate). It is obvious from the results that substitution of methoxy group at *meta* position increases the activity compared to the unsubstituted acetophenones

Table 6
Anti-fungal activity expressed in size (mm/100 μg ml^{-1}) of inhibition zone.

Sample	*Aspergillus fumigatus*	*Trichoderma vivide*	*Candida lipolytica*	*Aspergillus niger*
4a	18	03	04	04
4b	19	05	05	05
4c	20	09	10	08
4d	15	02	04	01
4e	10	06	07	02
4f	19	10	10	06
4g	20	06	07	04
4h	10	06	06	01
4i	17	05	05	03
4j	01	01	01	02
4k	19	04	03	04
4l	18	03	04	04
4m	15	05	07	04
4n	18	02	03	04
4o	18	09	08	04
4p	10	02	03	02
4q	16	08	07	03
4r	17	06	06	03
4s	10	04	04	03
4t	05	06	05	05
Nystatin	22	17	16	10

ring; also it is found that incorporation of halo (bromo and fluoro) groups at *ortho* and *meta* positions leads to more active compounds than that at *para* position. Introduction of substituents at adjacent position reduces the activity significantly even at 2,4-positions (**4e**, **4d**, **4h**).

5.2. Anti-fungal activity

The *in vitro* antimicrobial activity of the synthesized compounds against four strains of fungi i.e. *Aspergillus fumigatus*, *Trichoderma viride*, *Candida lipolytica*, *Aspergillus niger* was investigated and all the newly synthesized compounds were found active against all the strains under evaluation to certain extent (Table 6). The compounds **4a**–**4c**, **4g**, **4f**, **4i**, and **4k** are strongly active against *A. fumigatus* and moderately active against other strains.

5.3. Anti-leishmanial activity

All the compounds were tested for their anti-leishmanial activity using *Leishmania major* promastigotes as parasites for *in vitro* screening. The results are shown in Table 7. Compounds **4d**, **4j** and **4g** showed significant activity while the compounds **4o**, **4n** and **4k** exhibited moderate activity.

Table 7
Anti-leishmanial activity of the compound IC_{50}.

Compound	IC_{50}, μg/ml	Compound	IC_{50}, μg/ml
4a	0.91 ± 0.04	**4l**	0.89 ± 0.03
4b	0.93 ± 0.50	**4m**	0.97 ± 0.02
4c	0.92 ± 0.02	**4n**	0.86 ± 0.08
4d	0.72 ± 0.62	**4o**	0.86 ± 0.19
4e	0.99 ± 0.06	**4p**	0.92 ± 0.19
4f	0.99 ± 0.03	**4q**	0.98 ± 0.02
4g	0.67 ± 0.10	**4r**	0.98 ± 0.04
4h	0.63 ± 0.06	**4s**	0.82 ± 0.20
4i	0.98 ± 0.22	**4t**	0.96 ± 0.05
4j	0.71 ± 0.03	Standard drug (Amphotericin B)	0.56 ± 0.20
4k	083 ± 0.04		

6. Conclusion

In our experiments, we used a new catalyst for *N*-arylation of imidazole and synthesized a new series of imidazole based chalcones. Some of these showed significant anti-oxidant, anti-leishmanial and anti-fungal activities, especially against *A. fumigatus* which causes aspergillosis, a significant threat to human health in the form of allergic and life threatening invasive infections.

7. Experimental

All the chemicals were purchased from Merck, BDH and WAKO and used without purification. EIMS were recorded on MAT 312 instrument. ^{1}H NMR spectra were recorded on a Bruker XWIN-300 MHz and ^{13}C NMR on 100 MHz. Chemical shifts are reported in ppm referenced to the residual solvent signal. IR spectra (KBr) were recorded with an IR-spectrophotometer. Melting points were measured on a Stuart scientific SMP3 apparatus and are uncorrected. Elemental analysis was carried out using a Perkin Elmer 2400-CHN Analyzer. The purity of products was checked by TLC (Silica gel Merck). Visualization was achieved with UV light and Iodine vapor staining.

