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Design, synthesis, and structure elucidation of novel 3-aralkyl/arylamino-1-pyridin-3-ylpropenones and 3-adamantyl-5-nicotinoyl-1,2,3,4-tetrahydropyrimidine hybrids with promising anti-inflammatory activities[§]

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Aiming for the synthesis of unreported molecular hybrids of 1,2,3,4-tetrahydropyrimidine and adamantane moiety containing nicotinoyl group in position 5 of the tetrahydropyrimidine ring suitable for use as anti-inflammatory agents, the precursor enaminones **3a–h** have been reacted with 1-adamantanamine **4** and formaldehyde under thermal conditions producing the desired products **5a–h**. The enaminone derivatives **3a–h** are obtained by reacting formylated 3-acetylpyridine **2** with various primary amines. The structures of (3-((3s,5s,7s)-adamantan-1-yl)-1-aralkyl/aryl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)methanones **5a–h** prepared in this investigation have been determined by various analytical and spectroscopic methods, in addition to the X-ray crystallographic analysis. The anti-inflammatory study of the synthesized compounds demonstrates promising activity.

Keywords: Tetrahydropyrimidine, Anti-Inflammatory, Enaminones, X-Ray Crystallography, Nicotinoyl Group, Adamantane

Isonicotinoyl motifs are known for their pharmacological properties like anti-tubercular, anti-pyretic, anti-bacterial, antifungal, antioxidant properties[1] and chelating effects[2,3]. The scaffolds featuring isonicotinoyl groups have demonstrated remarkably high anti-inflammatory potency, highlighting their potential as promising therapeutic agents[4]. Isoniazid has been widely used as the most potent and widely used anti-tuberculosis agents typically administered alongside rifampicin, ethambutol, and pyrazinamide[5].

Considering the significant pharmacological effects of isonicotinoyl derivatives, our group also have reported[6] the synthesis and anti-bacterial activities of novel 5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines (THP), and bis-(5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines), and novel molecular hybrids of 5-isonicotinoyl-1,2,3,4-tetrahydropyrimidine-adamantane with significant anti-inflammatory and antibacterial activities[7] (Fig. 1) where the isonicotinoyl group is positioned at 5 of the THP ring.

In view of the promising developments associated with the isonicotinoyl group at the 5-position of THP ring, along with its potential antibacterial and anti-inflammatory activities, we decided to design THP derivatives with nicotinoyl group at C-5 of the ring. A variety of nicotinoyl based compounds like nicotinoyl organoselenium derivatives, nicotinoyl thioureas, quinolin-2-one hydrazones incorporating nitrophenyl or isonicotinoyl/nicotinoyl, curcumin-nicotinoyl derivatives have been synthesized and explored for their biological effects[8-11]. These compounds have been reported to exhibit anti-inflammatory, chemo- and redox-sensing, antioxidant, antimicrobial, antibacterial and anticancer properties[8-11]. Taking into accounts these insights, we herein describe the synthesis, structure elucidation and anti-inflammatory activities of this class of hitherto unreported molecular hybrids (3-((3s,5s,7s)-adamantan-1-yl)-1-aralkyl/aryl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridine-3-yl)methanones with nicotinoyl moiety incorporated in position-5 of the tetrahydropyrimidine ring.

§ This manuscript is a part of the Ph D thesis of Utpalparna Kalita (2015) which has already been uploaded on www.shodhganga.inflibnet.ac.in as mandated by the UGC.

