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RESEARCH ARTICLE

Synthesis and leishmanicidal activity of 2,3,4-substituted-5-imidazolones

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Abstract

Twenty-nine imidazolones **1–29** were synthesized and were randomly screened for their *in vitro* anti-leishmanial potential. Compound **17** showed a good anti-leishmanial activity with an IC_{50} value of 12.98 ± 0.32 µg/mL. Compounds **14** and **24** were also found to be moderately active (IC_{50} values 28.20 ± 0.03 and 41.12 ± 0.32 µg/mL, respectively). The activity was compared with that of standard drugs, amphotericin B (IC_{50} = 0.12 ± 0.41 µg/mL) and pentamidine (IC_{50} = 2.56 ± 0.10 µg/mL).

Keywords: *Imidazolone; substitution effect; Leishmania major; leishmanicidal activity*

Introduction

Leishmaniasis is a protozoan disease caused by parasites belonging to the genus *Leishmania,* which affects the skin, mucous membranes, and internal organs. These parasites are carried by the blood-sucking sandfly, *Phlebotomus* species. It also known as Kala azar, which is Hindi for "black fever". When the parasites are transmitted to humans or animals, the host's immune system attempts to consume the protozoa with immune cells called macrophages; these macrophages burst open, releasing the protozoa and allowing them to take over neighboring cells.

Leishmaniasis is classified into cutaneous, visceral, mucosal or mucocutaneous, and diffused cutaneous forms[1,2]. The symptoms of leishmaniasis include wounds, fever, weight loss, anorexia, change in hair color, abnormal growth and major dysfunction of the liver, damage to the spleen, bone marrow, and lymph nodes, ulcer, nasal blockage, swelling of the nose and lips with damage of the soft tissues of the oronasal cavity, wounds widely distributed on the skin, thickening of plaques, and multiplex nodules and anemia.

Leishmaniasis disease is distributed worldwide and causes considerable mortality and morbidity. It is present in approximately 88 countries ranging from Central and South America to West Asia. More than 90% of cases of visceral leishmaniasis are in Bangladesh, Brazil, India, Nepal, and Sudan. In Sudan, one epidemic lasted from 1984 to 1994 and claimed over 100,000 lives. Leishmaniasis is treatable, but existing medicines are costly. Treatment is generally with pentavalent antimonials such as Pentostam (sodium stibogluconate) or Glucantime (meglumine antimonite). Second-line drugs are amphotericin B and pentamidine; however, these are not used routinely because of toxicity[3–5].

Imidazolone is a five-membered heterocyclic ring system with three carbon atoms and two nitrogen atoms at positions 1 and 3. Imidazolones are carbonyl dihydro-imidazoles, also known as oxoimidazolines. In general, imidazolones are of many types, e.g. 2-, 4-, or 5-imidazolones. The number indicates the position of the carbonyl group.

The imidazolones are diverse bioactive heterocyclic compounds. They show numerous biological activities including anti-human immunodeficiency virus (HIV), antimalarial, local anesthetic, goitrogenic, antibiotic, antifungal, antiparasitic, anticonvulsant, monoamine oxidase (MAO) inhibitory, sedative, hypnotic, central nervous system (CNS) depressant, anti-inflammatory, anticancer, anti-parkinsonian, and immunomodulatory properties.

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Previously, the imidazolones were prepared by heating a mixture of 5-oxazolone derivatives with differently substituted aromatic or aliphatic amines in the presence of excess of pyridine for 10–15 h. The yields of the product were moderate and the reaction required a long time to complete[6–16].

In our ongoing research on leishmaniasis[17–20], we synthesized 29 imidazolones, **1–29**, by treating different oxazolones with varyingly substituted aromatic amines. In a typical reaction, a mixture of differently substituted *E*-oxazolones[21–23] (1 mmol) and substituted aromatic amines (1.1 mmol) in anhydrous pyridine were irradiated by microwaves to afford compounds **1–29**. Compounds **1–29** were randomly screened for their *in vitro* anti-leishmanial potential. Compound **17** showed a good anti-leishmanial activity, having an IC_{50} value of 12.98 ± 0.32 µg/mL. Compounds **14** and **24** were also found to be moderately active, having IC_{50} values of 28.20 ± 0.03 and 41.12 ± 0.32 µg/mL, respectively. However, compounds **1–3**, **5**, **6**, **9**, **11–13**, **15**, **18–23**, **25**, **26**, **28**, and **29** showed IC_{50} values greater than 50 µg/mL, while compounds **4**, **7**, **8**, **10**, **16**, and **27** showed IC_{50} values greater than 100 µg/mL, and thus were considered to be inactive. The activity was compared with that of the standard drugs amphotericin B (IC_{50} = 0.12 ± 0.41 µg/mL) and pentamidine (IC_{50} = 2.56 ± 0.10 µg/mL). The structures of all the synthesized compounds were determined by spectroscopic analysis.

Material and methods

General experimental

Melting points were determined on a Büchi 434 melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) experiments were performed on Bruker Avance AM 300 and 500 MHz spectrometers. CHN (carbon, hydrogen, and nitrogen) analysis was performed on a Carlo Erba Strumentazione-Mod-1106 elemental analyzer (Italy). Ultraviolet (UV) spectra were recorded on a PerkinElmer Lambda-5 UV/VIS spectrometer in MeOH. Infrared (IR) spectra were recorded on a Jasco IR-A-302 spectrometer as KBr (disk). Electron impact mass spectra (EI MS) were recorded on a Finnigan MAT-311A spectrometer (Germany). Reactions were carried out in a CEM Discover system, model 908010 (USA). Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254; E. Merck, Germany). Chromatograms were visualized under UV light at 254 and 365 nm or by using iodine vapors.

General procedure for the synthesis of compounds 1–29

A mixture of differently substituted *E*-oxazolones[22–24] (1 mmol) and substituted aromatic amines (1.1 mmol) in anhydrous pyridine were irradiated by microwaves (CEM Discover system, model 908010) for 10–15 min at 150°C. The input power of the microwave reactor was 300 W, and the same power was used for all reactions. The reactions were performed in an open vessel. The completion of reaction was monitored by TLC, and then 5 mL of ice-cool 5% HCl in water was added and the mixture was left overnight. The resultant solids were collected and washed with water before being crystallized by ethanol, filtered, and dried to afford compounds **1–29**.

