# 1-[4-(1*H*-Imidazol-1-yl)phenyl]-3-phenylprop-2-en-1-ones – a potential pharmacophore bearing anti-leishmanial activity

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A series of new potentially anti-microbial 1-[4-(1*H*-imidazol-1-yl)phenyl]-3-phenylprop-2-en-1-ones was synthesised by condensation of various substituted benzaldehydes with 1-[4-(1*H*-imidazol-1-yl)phenyl]ethanone, which was itself prepared by *N*-arylation of imidazole with *p*-haloacetophenones, using copper iodide and 1,3-di(pyridin-2-yl)propane-1,3-dione as a catalyst. All the synthesised compounds were subjected to preliminary evaluation for their anti-leishmanial and anti-fungal activities. Some of the synthesised compounds showed significant activities.

**Keywords:** imidazole, *N*-arylation, 1,3-di(pyridin-2-yl)propane-1,3-dione, anti-fungal activity, anti-leishmanial activity

Considerable work has been carried out during the past 20 years on the design, synthesis, characterisation and applications of various imidazole derivatives in order to explore their interesting physicochemical and biological properties. Some of these compounds have been found to possess activity against carboxypeptidase[1] and show anti-aging,[2] anti-microbial,[3] anti-cancer[4] and anti-malarial[5] activities while others show anti-hypertensive,[6] anti-diabetic[7] and anti-depressant[8] activities. Imidazole-based drugs such as ornidazole, metronidazole, nimorazole, miconazole and butoconazole (Fig. 1) are well known for their anti-microbial nature and are also used as sensitisers of hypoxic tumours in conjunction with radiotherapy.[9]

On the other hand, 1,3-diphenyl substituted prop-2-en-1-one derivatives, commonly known as chalcones (Fig. 2), correspond to one of the major classes of natural products with widespread distribution in fruits, vegetables and other foodstuffs.[10] Their wide range of biological activities such as anti-bacterial,[11] anti-fungal,[12] anti-oxidant,[13] anti-malarial,[14] anti-plasmodial[15] and anti-leishmanial[16] activities are largely attributed to their α,β-unsaturated ketone moieties.

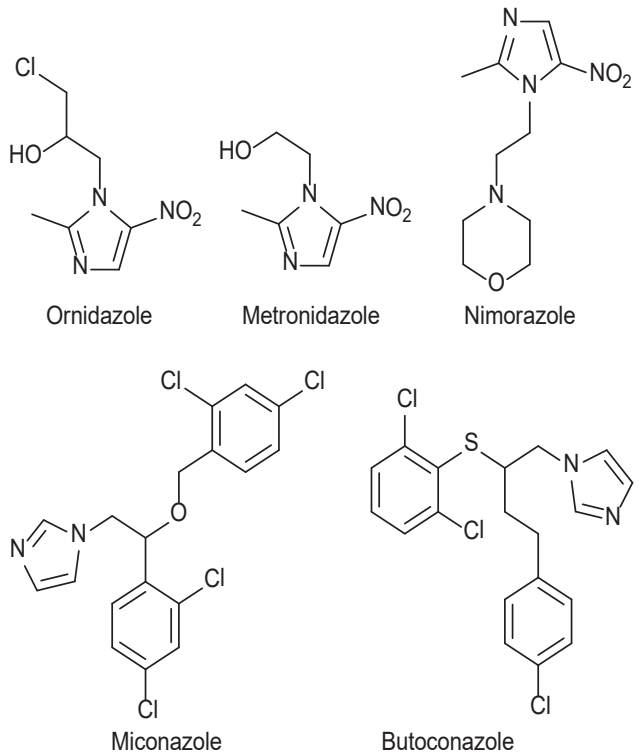


**Fig. 1** Structures of some well-known imidazole-based drugs.

The literature shows that the introduction of various substituents to the aromatic rings of chalcones is of interest in obtaining pharmacologically active compounds.[17,18] Our interest in the synthesis of biologically active heterocyclic compounds[19,20] has led us to synthesise new imidazole-based compounds bearing 1,3-diarylprop-2-en-1-one moieties with different substituents at the aryl ring and to investigate their anti-leishmanial and anti-fungal activities.

## Results and discussion

Synthesis of *N*-aryl imidazoles has attracted significant interest due to their frequent occurrence in biologically active inhibitors.[21] We have synthesised 1-(4-(1-*H*-imidazol-1-yl) phenyl)ethanone (**3**) by a mild and cost effective *N*-arylation of imidazole with *p*-fluoroacetophenone, using a combination of copper iodide and 1,3-di(pyridin-2-yl)propane-1,3-dione as a coupling catalyst.[22] Various *para*-substituted haloacetophenones were condensed to explore their structure–activity relationship and it was found that the 4-fluoro analogue is more reactive than the corresponding bromo and chloro analogues (Table 1). This may be attributed to the stronger (–) inductive effect of the fluoro group amongst the series, which causes electron deficiency at C-4 and thereby facilitates the nucleophilic attack of imidazole. We then reacted 1-[4-(1*H*-imidazol-1-yl)phenyl] ethanone (**3**) with a number of substituted aromatic aldehydes in the presence of 10% methanolic sodium hydroxide to obtain a series of novel potentially biologically active 1-(4-1*H*-imidazol-1-yl)-3-phenylprop-2-en-1-ones **4a–o** in good overall yields (Scheme 1).

