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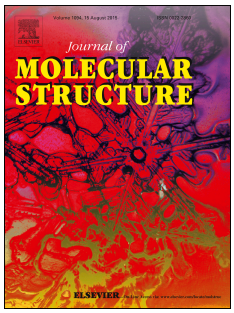

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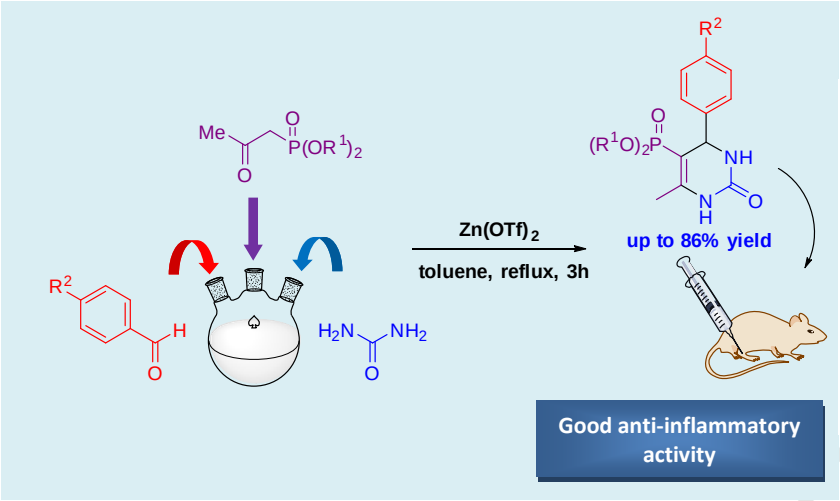

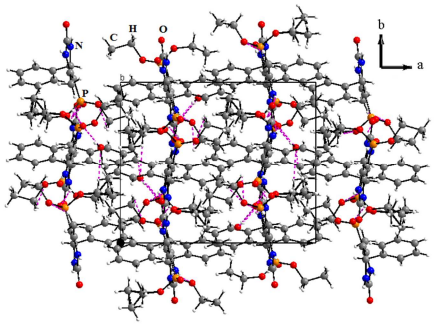

5-Phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones: Zinc triflate-catalyzed one-pot multi-component synthesis, X-ray crystal structure and anti-inflammatory activity

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HIGHLIGHTS

- One-pot three-component synthesis of 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones.
- Synthesized compound were characterized by single crystal X-ray diffraction.
- The synthesized compounds were screened for their anti-inflammatory activity.

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ABSTRACT

Herein we report a simple and efficient one-pot three-component synthesis of 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones, through the zinc triflate-catalyzed Biginelli-type reaction of β-ketophosphonates, aldehydes and urea. The compounds obtained were characterized by various spectroscopic tools including IR, NMR (^{1}H, ^{31}P, ^{13}C) spectroscopy, mass spectrometry and single crystal X-ray diffraction. All the synthesized compounds were screened, for the first time, for anti-inflammatory activity by carrageenan-induced hind paw edema method, using female Wister rats and they showed significant anti-inflammatory activity in some cases higher than the standard indomethacin.

1. Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones and their derivatives are an important class of compounds in medicinal chemistry with a wide range of biological properties, including antitumoral [1], antimalarial [2], anti-inflammatory [3] and anti-HIV [4] activities; some are also medicinally important as calcium channel modulators and α_{1a}-adrenergic receptor antagonists [5]. The introduction of a phosphonate functionality on 3,4-dihydropyrimidinones, may be very interesting for the enhancement of the biological properties of these molecules, in a similar way to that reported for other pharmaceuticals [6,7]. It is also known that phosphonate and phosphonic acid moieties regulate important biological functions by mimicking carboxylic acid groups [8].

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With this in mind, and in the continuation of our interest to develop efficient protocols for the synthesis of heterocyclic phosphonates with possible biological properties [9-11], we report herein a simple and efficient one-pot multi-component synthesis of 5-phosphonato-3,4-dihydropyrimidin-2-ones, through the zinc triflate-catalyzed Biginelli-type reaction [12-17] of β-ketophosphonates, aldehydes and urea.

To the best of our knowledge, there are only two reports on the use of β-ketophosphonates as substrates in the Biginelli reaction, which employed ytterbium triflate [18] or *p*-toluenesulfonic acid [19] as catalyst. However, in spite of their potential utility, these procedures suffer from one or the other drawbacks such as the unsatisfactory yields, tedious work-up or long reaction time.

By comparison with these existing strategies, our method offers significant advantages such as efficiency, short reaction time, easy work-up and high yields. In addition, the zinc triflate catalyst used is known for its low toxicity, low cost, and environmentally benignity. This is very beneficial for safely obtaining phosphonodihydropyrimidinone derivatives of pharmacological interest.

All the synthesized compounds were screened for anti-inflammatory activity by carrageenan-induced hind paw edema method [20], using female Wister rats and they showed significant anti-inflammatory activity in some cases higher than the standard indomethacin.

2. Experimental

2.1. Methods and Materials

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded with $CDCl_3$ or DMSO-d_6 as the solvent, on a Bruker AC-300 spectrometer operating at 300.1 MHz for ^{1}H, 121.5 MHz for ^{31}P and 75.5 MHz for ^{13}C. The chemical shifts are reported in ppm relative to TMS (internal reference) for ^{1}H and ^{13}C NMR and relative to 85% H_3PO_4 (external reference) for ^{31}P NMR. The coupling constants are reported in Hz. For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet and br s: broad singlet. Mass spectra were determined on an Agilent 5975B spectrometer, under electronic impact (EI) conditions. FT-IR spectra were recorded on a Nicolet IR200 spectrometer, the number of scans was 32, the scanning range was 4000–400 cm^{-1} and the resolution 4 cm^{-1}. The progress of the reactions was monitored by TLC. Purification of products was performed by column chromatography using silica gel (Fluka). The starting β-ketophosphonates **1** were synthesized by literature procedures [21].

*2.2. General procedure for the synthesis of 5-phosphonato-3,4-dihydropyrimidin-2(1H)-ones (**3**)*

A mixture containing the β-ketophosphonate (2 mmol), aldehyde (2 mmol), urea (3 mmol) and $Zn(OTf)_2$ (15 mol%) in toluene (8 mL), was refluxed for 3 h. After completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure, then $CHCl_3$ (30 mL) was added. The organic phase was washed with H_2O (2 × 10 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel column, using EtOAc as eluent.