*2-Methyl-3-phenyl-5-[(E)-phenylmethylidene]-3,5-dihydro-4H-imidazole-4-one (**1**)* Yield: 88%; m.p.: 155°C; R_f: 0.61 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 299 (log ε = 4.5) nm; IR (KBr): υ_{max} 3020, 2917, 1708, 1635, 1250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, $J_{2',3'} = J_{6',5'}$ = 8.2 Hz, 2H, H-2′/6′), 7.70 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.2 Hz, 2H, H-2″/6″), 7.50–7.55 (m, 3H, H-3″–5″), 7.43–7.45 (m, 3H, H-3′–5′), 7.04 (s, 1H, H-6), 2.35 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 262 (M^+, 34), 144 (10), 118 (52), 77 (100); Anal. calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68%; Found: C, 77.86; H, 5.39; N, 10.40%.

*2,3-Diphenyl-5-[(E)-phenylmethylidene]-3,5-dihydro-4H-imidazole-4-one (**2**)* Yield: 77%; m.p.: 166°C; R_f: 0.61 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 310 (log ε = 4.2) nm; IR (KBr): ν_{max} 3019, 2823, 1708, 1655, 1267 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.46 (m, 3H, H-2′/6′), 8.21 (m, 2H, H-2″/6″), 7.88 (m, 3H, H-3′–5′), 7.57 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 7.8 Hz, 2H, H-2‴/6‴), 7.51 (m, 3H, H-3‴–5‴), 7.42 (m, 3H, H-3″–5″), 7.06 (s, 1H, H-6); EI MS: *m/z* (rel. abund. %) 324 (M^+, 34), 193 (10), 118 (100), 77 (75); Anal. calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64%; Found: C, 81.48; H, 4.99; N, 8.66%.

*5-[(E)-[1,1′-Diphenyl]-4-ylmethylidene]-2-methyl-3-phenyl-3,5-dihydro-4H-imidazole-4-one (**3**)* Yield: 99%; m.p.: 158°C; R_f: 0.61 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 368 (log ε = 4.7) nm; IR (KBr): ν_{max} 3027, 2923, 1708, 1645, 1267 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, $J_{2',3'} = J_{6',5'}$ = 8.4 Hz, 2H, H-2′/6′), 7.70 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 8.2 Hz, 2H, H-2‴/6‴), 7.64 (d, $J_{3',2'} = J_{5',6'}$ = 8.3 Hz, 2H, H-3′/5′), 7.54–7.50 (m, 3H, H-3‴–5‴), 7.43–7.46 (m, 3H, H-3″–5″), 7.38 (d, $J_{2'',3''} = J_{6'',5''}$ = 7.2 Hz, 2H, H-2″/6″), 7.07 (s, 1H, H-6), 2.36 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 238 (M^+, 34), 193 (10), 118 (100), 77 (75); Anal. calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28%; Found: C, 81.68; H, 5.39; N, 8.30%.

*5-[(E)-[1,1′-Biphenyl]-4-ylmethylidene]-3-(3-methoxyphenyl)-2-methyl-3,5-dihydro-4H-imidazole-4-one (**4**)* Yield: 85%; m.p.: 147°C; R_f: 0.54 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 313 (log ε = 4.5) nm; IR (KBr): ν_{max} 3028, 2977, 1643, 1601, 1270 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.25 (d, $J_{2',3'} = J_{6',5'}$ = 8.3 Hz, 2H, H-2′/6′), 7.69 (d, $J_{3',2'} = J_{5',6'}$ = 8.3 Hz, 2H, H-3′/5′), 7.45 (m, 3H, H-3″–5″), 7.68 (d, $J_{6''',5'''}$ = 8.2 Hz, 1H, H-6‴), 7.63 (m, 1H, H-5‴), 7.37 (m, 2H, H-2″/6″), 7.25 (br.s, 1H, H-2‴), 7.23 (s, 1H, H-6), 6.99 (m, 1H, H-4‴), 3.88 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 368 (M^+, 100), 193 (19.1), 148 (61), 134 (40), 77 (10.3); Anal. calcd for $C_{24}H_{20}N_2O_2$: C, 81.63; H, 5.36; N, 8.28%; Found: C, 81.65; H, 5.37; N, 8.31%.

*5-[(E)-[1,1′-Biphenyl]-4-ylmethylidene]-2,3-diphenylidene-3,5-dihydro-4H-imidazole-4-one (**5**)* Yield: 97%; m.p.: 160°C; R_f: 0.62 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 313 (log ε = 3.45) nm; IR (KBr): ν_{max} 3255, 3030, 1640, 1440, 1290 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.45 (m, 2H, H-2′/6′), 8.21 (m, 2H, H-2″/6″), 7.86 (m, 3H, H-3′–5′), 7.65 (d, $J_{3'',2''} = J_{5'',6''}$ = 8.4 Hz, 2H, H-3″/5″), 7.57 (d, $J_{2'''',3''''} = J_{6'''',5''''}$ = 7.7 Hz, 2H, H-2⁗/6⁗), 7.50 (m, 3H, H-3⁗–5⁗), 7.41 (m, 3H, H-3‴–5‴), 7.37 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 7.2 Hz, 2H, H-2‴/6‴), 7.27 (s, 1H, H-6); EI MS: *m/z* (rel. abund. %) 400 (M^+, 6), 390 (17), 270 (22), 167

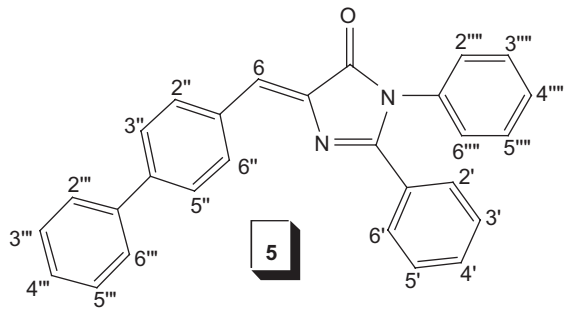


Figure 1. Structure of compound **5**.

(100), 105 (83); Anal. calcd for $C_{28}H_{20}N_2O$: C, 83.98; H, 5.03; N, 7.00%; Found: C, 83.99; H, 5.12; N, 7.08% (Figure 1).