Structures of the newly synthesised compounds were established on the basis of IR, NMR and mass spectrometry along with their elemental analyses, which were found to be in accordance with the calculated values. In the IR spectra, characteristic peaks around 1660 $cm^{-1}$ were noted, signals around δ 189 were observed in $^{13}C$ NMR for C=O, while proton NMR showed characteristic signals of α,β olefinic protons with $J$ = 14.0–16.7 Hz.[23]

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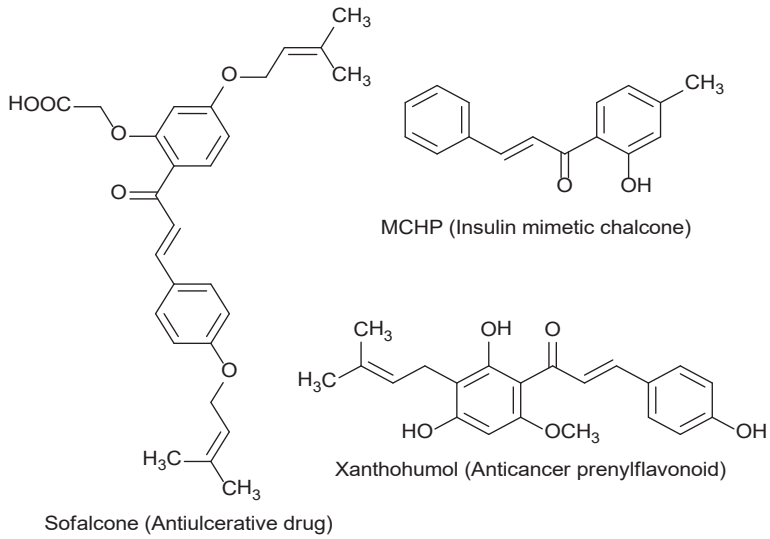
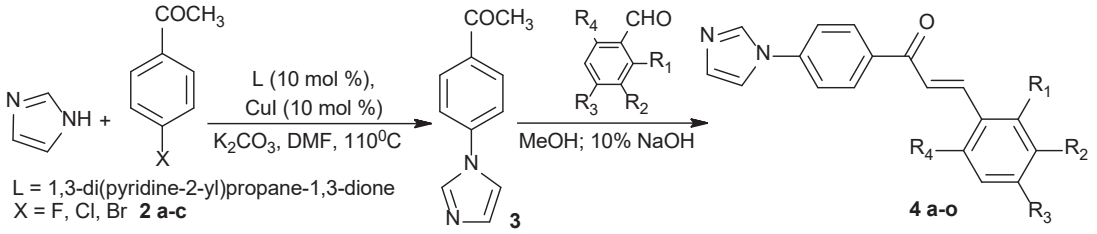



**Fig. 2** Structures of some medicinally important 1,3-disubstituted prop-2-en-1-ones.




| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **4a** | Cl | H | H | H |
| **4b** | H | Cl | H | H |
| **4c** | H | H | Cl | H |
| **4d** | Cl | H | Cl | H |
| **4e** | Cl | H | H | Cl |

| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **4f** | Br | H | H | H |
| **4g** | H | Br | H | H |
| **4h** | H | H | F | H |
| **4i** | H | $NO_2$ | Cl | H |
| **4j** | H | H | $NO_2$ | H |

| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **4k** | OMe | H | H | H |
| **4l** | H | Cl | OMe | H |
| **4m** | OMe | H | OMe | H |
| **4n** | OMe | OMe | OMe | H |
| **4o** | H | H | * | H |

* imidazol-1-yl

**Scheme 1** Synthesis of 1-[4-(1*H*-imidazol-1-yl)phenyl]-3-phenylprop-2-en-1-ones from imidazole.

**Table 1** Reaction conditions for the reaction of acetophenones with imidazole

| Entry | Acetophenone | Yield/% | Reaction time/h |
|---|---|---|---|
| 1 | 1-(4-Fluorophenyl)ethanone | 94 | 12 |
| 2 | 1-(4-Chlorophenyl)ethanone | 92 | 18 |
| 3 | 1-(4-Bromophenyl)ethanone | 93 | 16 |

*Stereochemistry and X-ray crystallography*

In order to investigate the stereochemistry (*E* or *Z* configuration) and for structural elucidation of the synthesised compounds, single crystals of the product **4n** were grown for X-ray crystallographic studies.

The asymmetric unit consists of discrete molecules devoid of any classical hydrogen bonds and it is stabilised by non-classical (C–H…O) hydrogen bonding interactions which link the molecules into a three dimensional network. In the crystal structure of compound **4n** (Fig. 3), the phenyl-prop-en-one moiety is not planar as evident from the associated torsion angles [O(1)-C(1)-C(2)-C(3) = –17.4(3)° and C(1)-C(2)-C(3)-C(31) = 173.42(19)°]. The mean-planes formed by the trimethoxyphenyl ring [C(31)–C(36)] and phenyl ring [C(11)–C(16)] subtend dihedral angles of 27.69(13)° and 17.06(11)° with the propenone moiety [O(1)/C(1)–C(3)] respectively. Moreover, the mean-plane of the imidazole ring [N(1)/N(2)/C(22)–C(25)] forms an angle of 7.91(15)° with the phenyl ring [C(11)–C(16)]. The mean-plane of the trimethoxyphenyl ring [C(31)–C(36)] is twisted by 43.89(7)° with respect to the plane of the other phenyl ring.

CCDC 739320 contains the supplementary data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* https://summary.ccdc.cam.ac.uk/structure-summary-form. Details of crystal data and structure refinement have been provided in Table 2.

