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Short Note

Diethyl (5-Benzyl-2-(4-(*N*′-hydroxycarbamimidoyl)phenyl)-5-methyl-4,5-dihydrofuran-3-yl)phosphonate

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Abstract: As part of our ongoing research into the antileishmanial properties of amidoxime derivatives, we report a preliminary assessment of the antiparasitic properties of a novel compound, diethyl (5-benzyl-2-(4-(*N*′-hydroxycarbamimidoyl)phenyl)-5-methyl-4,5-dihydrofuran-3-yl)phosphonate. This compound was evaluated in vitro for the first time against the promastigote form of *Leishmania amazonensis*. Compounds containing both amidoxime and phosphonyl functional groups in dihydrofuran scaffolds are relatively rare, despite the extensive study of this heterocycle in various biological applications. Therefore, this work makes a valuable contribution to the fight against *Leishmania* spp. as a neglected disease. The cyclized 4,5-dihydrofuran intermediate scaffold was obtained via a three-step synthetic route that had previously been developed for accessing other derivatives, including the sulfone moiety. This synthesis was performed using a manganese-based free radical oxidative method under microwave irradiation. The intermediary 4,5-dihydrofuran, which included a nitrile group, tolerated the subsequent reaction with hydroxylamine hydrochloride, resulting in the formation of the target product. The target compound showed moderate activity in vitro against the promastigote form of *L. amazonensis* (IC_{50} = 91.1 μM).

Keywords: amidoxime; 4,5-dihydrofuran-phosphonyl derivative; leishmaniasis; microwave irradiation

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1. Introduction

Leishmaniasis is a neglected tropical disease caused by a protozoan of the genus *Leishmania*. This parasitic infection affects nearly a billion people in over 90 countries worldwide, with up to 1 million new cases and 30,000 deaths estimated annually [1]. Conventional antileishmanial treatments available on the market have clinical limitations such as toxicity, drug resistance, or high cost (pentamidine, antimonials, amphotericin B, and miltefosine) [2]. Additionally, the three major clinical forms (cutaneous, mucocutaneous, and visceral leishmaniasis) can cause significant medical issues and even be fatal in the absence of treatment [3]. In this context, the research to find new cost-effective compounds designed for oral use is currently highly relevant.

Among heterocyclic compounds, dihydrofurans are important scaffolds that frequently appear in natural products [4] and are extensively studied in various biological applications, serving as intermediates in organic synthesis [5]. However, the derivatives of dihydrofuran derivatives bearing both the phosphonyl and amidoxime groups are relatively rare [6]. Thus, this work contributes to the efforts to combat *Leishmania* spp. As a neglected dis-

ease by providing preliminary information on the in vitro biological activity of the target compound against the promastigote form of *Leishmania amazonensis* for the first time.

The amidoxime functional group has demonstrated potential for pharmaceutical applications, particularly in their antiparasitic activity against *Leishmania* spp. [7]. As a part of our research program, the hit molecule 4-(5-benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-*N*′-hydroxybenzimidamide (**Hit 1**) was reported with promising activity (Figure 1) and obtained via a three-step synthetic route involving oxidative free radical cyclization mediated using manganese (III) acetate. [8]. In this work, given that phosphorus modification is widely employed in drug design to modulate selectivity or bioavailability [9], the replacement of the sulfone moiety at position **3** with a phosphate derivative (**A**) was considered useful for modulating physicochemical properties (e.g., aqueous solubility or Log P) with the expectation of an oral administration. Hence, our interest lies in verifying if the antiparasitic activity is retained.