5-[(E)-[1,1′-Biphenyl]-4-ylmethylidene]-3-(2-methoxyphenyl)-2-phenyl-3,5-dihydro-4H-imidazole-4-one ***(6)*** Yield: 85%; m.p.: 130°C; R_f: 0.52 (ethyl acetate/hexane, 3:7), UV (MeOH): λ_{max} 319 (log ε = 4.69) nm; IR (KBr): ν_{max} 3354, 3056, 1653, 1528, 1250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.44 (d, $J_{2',3'} = J_{6',5'} = 7.2$ Hz, 2H, H-2′/6′), 8.19 (d, $J_{2'',3''} = J_{6'',5''} = 7.2$ Hz, 2H, H-2″/6″), 7.91 (m, 3H, H-3′–5′), 7.65 (d, $J_{3',2'} = J_{5',6'} = 7.3$ Hz, 2H, H-3″/5″), 7.57 (d, $J_{6''',5'''} = 8.0$ Hz, 1H, H-6‴), 7.42 (m, 3H, H-3‴–5‴), 7.35 (d, $J_{2''',3'''} = J_{6''',5'''} = 7.3$ Hz, 2H, H-2‴/6‴), 7.31 (m, 2H, H-4‴, 5‴), 7.28 (s, 1H, H-6), 6.86 (d, $J_{3''',4'''} = 8.1$ Hz, 1H, H-3‴), 3.79 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 430 (M^+, 5), 326 (9.34), 123 (92), 105 (100), 77 (30); Anal. calcd for $C_{29}H_{22}N_2O$: C, 80.91; H, 5.15; N, 6.51%; Found: C, 80.93; H, 5.15; N, 6.52%.

5-[(E)-[1,1′-Biphenyl]-4-ylmethylidene]-3-(3-methoxyphenyl)-2-phenyl-3,5-dihydro-4H-imidazole-4-one ***(7)*** Yield: 83%; m.p.: 175°C; R_f: 0.53 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 314 (log ε = 4.6) nm; IR (KBr): ν_{max} 3256, 3062, 3029, 1641, 1481, 1260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, $J_{2',3'} = J_{6',5'} = 8.4$ Hz, 2H, H-2′/6′), 8.20 (d, $J_{2'',3''} = J_{6'',5''} = 7.1$ Hz, 2H, H-2″/6″), 7.90 (m, 3H, H-3′-5′), 7.70 (m, 1H, H-6‴), 7.65 (m, 1H, H-5‴), 7.52 (d, $J_{3'',2''} = J_{5'',6''} = 8.5$ Hz, 2H, H-3″/5″), 7.41 (m, 3H, H-3‴–5‴), 7.36 (d, $J_{2''',3'''} = J_{6''',5'''} = 8.4$ Hz, 2H, H-2‴/6‴), 7.25 (s, 1H, H-6), 7.21 (s, 1H, H-2‴), 7.05 (m, 1H, H-4‴), 3.80 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 430 (M^+, 2), 327 (11), 281 (2.6), 123 (40), 105 (100), 77 (29); Anal. calcd for $C_{29}H_{22}N_2O_2$: C, 80.91; H, 5.15; N, 6.51%; Found: C, 80.92; H, 5.16; N, 6.53%.

5-[(E)-[1,1′-Biphenyl]-4-ylmethylidene]-3-(4-methoxyphenyl)-2-phenyl-3,5-dihydro-4H-imidazole-4-one ***(8)*** Yield: 85%; m.p.: 175°C; R_f: 0.54 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 313 (log ε = 4.65); IR (KBr): ν_{max} 3257, 3060, 2930, 1638, 1510, 1242 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.54 (d, $J_{3'',2''} = J_{5'',6''} = 7.5$ Hz, 2H, H-3″/5″), 8.46 (m, 2H, H-2′/6′), 8.39 (m, 2H, H-2″/6″), 7.87 (m, 3H, H-3′-5′), 7.65 (d, $J_{2'''',3''''} = J_{6'''',5''''} = 8.9$ Hz, 2H, H-2‴‴/6‴‴), 7.43 (m, 3H, H-3‴–5‴), 7.40 (d, $J_{2''',3'''} = J_{6''',5'''} = 7.7$ Hz, 2H, H-2‴/6‴), 7.24 (s, 1H, H-6), 6.83 (d, $J_{3'''',2''''} = J_{5'''',6''''} = 8.8$ Hz, 2H, H-3‴‴/5‴‴), 3.76 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 430 (M^+, 5), 326 (9.34), 123 (92), 105 (100), 77 (30); Anal. calcd for $C_{29}H_{22}N_2O_2$: C, 80.91; H, 5.15; N, 6.51%; Found: C, 80.94; H, 5.17; N, 6.54%.

5-[(E)-(4-Fluorophenyl)methylidene]-2-methyl-3-phenyl-3,5-dihydro-4H-imidazole-4-one ***(9)*** Yield: 70%; m.p.: 122°C; R_f: 0.59 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 346 (log ε = 4.82) nm; IR (KBr): ν_{max} 3404, 3067, 1652, 1498, 1160 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, $J_{3'',2''} = J_{5'',6''} = 7.7$ Hz, 2H, H-3′/5′), 8.19 (d, $J_{2',3'} = J_{6',5'} = 8.6$ Hz, 2H, H-2′/6′), 7.52 (m, 2H, H-2″/6″), 7.44 (m, 3H, H-3″–5″), 7.15 (s, 1H, H-6), 2.28 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 280 (M^+, 31.62), 135 (10.0), 118 (98), 77 (100); Anal. calcd for $C_{17}H_{13}FN_2O$: C, 72.84; H, 4.67; N, 9.99%; Found: C, 72.86; H, 4.68; N, 9.10%.

5-[(E)-(4-Fluorophenyl)methylidene]-3-(2-methoxypheny)l-2-methyl-3,5-dihydro-4H-imidazole-4-one ***(10)*** Yield: 60%; m.p.: 124°C; R_f: 0.50 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 344 (log ε = 5.2) nm; IR (KBr): ν_{max} 3043, 2844, 1651, 1504, 1159 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, $J_{3'',2''} = J_{5'',6''} = 8.5$ Hz, 2H, H-3′/5′), 8.19 (d, $J_{2',3'} = J_{6',5'} = 8.5$ Hz, 2H, H-2′/6′), 7.43 (m, 2H, H-4″–6″), 7.24 (s, 1H, H-6), 7.03 (d, $J_{3'',4''} = 8.5$ Hz, 1H, H-3″), 3.80 (s, 3H, OCH_3), 2.17 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 310 (M^+, 35.2), 148 (100), 134 (53), 92 (19), 77 (29); Anal. calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03%; Found: C, 69.69; H, 4.89; N, 9.05%.