*Anti-leishmanial activity*

Leishmaniasis is a group of prevalent diseases caused by protozoan parasites belonging to the genus *Leishmania*. *Leishmania* cause a broad spectrum of diseases ranging from the cutaneous healing skin lesions caused by *Leishmania major* to a fatal visceral form called kala azar caused by *L. donovani*. The synthesised compounds were tested for their anti-leishmanial activity using *L. major promastigotes* as parasites for in *vitro* screening and the results are shown in Table 4. The obtained data are represented as mean ± S.D. The data were statistically analysed by one-way ANOVA, followed by Tukey's multiple comparison test. The $IC_{50}$ (minimum concentration necessary for inhibition of 50% of microorganism growth) values were calculated using sigmoid dose–response curves (Table 3)**.** It was found that compounds **4i** and **4j** showed significant activity almost comparable to the standard drug, amphotericin, while the compounds **4f**, **4g** and **4o** exhibited moderate activity. Compounds **4a**, **4b**, **4c**, **4d**, **4e** were found to be weakly active

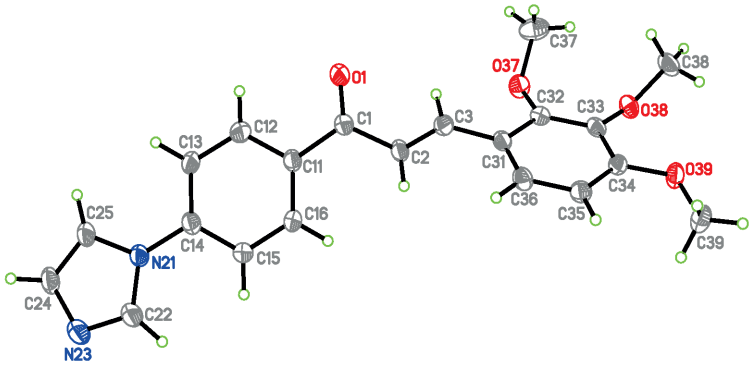



**Fig. 3** ORTEP3 diagram of compound **4n** showing the numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary radius.

**Table 2** Crystallographic parameters for compound **4n**

| | | | |
|---|---|---|---|
| Structural formula | $C_{21}H_{20}N_2O_4$ | Cell volume | 896.35(13) Å$^3$ |
| Formula weight | 364.39 | Z | 2 |
| Crystal system | Monoclinic | Absorption correction | None |
| Space group | Pc | Calculated density | 1.350 mg m$^{-3}$ |
| T/K | 173(2) | Crystal size | 0.48 × 0.45 × 0.44 mm$^3$ |
| a/Å | 14.4923(13) | Reflections collected | 5783 |
| b/Å | 7.9425(5) | Independent reflections | 1676 [R(int) = 0.0586] |
| c/Å | 7.7897(7) | Goodness-of-fit on F2 | 1.047 |
| θ range for data collection | 3.66–25.56° | F(000) | 384 |

**Table 3** Anti-leishmanial activity of the compounds ($IC_{50}$)

| Compd. | $IC_{50}$/μg mL$^{-1}$ | Compd. | $IC_{50}$/μg mL$^{-1}$ |
|---|---|---|---|
| **4a** | 0.81 ± 0.08 | **4i** | 0.59 ± 0.03 |
| **4b** | 0.83 ± 0.14 | **4j** | 0.58 ± 0.02 |
| **4c** | 0.85 ± 0.06 | **4k** | 0.82 ± 0.02 |
| **4d** | 0.76 ± 0.21 | **4l** | 0.97 ± 0.92 |
| **4e** | 0.72 ± 0.04 | **4m** | 0.93 ± 0.40 |
| **4f** | 0.68 ± 0.01 | **4n** | 0.91 ± 0.02 |
| **4g** | 0.62 ± 0.25 | **4o** | 0.67 ± 0.10 |
| **4h** | 0.99 ± 1.12 | Amphotericin B | 0.56 ± 0.20 |

whilst the compounds **4h**, **4k**, **4l**, **4m** and **4n** exhibited almost no activity against *L. major promastigotes*. It is evident from the results that compounds bearing nitro groups are the most active ones while introduction of electron-donating methoxy groups makes the pharmacophore almost inactive.

*Anti-fungal activity*

The *in vitro* antifungal activity of the synthesised compounds against four strains of fungi *i.e. Candida albicans, Aspergillus fumigatus, Trichoderma viride* and *Aspergillus niger* was investigated. Most of the newly synthesised compounds were found active against all the strains under evaluation to a certain extent (Table 4). The data are represented as mean of the triplicate ± S.D. An insight into the structure–activity relationship shows that the compounds bearing nitro groups *i.e.* **4i** and **4j** are moderately active along with the dichloro derivatives (**4d** and **4e**). It is also evident that the newly synthesised compounds are comparatively more active against *Candida albicans* than the rest of the strains. The compounds bearing methoxy groups at the benzene ring were found almost inactive with an $IC_{50}$ greater than 50.

## Experimental

*Chemistry*

All the chemicals were purchased from Merck, BDH, Aldrich and WAKO and were used without purification. EIMS was recorded on a MAT 312 instrument. $^1$H NMR spectra were recorded on a Bruker XWIN instrument at 400 MHz and $^{13}$C NMR spectra were recorded at 100 MHz. Chemical shifts are reported in ppm referenced to the residual solvent signal. IR spectra (in KBr disks) were recorded using a Thermo Nicolet FTIR 200 spectrometer. Melting points were recorded on a Stuart Scientific SMP3 apparatus and are uncorrected. Elemental analyses were carried out using a PerkinElmer 2400-CHN Analyser.