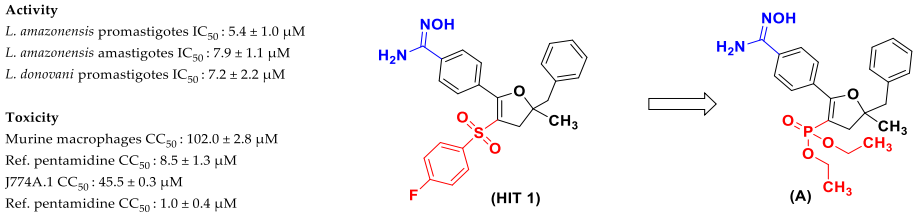
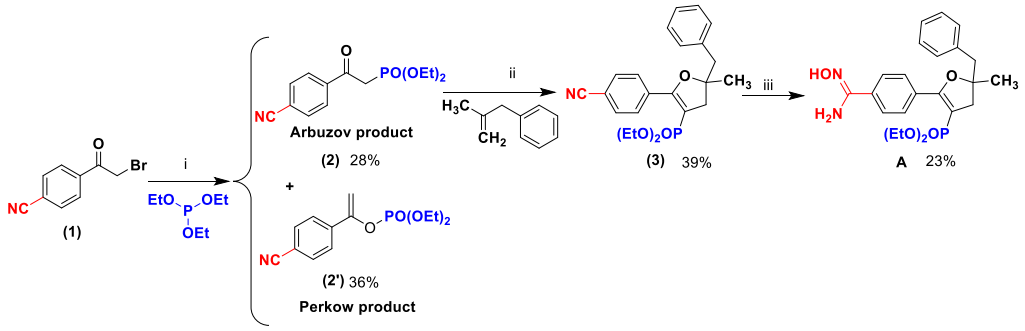


Figure 1. Antileishmanial amidoxime compounds.

2. Results and Discussion

2.1. Synthesis

Using a synthetic route previously developed in our team to access dihydrofuran derivatives [7], diethyl (5-benzyl-2-(4-(*N*′-hydroxycarbamimidoyl)phenyl)-5-methyl-4,5-dihydrofuran-3-yl)phosphonate was obtained via a three-step synthesis (Scheme 1).



Scheme 1. Synthesis of compound **A**, a 4,5-dihydrofuran scaffold bearing a phosphonyl group in position 3. Reagents and conditions: (i) triethyl phosphite (1 equiv.), 120 °C, 18 h. (ii) (2-methylallyl)benzene (2 equiv.), $Mn(OAc)_3$ (2.1 equiv.), $Cu(Oac)_2$ (1 equiv.), AcOH, MW, 80 °C, 2.5 h. (iii) *t*BuOK (10 equiv.), NH_2OH-HCl (10 equiv.), DMSO, 18 h, 0 °C to RT, N_2.

A Michaelis-Arbuzov reaction was performed with 4-(2-bromoacetyl)benzonitrile (**1**) and triethyl phosphite to yield diethyl (2-(4-cyanophenyl)-2-oxoethyl)phosphonate (**2**). Subsequently, a cyclization reaction leading to diethyl (5-benzyl-2-(4-cyanophenyl)-5-methyl-4,5-dihydrofuran-3-yl)phosphonate (**3**) was performed via a microwave-mediated reaction on a mixture of **2**, manganese (III) acetate (2.1 equiv.) and 2-methyl-3-phenyl-1-propene (2 equiv.). Finally, compound **3** was subjected to a reaction with a substantial excess of hydroxylamine hydrochloride and potassium *tert*-butoxide in DMSO, yielding the intended amidoxime derivative **A**.

The reaction to obtain **2** was limited by the formation of a by-product identified as a vinyl phosphate Perkow product (**2′**) [10]. This is concordant with the literature; the Arbuzov reaction yield is often described as decreased via a concomitant Perkow side reaction [11].

2.2. Biological Activity

The biological activity of compound **A** was evaluated in vitro against the promastigote form of *L. amazonensis* and showed moderate activity IC_{50} = 91.1 ± 1.06 μM. compared with HIT 1 (IC_{50} = 5.4 ± 1.0 μM). Cytotoxicity tests were not performed for this compound because the activity is notably far from the 10 μM of reference [12].