5-Diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (3a).

White Solid; mp 169-170 °C. IR (neat): $\nu_{P=O}$ = 1235 cm^{-1}; $\nu_{C=O}$ = 1703 cm^{-1}; ν_{NH} = 3116-3224 cm^{-1}. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 18.8. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$-O); 1.11 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$-O); 2.12 (d, 3H, $^4J_{PH}$ = 3.0 Hz, C*H*$_3$); 3.49 – 3.83 (m, 4H, 2 CH$_3$-C*H*$_2$-O); 5.05 (dd, 1H, $^3J_{PH}$ = 9.0 Hz, $^3J_{HH}$ = 3.0 Hz, C*H*-NH); 6.14 (br s, 1H, N-*H*) 7.18-7.30 (m, 5H, arom-H); 8.73 (d, 1H, $^3J_{HH}$ = 3.0 Hz, N-*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.0 (d, $^3J_{CP}$ = 7.5 Hz, *C*H$_3$-CH$_2$-O); 16.3 (d, $^3J_{CP}$ = 6.0 Hz, *C*H$_3$-CH$_2$-O); 18.2 (d, $^3J_{CP}$ = 3.7 Hz *C*H$_3$); 56.6 (d, $^2J_{CP}$ = 15.7 Hz, *C*H-NH); 61.3 (d, $^2J_{CP}$ = 5.1 Hz, CH$_3$-*C*H$_2$-O); 61.4 (d, $^2J_{CP}$ = 5.1 Hz, CH$_3$-*C*H$_2$-O); 96.0 (d, $^1J_{CP}$ = 206.8 Hz, P-*C*=C); 147.0 (d, $^2J_{CP}$ = 20.6 Hz, P-C=*C*); 154.23 (s, C=O); phenyl carbons: δ 126.9, 128.2, 128.7, 143.8; EI-HRMS: calculated for $C_{15}H_{21}N_2O_4P$: 324.1239 (M^+); Found: 324.1238.

5-Dimethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (3b).

White Solid; mp 198-200 °C. IR (neat): $\nu_{P=O}$ 1236 cm^{-1}; $\nu_{C=O}$ 1700 cm^{-1}; ν_{NH} = 3119-3258 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 22.9. ^1H NMR (300 MHz, DMSO-d_6): δ = 2.15 (d, 3H, $^4J_{HP}$ = 2.7 Hz, C*H*$_3$); 3.34 (d, 3H, $^3J_{PH}$ = 11.3 Hz, C*H*$_3$-O); 3.46 (d, $^3J_{PH}$ = 11.5 Hz, C*H*$_3$-O); 4.89 (dd, 1H, $^3J_{PH}$ = 8.6 Hz, $^3J_{HH}$ = 3.2 Hz, C*H*-NH); 7.32-7.40 (m, 5H, arom-H); 7.77 (br s, 1H, N-H); 9.28 (d, 1H, $^3J_{HH}$ = 3.1 Hz, N-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.3 (d, $^3J_{CP}$ = 3.5 Hz, *C*H$_3$); 51.3 (d, $^2J_{CP}$ = 4.9 Hz, CH$_3$-O); 51.4 (d, $^2J_{CP}$ = 5.2 Hz, CH$_3$-O); 54.9 (d, $^2J_{CP}$ = 15.2 Hz, *C*H-NH); 92.5 (d, $^1J_{CP}$ = 205.8 Hz, P-*C*=C); 148.8 (d, $^2J_{CP}$ = 20.7 Hz, P-C=*C*); 152.5 (s, C=O); phenyl carbons: 126.5, 127.4, 128.4, 144.5; EI-HRMS: calculated for $C_{13}H_{17}N_2O_4P$: 296.0926 (M^+); Found: 296.0922.

5-Diethoxyphosphoryl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (3c).

Yellow Solid; mp 219-220 °C. IR (neat): $\nu_{P=O}$ = 1225 cm^{-1}; $\nu_{C=O}$ = 1700 cm^{-1}; ν_{NH} = 3120-3232 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 19.2. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.00 (t, 3H, $^3J_{HH}$ = 7.0 Hz, C*H*$_3$-CH$_2$-O); 1.13 (t, 3H, $^3J_{HH}$ = 7.0 Hz, C*H*$_3$-CH$_2$-O); 2.12 (d, 3H, $^4J_{PH}$ = 2.2 Hz, C*H*$_3$); 3.59-3.84 (m, 4H, 2 CH$_3$-C*H*$_2$-O); 5.01 (dd, 1H, $^3J_{PH}$ = 8.5 Hz, $^3J_{HH}$ = 3.4 Hz, C*H*-NH); 7.53-8.25 (m, 4H, , arom-H); 7.81 (d, 1H, $^4J_{PH}$ = 1.7 N-*H*); 9.31 (d, 1H, $^3J_{HH}$ = 3.0 Hz, N-*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.7 (d, $^3J_{CP}$ = 6.6 Hz, *C*H$_3$-CH$_2$-O); 16.0 (d, $^3J_{CP}$ =

6.2 Hz, *C*H_3-CH_2-O); 17.4 (d, $^3J_{CP}$ = 3.4, *C*H_3); 54.6 (d, $^2J_{CP}$ =15.1 Hz, *C*H-NH); 60.6 (d, $^2J_{CP}$ = 5.1 Hz, CH_3- *C*H_2-O); 60.7 (d, $^2J_{CP}$ = 5.2 Hz, CH_3-*C*H_2-O); 92.7 (d, $^1J_{CP}$ = 206.4 Hz, P-*C*=C); 149.1 (d, $^2J_{CP}$ = 20.6 Hz, P-C=*C*); 152.2 (s, C=O); phenyl carbons: 123.7, 127.8, 146.7, 151.6; EI-HRMS: calculated for $C_{15}H_{20}N_3O_6P$: 369.1090 (M^+); found: 369.1092.