**Table 4** Anti-fungal activity of the compounds ($IC_{50}$)

| Compound | *Candida albicans* | *Aspergillus fumigatus* | *Trichoderma viride* | *Aspergillus niger* |
|---|---|---|---|---|
| **4a** | 39.84 ± 0.112 | 34.17 ± 0.318 | > 50 | > 50 |
| **4b** | 37.76 ± 0.192 | > 50 | > 50 | > 50 |
| **4c** | 42.15 ± 0.189 | 38.72 ± 0.183 | 36.53 ± 0.174 | 44.27 ± 0.741 |
| **4d** | 22.07 ± 0.221 | 38.79 ± 0.194 | 34.28 ± 0.183 | 28.65 ± 0.512 |
| **4e** | 20.07 ± 0.241 | 34.29 ± 0.166 | 34.28 ± 0.183 | 31.98 ± 0.211 |
| **4f** | 31.09 ± 0.231 | 41.98 ± 0.211 | 40.69 ± 0.062 | 44.61 ± 0.060 |
| **4g** | 33.77 ± 0.123 | 42.07 ± 0.221 | 48.42 ± 0.123 | 43.94 ± 0.251 |
| **4h** | 33.77 ± 0.143 | 40.07 ± 0.241 | 49.42 ± 0.113 | 46.24 ± 0.271 |
| **4i** | 18.37 ± 0.999 | 21.09 ± 0.231 | 21.98 ± 0.136 | 24.34 ± 0.141 |
| **4j** | 19.86 ± 0.132 | 23.77 ± 0.193 | 29.31 ± 0.182 | 28.87 ± 0.214 |
| **4k** | 31.98 ± 0.136 | 23.77 ± 0.193 | 7.31 ± 0.082 | 24.87 ± 0.264 |
| **4l** | > 50 | > 50 | > 50 | > 50 |
| **4m** | > 50 | > 50 | > 50 | > 50 |
| **4n** | > 50 | > 50 | > 50 | > 50 |
| **4o** | > 50 | > 50 | > 50 | > 50 |
| Clotrimazole | 9.36 ±0.11 | 9.56 ± 0.129 | 11.07 ± 0.241 | 13.42 ± 0.113 |

*1-[4-(1H-Imidazol-1-yl)phenyl]ethanone* (**3**)

The compound was prepared according to a modified literature procedure.[22] A mixture of imidazole (1.021 g, 15 mmol), anhydrous potassium carbonate (2.76 g, 20 mmol), copper iodide (0.119 g, 1.0 mmol), 1,3-di(pyridin-2-yl)propane-1,3-dione (10.0 mmol), 4-haloacetophenone (10.0 mmol) and DMF (15 mL) was stirred for 30 min at room temperature under a nitrogen atmosphere. This was followed by heating at 110 °C for 12–18 h. After the completion of the reaction (as indicated by TLC), the contents were cooled to room

temperature and passed through a plug of Celite. The filtrate was diluted with ethyl acetate (50 mL) and washed three times with saturated brine (10 mL each time). Treatment of the organic layer with activated charcoal and evaporation of the solvent under vacuum afforded the product: Yield (see Table 1); m.p. 115–116 °C (lit.[22] 114–116 °C).

*Synthesis of 1-[4-(1*H*-imidazol-1-yl)phenyl]-3-phenylprop-2-en-1-ones* **4a–o***; general procedure*

A methanolic sodium hydroxide solution (10%; 10.0 mL) was added drop-wise to a mixture of 1-(4-(1*H*-imidazol-1-yl)phenyl)ethanone (**3**) (10.0 mmol, 1.86 g), aromatic aldehyde (10.0 mmol) and methanol (50 mL) over a period of 30–40 min with continuous stirring at room temperature until completion of the reaction (as indicated by TLC). The reaction flask was kept in the freezer overnight. The obtained precipitates were filtered off and washed with a cold methanol–water mixture (1:10). Finally the product was purified by column chromatography using $CHCl_3$:MeOH (97:3) as a solvent.

*3-(2-Chlorophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4a**): Light yellow powder; yield 57%; m.p. 136–137 °C; IR (KBr): 3106, 1662, 1509, 642 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.15 (d, 2H, *J* = 7.8 Hz), 7.95 (s, 1H), 7.78 (d, 1H, *J* = 15.6 Hz), 7.63 (t, 1H, *J* = 6.9 Hz), 7.54 (m, 5H), 7.40 (m, 3H); $^{13}C$ NMR ($CDCl_3$): δ 188.5, 143.9, 140.8, 136.7, 136.6, 135.2, 131.3, 131.0, 130.5, 129.2, 128.1, 127.1, 126.5, 124.0, 123.0, 122.6 , 121.5, 121.0; EIMS *m/z* (%): 310.9 (7.98), 310.0 (34.72), 309.0 (33.30), 308.0 (100.00), 307.0 (41.52), 273.1 (48.26), 241.0 (26.71), 171.1 (56.79), 143.1 (27.88), 137.0 (29.56), 116.0 (52.79), 102.1 (52.30). Anal. calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07; found: C, 70.01; H, 4.29; N, 9.16%.

*3-(3-Chlorophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4b**): Yellow powder; yield 64%; m.p. 138–139 °C; IR (KBr): 3125, 1662, 1529 $cm^{-1}$; EIMS *m/z* (%): 311.0 (7.34), 310.0 (34.89), 309.0 (34.62), 308.0 (100.00), 273.1 (47.95), 241.0 (22.44), 171.1 (57.20), 137.0 (26.93), 116.0 (46.90), 102.1 (50.58); $^1H$ NMR ($CDCl_3$): δ 8.13 (d, 2H, *J* = 8.6 Hz), 8.02 (d, 1H, *J* = 15.8 Hz), 7.94 (s, 1H), 7.56 (d, 1H, *J* = 15.8 Hz), 7.52 (t, 2H, *J* = 8.7 Hz), 7.38 (d, 1H, *J* = 8.7 Hz), 7.35 (t, 1H, *J* = 1.8 Hz), 6.73 (d, 1H, *J* = 8.8 Hz), 3.94 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H); $^{13}C$ NMR ($CDCl_3$): δ 188.3, 143.6, 143.1, 138.6, 134.7, 131.2, 129.5, 129.1, 128.0, 127.1, 125.3, 123.3, 123.1, 122.0, 121.5, 120.2, 119.8, 117.3. Anal. calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07; found: C, 69.91; H, 4.31; N, 9.01%.