5-[(E)-(4-Fluorophenyl)methylidene]-3-(3-methoxyphenyl)-2-methyl-3,5-dihydro-4H-imidazole-4-one ***(11)*** Yield: 56%; m.p.: 125°C; R_f: 0.51 (ethyl acetate/hexane, 3:7); UV (MeOH): λ_{max} 346 (log ε = 4.75) nm; IR (KBr): ν_{max} 3075, 3004, 2968, 1651, 1497, 1392 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, $J_{3',2'} = J_{5',6'} = 8.5$ Hz, 2H, H-3′/5′), 8.19 (d, $J_{2',3'} = J_{6',5'} = 8.5$ Hz, 2H, H-2′/6′), 7.40 (d, $J_{6'',5''} = 7.5$ Hz, 1H, H-6″), 7.24 (s, 1H, H-2″), 7.23 (s, 1H, H-6), 6.99 (m, 2H, H-4″, 5″), 3.82 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 310 (M^+, 100), 221 (4), 148 (69), 134 (32), 77 (16); Anal. calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03%; Found: C, 69.70; H, 4.90; N, 9.05%.

5-[(E)-(4-Fluorophenyl)methylidene]-3-(4-methoxyphenyl)-2-methyl-3,5-dihydro-4H-imidazole-4-one ***(12)*** Yield: 99%; m.p.: 122°C R_f: 0.52 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 342 (log ε = 4.69) nm; IR (KBr): ν_{max} 3056, 2940, 1644, 1511, 1159 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, $J_{3',2'} = J_{5',6'} = 8.5$ Hz, 2H, H-3′/5′), 8.19 (d, $J_{2',3'} = J_{6',5'} = 8.5$ Hz, 2H, H-2′/6′), 7.65 (d, $J_{2'',3''} = J_{6'',5''} = 8.9$ Hz, 1H, H-2″/6″), 7.23 (s, 1H, H-6), 7.00 (d, $J_{3'',2''} = J_{5'',6''} = 8.8$ Hz, 1H, H-3″/5″), 3.83 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 311 (M^+, 52), 148 (100), 134 (76), 77 (44). Anal. calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03%; Found: C, 69.68; H, 4.88; N, 9.04%.

5-[(E)-(4-Fluorophenyl)methylidene]-2,3-diphenyl-3,5-dihydro-4H-imidazole-4-one ***(13)*** Yield: 40%; m.p.: 242°C; R_f: 0.63 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 282 (log ε = 4.46) nm; IR (KBr): ν_{max} 3271, 3135, 3062, 1648, 1474, 1326 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, $J_{3'',2''} = J_{5'',6''} = 8.5$ Hz, 2H, H-3″/5″), 8.26 (m, 2H, H-2′/6′), 8.20 (d, $J_{2'',3''} = J_{6'',5''} = 8.5$ Hz, 2H, H-2″/6″), 7.86 (m, 3H, H-3′–5′), 7.56 (d, $J_{2''',3'''} = J_{6''',5'''} = 7.7$ Hz, 2H, H-2‴/6‴), 7.48 (m, 3H, H-3‴–5‴), 7.22 (s, 1H, H-6); EI MS: *m/z* (rel. abund. %) 343 (M^+, 3), 267 (9), 135 (4), 105 (100), 93 (66), 77 (46); Anal. calcd for $C_{22}H_{15}FN_2O$: C, 77.18; H, 4.42; N, 8.18%; Found: C, 77.00; H, 4.03; N, 8.20%.

5-[(E)-(4-Fluorophenyl)methylidene]-3-(2-methoxyphenyl)-2-methyl-3,5-dihydro-4H-imidazole-4-one ***(14)***

Yield: 80%; m.p.: 196°C; R_f: 0.57 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 290 (log ε = 4.6) nm; IR (KBr): ν_{max} 3219, 3062, 2923, 1643, 1462, 1227 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, $J_{3'',2''} = J_{5'',6''}$ = 7.8 Hz, 2H, H-3″/5″), 8.25 (m, 2H, H-2′/6′), 8.19 (d, $J_{2'',3''} = J_{6'',5''}$ = 7.8 Hz, 2H, H-2″/6″), 7.88 (m, 3H, H-3′–5′), 6.84 (d, $J_{3''',4'''}$ = 8.0 Hz, 1H, H-3‴), 7.55 (d, $J_{5''',6'''}$ = 7.5 Hz, 1H, H-6‴), 7.46 (m, 2H, H-4‴, 5‴), 7.22 (s, 1H, H-6), 3.77 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 309 (M$^+$, 42), 177 (4.1), 105 (100), 77 (22); Anal. calcd for $C_{23}H_{17}FN_2O_2$ C, 74.18; H, 4.60; N, 7.52%; Found: C, 74.22; H, 4.63; N, 7.56%.

5-[(E)-(4-Fluorophenyl)methylidene]-3-(3-methoxyphenyl)-2-methyl-3,5-dihydro-4H-imidazole-4-one (***15***) Yield: 75%; m.p.: 204°C; R_f: 0.59 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 288 (log ε = 4.8) nm; IR (KBr): ν_{max} 3152, 3083, 2933, 1648, 1415, 1227 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, $J_{3'',2''} = J_{5'',6''}$ = 7.8 Hz, 2H, H-3″/5″), 8.26 (m, 2H, H-2′/6′), 8.19 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.3 Hz, 2H, H-2″/6″), 7.88 (m, 3H, H-3′–5′), 7.43 (m, 1H, H-6‴), 7.36 (s, 1H, H-2‴), 7.23 (s, 1H, H-6), 7.04 (m, 2H, H-4‴, 5‴), 3.79 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 373 (M$^+$, 3), 269 (17), 242 (5), 123 (62), 105 (100), 77 (45); Anal. calcd for $C_{23}H_{17}FN_2O_2$ C, 74.18; H, 4.60; N, 7.52%; Found: C, 74.21; H, 4.62; N, 7.55%.

5-[(E)-(4-Fluorophenyl)methylidene]-3-(4-methoxyphenyl)-2-methyl-3,5-dihydro-4H-imidazole-4-one (***16***) Yield: 98%; m.p.: 185°C; R_f: 0.58 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 282 (log ε = 4.7) nm; IR (KBr): ν_{max} 3131, 3069, 2958, 1650, 1478, 1241 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, $J_{3'',2''} = J_{5'',6''}$ = 8.3 Hz, 2H, H-3″/5″), 8.25 (m, 2H, H-2′/6′), 8.18 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.3 Hz, 2H, H-2″/6″), 7.85 (m, 3H, H-3′-5′), 7.46 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 8.9 Hz, 2H, H-2‴/6‴), 7.23 (s, 1H, H-6), 6.85 (d, $J_{3''',2'''} = J_{5''',6'''}$ = 8.9 Hz, 2H, H-3‴/5‴), 3.78 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 373 (M$^+$, 2), 267 (6), 123 (100), 105 (84), 77 (37); Anal. calcd for $C_{23}H_{17}FN_2O_2$: C, 74.18; H, 4.60; N, 7.52%; Found: C, 74.20; H, 4.61; N, 7.53%.