7.1. Procedure for synthesis of 4-(1H-imidazol-1-yl) benzaldehyde (**3**)

A mixture of imidazole (6.80 g, 100 mmol), anhydrous potassium carbonate (13.80 g, 100 mmol), 4-fluorobenzaldehyde (12.40 g, 100 mmol), hexadecyltrimethylammonium bromide (20 mg) and dimethylformamide (50.0 ml) was stirred for a period of 18 hours at 100 °C and after cooling to room temperature, was poured onto crushed ice (200 ml). Pale yellow precipitates obtained were filtered, dried and crystallized from methanol. Yield: 78.3%; mp 150–152 °C.

7.2. 3-[4-(1H-Imidazol-1-yl) phenyl]prop-2-en-1-ones

A methanolic sodium hydroxide solution (40%; 10.0 ml) was added dropwise to a mixture of 4-(1*H*-imidazol-I-yl)benzaldehyde (10.0 mmol, 1.72 g), acetophenone (10.0 mmol) and methanol (50 ml) over a period of 30–40 minutes with continuous stirring at room temperature till completion of the reaction (as indicated by TLC). Precipitates obtained, were filtered, washed with cold methanol–water mixture (1:10). Finally the product was recrystallized from methanol.

7.2.1. 3-[4-(1H-Imidazol-1-yl)phenyl]-1-phenyl-prop-2-en-1-one (***4a***)

Yellowish solid. IR (KBr, cm^{-1}) 3099, 1662, 1521, 653; ^{1}H NMR ($CDCl_3$): δ 8.02 (d, 2H, $J = 7.1$ Hz), 7.90 (s, 1H), 7.83 (d, 1H, $J = 15.7$ Hz), 7.76 (t, 2H, $J = 8.5$ Hz), 7.61 (m, 1H), 7.57 (d, 1H, $J = 15.7$ Hz), 7.53 (m, 4H), 7.31 (t, 1H, $J = 1.2$ Hz), 7.22 (s, 1H); ^{13}C NMR: 190.3, 143.2, 138.7, 138.1, 135.5, 133.2, 131.0, 130.2, 128.9, 128.7, 122.8, 121.6, 118.0. EIMS (*m*/*z*, %) 275.2 (15.27), 274.2 (M^+, 75.12), 197.1 (27.80), 169.0 (9.49) 144.1 (7.53), 105.0 (36.48), 77 (100).

7.2.2. 3-(2-Chlorophenyl)-3-[4-(1H-imidazol-1-yl)phenyl]prop-2-en-1-one (***4b***)

Yellowish solid. IR (KBr, cm^{-1}) 3119, 1640, 1525, 653; ^{1}H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.68 (d, 2H, $J = 8.5$ Hz), 7.50 (m, 7H), 7.29 (t, 1H, $J = 7.8$ Hz), 7.21 (d, 1H, $J = 7.8$ Hz), 7.17 (d, 1H, $J = 16.6$ Hz); ^{13}C

NMR: 188.5, 143.8, 136.9, 136.7 (2C), 133.7 (2C), 131.0 (2C), 130.7 (4C), 127.6 (2C), 123.3, 122.6, 121.0. EIMS (*m*/*z*, %) 310.2 ($M^+ + 2$, 31.03), 309.2 (35.69), 308.2 (M^+, 100), 273.2 (30.28), 241.1 (26.55), 197.1 (58.56), 139.0 (94.87), 111.0 (15.20), 102.0 (35.0).