*3-(4-Chlorophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4c**): Colourless solid; yield 58%; m.p. 135–136 °C; IR (KBr): 3124, 1660, 1519, 650 $cm^{-1}$; EIMS *m/z* (%): 310.0 (34.93), 308.0 (100.00), 307.0 (44.78), 273.1 (29.82), 241.0 (28.83), 186.1 (6.99), 171.1 (59.40), 143.1 (29.62), 137.1 (35.29), 116.0 (56.08), 102.1 (49.54); $^1H$ NMR ($CDCl_3$): δ 8.14 (d, 2H, *J* = 7.0 Hz), 7.95 (s, 1H), 7.80 (d, 1H, *J* = 15.6 Hz), 7.58 (d, 2H, *J* = 8.5 Hz), 7.53 (d, 2H, *J* = 8.6 Hz), 7.50 (d, 1H, *J* = 15.6 Hz), 7.40 (d, 2H, *J* = 8.5 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 7.24 (s, 1H); $^{13}C$ NMR ($CDCl_3$): δ 189.7, 144.2, 143.0, 136.9, 136.8, 133.3, 132.5, 130.7, 130.3, 129.5, 128.6, 128.4, 127.1, 126.8, 124.0, 123.1, 122.7, 121.0. Anal. calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07; found: C, 70.15; H, 4.30; N, 9.02%.

*3-(2,4-Dichlorophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4d**): Yellow powder; yield 76%; m.p. 169–170 °C; IR (KBr): 3116, 1656, 1508, 648 $cm^{-1}$; EIMS *m/z* (%): 342.0 (6.26), 308.0 (100.00), 273.1 (29.82), 241.0 (28.83), 186.1 (6.99), 171.1 (59.46), 143.1 (29.62), 137.1 (35.29), 116.0 (56.08), 102.1 (49.54); $^1H$ NMR ($CDCl_3$): δ 8.14 (d, 2H, *J* = 8.8 Hz), 8.10 (d, 1H, *J* = 15.1 Hz), 7.95 (s, 1H), 7.69 (d, 1H, *J* = 8.5 Hz), 7.54 (d, 2H, *J* = 8.9 Hz), 7.51 (d, 1H, *J* = 6.9 Hz), 7.47 (d, 1H, *J* = 15.6 Hz), 7.36 (t, 1H, *J* = 6.9 Hz), 7.31 (dd, 2H, *J* = 1.9 Hz, 8.4 Hz); $^{13}C$ NMR ($CDCl_3$): δ 188.6, 140.2, 137.0, 136.5, 136.3, 133.8, 132.4, 131.7, 130.4, 129.8, 129.2, 128.8, 127.8, 124.5, 123.3, 123.0, 121.4, 121.1. Anal. calcd for $C_{18}H_{12}Cl_2N_2O$: C, 62.99; H, 3.52; N, 8.16; found: C, 63.06; H, 3.62; N, 8.09%.

*3-(2,6-Dichlorophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4e**): Light brown powder; yield 76%; m.p. 162–163 °C. IR (KBr): 3106, 1665, 1508 $cm^{-1}$; EIMS *m/z* (%): 346.0 (5.10), 345.0 (6.33), 344.0 (30.63), 343.0 (10.72), 342.0 (45.15), 309.0 (34.45), 308.0 (21.43), 307.1 (100.00), 275.0 (14.15), 171.1 (49.42), 116.0 (40.91); $^1H$ NMR ($CDCl_3$): δ 8.15 (d, 2H, *J* = 7.6 Hz), 7.95 (s, 1H), 7.90 (d, 1H, *J* = 16.1 Hz), 7.67 (d, 1H, *J* = 16.1 Hz), 7.54 (d, 2H, *J* = 7.7 Hz), 7.39 (d, 2H, *J* = 8.0 Hz), 7.35 (t, 1H, *J* = 1.8 Hz), 7.21 (d, 2H, *J* = 8.2 Hz); $^{13}C$ NMR ($CDCl_3$): δ 188.4, 143.3, 138.0, 136.5, 136.2, 133.7, 132.9, 131.6, 130.5, 129.9, 129.6, 129.0, 128.4, 127.2, 124.0, 123.3, 122.8, 121.4. Anal. calcd for $C_{18}H_{12}Cl_2N_2O$: C, 62.99; H, 3.52; N, 8.16; found: C, 65.01; H, 3.55; N, 8.11%.