5-Dimethoxyphosphoryl-6-méthyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (3d). Yellow Solid; mp 235-237 °C. IR (neat): $\nu_{P=O}$ = 1228 cm^{-1}; $\nu_{C=O}$ = 1701 cm^{-1} ; ν_{NH} = 3142-3232 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 22.3. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (d, 3H, $^4J_{PH}$ = 2.2 Hz, C*H*$_3$); 3.41 (d, 3H, $^3J_{PH}$ = 11.2 Hz, C*H*$_3$-O); 3.50 (d, 3H, $^3J_{PH}$ = 11.4 Hz, C*H*$_3$-O); 5.05 (dd, 1H, $^3J_{PH}$ = 8.5 Hz, $^3J_{HH}$ = 3.4 Hz, C*H*-NH); 7.59-8.30 (m, 4H, arom-H); 7.90 (d, 1H, $^4J_{PH}$ = 1.7 Hz, N-H); 9.42 (d, 1H, $^3J_{HH}$ = 3.0 Hz, N-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.3 (d, $^3J_{CP}$ = 3.5 Hz, *C*H_3); 51.5 (d, $^2J_{CP}$ = 5.1 Hz, *C*H_3-O); 51.6 (d, $^2J_{CP}$ = 5.3 Hz, *C*H_3-O); 54.5 (d, $^2J_{CP}$ = 15.3 Hz, *C*H-NH); 91.5 (d, $^1J_{CP}$ = 206.9 Hz, P-*C*=C);149.7 (d, $^2J_{CP}$ = 20.5 Hz, P-C=*C*); 152.1 (s, C=O); phenyl carbons: 123.8, 127.8, 146.7, 151.5; EI-HRMS: calculated for $C_{13}H_{16}N_3O_6P$: 341.0777 (M^+); found: 341.0776.

5-Diethoxyphosphoryl-6-méthyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (3e). White Solid; mp 120-122 °C. IR (neat): $\nu_{P=O}$ = 1227 cm^{-1}; $\nu_{C=O}$ = 1700 cm^{-1}; ν_{NH} = 3127-3243 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 19.1. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.03 (t, 3H, $^3J_{HH}$ = 7.0 Hz, C*H*$_3$-CH_2-O); 1.13 (t, 3H, $^3J_{HH}$ = 7.0 Hz, C*H*$_3$-CH_2-O); 2.12 (d, 3H, $^4J_{PH}$ = 2.1 Hz, C*H*$_3$); 3.57-3.86 (m, 4H, 2 CH_3-C*H*$_2$-O); 5.02 (dd, 1H, $^3J_{PH}$ = 8.1 Hz, $^3J_{HH}$ = 2.8 Hz, C*H*-NH); 7.07 (br s, 1H, N-H), 7.17-7.27 (m, 4H, arom-H); 9.00 (br s, 1H, N-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.0 (d, $^3J_{CP}$ = 7.0 Hz, *C*H_3-CH_2-O); 15.2 (d, $^3J_{CP}$ = 6.7 Hz, *C*H_3-CH_2-O); 16.9 (d, $^3J_{CP}$ = 3.6 Hz, C*H*$_3$); 54.5 (d, $^2J_{CP}$ = 15.6 Hz, C*H*-NH); 60.2 (d, $^2J_{CP}$ = 5.2 Hz, 2 CH_3-*C*H_2-O); 93.7 (d, $^1J_{CP}$ = 207.4 Hz, P-*C*=C); 146.9 (d, $^2J_{CP}$ = 20.6 Hz, P-C=*C*); 152.8 (s, C=O); phenyl carbons: 127.4, 127.5, 132.2, 141.8. EI-HRMS calculated for $C_{15}H_{20}ClN_2O_4P$: 358.0849 (M^+); found: 358.0811.

5-Dimethoxyphosphoryl-6-méthyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (3f). White Solid; mp 226-227 °C. IR (neat): $\nu_{P=O}$ = 1227 cm^{-1}; $\nu_{C=O}$ = 1702 cm^{-1}; ν_{NH} = 3128-3251 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 22.7. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.14 (d, 3H, $^4J_{PH}$ = 2.0 Hz, C*H*$_3$); 3.39 (d, 3H, $^3J_{PH}$ = 11.3 Hz, C*H*$_3$-O); 3.48 (d, 3H, $^3J_{PH}$ = 11.4 Hz, C*H*$_3$-O); 4.91 (dd, 1H, $^3J_{PH}$ = 8.6 Hz, $^3J_{HH}$ = 3.4 Hz, C*H*-NH); 7.33-7.48 (m, arom-H); 7.80 (d, 1H, $^4J_{PH}$ = 1.6 Hz N-H) ; 9.33 (d, 1H, $^3J_{HH}$ = 3.1 Hz, N-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.3 (d, $^3J_{CP}$ = 3.5 Hz, *C*H_3); 51.4 (d, $^2J_{CP}$ = 5.0 Hz, *C*H_3-O); 51.5 (d, $^2J_{CP}$ = 5.3 Hz, *C*H_3-O); 54.3 (d, $^2J_{CP}$ = 15.3 Hz, *C*H-NH); 92.1(d, $^1J_{CP}$ = 206.3 Hz, P-*C*=C); 149.1 (d, $^2J_{CP}$ = 20.7 Hz, P-C=*C*); 152.3 (s, C=O); phenyl carbons: 128.4, 131.9, 143.4.

5-Diethoxyphosphoryl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (3g).

White Solid; mp 138-140 °C. IR (neat): $\nu_{P=O}$ = 1229 cm^{-1}; $\nu_{C=O}$ = 1703 cm^{-1}; ν_{NH} = 3116-3242 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 19.9. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.04 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, C*H*$_3$-CH$_2$-O); 1.19 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, C*H*$_3$-CH$_2$-O); 2.16 (d, 3H, $^{4}J_{PH}$ = 2.2 Hz, C*H*$_3$); 3.42-3.87 (m, 4H, CH$_3$-C*H*$_2$-O); 3.78 (s, 3H, OC*H*$_3$); 4.85 (dd, 1H, $^{3}J_{PH}$ = 8.7 Hz, $^{3}J_{HH}$ = 3.2 Hz, C*H*-NH); 6.93-7.26 (m, 4H, arom-H); 7.64 (d, 1H, $^{4}J_{PH}$ = 1.6 Hz, N-H); 9.16 (d, 1H, $^{3}J_{HH}$ = 3.1 Hz, N-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.8 (d, $^{3}J_{CP}$ = 6.8 Hz, *C*H$_3$-CH$_2$-O); 16.0 (d, $^{3}J_{CP}$ = 6.3 Hz, *C*H$_3$-CH$_2$-O); 17.3 (d, $^{3}J_{CP}$ = 3.5 Hz, *C*H$_3$); 54.4 (d, $^{2}J_{CP}$ = 15.0 Hz, *C*H-NH); 55.1 (s, CH$_3$-O); 60.4 (d, $^{2}J_{CP}$ = 5.5 Hz, CH$_3$-*C*H$_2$-O); 60.5 (d, $^{2}J_{CP}$ = 5.6 Hz, CH$_3$-*C*H$_2$-O); 94.0 (d, $^{1}J_{CP}$ = 205.1 Hz, P-*C*=C); 147.9 (d, $^{2}J_{CP}$ = 20.9 Hz, P-C=*C*); 152.5 (s, C=O); phenyl carbons: 113.6, 127.7, 136.7, 158.5; EI-HRMS: calculated for $C_{16}H_{23}N_3O_5P$: 354.1344 (M^+); found: 354.1343.