*7.2.3. 3-(4-Chlorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4c**)*

Yellow crystalline solid. IR (KBr, cm^{-1}) 3107, 1659, 1518, 656; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 2H, $J = 8.5$ Hz), 7.90 (s, 1H), 7.83 (d, 1H, Hβ, $J = 15.7$ Hz), 7.75 (t, 2H, $J = 7.5$ Hz), 7.51 (d, 1H, $J = 8.2$ Hz), 7.49 (d, 1H, $J = 14.8$ Hz), 7.46 (t, 2H, $J = 8.5$ Hz), 7.43 (d, 1H, $J = 8.5$ Hz), 7.31 (t, 1H), 7.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 189.9, 143.7, 143.7, 139.7, 138.8, 136.4, 134.0, 131.2, 130.9, 130.5, 130.3, 130.1, 129.9, 129.2, 129.4, 122.3, 121.7, 118.0; EIMS (*m*/*z*, %) 310.2 ($M^+ + 2$, 34.08), 308.2 (M^+, 100), 273.2 (99.45), 241.1 (21.34), 197.1 (42.76), 142.0 (53.72), 113.0 (75.5), 111.0 (61.23).

*7.2.4. 3-(2,4-Dichlorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4d**)*

Off white solid. IR (KBr, cm^{-1}) 3133, 1663, 1523, 648; ^1H NMR ($CDCl_3$): 7.89 (s, 1H), 7.68 (d, 2H, $J = 8.5$ Hz), 7.51 (d, 1H, $J = 15.7$ Hz), 7.48 (m, 4H), 7.36 (dd, 1H, $J = 6.3$ Hz), 7.30 (s, 1H), 7.21 (s, 1H), 7.15 (d, 1H, $J = 16.0$ Hz); ^{13}C NMR: 192.3, 144.6, 138.5, 137.4, 136.2, 135.6, 133.1, 130.7, 130.4 (3C), 127.6, 126.6, 121.6 (2C), 118.0; EIMS (*m*/*z*, %) 344.2 (20.71), 343.2 (M^+, 11.14), 342.2 (35.8), 307.2 (16.27), 197.1 (40.98), 172.9 (61.00), 145.0 (27.31) 116.1 (100), 102 (92.60), 76.0 (53.45), 75.0 (58.76).

*7.2.5. 3-(3,4-Dichlorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4e**)*

White amorphous solid. IR (KBr, cm^{-1}) 3110, 1661, 1521, 659; ^1H NMR ($CDCl_3$): δ 8.09 (d, 1H, $J = 1.9$ Hz), 7.91 (s, 1H), 7.86 (d, 1H, Hβ, $J = 15.7$ Hz), 7.85 (dd, 1H, $J = 7.7$ Hz, 2.0 Hz), 7.76 (t, 2H, $J = 8.5$ Hz); 7.60 (d, 1H, $J = 8.3$ Hz), 7.46 (d, 1H, $J = 15.9$ Hz), 7.43 (d, 2H, $J = 7.7$ Hz), 7.31 (t, 1H), 7.22 (s, 1H); ^{13}C NMR: 188.8, 142.9, 138.8, 136.9, 136.0, 133.2, 132.9, 132.8, 130.9, 129.9, 129.8, 129.6, 129.2, 126.2, 124.3, 124.1, 119.8, 117.8; EIMS (*m*/*z*, %) 344.1 (M + 2, 54.93), 343.2 (33.26), 342.3 (M^+, 100), 307.2 (46.83), 275.1 (17.79), 197.1 (52.57), 145.0 (28.64), 115.0 (38.26), 102.1 (32.86).

*7.2.6. 3-(2,5-Dichlorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4f**)*

Yellow solid. IR (KBr, cm^{-1}) 3115, 1661, 1523, 651; ^1H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.69 (d, 2H, $J = 8.5$ Hz), 7.51 (d, 1H, $J = 16.7$ Hz), 7.45 (d, 2H, $J = 1.8$ Hz), 7.42 (t, 1H, $J = 7.8$ Hz), 7.39 (d, 2H, $J = 1.3$ Hz), 7.30 (t, 1H, $J = 7.2$ Hz), 7.21 (s, 1H), 7.13 (d, 1H, $J = 16.1$ Hz); ^{13}C NMR: 192.0, 145.0, 140.3, 139.2, 135.5, 133.5, 133.3, 132.1, 131.8, 131.1, 130.5, 129.8, 129.4, 126.7, 126.4, 121.6, 118.0; EIMS (*m*/*z*, %) 346.2 (2.62), 343.1 (15.6), 342.2 (M^+, 50.19), 307.2 (14.11), 275.0 (20.38), 197.1 (100), 169.1 (39.10), 116.0 (68.10), 102 (74.70).