3. Materials and Methods

3.1. Chemistry

Reagents were purchased from Sigma-Aldrich (3050 Spruce Street St. Louis, MO, 63103, USA), Fluorochem (Unit 14 Graphite Way, Hadfield, Glossop SK13 1QH, UK), Fisher Scientific (168 3rd Ave, Waltham, MA 02451, USA), or TCI chemicals (9211 North Harborgate Street, Portland, OR 97203, USA) and used without further purification. Microwave reactions were performed using monomode reactors: Biotage Initiator® classic (Uppsala, Sweden) in sealed vials with output power from 0 to 400 W. The following adsorbent was used for column chromatography: silica gel 60 (Merck KgaA, Darmstadt, Germany, particle size 0.063–0.200 mm, 70–230 mesh ASTM). Reaction monitoring of intermediary compounds **2**, **2′**, and **3** was performed either using aluminum TLC plates (5 × 5 cm) with silica gel coated 60F-254 (Merck) in an appropriate eluent and visualized using ultraviolet light in a UV-Lamp VL-6.CL., 254 nm (6 W) and 365 nm (6 W) or using an LC-MS apparatus Thermo Scientific Accela High Speed LC System® coupled to a Thermo MSQ Plus® quadrupole mass spectrometer, with an HPLC column Thermo Hypersil Gold® (168 3rd Ave, Waltham, MA 02451, USA) 50 × 2.1 mm (C_{18} bounded), with particles of a diameter of 1.9 mm. The volume of sample injected into the column was 1 μL. Chromatographic analysis, total duration of 8 min, was on the gradient of the following solvents: t = 0 min, methanol/water 50:50; 0 < t < 4 min, linear increase in the proportion of methanol to a methanol/water ratio of 95:5; 4 < t < 6 min, methanol/water 95:5; 6 < t < 7 min, linear decrease in the proportion of methanol to return to a methanol/water ratio of 50:50; 6 < t < 7 min, methanol/water 50:50. The water used was buffered with ammonium acetate 5 mM. The flow rate of the mobile phase was 0.3 mL/min.

Low-resolution mass spectra were recorded for products **2**, **2′**, **3**, and **A**, in an Agilent SQ G6120B mass spectrometer (5301 Stevens Creek Blvd, Santa Clara, CA 95051, USA) in positive and negative electrospray mode using liquid chromatography with Diode-Array Detection at 254 nM, column Agilent Poroshell (5301 Stevens Creek Blvd, Santa Clara, CA 95051, USA) 120 EC-C18 2.7 μm (4.6 × 50 mm), mobile phase (A: H_2O + 0.1% Formic acid, B: MeCN + 0.1% Formic acid), method flow rate 0.5 mL/min, time/%B 0/10, 5/100, 9/100, at the Faculté de Pharmacie of Marseille.

The high-resolution mass spectrum of compound **A** was recorded on an SYNAPT G2 HDMS (Waters, 34 Maple St., Milford, MA 01757, USA) equipped with a pneumatically assisted atmospheric pressure ionization (API) source. The sample was ionized in positive electrospray mode under the following conditions: electrospray voltage: 2.8 kV; orifice voltage: 20 V; nebulizing gas flow rate (nitrogen): 100 L/h. The sample was dissolved in 300μL of dichloromethane and then diluted 1:103 in a solution of methanol with 3 mM ammonium acetate. The extract solution was introduced into the ionization source via infusion at a flow rate of 10 μL/min. Exact mass measurement was performed in triplicate with external calibration. HRMS was performed at the Faculté des Sciences de Saint-Jérôme (Marseille).

NMR spectra were recorded on a Bruker Avance NEO 400 MHz NanoBay spectrometer at the Faculté de Pharmacie of Marseille. Residual ^1H and ^{13}C peaks in deuterated solvents ($CDCl_3$ and DMSO-d_6) were used for chemical shift calibration without the need for an additional internal standard. ^1H NMR: reference $CDCl_3$ δ = 7.26 ppm, reference DMSO-d_6 δ = 2.50 ppm and ^{13}C NMR: reference $CDCl_3$ δ = 77.16 ppm, reference DMSO-d_6 δ = 39.52 ppm. Data for ^1H NMR are reported as follows: chemical shifts (δ) in parts per million (ppm), multiplicity (described as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublet; ddd, doublet of doublet of doublet;

m, multiplet), coupling constants (*J*) in Hertz (Hz) and integration. Data for ^{13}C NMR are reported as follows: chemical shifts (δ) in parts per million (ppm).