5-Diethoxyphosphoryl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (3h). Yellow Solid; mp 158-159 °C. IR (neat): $\nu_{P=O}$ = 1230 cm^{-1}; $\nu_{C=O\ (amide)}$ = 1701 cm^{-1}; ν_{NH} = 3120-3252 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 19.8. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.98 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, C*H*$_3$-CH$_2$-O); 1.13 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, C*H*$_3$-CH$_2$-O); 2.11 (d, 3H, $^{4}J_{PH}$ = 2.3 Hz, C*H*$_3$); 2.27 (s, CH$_3$); 3.38-3.80 (m, 4H, 2 CH$_3$-C*H*$_2$-O); 4.82 (dd, 1H, $^{3}J_{PH}$ = 8.8 Hz, $^{3}J_{HH}$ = 3.3 Hz, C*H*-NH); 7.11-7.19 (m, 4H, arom-H); 7.61 (d, 1H, $^{4}J_{PH}$ = 1.7 Hz, N-H); 9.12 (d, 1H, $^{3}J_{HH}$ = 3.0 Hz, N-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.7 (d, $^{3}J_{CP}$ = 6.7 Hz, *C*H$_3$-CH$_2$-O); 16.0 (d, $^{3}J_{CP}$ = 6.3 Hz, *C*H$_3$-CH$_2$-O); 17.3 (d, $^{3}J_{CP}$ = 3.5 Hz, *C*H$_3$); 30.6 (s, CH$_3$); 54.7 (d, $^{2}J_{CP}$ = 15.1 Hz, *C*H-NH); 60.4 (d, $^{2}J_{CP}$ = 5.0 Hz, CH$_3$-*C*H$_2$-O); 60.5 (d, $^{2}J_{CP}$ = 5.2 Hz, CH$_3$-*C*H$_2$-O); 93.9 (d, $^{1}J_{CP}$ = 205.4 Hz, P-*C*=C); 148.1 (d, $^{2}J_{CP}$ = 20.9 Hz, P-C=*C*); 152.6 (s, C=O); phenyl carbons: 126.4, 128.7, 136.5, 141.5.

*2.3 X-ray diffraction data of compound **3a***

A single crystal was carefully selected under a polarizing microscope in order to perform its structural analysis by X-ray diffraction. The data were integrated and scaled using hkl-SCALEPACK [22]. Solution by direct methods (SHELXS, SIR97 [23]) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97 [24-27]. Scattering factors are from Waasmair and Kirfel [28]. Hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters Ueq were fixed such that they were 1.2Ueq of their parent atom Ueq for CH's and 1.5Ueq of their parent atom Ueq in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares. The drawings were made with Diamond

[29] and Mercury [30]. Crystal data and experimental parameters used for the intensity data collection are summarized in Table 1.

Table 1. Crystal data and structure refinement of $C_{15}H_{21}N_2O_4P$, 0.065(H_2O).

Empirical formula	C15 H21.13 N2 O4.06 P	Crystal size	0.30 x 0.27 x 0.21 mm^3
Formula weight	325.43	Theta range for data collection	2.06 to 28.30°.
Temperature	130(2) K	Crystal size	0.30 x 0.27 x 0.21 mm^3
Wavelength	0.71073 Å	Theta range for data collection	2.06 to 28.30°.
Crystal system	*Monoclinic*	Index ranges	-20<=h<=20, -14<=k<=15, -25<=l<=25
Space group	P $2_1/n$	Reflections collected	68023
Unit cell dimensions	a = 15.3175(5) Å	Independent reflections	8056 [R(int) = 0.0594]
	b = 11.7656(5) Å	Completeness to theta = 25.00°	99.8 %
	c = 19.4907(6) Å	Max. and min. transmission	0.9616 and 0.9458
	β= 111.483(3)°	Refinement method	Full-matrix least-squares on F^2
Volume	3268.6(2) $Å^3$	Data / restraints / parameters	8056 / 6 / 426
Z	8	Goodness-of-fit on F^2	1.038
Density (calculated)	1.323 Mg/m^3	Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1298
Absorption coefficient	0.188 mm^{-1}	R indices (all data)	R1 = 0.1001, wR2 = 0.1457
F(000)	1381	Largest diff. peak and hole	0.397 and -0.441 e.$Å^{-3}$

2.4. Anti-inflammatory activity

Anti-inflammatory activity of the synthesized compounds **3a-h** and indomethacin used as standard, was determined by carrageenan-induced hind paw edema method [20], using female Wister rats. Test compounds, dissolved in ethanol 10%, were given to rats intraperitoneally at a dose of 10 mg/kg of body weight of rats and at a volume of 100 µL/100 g of body weight of rats. The same volume of ethanol 10% was given to the control group. One hour after treatment, the

right hind paw volume of all rats was measured with a plethysmometer, then, carrageenan 0.1 mL (1%, w/v) solution in ultrapure water was subcutaneously injected into the planter surface of the right hind paw of all rats. Carrageenan-induced paw edema was measured at 1 h, 2 h, 3 h, 4 h and 6 h following Carrageenan-treatment. All experiments were done in triplicate.