*7.2.7. 3-(2,6-Dichlorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4g**)*

Off white solid. IR (KBr, cm^{-1}) 3102, 1646, 1522, 654; ^1H NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.65 (d, 2H, $J = 8.4$ Hz), 7.43 (d, 1H, $J = 8.4$ Hz), 7.40 (m, 5H), 7.29 (d, 1H, $J = 16.3$ Hz), 7.21 (s, 1H), 6.97 (d, 1H, $J = 16.2$ Hz); ^{13}C NMR: 188.4, 144.1, 138.5, 138.2, 138.0, 136.9, 136.0, 135.0, 130.7, 129.5, 129.3, 129.0, 126.5, 126.1, 124.6, 124.4, 122.5, 118.6; EIMS (*m*/*z*, %), 344.1 ($M^+ + 2$, 40.17), 343.2 (30.12), 342.1 (M^+, 63.89), 307.2 (8.94), 275.1 (32.86), 197.1 (100), 115 (24.25), 102 (41.23).

*7.2.8. 3-[4-(1*H*-Imidazol-1-yl)phenyl]-1-(2,3,4-trichlorophenyl)prop-2-en-1-one (**4h**)*

Yellow solid. IR (KBr, cm^{-1}) 3108, 1640, 1520, 658; ^1H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.67 (d, 2H, $J = 8.4$ Hz), 7.50 (d, 1H, $J = 16.0$ Hz), 7.42 (m, 3H), 7.30 (d, 1H, $J = 8.2$ Hz), 7.27 (t, 2H, $J = 6.8$ Hz), 7.08 (d, 1H, $J = 16.0$ Hz); ^{13}C NMR: 191.0, 144.8, 143.1, 138.3, 137.1, 136.9, 135.8, 135.0, 131.8, 131.2, 131.0, 130.9, 130.7, 124.6, 123.8, 123.6, 122.1, 118.5; EIMS (*m*/*z*, %) 380.1 ($M^+ + 2$, 11.78), 378 (M^+, 26.14), 377 (48.05), 376 (31.44), 341.2 (13.55), 309.1 (13.60), 197.1 (82.99), 141.0 (100), 102.0 (64.80), 76 (36.96).

*7.2.9. 1-(2-Fluorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4i**)*

Yellow solid. IR (KBr, cm^{-1}) 3113, 1659, 1515, 659; ^1H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.85 (d, 1H, $J = 15.1$ Hz), 7.79 (dd, 2H, $J = 1.7$ Hz, 8.5 Hz), 7.73 (d, 1H, $J = 8.3$ Hz), 7.57 (m, 1H), 7.44 (d, 1H, $J = 14.8$ Hz), 7.41 (t, 1H, $J = 6.0$ Hz), 7.38 (d, 1H, $J = 2.8$ Hz), 7.30 (t, 1H, $J = 7.5$ Hz), 7.29 (t, 1H, $J = 7.5$ Hz), 7.21 (s, 1H), 7.17 (dd, 1H, $J = 1.9$ Hz, 7.6 Hz); ^{13}C NMR: 189.8, 162.5, 144.3, 138.0, 137.6, 135.8, 135.0, 130.7, 129.9, 129.7, 129.5, 123.9 (2C), 123.3, 122.1, 121.8, 117.6, 114.5; EIMS (*m*/*z*, %) 292.2 (M^+, 43.48), 225.1 (12.74), 197.1 (16.40), 169.1 (6.72), 144.1 (23.31), 123.1 (100), 95 (27.82).