5-[(E)-(4-Fluorophenyl)methylidene]-2-methyl-3-phenyl-3,5-dihydro-4H-imidazole-4-one (***17***) Yield: 88%; m.p.: 118°C; R_f: 0.55 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 276 (log ε = 4.5) nm; IR (KBr): ν_{max} 3374, 3097, 1642, 1523, 1265 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.13 (s, 1H, H-6′), 8.12 (d, $J_{4',3'}$ = 8.8 Hz, 1H, H-4′), 8.09 (d, $J_{3',4'}$ = 8.8 Hz, 1H, H-3′), 7.58 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.8 Hz, 2H, 2″/6″), 7.48 (m, 3H, H-3″–5″), 7.25 (s, 1H, H-6), 2.32 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 341 (M$^+$, 14), 306 (65), 276 (42), 118 (73), 77 (63); Anal. calcd for $C_{17}H_{12}ClN_3O_3$: C, 59.75; H, 3.54; N, 12.30%; Found: C, 59.76; H, 3.55; N, 12.31%.

5-[(E)-(2-Chloro-5-nitrophenyl)methylidene]-3-(3-methoxyphenyl)-2-methyl-3,5-dihydro-4H-imidazole-4-one (***18***) Yield: 99%; m.p.: 130°C; R_f: 0.52 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 208 (log ε = 4.8) nm; IR (KBr): ν_{max} 3378, 3091, 1602, 1525, 1270 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.14 (s, IH, H-6′), 8.12 (d, $J_{4',3'}$ = 8.8 Hz, 1H, H-4′), 8.10 (d, $J_{3',4'}$ = 8.8 Hz, 1H, H-3′), 7.58 (d, $J_{6'',5''}$ = 8.8 Hz, 1H, H-6″), 7.41 (t, $J_{5'',4''} = J_{5'',6''}$ = 8.8 Hz, 1H, 5″), 7.24 (s, 1H, H-6), 7.01 (d, $J_{4'',5''}$ = 8.8 Hz, 1H, 4″), 6.99 (s, 1H, H-2″), 3.82 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 371 (M$^+$, 20), 336 (100), 148 (34), 77 (14); Anal. calcd for $C_{18}H_{14}ClN_3O_4$: C, 58.15; H, 3.80; N, 11.30%; Found: C, 58.19; H, 3.84; N, 11.33%.

5-[(E)-(2-Chloro-5-nitrophenyl)methylidene]-2,3-diphenyl-3,5-dihydro-4H-imidazole-4-one (***19***) Yield: 87%; m.p.: 192°C; R_f: 0.56 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 204 (log ε = 4.8) nm; IR (KBr): ν_{max} 3277, 3070, 1642, 1474, 1263 cm–^{1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.16 (s, 1H, H-6″), 8.14 (m, 1H, H-4″), 8.12 (m, 1H, H-3″), 7.89 (d, $J_{2',3'} = J_{6',5'}$ = 7.5 Hz, 2H, H-2′/6′), 7.79 (m, 3H, H-3′–5′), 7.64 (d, $J_{2'',3''} = J_{6'',5''}$ = 7.5 Hz, 2H, H-2″/6″), 7.46 (m, 3H, H-3″–5″), 7.34 (s, 1H, H-6); EI MS: *m/z* (rel. abund. %) 403 (M$^+$, 2), 367 (14), 273 (25), 180 (22), 105 (94), 93 (9), 77 (100), 121 (100); Anal. calcd. for $C_{22}H_{14}ClN_3O_3$: C, 65.43; H, 3.49; N, 10.41%; Found: C, 65.44; H, 3.50; N, 10.42%.

5-[(E)-(2-Chloro-5-nitrophenyl)methylidene]-3-(3-methoxyphenyl)-2-phenyl-3,5-dihydro-4H-imidazole-4-one (***20***) Yield: 53%; m.p.: 135°C; R_f: 0.54 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 207 (log ε = 5.0) nm; IR (KBr): ν_{max} 3369, 3078, 2937, 1604, 1345, 1284 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, $J_{4'',5''}$ = 8.8 Hz, 1H, H-4″), 8.12 (s, 1H, H-6″), 8.00 (d, $J_{3'',4''}$ = 8.8 Hz, 1H, H-3″), 7.92 (d, $J_{2',3'} = J_{6',5'}$ = 7.6Hz, 2H, H-2′/6′), 7.77 (m, 3H, H-3′–5′), 7.64 (d, $J_{6''',5'''}$ = 7.4 Hz, 1H, H-6‴), 7.45 (t, $J_{5''',4'''} = J_{5''',6'''}$ = 7.6 Hz, 1H, H-5‴), 7.20 (s, 1H, H-6), 7.07 (s, 1H, H-2‴), 6.99 (d, $J_{4''',5'''}$ = 7.5 Hz, 1H, H-4‴), 3.82 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 433 (M$^+$, 2.0), 398 (5), 292 (8), 123 (21), 105 (100), 77(56); Anal. calcd for $C_{23}H_{16}ClN_3O_4$: C, 63.67; H, 3.72; N, 9.69%; Found: C, 63.68; H, 3.76; N, 9.74%.

5-[(E)-(2-Chloro-5-nitrophenyl)methylidene]-3-(4-methoxyphenyl)-2-phenyl-3,5-dihydro-4H-imidazole-4-one (***21***) Yield: 62%; m.p.: 198°C; R_f: 0.55 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 203 (log ε = 4.9); IR (KBr): ν_{max} 3282, 3004, 2839, 1641, 1468, 1251 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.13 (s, 1H, H-6″), 8.11 (d, $J_{4'',5''}$ = 8.8 Hz, 1H, H-4″), 8.03 (d, $J_{3'',4''}$ = 8.8 Hz, 1H, H-3″), 7.84 (d, $J_{2',3'} = J_{6',5'}$ = 7.6Hz, 2H, H-2′/6′), 7.72 (m, 3H, H-3′–5′), 7.63 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 7.5 Hz, 2H, H-2‴/6‴), 7.34 (s, 1H, H-6), 6.80 (d, $J_{3''',2'''} = J_{5''',6'''}$ = 7.5 Hz, 2H, 3‴/5‴), 3.82 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 433 (M$^+$, 2), 415 (11), 293 (9), 210 (14), 123 (50), 105 (100), 77 (41); Anal. calcd for $C_{23}H_{16}ClN_3O_4$: C, 63.67; H, 3.72; N, 9.69%; Found: C, 63.68; H, 3.73; N, 9.70%.