*3-(2-Fluorophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4f**): Off-white powder; yield 60%; m.p. 140–141 °C; IR (KBr): 3114, 1662, 1510, 648 $cm^{-1}$; EIMS *m/z* (%): 293.0 (22.03), 292.0 (100.00), 291.1 (32.91), 225.0 (27.48), 171.1 (49.06), 116.0 (41.36), 102.1 (10.89), 101.0 (63.08); $^1H$ NMR ($CDCl_3$): δ 8.15 (d, 2H, *J* = 7.8 Hz), 7.95 (s, 1H), 7.93 (d, 1H, *J* = 15.8 Hz), 7.65 (d, 1H, *J* = 15.8 Hz), 7.62 (d, 1H, *J* = 6.7 Hz), 7.53 (d, 2H, *J* = 8.6 Hz), 7.40 (m, 2H), 7.20 (m, 3H); $^{13}C$ NMR ($CDCl_3$): δ 189.3, 142.8, 140.1, 136.2, 133.8, 132.9, 131.2, 129.4, 128.0, 124.8, 124.2, 123.8, 123.6, 122.8, 122.4, 119.8, 118.2, 116.1. Anal. calcd for $C_{18}H_{13}BrN_2O$: C, 61.21; H, 3.71; N, 7.93; found: C, 61.29; H, 3.73; N, 7.98%.

*3-(3-Bromophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4g**): Yellow powder; yield 89%; m.p. 171 °C; IR (KBr): 3106, 1652, 1510, 643 $cm^{-1}$; EIMS *m/z* (%): 354.9 (8.71), 353.9 (38.63), 353.0 (20.25), 352.0 (37.82), 273.1 (44.46), 171.1 (39.21), 116.1 (45.79), 102.1 (100.00); $^1H$ NMR ($CDCl_3$): δ 8.15 (dd, 2H, *J* = 1.7 Hz, 8.8 Hz), 7.95 (s, 1H), 7.80 (t, 1H, *J* = 1.5 Hz), 7.77 (d, 1H, *J* = 15.7 Hz), 7.55 (m, 5H), 7.36 (t, 1H, *J* = 1.2 Hz), 7.31 (t, 2H, *J* = 7.8 Hz); $^{13}C$ NMR ($CDCl_3$): δ 189.4, 144.3, 143.8, 137.4, 137.0, 136.3, 131.7, 131.2, 130.8, 130.6, 130.4, 129.2, 128.6, 125.8, 123.6, 123.0, 121.6, 120.8. Anal. calcd for $C_{18}H_{13}BrN_2O$: C, 61.21; H, 3.71; N, 7.93; found: C, 61.13, H, 3.76, N, 7.96%.

*3-(4-Fluorophenyl)-1-[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4h**): Colourless solid; yield 51%; m.p. 149 °C; IR (KBr): 3116, 1659, 1526, 644 $cm^{-1}$; EIMS *m/z* (%): 293.9 (3.73), 293.0 (19.79), 292.0 (100.00), 291.0 (36.10), 225.0 (33.71), 196.0 (11.87), 171.1 (38.30), 116.0 (38.10), 102.1 (10.83), 101.0 (56.74); $^1H$ NMR ($CDCl_3$): δ 8.14 (dd, 2H, *J* = 6.8 Hz, 1.8 Hz), 7.95 (s, 1H), 7.82 (d, 1H, *J* = 15.6 Hz), 7.66 (dd, 2H, *J* = 9.2 Hz, 1.9 Hz), 7.54 (d, 2H, *J* = 7.7 Hz), 7.46 (d, 1H, *J* = 15.6 Hz), 7.35 (t, 1H, *J* = 1.9 Hz), 7.13 (t, 3H, *J* = 7.7 Hz); $^{13}C$ NMR ($CDCl_3$): δ 189.0, 142.2, 140.0, 136.1, 134.0, 132.8, 131.0, 129.2, 128.0, 125.0, 124.4, 123.7, 123.3, 122.6, 122.2, 119.6, 118.0, 116.0. Anal. calcd for $C_{18}H_{13}FN_2O$: C, 73.96; H, 4.48; N, 9.58; found: C, 73.93, H, 4.57, N, 9.59%.

*1-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(3-nitrophenyl)prop-2-en-1-one* (**4i**): Off-white powder; yield 86%; m.p. 159–160 °C; IR (KBr): 3128, 1661, 1512, 640 $cm^{-1}$; EIMS *m/z* (%): 321.0 (3.44), 320.0 (23.12), 319.0 (100.00), 291.0 (14.65), 252.0 (16.07), 171.1 (79.77), 143.1 (28.07), 116.1 (45.05), 102.1 (41.04); $^1H$ NMR ($CDCl_3$): δ 8.52 (t, *J* = 1.5 Hz), 8.27 (dd, 1H, *J* = 1.3 Hz, 8.1 Hz), 8.18 (d, 2H, *J* = 8.5 Hz), 8.08 (d, 1H, *J* = 8.6 Hz), 7.96 (d, 1H, *J* = 15.5 Hz), 7.91 (t, 2H, *J* = 7.5 Hz), 7.85 (s, 1H), 7.66 (d, 1H, *J* = 15.3 Hz), 7.62 (d, 1H, *J* = 7.4 Hz), 7.55 (d, 1H, *J* = 6.8 Hz), 7.37 (t, 1H, *J* = 1.3 Hz); $^{13}C$ NMR ($CDCl_3$): δ 188.2, 149.0, 142.5, 141.8, 136.6, 136.4, 134.7, 132.6, 130.9, 130.4, 127.2, 125.0, 124.0, 123.8, 122.6, 122.1, 121.0, 120.9. Anal. calcd for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16; found: C, 67.70, H, 4.14, N, 13.10%.