*7.2.10. 1-(4-Fluorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4j**)*

Yellow crystalline solid. IR (KBr, cm^{-1}) 3097, 1660, 1515, 656; ^1H NMR ($CDCl_3$): δ 8.08 (dd, 2H, $J = 2.0$ Hz, 6.8 Hz), 7.90 (s, 1H), 7.83 (d, 1H, $J = 15.7$ Hz), 7.75 (d, 2H, $J = 8.5$ Hz), 7.53 (d, 1H, $J = 15.7$ Hz), 7.46 (t, 2H, $J = 8.5$), 7.31 (t, 1H, $J = 7.5$ Hz), 7.20 (m, 3H); ^{13}C NMR: 188.6, 167.1, 143.4, 138.8, 135.5, 134.5, 134.0, 131.4, 131.2, 131.0, 130.2, 130.4, 122.3, 122.1, 121.6, 118.0, 116.2, 115.9; EIMS (*m*/*z*, %) 292.2 (M^+, 57.36), 291.2 (22.56), 225.1 (14.25), 197.1 (18.80), 169.1 (7.64), 144.1 (75.25), 123.1 (100), 95 (34.04).

*7.2.11. 1-(2,3-Difluorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4k**)*

White solid. IR (KBr, cm^{-1}) 3126, 1661, 1523, 659; ^1H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.76 (d, 1H, $J = 13.2$ Hz), 7.73 (d, 2H, $J = 8.2$ Hz), 7.57 (m, 1H), 7.45 (d, 1H, $J = 8.4$ Hz), 7.43 (d, 1H, $J = 13.3$ Hz), 7.37 (m, 2H), 7.31 (t, 1H), 7.22 (s, 1H), 7.18 (d, 1H, $J = 6.8$ Hz); ^{13}C NMR: 188.2, 160.2, 154.6, 143.1, 138.3, 135.1, 135.0, 131.9, 131.3, 131.1, 126.6, 126.0, 123.7, 121.7, 120.9, 120.7, 119.3, 117.5; EIMS (*m*/*z*, %) 311.0 (19.52), 310.0 (M^+, 100), 309 (37.61), 243.0 (33.57), 199.1 (45.71), 167.1 (26.31), 141.0 (46.45), 113.0 (38.57).

*7.2.12. 1-(3,4-Difluorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4l**)*

White solid. IR (KBr, cm^{-1}) 3124, 1665, 1520, 657; ^1H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.86 (d, 1H, $J = 5.7$ Hz), 7.85 (t, 1H, $J = 6.8$ Hz), 7.84 (d, 1H, $J = 15.7$ Hz), 7.75 (d, 2H, $J = 8.5$ Hz), 7.47 (d, 1H, $J = 15.8$ Hz), 7.44 (d, 1H, $J = 8.5$ Hz), 7.31 (t, 1H, $J = 1.9$ Hz), 7.27 (m, 2H), 7.22 (s, 1H); ^{13}C NMR: 188.8, 158.6, 156.1, 143.8, 138.2, 136.1, 135.6, 134.0, 130.6, 129.4, 129.2, 123.3, 123.0, 122.7, 122.0, 117.0, 114.2; EIMS (*m*/*z*, %) 311 (20.50), 310 (M^+, 100), 309 (34.87), 243 (23.40), 197.1 (25.55), 169 (16.31), 141 (49.80), 113 (57.82), 102.1 (18.02).