Diethyl (2-(4-cyanophenyl)-2-oxoethyl)phosphonate (**2**)

The Michaelis–Arbuzov reaction was performed in a round-bottom flask dried, mixing 4-(2-bromoacetyl)benzonitrile (2 g, 8.92 mmol, 1 equiv.) and triethyl phosphite (1 equiv.) and heated at 120 °C for 18 h. The TLC monitoring reaction was performed using DCM-AcOEt (4:1) as eluent and visualized with ultraviolet light in a UV-Lamp VL-6.CL., 254 nm (6 W), with a retardation factor of 0.28, and verified via low-resolution LC-MS. The mixture was allowed to cool down to room temperature and concentrated in vacuo. The crude product was purified via column chromatography (silica gel; eluent: dichloromethane/cyclohexane/AcOEt 80/10/10) affording the title product. Yield 28% (678 mg). The product was obtained in the keto form principally, with traces of enol form as an orange oily solid. The NMR data were in agreement with the literature values [13,14] (Supplementary Materials). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12 (d, $^{3}J_{H\text{-}H}$ = 8.8 Hz, 2H, $2CH_{Ar}$), 7.78 (d, $^{3}J_{H\text{-}H}$ = 8.8 Hz, 2H, $2CH_{Ar}$), 4.18–4.09 (m, 4H, $2CH_2$), 3.63 (d, $^{3}J_{H\text{-}H}$ = 22.9 Hz, 2H, CH_2), 1.28 (t, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 190.9 (d, $J_{P\text{-}C}$ = 6.6 Hz, C), 139.5 (C), 132.6 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 117.9 (C), 117.0 (C), 63.1 (d, $J_{P\text{-}C}$ = 6.8 Hz, $2CH_2$), 39.2 (d, $J_{P\text{-}C}$ = 131.5 Hz, CH_2), 16.3 (d, $J_{P\text{-}C}$ = 6.0 Hz, $2CH_3$). $C_{13}H_{16}NO_4P$: LC/MS ESI+ t_R 4.45 min, (*m*/*z*) $[M + H]^+$ 281.25/282.70.

1-(4-Cyanophenyl)vinyl diethyl phosphate (**2′**)

The Perkow product was achieved with the same method to obtain 2. The TLC monitoring reaction was performed using DCM-AcOEt (4:1) as eluent and visualized with ultraviolet light in a UV-Lamp VL-6.CL., 254 nm (6 W), with a retardation factor of 0.63, and verified via low-resolution LC-MS. The crude product was purified via column chromatography (silica gel; eluent: dichloromethane/cyclohexane/AcOEt 40/50/10) affording the title product. Yield 36% (875 mg). The product was obtained as a brown oily solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72–7.62 (m, 4H, $4CH_{Ar}$), 5.45–5.38 (m, 2H, CH_2), 4.29–4.15 (m, 4H, $2CH_2$), 1.35 (td, $J_{H\text{-}H}$ = 1.2 Hz, $J_{H\text{-}H}$ = 7.2 Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 150.7 (d, *J* = 7.4 Hz, C), 138.7 (d, *J* = 6.6 Hz, C), 132.4 ($2CH_{Ar}$), 125.9 ($2CH_{Ar}$). $C_{13}H_{16}NO_4P$: LC/MS ESI+ t_R 5.10 min, (*m*/*z*) $[M + H]^+$ 281.25/282.60.

Diethyl (5-benzyl-2-(4-(N′-hydroxycarbamimidoyl)phenyl)-5-methyl-4,5-dihydrofuran-3-yl)phosphonate (**3**)