*1-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(4-nitrophenyl)prop-2-en-1-one* (**4j**): Colourless solid; yield 47%; m.p. 202–204 °C; IR (KBr): 3112, 1648, 1521, 644 $cm^{-1}$; EIMS *m/z* (%): 321.0 (3.48), 320.0 (22.79), 319.0 (100.00), 318.0 (10.48), 272.0 (20.03), 252.0 (18.94), 171.1 (72.29), 116.0 (57.52), 102.1 (52.32); $^1H$ NMR ($CDCl_3$): δ 8.29 (d, 2H, *J* = 8.7 Hz), 8.17 (d, 2H, *J* = 8.6 Hz), 7.96 (s, 1H), 7.87 (d, 1H, *J* = 15.7 Hz), 7.80 (d, 3H, *J* = 8.7 Hz), 7.64 (d, 1H, *J* = 15.7 Hz), 7.56 (d, 2H, *J* = 5.6 Hz), 7.36 (t, 1H, *J* = 4.9 Hz); $^{13}C$ NMR ($CDCl_3$): δ 189.0, 146.7, 143.0, 142.8, 139.5, 137.0, 135.7, 131.4, 131.0, 129.0, 125.6, 125.4, 123.0, 122.5, 122.1, 121.8, 121.5, 121.2. Anal. calcd for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16; found: C, 67.78, H, 4.16, N, 13.12%.

*1-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(2-methoxyphenyl)prop-2-en-1-one* (**4k**): Light yellow powder; yield 67%; m.p. 127–128 °C; IR (KBr): 3110, 1648, 1510, 641 $cm^{-1}$; EIMS m/z (%): 304.1 (6.66), 274.0 (21.50), 273.0 (100.00), 171.1 (10.94), 116.0 (21.85), 102.1 (5.80); $^1H$ NMR

($CDCl_3$): δ 8.14 (dd, 3H, *J* = 1.9 Hz, 8.6 Hz), 7.94 (s, 1H), 7.63 (d, 2H, *J* = 7.4 Hz), 7.61 (d, 1H, *J* = 14.0 Hz), 7.52 (d, 2H, *J* = 8.5 Hz), 7.40 (dd, 1H, *J* = 1.5 Hz, 7.8 Hz), 7.36 (d, 1H, *J* = 13.6 Hz), 6.95 (m, 2H), 3.91 (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 189.0, 162.0, 145.6, 145.0, 137.8, 137.2, 130.2, 130.0, 127.4, 124.5, 123.6, 123.4, 121.8, 121.5, 120.9, 119.8, 119.2, 114.7, 55.6. Anal. calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20; found: C, 75.05, H, 5.35, N, 9.15%.

*1-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(4-methoxyphenyl)prop-2-en-1-one* (**4l**): Colourless solid; yield 77%; m.p. 158 °C; IR (KBr): 3103, 1658, 1510 cm$^{-1}$; EIMS *m/z* (%): 305.9 (4.01), 305.1 (22.17), 304.1 (100.00), 303.1 (36.12), 289.1 (16.30), 273.1 (13.18), 196.0 (4.04), 116.0 (23.67), 102.1 (7.78); $^1$H NMR ($CDCl_3$): δ 8.13 (dd, 2H, *J* = 1.7 Hz, 6.8 Hz), 7.94 (s, 1H), 7.83 (d, 1H, *J* = 15.6 Hz), 7.61 (d, 2H, *J* = 8.7 Hz), 7.52 (d, 2H, *J* = 7.0 Hz), 7.41 (d, 1H, *J* = 15.5 Hz), 7.35 (t, 1H, *J* = 1.7 Hz), 6.94 (d, 2H, *J* = 8.7 Hz), 3.85 (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 188.9, 161.8, 145.2, 144.8, 137.5, 137.0, 130.1, 130.2, 127.2, 124.3, 123.3, 123.2, 121.8, 121.2, 121.0, 120.0, 119.4, 114.9, 55.4. Anal. calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20; found: C, 75.03, H, 5.33, N, 9.26%.

*1-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(2,4-dimethoxyphenyl)prop-2-en-1-one* (**4m**): Yellow crystalline solid; yield 63%; m.p. 158–159 °C; IR (KBr): 3126, 1658, 1519, 650 cm$^{-1}$; EIMS *m/z* (%): 334.1 (22.88), 304.1 (22.97), 303.1 (100.00), 171.1 (10.59), 116.0 (17.86), 102.1 (4.13); $^1$H NMR ($CDCl_3$): δ 8.13 (d, 2H, *J* = 8.7 Hz), 8.08 (d, 1H, *J* = 15.7 Hz), 7.94 (s, 1H), 7.57 (t, 2H, *J* = 8.6 Hz), 7.54 (d, 1H, *J* = 15.0 Hz), 7.51 (d, 2H, *J* = 8.2 Hz), 7.35 (t, 1H, *J* = 6.8 Hz), 6.55 (dd, 1H, *J* = 2.2, 8.5 Hz), 6.47 (d, 1H, *J* = 2.3 Hz), 3.90 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 189.7, 163.5, 160.7, 141.5, 137.8, 136.5, 130.6, 130.4, 128.3, 124.4, 123.2, 122.9, 119.9, 119.8, 113.2, 105.7, 98.6, 55.8, 55.7. Anal. calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38; found: C, 71.89, H, 5.49, N, 8.44%.

*1-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one* (**4n**): Pale yellow powder; yield 80%; m.p. 134–135 °C; IR (KBr): 3101, 1658, 1520 cm$^{-1}$; EIMS *m/z* (%): 364.1 (4.40), 334.0 (22.66), 333.0 (100.00), 171.1 (8.82), 116.0 (11.29); $^1$H NMR ($CDCl_3$): δ 8.13 (d, 2H, *J* = 8.6 Hz), 8.02 (d, 1H, *J* = 15.8 Hz), 7.94 (s, 1H), 7.56 (d, 1H, *J* = 15.8 Hz), 7.52 (t, 2H, *J* = 8.7 Hz), 7.38 (d, 1H, *J* = 8.7 Hz), 7.35 (s, 1H), 6.73 (d, 1H, *J* = 8.8 Hz), 3.94 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 189.4, 156.3, 153.9, 142.7, 142.5, 137.6, 136.0, 134.4, 133.8, 133.6, 124.0, 123.8, 122.9, 120.9, 120.8, 112.9, 107.8, 61.6, 61.1, 56.4. Anal. calcd for $C_{21}H_{21}N_2O_4$: C, 69.22; H, 5.53; N, 7.69; found: C, 69.42, H, 5.63, N, 7.76%.