*7.2.13. 1-(2,6-Difluorophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4m**)*

White amorphous solid. IR (KBr, cm^{-1}) 3108, 1658, 1523; ^1H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.68 (d, 2H, $J = 8.5$ Hz), 7.53 (d, 1H, Hβ, $J = 16.1$ Hz), 7.47 (m, 3H), 7.30 (t, 1H, $J = 7.8$ Hz), 7.21 (s, 1H), 7.08 (d, 1H, $J = 16.1$), 7.02 (dd, 2H, $J = 7.8$, 2.8 Hz); ^{13}C NMR: 189.3, 160.5, 160.3, 143.8, 136.6, 135.3, 135.1, 134.0, 130.8, 129.8, 129.6, 124.9, 121.1, 116.5, 109.8, 109.5, 106.3; EIMS (*m*/*z*, %), 311.2 (8.61), 310.2 (M^+, 48.70), 243.2 (40.47), 197.2 (28.23), 169.1 (12.51), 141.0 (100).

*7.2.14. 1-(2-Bromophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4n**)*

Yellow solid. IR (KBr, cm^{-1}) 3128, 1663, 1522, 648; ^1H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.67 (m, 3H), 7.46 (d, 1H, $J = 15.8$ Hz), 7.43 (d, 4H, $J = 7.2$ Hz), 7.38 (m, 2H), 7.29 (t, 1H, $J = 8.2$ Hz), 7.21 (s, 1H), 7.13 (d, 1H, $J = 16.0$ Hz); ^{13}C NMR: 188.7, 143.8, 137.1, 136.0, 135.6, 134.0, 132.9, 132.8, 132.6, 128.8, 128.6, 128.4, 123.5, 123.4, 123.2, 121.4, 119.2, 116.8; EIMS (*m*/*z*, %) 354.1 (70.49), 353.1 (M^+, 30.25), 273.2 (55.25), 197.1 (100), 155 (39.41); 115.0 (19.94), 102.0 (38.41).

*7.2.15. 1-(4-Bromophenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4o**)*

White amorphous solid. IR (KBr, cm^{-1}) 3109, 1658, 1525, 649; ^1H NMR ($CDCl_3$): δ 7.90 (d, 2H, $J = 8.7$), 7.83 (s, 1H), 7.78 (d, 1H, Hβ, $J = 15.7$ Hz), 7.75 (t, 2H, $J = 8.4$ Hz), 7.66 (d, 2H, $J = 8.5$ Hz), 7.50 (d, 1H, $J = 15.7$ Hz), 7.46 (t, 2H, $J = 8.5$ Hz), 7.31 (t, 1H, $J = 8.3$ Hz), 7.22 (s, 1H); ^{13}C NMR: 189.0, 143.6, 138.8, 136.7, 133.8, 132.0 (3C), 130.1, 130.0 (4C), 128.2 (3C), 121.5, 117.8; EIMS (*m*/*z*, %) 354.2 ($M^+ + 2$, 42.48), 353.1 (M^+, 29.36), 352.2 (47.17), 273.2 (100), 197.1 (44.67), 157.0 (51.25), 141.1 (60.49), 102.0 (27.41).

*7.2.16. 3-[4-(1*H*-Imidazol-1-yl)phenyl]-1-(4-iodophenyl)prop-2-en-1-one (**4p**)*

Yellow crystalline solid. IR (KBr, cm^{-1}) 3116, 1656, 1521, 652; ^1H NMR ($CDCl_3$): δ 7.90 (d, 2H, $J = 6.2$ Hz), 7.85 (s, 1H), 7.82 (d, 1H, $J = 15.7$ Hz), 7.72 (m, 4H), 7.48 (d, 1H, $J = 15.8$ Hz), 7.43 (d, 2H, $J = 7.6$ Hz), 7.31 (t, 1H, $J = 8.5$ Hz), 7.22 (s, 1H); ^{13}C NMR: 189.0, 143.7, 138.2, 138.0, 137.1, 136.8, 135.7, 132.2, 130.4, 130.3, 130.2, 130.1, 129.8, 122.2, 122.0, 121.7, 117.6, 101.1; EIMS (*m*/*z*, %) 401.1 (23.10), 400.2 (M^+, 100), 333.1 (11.66), 273.2 (96.34), 231 (51.78), 197.1 (46.88), 169.1 (20.29), 102 (32.83).