2-Methyl-3-phenyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (***22***) Yield: 70%; m.p.: 151°C; R_f: 0.48 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 373 (log ε = 4.5) nm; IR (KBr): ν_{max} 3397, 3071, 2923, 1640, 1387, 1263 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, $J_{5',4'}$ = 4.7 Hz, 1H, H-5′), 7.54 (d, $J_{3',4'}$ = 3.5 Hz, 1H, H-3′), 7.49 (d, $J_{2'',3''} = J_{6'',5''}$ = 7.7 Hz, 2H, H-2″/6″), 7.43 (m, 3H, H-3″–5″), 7.42 (s, 1H, H-6), 7.12 (dd, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 3.5 Hz, 1H, H-4′), 2.37 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 268, (M$^+$, 31), 118 (88), 77 (100), 51 (41); Anal. calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44%; Found: C, 67.15; H, 52.00; N, 10.45%.

3-(2-Methoxyphenyl)-2-methyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (***23***) Yield: 78%; m.p.: 151°C; R_f: 0.43 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 368 (log ε = 4.61) nm; IR (KBr): ν_{max} 3072, 2838, 1640, 1391, 1247 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, $J_{5',4'}$ = 4.7 Hz, 1H, H-5′), 7.54 (d, $J_{3',4'}$ = 3.5 Hz, 1H, H-3′), 7.45 (d, $J_{6'',5''}$ = 8.3 Hz, 1H, H-6″), 7.42 (s, 1H, H-6), 7.42 (m, 2H, H-3″, 4″), 7.14 (d, $J_{2'',3''}$ = 8.8 Hz, 1H, H-2″), 7.12 (dd, $J_{4',3'}$ = 4.7,

$J_{4',5'}$ = 3.5 Hz, 1H, H-4′), 3.80 (s, 3H, OCH_3), 2.31 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 298 (M^+, 53), 283 (4), 148 (100), 134 (24), 92 (38), 77 (68); Anal. calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39%; Found: C, 64.45; H, 4.77; N, 9.42%.

*3-(3-Methoxyphenyl)-2-methyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (**24**)* Yield: 65%; m.p.: 170°C; R_f: 0.44 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 372 (log ε = 5.2) nm; IR (KBr): ν_{max} 3072, 3001, 2935, 1639, 1320, 1241 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, $J_{5',4'}$ = 4.7 Hz, 1H, H-5′), 7.54 (d, $J_{3',4'}$ = 3.5 Hz, 1H, H-3′), 7.42 (s, 1H, H-6), 7.42 (d, $J_{6'',5''}$ = 8.1 Hz, 1H, H-6″), 7.22 (s, 1H, H-2″), 7.12 (dd, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 3.5 Hz, 1H, H-4′), 7.20 (t, $J_{5'',4''} = J_{5''''6''''}$ = 8.1 Hz, 1H, H-5″), 6.81 (d, $J_{4'',5''}$ = 8.7 Hz, 1H, H-4″), 3.85 (s, 3H, OCH_3), 2.50 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 298 (M^+, 57), 148 (100), 134 (19), 107 (12); Anal. calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41%; H, 4.73; N, 9.39; Found: C, 64.46; H, 4.78; N, 9.43%.

*3-(4-Methoxyphenyl)-2-methyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (**25**)* Yield: 78%; m.p.: 109°C; R_f: 0.45 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 372 (log ε = 4.67) nm; IR (KBr): ν_{max} 3039, 2966, 1635, 1510, 1247 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, $J_{5',4'}$ = 4.7 Hz, 1H, H-5′), 7.63 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.7 Hz, 2H, H-2″/6″), 7.54 (d, $J_{3',4'}$ = 3.5 Hz, 1H, H-3′), 7.42 (s, 1H, H-6), 7.12 (dd, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 3.5 Hz, 1H, H-4′), 6.99 (d, $J_{3'',4''} = J_{5'',6''}$ = 8.8 Hz, 2H, H-3″/5″), 3.83 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); EI MS: *m/z* (rel. abund. %) 298, (M^+, 64), 148 (100), 134 (56), 92 (28), 77 (44); Anal. calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39%; Found: C, 64.43; H, 4.75; N, 9.40%.

*2,3-Diphenyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (**26**)* Yield: 96%; m.p.: 205°C; R_f: 0.49 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 318 (log ε = 4.37) nm; IR (KBr): ν_{max} 3254, 3131, 3063, 1649, 1473, 1280 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, $J_{2',3'} = J_{6',5'}$ = 8.7 Hz, 2H, H-2′/6′), 8.30 (m, 3H, H-3′–5′), 7.63 (d, $J_{5'',4''}$ = 4.7 Hz, 1H, H-5″), 7.61 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 7.3 Hz, 2H, H-2‴/6‴), 7.55 (d, $J_{3'',4''}$ = 3.5 Hz, 1H, H-3″), 7.54 (m, 3H, H-3‴–5‴), 7.32 (dd, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 3.5 Hz, 1H, H-4″), 7.30 (s, 1H, H-6); EI MS: *m/z* (rel. abund. %) 330 (M^+, 3.4), 255 (17.35), 227 (9.2), 105 (100), 77 (56); Anal. calcd for $C_{20}H_{14}N_2OS$ $C_{27}H_{18}O_6$: C, 72.70; H, 4.27; N, 8.48%; Found: C, 72.72; H, 4.26; N, 8.86%.

*3-(2-Methoxyphenyl)-2-phenyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (**27**)* Yield: 90%; m.p.: 171°C; R_f: 0.47 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 323 (log ε = 4.8) nm; IR (KBr): ν_{max} 3285, 3072, 2936, 1671, 1462, 1248 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, $J_{2',3'} = J_{6',5'}$ = 7.5 Hz, 2H, H-2′/6′), 7.79 (m, 3H, H-3′–5′), 7.63 (d, $J_{5'',4''}$ = 4.7 Hz, 1H, H-5″), 7.61 (d, $J_{6''',5'''}$ = 7.3 Hz, 1H, H-6‴), 7.56 (d, $J_{3'',4''}$ = 3.5 Hz, 1H, H-3″), 7.45 (m, 2H, H-4‴–5‴), 7.33 (dd, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 3.5 Hz, 1H, H-4″), 7.33 (s, 1H, H-6), 6.98 (d, $J_{3''',4'''}$ = 7.6 Hz, 1H, H-3‴), 3.37 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 360 (M^+, 10.6), 210 (13.50), 173 (100), 145 (42), 105 (41), 69 (63), 57 (65); Anal. calcd for $C_{21}H_{16}N_2O_2S$: C, 69.98; H, 4.47; N, 7.77%; Found: C, 69.20; H, 4.50; N, 7.80%.