In a microwave vial of 20 mL equipped with a stirring bar, a solution of manganese (III) acetate dihydrate (2.1 equiv.) and copper (II) acetate (1 equiv.) in 12 mL of glacial acetic acid was heated at 80 °C under microwave irradiation for 15 min. Then, the reaction mixture was cooled and compound **2** (300 mg, 1.07 mmol, 1 equiv.) and 2-methyl-3-phenyl-1-propene (2 equiv.) in 13 mL of acetic acid was added. The reaction mixture was heated for 2.5 h under microwave irradiation under the same conditions. The TLC monitoring reaction was performed using DCM-AcOEt (4:1) as eluent and visualized with ultraviolet light in a UV-Lamp VL-6.CL., 254 nm and 365 nm (6 W), with a retardation factor of 0.58, and verified via low-resolution LC-MS. The resulting product was poured into 50 mL of cold water and extracted with dichloromethane (3 × 40 mL). The organic extracts were collected and washed with saturated aqueous $NaHCO_3$ (3 × 40 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified via column chromatography (silica gel; eluent: dichloromethane/MeOH 98/2) affording the title product as a yellow oily solid, Yield 39% (171 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.91 (d, $^{3}J_{H\text{-}H}$ = 8.4 Hz, 2H, $2CH_{Ar}$), 7.65 (d, $^{3}J_{H\text{-}H}$ = 8.4 Hz, 2H, $2CH_{Ar}$), 7.31–7.19 (m, 5H, CH), 3.97–3.68 (m, 4H, $2CH_2$), 3.06 (dd, $^{4}J_{H\text{-}H}$ = 3.4 Hz, $^{2}J_{H\text{-}H}$ = 15.3 Hz, 1H, H-(CH_2)), 3.00 (dd, $^{4}J_{H\text{-}H}$ = 14.1 Hz, $^{2}J_{H\text{-}H}$ = 40.1 Hz, 2H, H-(CH_2)), 2.80 (dd, $^{4}J_{H\text{-}H}$ = 3.3 Hz, $^{2}J_{H\text{-}H}$ = 15.5 Hz, 1H, H-(CH_2)), 1.50 (s, 3H, CH_3), 1.18 (t, $^{3}J_{H\text{-}H}$ = 7.0 Hz, 3H, CH_3), 1.13 (t, $^{3}J_{H\text{-}H}$ = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.7 (d, *J* = 26.2 Hz, C), 136.5 (C), 134.5 (C), 131.7 ($2CH_{Ar}$), 130.6 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 128.4 ($2CH_{Ar}$), 127.0 (CH_{Ar}), 118.7 (C), 113.6 (C), 97.3 (d, *J* = 213.8 Hz, C), 88.1 (d, *J* = 11.8 Hz, C), 61.7 (t, *J* = 6.3 Hz, $2CH_2$), 46.8 (CH_2), 44.3 (d, *J* = 8.6 Hz, CH_2), 27.1 (CH_3), 16.3 (t, *J* = 6.4 Hz, $2CH_3$). ^{31}P NMR

(161.9 MHz, $CDCl_3$) δ (ppm) 17.0. $C_{23}H_{26}NO_4P$: LC/MS ESI+ t_R 6.23 min, (*m*/*z*) [M + H] + 412.51. $[M + H]^+$ 411.16/411.60.

Diethyl (5-benzyl-2-(4-(N′-hydroxycarbamimidoyl)phenyl)-5-methyl-4,5-dihydrofuran-3-yl)phosphonate (**A**)

A suspension of hydroxylamine hydrochloride (10 equiv.) in DMSO was stirred under inert atmosphere and cooled to 0 °C. Potassium *tert*-butoxide (10 equiv.) was added gradually, and the reaction mixture was stirred for 30 min. Then, compound **3** was added (160 mg, 0.38 mmol, 1 equiv.), and the reaction mixture was stirred for 18 h at room temperature. The TLC monitoring reaction was performed using DCM-MeOH (95:5) as eluent and visualized with ultraviolet light in a UV-Lamp VL-6.CL., 254 and 365 nm (6 W), with a retardation factor of 0.55, and verified via low-resolution LC-MS. The resulting mixture was poured into cold water. Then, the reaction mixture was extracted with EtOAc (3 × 15 mL), and the organic layers were combined, washed with water (1 × 20 mL), brine (1 × 20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified via column chromatography (eluent: dichloromethane/MeOH 98/2), Rf 0.32. Yield 23% (40 mg). The product was obtained as a yellow solid and verified via HRMS. Mp 110–111 °C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) 9.82 (s, 1H, OH), 7.77–7.66 (m, 4H, $4CH_{Ar}$), 7.33–7.17 (m, 5H, $5CH_{Ar}$), 5.96 (br s, 2H, NH_2), 3.83–3.68 (m, 2H, CH_2), 3.65–3.54 (m, 2H, CH_2), 3.01 (q, $J_{H\text{-}H}$ = 16.5 Hz, 2H, CH_2), 2.93 (dd, $^4J_{H\text{-}H}$ = 2.9 Hz, $^2J_{H\text{-}H}$ = 15.2 Hz, 1H, H-(CH_2)), 2.70 (dd, $^4J_{H\text{-}H}$ = 2.8 Hz, $^2J_{H\text{-}H}$ = 15.3 Hz, 1H, H-(CH_2)), 1.44 (s, 3H, CH_3), 1.08 (t, $^3J_{H\text{-}H}$ = 7.0 Hz, 3H, CH_3), 1.01 (t, $^3J_{H\text{-}H}$ = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.5 (d, *J* = 26.2 Hz, C), 152.5 (C), 136.6 (C), 133.6 (C), 131.8 (C), 130.6 ($2CH_{Ar}$), 129.2 ($2CH_{Ar}$), 128.3 ($2CH_{Ar}$), 126.8 (CH_{Ar}), 125.4 ($2CH_{Ar}$), 94.8 ((d, *J* = 214.7 Hz, C), 87.6 (d, *J* = 11.8 Hz, C), 61.6 (t, *J* = 6.3 Hz, $2CH_2$), 46.8 (CH_2), 44.3 (d, *J* = 8.6 Hz, CH_2), 27.1 (CH_3), 16.3 (t, *J* = 6.4 Hz, $2CH_3$). ^{31}P NMR (161.9 MHz, $CDCl_3$) δ (ppm) 17.0. $C_{23}H_{29}N_2O_5P$: LC/MS ESI+ t_R 5.14 min, *(m/z)* $[M + H]^+$ 444.47/445.90; HRMS: *m*/*z* $[M + H]^+$ calculated 445.1887; found 445.1884.