Anti-inflammatory activities of compounds **3a-h** and indomethacin were determined by comparing their results with the ones obtained in the control group. The anti-inflammatory effect of the test compounds was calculated by the following equation:

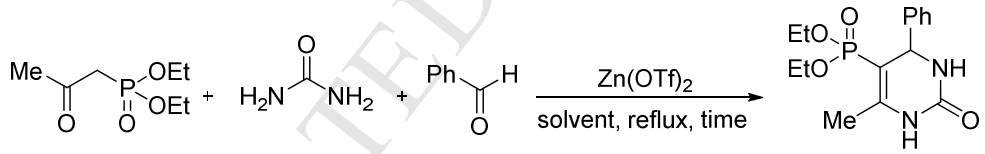
Anti-inflammatory activity $(I\ \%) = (1 - D/C) \times 100$, where D represents the percentage difference in paw volume after the test compound administration to the rats, and C represents the percentage difference of volume in the control group.

3. Results and discussion

3.1 Chemistry

In order to establish the optimum reaction conditions for the formation of the target compounds, we used β-ketophosphonate **1a**, benzaldehyde and urea as model substrates. The reaction was studied with various mole ratios of zinc triflate in different conditions. As shown in Table 1, the best results were obtained with 15 mol% of the catalyst, in refluxing toluene, for 3 h (Table 2, entry 8).

Table 2. Optimization of the reaction conditions



1a **3a**

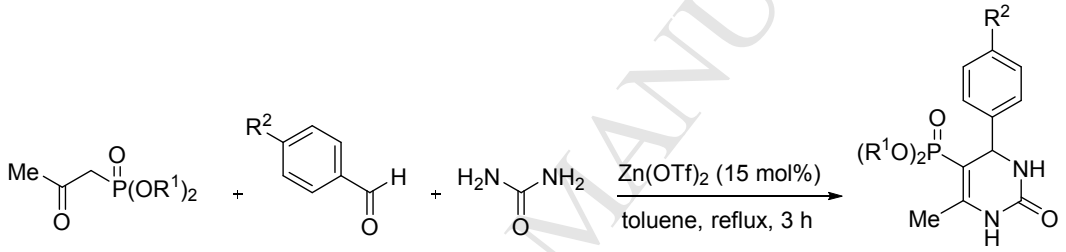
Entry	$Zn(OTf)_2$ ratio (mol%)	Solvent	Time (h)	Yield (%)[a]
1	0	toluene	24	0
2	5	toluene	3	70
3	5	MeCN	3	66
4	5	dioxane	3	26
5	5	THF	3	0
6	5	DCE	3	41
7	10	toluene	3	76
8	15	toluene	3	82

9	20	toluene	3	82

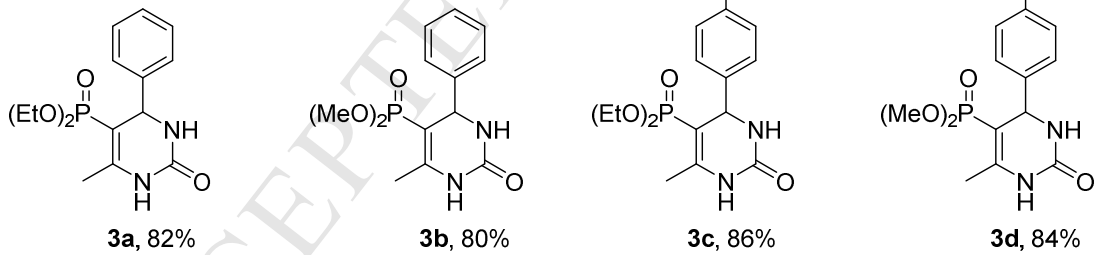
[a] Isolated yield.

With these optimized reaction conditions in hand, we next studied the scope of this methodology. A variety of structurally diverse aldehydes and β-ketophosphonates were investigated and a series of 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones of type **3** were afforded in good yields (Table 3). It is noteworthy to mention that the present method was found to be tolerant toward various aromatic aldehydes bearing either electron-withdrawing or electron-donating substituents. In general, aromatic aldehydes with electron-withdrawing groups, which are more reactive, afforded higher yields than those with electron-donating ones.

Table 3. Substrate scope studies



1 **2** **3**

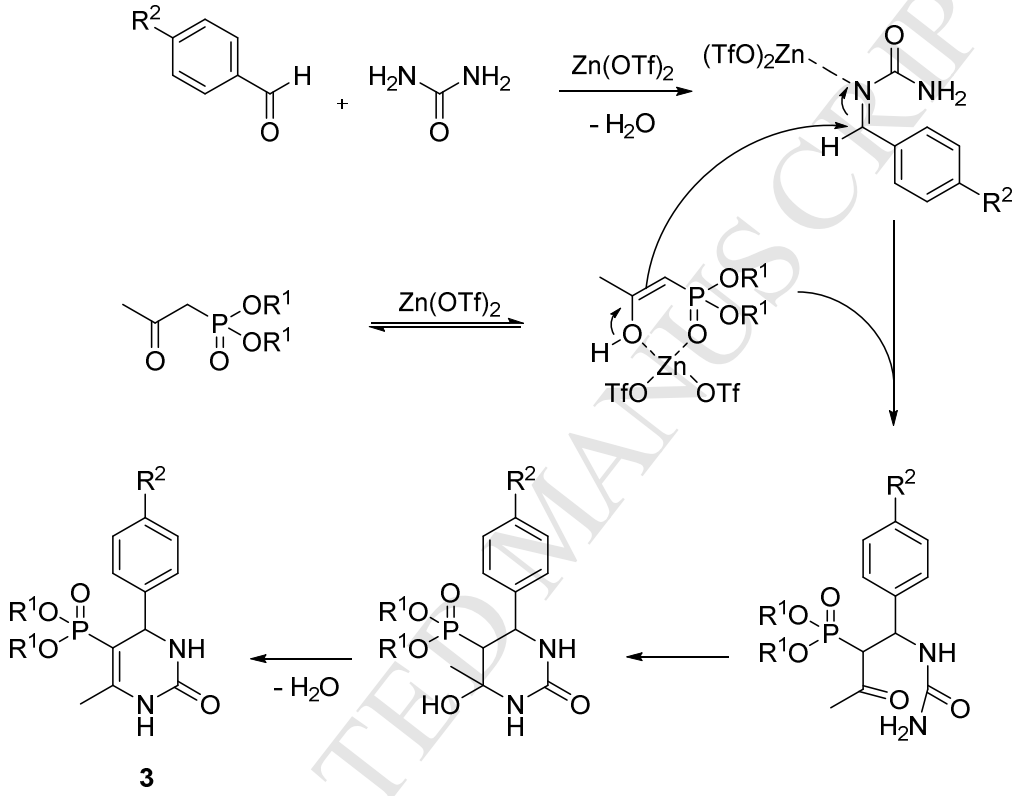


3a, 82% **3b**, 80% **3c**, 86% **3d**, 84%

3e, 85% **3f**, 83% **3g**, 75% **3h**, 72%

[a] Isolated yield.