*3-(3-Methoxyphenyl)-2-phenyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (**28**)* Yield: 82%; m.p.: 189°C; R_f: 0.48 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 319 (log ε = 4.5) nm; IR (KBr): ν_{max} 3144, 3073, 2958, 1643, 1478, 1267 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, $J_{2',3'} = J_{6',5'}$ = 7.5 Hz, 2H, H-2′/6′), 7.77 (m, 3H, H-3′-5′), 7.64 (d, $J_{6''',5'''}$ = 7.4 Hz, 1H, H-6‴), 7.63 (d, $J_{5'',4''}$ = 4.7 Hz, 1H, H-5″), 7.56 (d, $J_{3'',4''}$ = 3.5 Hz, 1H, H-3″), 7.45 (t, $J_{5''',4'''} = J_{5''''6''''}$ = 7.6 Hz, 1H, H-5‴), 7.33 (dd, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 3.5 Hz, 1H, H-4″), 7.32 (s, 1H, H-6), 7.07 (s, 1H, H-2‴), 6.99 (d, $J_{4''',5'''}$ = 7.5 Hz, 1H, H-4‴), 3.37 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 360 (M^+, 10), 257 (4), 123 (38), 105 (100), 7 (52); Anal. Calcd for $C_{21}H_{16}N_2O_2S$: C, 69.98; H, 4.47; N, 7.77%; Found: C, 69.22; H, 4.52; N, 7.83%.

*3-(4-Methoxyphenyl)-2-phenyl-5-[(E)-2-thienylmethylidene]-3,5-dihydro-4H-imidazol-4-one (**29**)* Yield: 90%; m.p.: 192°C; R_f: 0.48 (ethyl acetate/hexane, 3:7); UV (MeOH) λ_{max} 400 (log ε = 2.15) nm; IR (KBr): ν_{max} 3132, 3071, 2951, 1634, 1511, 1248 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, $J_{2',3'} = J_{6',5'}$ = 7.6 Hz, 2H, H-2′/6′), 7.79 (m, 3H, H-3′-5′), 7.63 (d, $J_{5'',4''}$ = 4.7 Hz, 1H, H-5″), 7.63 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 7.5 Hz, 2H, H-2‴/6‴), 7.55 (d, $J_{3'',4''}$ = 3.5 Hz, 1H, H-3″), 7.32 (dd, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 3.5 Hz, 1H, H-4″), 7.30 (s, 1H, H-6), 6.80 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 7.5 Hz, 2H, H-3‴/5‴), 3.77 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund. %) 360 (M^+, 100), 210 (37), 105 (77), 77 (16); Anal. calcd for $C_{21}H_{16}N_2O_2S$: C, 69.98; H, 4.47; N, 7.77%; Found: C, 69.99; H, 4.49; N, 7.78%.

Assay for leishmaniasis[24]

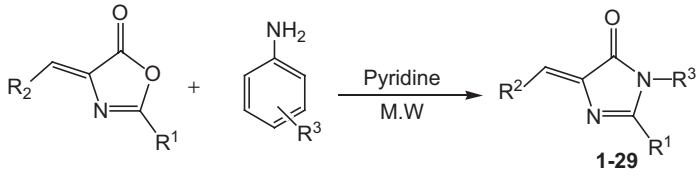
Leishmania major were grown in bulk in modified Novy–MacNeal–Nicolle (NNN) biphasic medium by using normal physiological saline. *Leishmania* promastigotes were cultured with RPMI-1640 medium, supplemented with 10% heat inactivated fetal bovine serum (FBS). Parasites at the log phase were centrifuged at 2000 rpm for 10 min, and washed three times with saline at the same speed and for the same time. Parasites were diluted with fresh culture medium to a final density of 10^6 cells/mL.

In a 96-well microtiter plate, 180 µL of medium was added in the first row and 100 µL of medium was added in other wells; 20 µL of the experimental compound was added in the medium and serially diluted; 100 µL of parasite culture was added to all wells. Two rows were left for negative and positive controls. Negative controls received only the medium, while the positive control contained a varying concentration of standard anti-leishmanial drugs, amphotericin B and pentamidine. The plate was incubated at 21–22°C for 72 h. The culture was examined microscopically on an improved Neubauer counting chamber, and IC_{50} values of compounds were calculated by Software Ezfit 5.03 (Perella Scientific). All assays were performed in triplicate.

Results and discussion

Chemistry

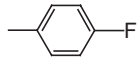
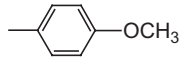
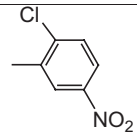
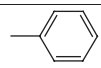
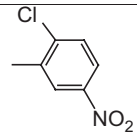
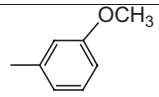
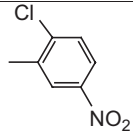
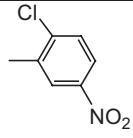
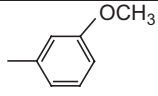
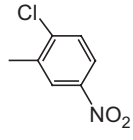
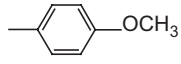
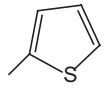
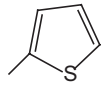
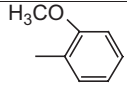
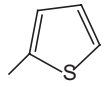
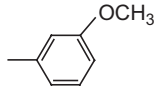
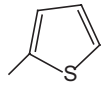
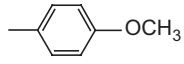
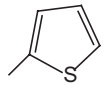
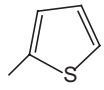
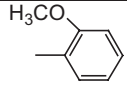
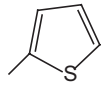
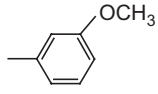
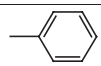
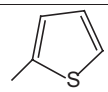
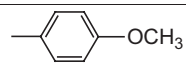
Imidazolones **1–29** were synthesized from differently substituted *E*-oxazolones[21–23] (1 mmol) and substituted aromatic amines (1.1 mmol) in anhydrous pyridine through microwave irradiation (Scheme 1). The structures of imidazolones **1–29** were determined using different spectroscopic techniques, including ^{1}H-NMR, EI, IR, and UV, and by elemental analysis.



1-29

Compound no.	R^1	R^2	R^3	Time of reaction (min)
1	—CH_3			7
2				10
3	—CH_3	—Ph		15
4	—CH_3	—Ph	OCH_3	14
5		—Ph		13
6		—Ph	H_3CO	12
7		—Ph	OCH_3	15
8		—Ph	—OCH_3	12
9	—CH_3	—F		13
10	—CH_3	—F	H_3CO	15
11	—CH_3	—F	OCH_3	14
12	—CH_3	—F	—OCH_3	12
13		—F		14
14		—F	H_3CO	13
15		—F	OCH_3	14

Continued.