*1,3-Bis[4-(1*H*-imidazol-1-yl)phenyl]prop-2-en-1-one* (**4o**): Off white powder; yield 76%; m.p. 202–203 °C; IR (KBr): 3109, 1663, 1518 cm$^{-1}$; EIMS *m/z* (%): 342.0 (5.29), 341.1 (24.78), 340.1 (100.00), 273.1 (31.37), 197.1 (22.50), 171.0 (42.09), 116.1 (51.26), 102.1 (29.07); $^1$H NMR ($CDCl_3$): δ 8.16 (dd, 2H, *J* = 7.0 Hz, 1.6 Hz), 7.95 (s, 1H), 7.86 (d, 1H, *J* = 15.7 Hz), 7.77 (d, 2H, *J* = 8.5 Hz), 7.55 (d, 2H, *J* = 2.1 Hz), 7.52 (d, 1H, *J* = 13.6 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 7.36 (s, 1H), 7.32 (t, 1H, *J* = 1.2 Hz), 7.22 (d, 2H, *J* = 4.8 Hz); $^{13}$C NMR ($CDCl_3$): δ 189.4, 141.1, 139.9, 138.2, 138.0, 136.8, 135.9, 134.0, 131.3, 131.4, 126.9, 126.7, 124.6, 124.3, 123.2, 122.9, 122.7, 121.6, 121.4, 120.8, 120.6. Anal. calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46; found: C, 74.18, H, 4.78, N, 16.54%.

*X-ray crystallography*

Crystals of the compound 1-[4-(1*H*-imidazol-1-yl)phenyl]-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (**4n**) were grown by slow evaporation from methanol solution at room temperature. The colourless crystal was mounted in a random orientation on a glass fibre in a Stoe IPDS-II two circle diffractometer equipped with graphite monochromated MoKα radiation (λ = 0.71073 Å). The data were corrected for Lorentz and polarisation effects and for absorption using the multi-scan method. The structure was solved by direct methods using SHELXS-97 and was refined using full-matrix least-squares methods on $F^2$ with SHELXL-97.[24] All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were located with a difference map and refined using a riding model.

*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 in a shaking incubator.[21] Each compound (1 mg) 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 1 g phase were centrifuged at 3000 rpm for 3 min. Parasites were diluted in fresh culture medium to a final density of $2 \times 10^6$ cells/mL. In 96-well plates, 180 μL of medium was added in different wells. The experimental compound (20 μL) was added to the medium and serially diluted. Parasite culture (100 μL) was added to 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 h at 24 °C. The culture was examined microscopically on an improved Neubaur counting chamber and $IC_{50}$ values of compounds possessing anti-leishmanial activity were calculated. All the assays were run in duplicate and the data obtained are represented as mean ± S.D. The data were statistically analysed by one-way ANOVA, followed by Tukey's multiple comparison test. The $IC_{50}$ (minimum concentration necessary for inhibition of 50% of microorganism growth) values were calculated using sigmoid dose–response curves.

*Anti-fungal activity*

The assay for anti-fungal activity was performed in sterile 96-well microplates according to the reported method,[25,26] which is based on the principle that the microbial cell number is directly proportional to the microbial growth. This proceeds in the log phase resulting in increased absorbance of broth medium. The fungal strains used for the experiments were obtained from the Department of Pathology, Quaid-e-Azam Medical College Bahawalpur. The organisms were maintained on stock sabroud dextrose agar culture before use. The test sample solutions, standard drug (clotrimazole) and their dilutions were pipetted into the wells (20 μg/well) along with the overnight maintained fresh fungal culture (180 μL). The initial absorbance of the culture was strictly maintained between 0.12–0.19 at 405 nm. The total volume in each well was kept to 200 μL, while incubation was carried out at 28 °C for 72 h with lids on the microplates. The absorbance was measured at 405 nm using a Synergy HT BioTek USA microplate reader before and after incubation and the difference was noted as an index of fungal growth. The percent inhibition was calculated using the formula:

$$\text{Inhibition (\%)} = 100\ (X - Y) / X$$

where X is the absorbance in the control with fungal culture and Y is the absorbance in the test sample.

All the results were calculated as the mean of triplicate measurements ($n = 3$, ± SD) and the minimum inhibitory concentration (MIC) was measured with suitable dilutions (10–30 μg/well). Results were calculated using EZ-Fit5 (Perrella Scientific Inc. Amherst USA) software and data expressed as $IC_{50}$.

## Conclusion

Prompted by the well-established anti-leishmanial and anti-fungal properties of imidazoles and chalcones, a series of novel 1-[4-(1*H*-imidazol-1-yl)phenyl]-3-phenylprop-2-en-1-ones **4a–o** were synthesised emphasising, in particular, the strategy of combining two chemically different but pharmacologically compatible pharmacophores in one frame. The title compounds were synthesised by the condensation of a series of benzaldehydes with 1-[4-(1*H*-imidazol-1-yl)phenyl]ethanone and were assayed for their anti-leishmanial and anti-fungal activities. Biological evaluation revealed that some of the compounds obtained were found to be active and could be useful as a template for further development through modification or derivatisation to design more potent biologically active compounds.

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