Based on our experimental results and the known literature precedents [12-16, 31,32], a mechanistic rationalization for this reaction is provided in Scheme 1. This proposed mechanism involves the nucleophilic addition of urea to the aldehyde, catalysed by the Lewis acid $Zn(OTf)_2$, giving rise to an imine intermediate. The interception of this last one by the β-ketophosphonate through its enol tautomer leads, after intramolecular cyclization and dehydration, to the dihydropyrimidinone **3**.



3

Scheme 1. Proposed mechanism for the formation of compounds **3**

3.2. Molecular structure

The structures of compounds **3** were established using various spectroscopic techniques including IR, NMR (^{1}H, ^{31}P, ^{13}C) spectroscopy, mass spectrometry as well as single crystal X-ray diffraction. The IR spectra revealed the presence of absorption bands towards 1230, 1700 and 3300 cm^{-1} corresponding, respectively to the P=O, C=O and N-H vibrators. The ^{1}H NMR spectra of compounds **3** showed, in particular, a doublet of doublets around 5 ppm relative to the CH proton at the β position with respect to the phosphorus atom. Such a multiplicity is characteristic of the coupling with phosphorus ($^3J_{PH}$ ~ 9 Hz) and the vicinal NH proton ($^3J_{HH}$ ~3 Hz). This last NH proton resonates then as a doublet ($^3J_{HH}$ ~3 Hz) at 8-9 ppm, while the other NH proton gives

a broad singlet (in some cases a doublet with a small $^{4}J_{PH}$ coupling constant of about 2 Hz) towards 6-7 ppm. The alkoxy groups on the phosphorus atom showed a signal doubling indicating that they are not magnetically equivalent, probably due to the neighbouring chiral carbon. The ^{31}P NMR shift recorded for compounds **3** was δ = 18-22 ppm which is consistent with the dialkyl phosphonate chemical shift values. The ^{13}C NMR spectra display the characteristic signals of all carbons and particularly those corresponding to the dihydropyrimidinone ring. The sp^2 carbons at the α and β positions to the phosphorus atom resonate each one as a doublet towards 92 ppm ($^{1}J_{CP}$ ~ 205 Hz) and 148 ppm ($^{2}J_{CP}$ ~ 20 Hz) respectively. The CH-N carbon gives also a doublet around 55 ppm. Such a doublet is characteristic of the coupling with phosphorus with a $^{2}J_{CP}$ coupling constant of about 15 Hz. As for the C=O carbon, it resonates as a singlet at near 152 ppm. Structures of compounds **3** were supported additionally by the mass spectra which showed the correct molecular ion peaks.

Unambiguous structure elucidation of phosphonodihydropyrimidinones **3** was achieved by X-ray crystallography. Single crystals of $C_{15}H_{21}N_2O_4P$,0.065(H_2O) were obtained by slow evaporation at room temperature of n-hexane into a chloroform (**3a**) solution. The molecular structure of (**3a**) as the result of a single crystal X-ray study is shown in Figure 1. It contains two crystallographically independent molecules with one of the ethyl groups of the second molecule is disordered over two orientations in a 0.729(2):0.271(8) ratio. In the atomic arrangement, these molecules are interconnected via N—H···O hydrogen bonds to form layers parallel to (b, c) plan (Figure 2, Table 4). Within the layers, $R_2^2(8)$ graph-set motif connecting two adjacent molecules are observed. These layers, located around x = 1/4 and x = 3/4, connect each other via C—H···O to form a three dimensional network (Figure 3, Table 5). A small amount of water (about 12.5%) can be incorporated into the structure, causing disorder in the ethyl moiety C29 and C30. The water contributes to connect the aforementioned layers by O—H···O hydrogen bond interactions.

Within the dihydropyrimidin-2(1*H*)-one rings, an examination of the bond length data (Table 5) shows that N1-C3 [1.348(3) Å], N2-C3 [1.367(3) Å], N2-C4 [1.385(3) Å], N3-C18 [1.342(3) Å], N4-C18 [1.370(3) Å] and N4-C19 [1.384(3) Å] can be attributed as having clear double bond character, which is due to the n-σ-π conjugation. The C1-C4 [1.353(3) Å] and C16-C19 [1.341(3) Å] in agreement with the presence of the C-C double bonds. The N1-C2 [1.466(3) Å], N3-C17 [1.463(3) Å], C1-C2 [1.531(3) Å] and C16-C17 [1.530(3) Å], clearly indicate the presence of C-C single bonds.

These molecules exhibit a regular spatial configuration with normal C-C distances and C-C-C, angles. The average value of the C-C bond lengths of the two phenyl rings is 1.388(3) and 1.387(3) Å which are between a single and double bond and agree with those in the literature [29, 30].

Concerning the P-O, the P1-O2 [1.469(1) Å] and P2-O6 [1.472(1) Å] are consistent with P-O double bonds, while P1-O3 [1.582(2) Å], P1-O4 [1.575(2) Å], P2-O7 [1.575(2) Å] and P2-O8 [1.583(2) Å] correspond to P-O single bonds.