Compound no.	R^1	R^2	R^3	Time of reaction (min)
16				12
17	$-CH_3$			13
18	$-CH_3$			15
19				11
20				15
21				8
22	$-CH_3$			10
23	$-CH_3$			13
24	$-CH_3$			11
25	$-CH_3$			10
26				13
27				15
28				11
29				9

Scheme 1. Synthesis of imidazolones **1–29**.

Biology

All the synthesized imidazolones **1–29** were evaluated for their leishmanicidal activity according to the literature protocol[24].

Compounds **1–29** demonstrated a varying degree of *in vitro* anti-leishmanial activities, with IC_{50} values in the range of 12.98 ± 0.32–96.17 ± 0.11 µg/mL, and compared with standard drugs amphotericin B and petamidine (IC_{50} = 0.12 ± 0.41 and 2.56 ± 0.10 µg/mL, respectively). Compound **17** (IC_{50} = 12.98 ± 0.32 µg/mL) was found to be the most active member of the series. Compounds **14** and **24** also showed good anti-leishmanial activities, with IC_{50} values of 28.20 ± 0.03 and 41.12 ± 0.32 µg/mL, respectively. Compounds **9**, **13**, **15**, **18**, **19**, and **21** showed only moderate activity against *Leishmania major*, with IC_{50} values 57.00 ± 0.21, 60.00 ± 0.13, 54.44 ± 0.05, 57.30 ± 0.04, 51.00 ± 0.03, and 51.32 ± 0.33 µg/mL, respectively. Compounds **1–3**, **5**, **6**, **11**, **12**, **20**, **22**, **23**, **25**, **26**, **28**, and **29** showed IC_{50} values greater than 60 µg/mL. Compounds **4**, **7**, **8**, **16**, and **27** showed IC_{50} values more than 100 µg/mL and were considered to be inactive (Table 1).

Compound **17** (IC_{50} = 12.98 ± 0.32 µg/mL) proved to be the most active anti-leishmanial molecule among the screened compounds. Limited structure–activity relationship (SAR) study suggests that the activity of the tested compounds mainly depends upon the substitution on the imidazolone moiety. Compound **17**, having R^1, R^2, and R^3 groups phenyl, methyl, and 2-chloro,5-nitrophenyl, respectively, showed the highest degree of anti-leishmanial activity; however, closely related compound **19** (IC_{50} = 51.00 ± 0.03 µg/mL), having a phenyl residue instead of methyl, was found to be less active than most compounds of the series. Nonetheless, when R^1 in compound **18** was changed for 3-methoxyphenyl, a decrease in activity (IC_{50} = 57.30 ± 0.04 µg/mL) was observed. In compound **21**, where R^1 was 4-methoxyphenyl and R^2 was phenyl, a slight increase in activity (IC_{50} = 51.32 ± 0.33 µg/mL) occurred, and in compound **20**, where R^1 was 3-methoxyphenyl and R^2 was phenyl, a sharp decline in activity was observed. This clearly indicates that substitution on the imidazolone plays a vital role for leishmanicidal activity. 5-[(*E*)-(4-Fluorophenyl)methylidene]-3-(2-methoxyphenyl)-2-methyl-3,5-dihydro-4*H*-imidazole-4-one (**14**) was found to be the second most active compound of the series, with an IC_{50} value of 28.20 ± 0.03 µg/mL. When the position of the methoxy group of R^1 was changed from C-2 to C-3 in a closely related molecule, 5-[(*E*)-(4-fluorophenyl)methylidene]-3-(3-methoxyphenyl)-2-methyl-3,5-dihydro-4*H*-imidazole-4-one (**15**), the activity decreased sharply, with an IC_{50} value 54.44 ± 0.05 µg/mL. If the activity of compounds **14** and **15** was compared, it was concluded that a slight change in position of the methoxy group increased the activity of compound **14**. In addition, surprisingly, if the methoxy group of R^1 was placed at position 4 of the phenyl ring as in compound **16**, complete loss in activity was observed. In compounds **1–8** and **9–13** containing nearly the same R^1, R^2, and R^3 groups, only slight variation in activity was observed.

3-(3-Methoxyphenyl)-2-methyl-5-[(*E*)-2-thienylmethylidene]-3,5-dihydro-4*H*-imidazol-4-one (**24**) was found to be the third most active compound of the series with an IC_{50} value of 41.12 ± 0.32 µg/mL. When the position of the methoxy group of R^1 was changed from 3 to 2 or 3 to 4 in closely related molecules **23** and **25**, the activity was sharply decreased, with IC_{50} values 61.43 ± 0.31 and 96.17 ± 0.11 µg/mL, respectively. However, the remaining compounds **22**, **26**, **28**, and **29** were found to be moderately active.

During the current study, varyingly substituted imidazolones were randomly screened for their anti-leishmanial activity, and compounds **14**, **17**, and **24** were found to be the active members of the series. Apparently, substitution on imidazolone plays a vital role, in addition to the imidazolone ring itself. Compounds **14** and **17** may therefore serve as lead compounds for further studies on leishmanicidal imidazolones. However, compound **24** is the best candidate in the thiophenic series but really needs improvements to become a lead.

Table 1. Results for anti-leishmanial activity of compounds **1–29**.

Compound	IC_{50} ± SEM[a] (µg/mL)	Compound	IC_{50} ± SEM[a] (µg/mL)
1	64.12 ± 0.21	**16**	>100
2	75.08 ± 0.05	**17**	12.98 ± 0.32
3	67.16 ± 0.31	**18**	57.30 ± 0.04
4	>100	**19**	51.00 ± 0.03
5	77.70 ± 0.11	**20**	63.24 ± 0.24
6	75.00 ± 0.24	**21**	51.32 ± 0.33
7	>100	**22**	78.34 ± 0.55
8	>100	**23**	61.43 ± 0.31
9	57.00 ± 0.21	**24**	41.12 ± 0.32
10	>100	**25**	96.17 ± 0.11
11	80.00 ± 0.23	**26**	72.30 ± 0.23
12	84.80 ± 0.25	**27**	>100
13	60.00 ± 0.13	**28**	65.39 ± 0.12
14	28.20 ± 0.03	**29**	77.92 ± 0.21
15	54.44 ± 0.05		
Amphotericin B[b]	0.12 ± 0.41	Pentamidine[c]	2.56 ± 0.10

[a]SEM is the standard error of the mean.
[b]Amphotericin B and
[c]pentamidine are standard drugs for leishmanicidal activity.

Acknowledgements

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***Declaration of interest*:** The authors report no conflicts of interest.

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