*7.2.17. 3-[4-(1*H*-Imidazol-1-yl)phenyl-1-(3-methoxyphenyl)]prop-2-en-1-one (**4q**)*

Yellow solid. IR (KBr, cm^{-1}) 3120, 1655, 1520, 654; ^1H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.82 (d, 1H, $J = 15.6$ Hz), 7.75 (t, 2H, $J = 8.5$ Hz), 7.60 (d, 1H, $J = 7.5$ Hz), 7.53 (d, 1H, $J = 15.6$ Hz), 7.48 (m, 5H), 7.31 (t, 1H, $J = 8.3$ Hz), 7.12 (dd, 1H, $J = 5.7$ Hz, 2.3 Hz), 3.87 (s, 3H, OCH_3); ^{13}C NMR: 190.0, 160.1, 143.2, 138.8, 137.1, 135.2, 131.0, 130.2 (3C), 129.9, 122.8, 121.6, 121.4, 121.2, 119.6, 118.0, 113.1, 55.7; EIMS (*m*/*z*, %) 305.2 (21.61), 304.2 (M^+, 100), 273.1 (9.20), 237.1 (9.37), 197.1 (38.51), 144.0 (25.76), 102.0 (23.83).

*7.2.18. 3-[4-(1*H*-Imidazol-1-yl)phenyl]-1-(4-methoxyphenyl)prop-2-en-1-one (**4r**)*

White solid. IR (KBr, cm^{-1}) 3101, 1659, 1523, 658; ^1H NMR ($CDCl_3$): δ 8.03 (d, 2H, $J = 8.8$ Hz), 7.88 (s, 1H), 7.79 (d, 1H, Hβ, $J = 15.7$ Hz), 7.74 (t, 2H, $J = 8.5$ Hz), 7.55 (d, 1H, $J = 15.6$ Hz), 7.42 (d, 2H, $J = 8.4$ Hz), 7.29 (t, 1H, $J = 8.0$ Hz), 7.20 (d, 1H, $J = 10.5$ Hz), 6.97 (d, 2H, $J = 8.8$ Hz), 3.86 (s, 3H, $-OCH_3$); ^{13}C NMR: 188.4, 163.8, 142.3, 139.0, 135.5, 134.3, 130.9, 130.8, 130.0 (3C), 128.6, 121.7, 121.6, 121.5, 118.0, 114.1, 113.9; EIMS (*m*/*z*, %) 304.2 (M^+, 32.57), 289.2 (4.35), 237.1 (2.06), 197.1 (3.30) 135.1 (100), 107 (7.07), 77 (23.11), 76 (5.60).

*7.2.19. 1-(3,4-Dimethoxyphenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4s**)*

Yellow solid. IR (KBr, cm^{-1}) 3110, 1655, 1516, 659; ^1H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.82 (d, 1H, $J = 15$ .6 Hz), 7.76 (t, 2H, $J = 8.5$ Hz), 7.66 (dd, 1H, $J = 6.5$ Hz), 7.61 (d, 2H, $J = 10.5$), 7.58 (d, 1H, $J = 15.6$ Hz), 7.45 (d, 2H, $J = 8.4$ Hz), 7.31 (t, 1H, $J = 7.6$ Hz), 7.22 (s, 1H), 6.94 (d, 1H, $J = 8.4$ Hz), 3.96 (s, 6H, 2 (OCH_3)); ^{13}C NMR: 188.3, 153.6, 149.5, 142.3, 138.6, 135.2, 134.3, 131.2, 131.0, 130.0 (3C), 123.3, 122.4, 121.6, 118.0, 110.8, 110.1, 56.3, 56.2; EIMS (*m*/*z*, %) 335.2 (23.43), 334.2 (M^+, 100), 303 (31.98), 197.1 (16.71), 165.1 (59.67), 115.0 (17.85), 102.0 (26.91).