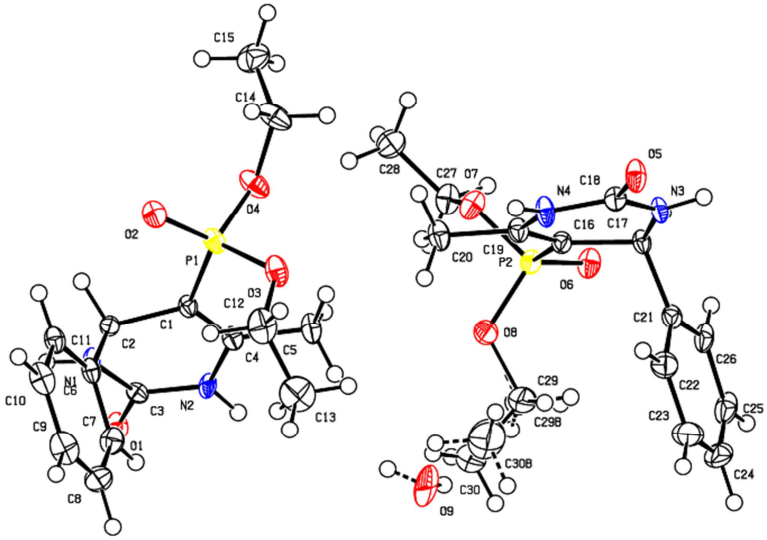


Figure 1. Asymmetric unit of $C_{15}H_{21}N_2O_4P$, 0.065(H_2O). Displacement ellipsoids are drawn at the 50% probability level.

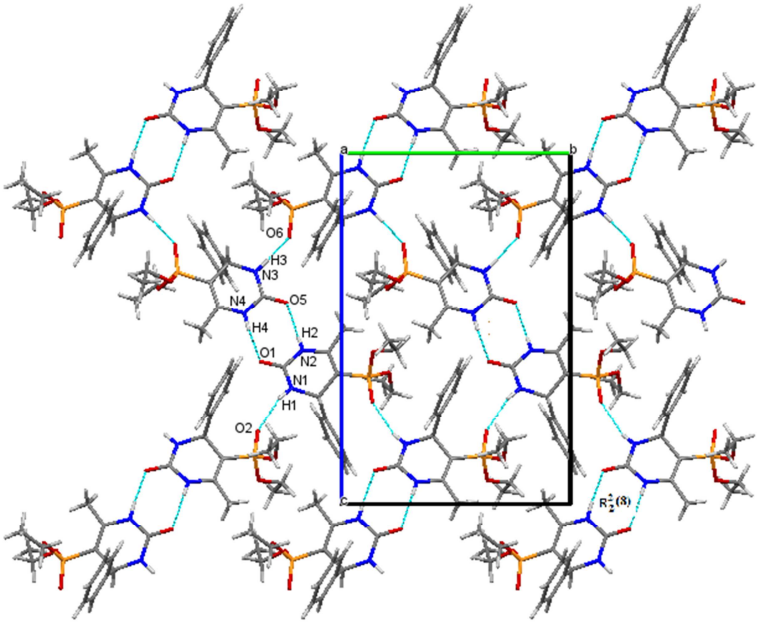


Figure 2. View of a layer parallel to the (a, b) plane in $C_{15}H_{21}N_2O_4P$, 0.065(H_2O). Dotted lines indicate hydrogen bonds. Disorder of ethyl groups are omitted for clarity.

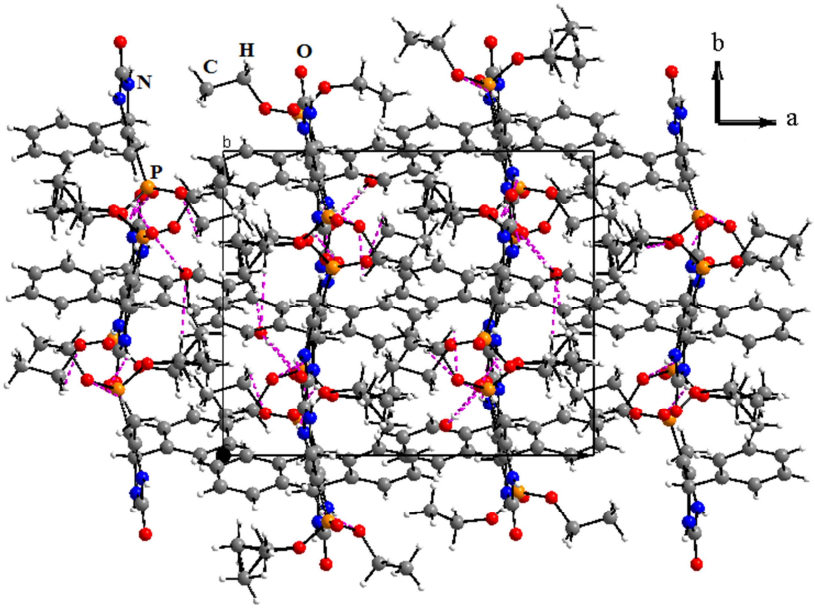


Figure 3. Crystal packing of $C_{15}H_{21}N_2O_4P$, 0.065(H_2O). Hydrogen bonds are denoted by dotted. Disorder of ethyl groups are omitted for clarity.

Table 4. Hydrogen-bond geometry (Å, º) in $C_{15}H_{21}N_2O_4P$, 0.065(H_2O).

D*—H···*A	***D*—H**	**H···*A***	***D*···*A***	***D*—H···*A***
C30—H30*C*···O9	0.98	1.52	2.449	157
C29*B*—H29*D*···O9	0.99	2.47	3.349	148
C5—H5*A*···O3	0.98	2.54	3.249 (3)	130
C20—H20*A*···O7	0.98	2.36	3.103 (3)	132
C24—H24···O2^{i}	0.95	2.59	3.492 (4)	159
N1—H1···O2^{ii}	0.88	2.07	2.823 (2)	143
N2—H2···O5^{iii}	0.88	2.01	2.830 (2)	155
N3—H3···O6^{iv}	0.88	2.04	2.842 (2)	151
N4—H4···O1^{v}	0.88	1.98	2.822 (2)	160
O9—H9*P*···O6^{vi}	0.80	2.23	3.020	171
O9—H9*O*···O5^{iii}	0.80	2.01	2.750	154

Symmetry codes : (i) $x-1/2, -y+3/2, z+1/2$; (ii) $-x+5/2, y-1/2, -z+3/2$; (iii) $x, y-1, z$; (iv) $-x+5/2, y+1/2, -z+5/2$; (v) $x, y+1, z$; (vi) $-x+5/2, y-1/2, -z+5/2$.

Table 5. Selected and important bond length and bond angle values (Å, °) in $C_{15}H_{21}N_2O_4P$, 0.065(H_2O).