3.2. Biology

3.2.1. Parasites

Leishmania amazonensis (MHOM/BR/77/LTB0016) was maintained as promastigotes at 26 °C in Schneider's insect medium (Sigma-Aldrich, St. Louis, MO, USA) with 10% heat-inactivated fetal calf serum (HIFCS), 100 µg/mL streptomycin and 100 U/mL penicillin. Parasites were maintained until the 10th passage; subsequently, new cultures were obtained from infected animals.

3.2.2. Antipromastigote Activity

L. amazonensis promastigotes were cultivated in Schneider's insect medium supplemented with 10% HIFCS, as indicated above, in either absence or presence of different concentrations of the substances. Culture was initiated with 1.0×10^6 cells/mL and maintained at 26 °C for 72 h. Cell viability was estimated via reduction of resazurin. The 50% inhibitory concentration (IC_{50}) was determined via logarithmic regression analysis using GraphPrism 5 software.

4. Conclusions

We reported the synthesis of diethyl (5-benzyl-2-(4-(*N′*-hydroxycarbamimidoyl) phenyl)-5-methyl-4,5-dihydrofuran-3-yl)phosphonate. This dihydrofuran derivative, which bears a phosphonyl and an amidoxime group, showed low in vitro activity against the promastigote form of *L. amazonensis* compared to previously identified **Hit 1**. This compound was obtained with a synthetic route that demonstrates the versatility of $Mn(OAc)_3$ to perform the cyclization of β-ketophosphonate type substrate under microwave irradiation and access to the dihydrofuran scaffold in moderate yield. This information may be useful in further structure–activity relationship analysis either for an antileishmanial activity or for other biological applications of the 4,5-dihydrofuran derivatives.

Supplementary Materials: The following are available online, Figure S1: LC-MS spectra of compounds **2** and **2′**. Figure S2: LC-MS spectra of compound **3**. Figure S3: LC-MS spectra of compound **A**. Figure S4: HRMS spectra of compound A. Figures S5–S12: ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **2′**, **3** and **A**.

Author Contributions: Conceptualization, O.L.A.L., C.C., Y.K., S.R. and P.V.; methodology, O.L.A.L., C.C., Y.K., S.R., F.M.S.U.M. and E.C.T.-S.; formal analysis, O.L.A.L., C.C., Y.K., S.R., F.M.S.U.M. and E.C.T.-S.; investigation, O.L.A.L., C.C., Y.K., S.R., F.M.S.U.M. and E.C.T.-S.; resources, C.C., O.L.A.L., E.C.T.-S. and P.V.; writing—original draft preparation, O.L.A.L.; writing—review and editing, O.L.A.L., C.C., Y.K., S.R., R.P.-L. and P.V.; visualization, O.L.A.L., C.C., Y.K., S.R., R.P.-L. and P.V.; supervision, C.C., E.C.T.-S. and P.V.; project administration, P.V. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