*7.2.20. 1-(3-Hydroxyphenyl)-3-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one (**4t**)*

White amorphous solid. IR (KBr, cm^{-1}) 3432, 3115, 1664, 1518, 658; ^1H NMR ($CDCl_3$): δ 8.23 (s, 1H), 7.92 (d, 2H, $J = 8.6$ Hz), 7.83 (d, 1H, Hβ, $J = 15.7$ Hz), 7.77 (d, 2H, $J = 7.2$), 7.70 (d, 1H, Hα, $J = 15.7$ Hz), 7.65 (t, 2H, $J = 8.9$ Hz), 7.58 (d, 1H, $J = 7.6$ Hz), 7.44 (t, 1H, $J = 2.1$ Hz), 7.36 (t, 1H, $J = 7.9$ Hz), 7.06 (dd, 1H, $J = 1.74$ Hz, 9.7 Hz); ^{13}C NMR: 190.0, 159.2, 143.4, 139.0, 138.0, 136.0, 131.5, 131.4, 130.8, 124.8, 123.1, 122.5, 122.3, 122.0, 121.2, 120.0, 116.8; EIMS (*m*/*z*, %) 291.3 (45.27), 290.2 (M^+, 31.36), 223.2 (4.90), 197.1 (12.05), 169.1 (7.29), 121.1 (100), 93 (34.01).

7.3. Antimicrobial testing

All the synthesized compounds (dissolved in DMSO) were subjected to anti-fungal screening for determining the zone of inhibition by cup diffusion method. The Petri plates were inoculated in cultures of fungus on potato dextrose agar medium. Plates were incubated at 37 °C for 24 hours for bacteria, at 30 °C for fungus species and at 45 °C for *A. fumigatus*. After inoculation, the diameter of clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism [29].

7.4. Superoxide scavenging assay

Compounds were assessed by the literature method [30] The reaction mixture comprises 40 μl of 280 μM β-nicotinamide adenine dinucleotide reduced form (NADH), 40 μl of 80 μM nitro blue tetrazolium (NBT), 20 μl of 8 μM phenazine methosulphate (PMS) 10 μl of 1 mM sample and 90 μl of 0.1 M phosphate buffer (pH 7.4). The reagents were prepared in buffer and sample in DMSO. The reaction was performed in 96-well microtitre plate at room temperature and absorbance was measured at 560 nm. The formation of superoxide was monitored by measuring the formation of water soluble blue formazan dye. A lower absorbance of reaction mixture indicates a higher scavenging activity of sample. Percent Radical Scavenging Activity was determined in comparison with control as:

$$\%\,\mathrm{RSA} = 100 - \{(\mathrm{OD\ test\ compound}/\mathrm{OD\ control}) \times 100\}$$

7.5. Anti-leishmanial activity

Anti-leishmanial activity of the title compounds was carried out on the pre-established culture of *L. major*. Parasites were cultured in medium M 199 with 10% foetal bovine serum; 25 mM of HEPES, and 0.22 μg of penicillin and streptomycin respectively at 24 °C in a shaking incubator [30].

1 mg of each compound was dissolved in 1 ml of DMSO and as a positive control 1 mg of Amphotericin B was also dissolved in 1 ml of DMSO.

Parasites at log phase were centrifuged at 3000 rpm for 3 minutes. Parasites were diluted in fresh culture medium to a final density of 2×10^6 cells/ml. In 96-well plates, 180 μl of medium was added in different wells. 20 μl of the experimental compound was added in medium and serially diluted. 100 μl of parasite culture was added in all wells. In negative controls, DMSO was serially diluted in medium while the positive control contained varying concentrations of standard anti-leishmanial compound i.e. Amphotericin B. The plates were incubated for 72 hours at 24 °C. The culture was examined microscopically on an improved Neubauer counting chamber and IC_{50} values of compounds possessing anti-leishmanial activity were calculated. All the assays were run in duplicate.

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