Atoms	Bond Length (Å)	Atoms	Bond Angle (°)
C1-C4	1.353(3)	C11-C6-C2	119.7(2)
C1-C2	1.531(3)	C8-C7-C6	120.2(2)
C2-N1	1.466(3)	C9-C8-C7	120.3(2)
C3-O1	1.237(3)	C8-C9-C10	120.0(2)
C3-N1	1.348(3)	C9-C10-C11	119.7(2)
C3-N2	1.367(3)	C10-C11-C6	120.6(2)
C4-N2	1.385(3)	C22-C21-C26	119.2(2)
C16-C19	1.341(3)	C21-C22-C32	120.3(2)
C16-C17	1.530(3)	C24-C23-C22	120.3(3)
C17-N3	1.463(3)	C25-C24-C23	119.6(2)
C18-O5	1.246(3)	C24-C25-C26	120.7(2)
C18-N3	1.342(3)	C25-C26-C21	119.9(2)
C18-N4	1.370(3)	-	-
C19-N4	1.384(3)	-	-
C19-C20	1.503(3)	-	-
C29-O8	1.455(6)	-	-
C6-C7	1.390(3)	-	-
C6-C11	1.391(3)	-	-
C7-C8	1.390(3)	-	-
C9-C9	1.382(3)	-	-
C9-C10	1.386(4)	-	-
C10-C11	1.390(3)	-	-
C21-C22	1.387(2)	-	-
C21-C26	1.397(3)	-	-
C22-C23	1.391(3)	-	-
C23-C24	1.389(4)	-	-
C24-C25	1.372(4)	-	-
C25-C26	1.394(3)	-	-
O8-P2	1.582(2)	-	-
O2-P1	1.469(2)	-	-
O3-P1	1.582(2)	-	-
O4-P1	1575(2)	-	-
O6-P2	1.472(2)	-	-
O7-P2	1.574(2)	-	-

3.3. Anti-inflammatory activity

Given that 3,4-dihydropyrimidinones are well-known for their promising anti-inflammatory properties [3,33-37], we focused our efforts, in the second part of this work, to evaluate the *in vivo* anti-inflammatory activity of the synthesized 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones **3a-h**. We shall note here that the search for novel anti-inflammatory agents to treat an inflammatory reaction and consequent diseases such as rheumatic manifestations, fractures and stomatitis, is a contemporary field.

Anti-inflammatory activity of the synthesized compounds **3a-h** and indomethacin used as standard, was determined by carrageenan-induced hind paw edema method [20], using female Wister rats. The results of these experiments are summarized in Figures 4 and 5. They showed that the synthesized compounds **3a-h** exhibited significant anti-inflammatory activity in some cases higher than the standard drug indomethacin. It was found that compound **3g** has the highest anti-inflammatory activity at 58.42 % when compared with other compounds. The remaining compounds exhibited an anti-inflammatory activity in the following order: **3c** (52.45 %), **3b** (48.29 %), **3d** (33.37 %), **3h** (29.95 %), **3e** (23.76 %), **3f** (17.11 %), **3a** (13.06 %), and compared with indomethacin (37.77 %). Thus, the most promising compounds in the present series are **3g**, **3c** and **3b** which showed excellent anti-inflammatory activity, higher than the standard drug indomethacin.

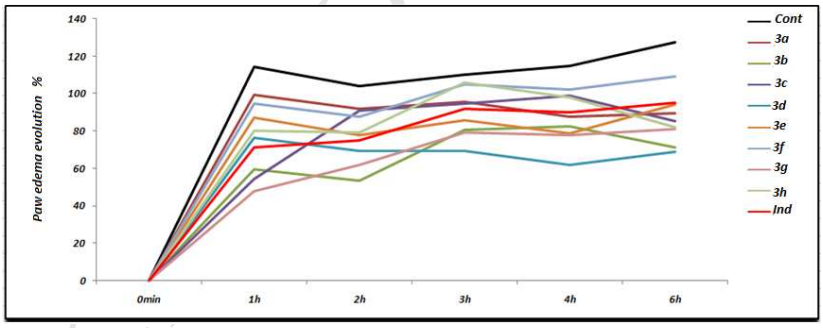


Figure 4: Anti-inflammatory activity (**3a-h**: tested compounds, Ind: indomethacin, Cont: control)

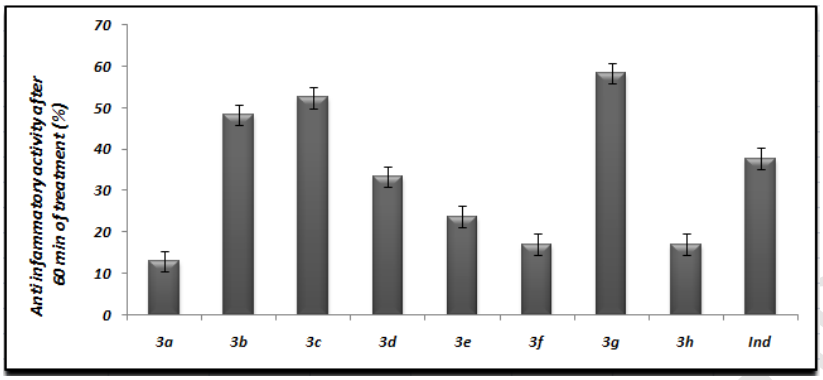


Figure 5: Anti-inflammatory activity after 60 min of treatment

4. Conclusion

We have developed a novel one-pot three-component protocol for the synthesis of 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones, through the zinc triflate-catalyzed Biginelli-type reaction of β-ketophosphonates, aldehydes and urea. This method offers significant advantages over prior reports, such as efficiency, good yields, shorter reaction time and easy work-up. Furthermore, the zinc triflate catalyst used is known for its low toxicity, low cost, and environmentally benignity, which is very beneficial for safely obtaining phosphonodihydropyrimidinone derivatives for biological screening. The compounds obtained were characterized by various spectroscopic tools including IR, NMR (^{1}H, ^{31}P, ^{13}C) spectroscopy, mass spectrometry and single crystal X-ray diffraction. All the synthesized compounds were evaluated for the first time for the anti-inflammatory activity and were found to be promising anti-inflammatory agents for further drug discoveries.

Acknowledgement

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Supplementary material

Supporting Information [Copy of NMR (^{1}H, ^{31}P, ^{13}C) and IR spectra for 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones **3**] is available on the publishers Web site along with the published article.

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