References

1. World Health Organization (WHO). World Health Statistics 2023: Monitoring Health for the SDGs, Sustainable Development Goals. Available online: www.who.int/data/gho/publications/world-health-statistics (accessed on 29 August 2023).
2. Mann, S.; Frasca, K.; Scherrer, S.; Henao-Martínez, A.F.; Newman, S.; Ramanan, P.; Suarez, J.A. A Review of Leishmaniasis: Current Knowledge and Future Directions. *Curr. Trop. Med. Rep.* **2021**, *8*, 121–132. [CrossRef] [PubMed]
3. Burza, S.; Croft, S.L.; Boelaert, M. Leishmaniasis. *Lancet* **2018**, *392*, 951–970. [CrossRef] [PubMed]
4. Quintavalla, A.; Veronesi, R.; Carboni, D.; Martinelli, A.; Zaccheroni, N.; Mummolo, L.; Lombardo, M. Chemodivergent Photocatalytic Synthesis of Dihydrofurans and β,γ-Unsaturated Ketones. *Adv. Synth. Catal.* **2021**, *363*, 3267–3282. [CrossRef]
5. Ma, S.; Zheng, Z.; Jiang, X. Pd(0)-Catalyzed Coupling−Cyclization of 2-(2′,3′-Allenyl)Acetylacetates and Organic Halides: An Efficient Synthesis of 4,5-Dihydrofuran Derivatives. *Org. Lett.* **2007**, *9*, 529–531. [CrossRef] [PubMed]
6. Lu, G.; Lin, B.; Gao, Y.; Ying, J.; Tang, G.; Zhao, Y. Mn(OAc)3-Mediated Synthesis of 3-Phosphonyldihydrofurans from β-Ketophosphonates and Alkenes. *Synlett* **2016**, *28*, 724–728. [CrossRef]
7. Curti, C.; Crozet, M.D.; Vanelle, P. Microwave-Assisted Manganese(III) Acetate Based Oxidative Cyclizations of Alkenes with β-Ketosulfones. *Tetrahedron* **2009**, *65*, 200–205. [CrossRef]
8. Tabélé, C.; Faiões, V.D.S.; Grimaud, F.; Torres-Santos, E.C.; Khoumeri, O.; Curti, C.; Vanelle, P. Original Antileishmanial Hits: Variations around Amidoximes. *Eur. J. Med. Chem.* **2018**, *148*, 154–164. [CrossRef] [PubMed]
9. Yu, H.; Yang, H.; Shi, E.; Tang, W. Development and Clinical Application of Phosphorus-Containing Drugs. *Med. Drug Discov.* **2020**, *8*, 100063. [CrossRef] [PubMed]
10. Borowitz, I.J.; Firstenberg, S.; Borowitz, G.B.; Schuessler, D. Organophosphorus Chemistry. XVII. Kinetics and Mechanism of the Perkow Reaction. *J. Am. Chem. Soc.* **1972**, *94*, 1623–1628. [CrossRef]
11. Afarinkia, K.; Cadogan, J.I.G.; Rees, C.W. Synthesis of 1,2-Azaphosphetidines. *J. Chem. Soc. Chem. Commun.* **1992**, *3*, 285. [CrossRef]
12. Katsuno, K.; Burrows, J.N.; Duncan, K.; Van Huijsduijnen, R.H.; Kaneko, T.; Kita, K.; Mowbray, C.E.; Schmatz, D.; Warner, P.; Slingsby, B.T. Hit and Lead Criteria in Drug Discovery for Infectious Diseases of the Developing World. *Nat. Rev. Drug Discov.* **2015**, *14*, 751–758. [CrossRef] [PubMed]
13. Zhou, P.; Hu, B.; Li, L.; Rao, K.; Yang, J.; Yu, F. Mn(OAc)s_3–Promoted Oxidative $C_{sp}{}^3$–P Bond Formation through C $_{sp}{}^2$–C $_{sp}{}^2$ and P–H Bond Cleavage: Access to β-Ketophosphonates. *J. Org. Chem.* **2017**, *82*, 13268–13276. [CrossRef] [PubMed]
14. Zhou, M.; Chen, M.; Zhou, Y.; Yang, K.; Su, J.; Du, J.; Song, Q. β-Ketophosphonate Formation via Aerobic Oxyphosphorylation of Alkynes or Alkynyl Carboxylic Acids with H-Phosphonates. *Org. Lett.* **2015**, *17*, 1786–1789. [CrossRef] [PubMed]