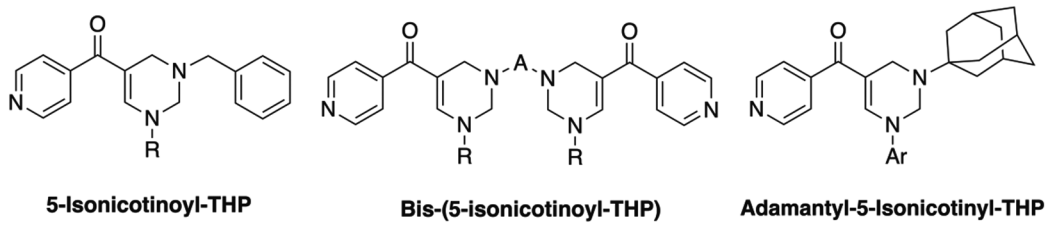


Fig. 1 — Examples of reported 5-isonicotinoyl-tetrahydropyrimidine derivatives

Experimental Section

Chemistry

Open capillary method was employed for recording melting points and are uncorrected. Perkin-Elmer 983 spectrometer were engaged for IR spectral data recording. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECS 400 and Varian 400 spectrometer; Bruker AV III 500 MHz taking Me4Si as the internal standard in $CDCl_3$ and DMSO-d_6. Data were recorded in following order: chemical shifts are expressed in δ values (ppm) relative to TMS as an internal standard, multiplets are presented as s = singlet, d = doublet, t = triplet, dd = double doublet, brs = broad singlet. The adamantyl and tetrahydropyrimidine groups are represented as Adam and THP. The X-ray diffraction data were collected at 293 K with Mo Kα radiation (k = 0.71073 A˚) using a Bruker Nonius SMART APEX II CCD diffractometer equipped with a graphite monochromator. Using Olex2, the structure was solved with the olex2.solve[12] structure solution program using Charge Flipping and refined with the SHELXL[13] refinement package using Least Squares Minimization on F^2. The H atoms were located at calculated positions and all the non-H atoms were refined in the anisotropic approximation: the H atoms were located at calculated positions. The structure was drawn using Olex[2] software. The electron spray mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer and Waters ZQ-4000 mass spectrometer. Mass analyser, make – Walters, model – Xevo G2-XS OTof, with software – MassLynx V 4.1 and Orbitrap Fusion Tribid mass spectrometer, Thermofisher Scientific was employed for HR-MS.

General Procedure

Synthesis of 3-aralkyl/arylamino-1-pyridine-3-yl-prop-2-en-1-ones (3a–h)

To a solution of 3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one **2** (1 mmol) in 2 mL acetic acid, aniline (1 mmol) was added in one lot and the resulting mixture was stirred at RT for 6–26 h when a solid product precipitated out. After completion of the reaction (tlc), the mixture was poured over chilled water and the precipitated product was collected by filtration, washed repeatedly by water to ensure complete removal of the acid and dried to give practically pure product **3a**–**h** in 87–95% overall yields. Further purification was achieved by column chromatography (silica gel, 20% EtOAc-Hexane).

(*Z*)-3-(Phenylamino)-1-(pyridin-3-yl)prop-2-en-1-one, 3a: Light yellow solid. Yield 195 mg, 87%. m.p.130°C. IR: 3219 (NH), 1649 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.00 (d, 1H, *J* = 8 Hz, $H_{2'}$), 7.08–7.13 (m, 3H, ArH), 7.33–7.41 (m, 3H, $H_{5''}$, 2H-ArH), 7.57 (dd, 1H, *J* = 8 Hz, 12.8 Hz, $H_{1'}$), 8.22 (d, 1H, *J* = 7.6 Hz, $H_{6''}$), 8.71 (d, 1H, *J* = 6.0 Hz, $H_{4''}$), 9.14 (s, 1H, $H_{2''}$), 12.17 (d, 1H, *J* = 12.8 Hz, H_{3a}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 93.1, 116.6, 123.5, 124.2, 129.8, 134.4, 134.8, 139.8, 145.9, 148.7, 151.9, 188.7; ESI-MS: *m/z* 224 $[M]^+$.

(*Z*)-1-(Pyridin-3-yl)-3-(*p*-tolylamino)prop-2-en-1-one, 3b: Light yellow solid. Yield 219 mg, 92%. m.p.136-138°C. IR: 3219 (NH), 1662 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.34 (s, 3H, CH_3), 5.97 (d, 1H, *J* = 7.5 Hz, $H_{2'}$), 7.04 (d, 2H, *J* = 8.0 Hz, ArH), 7.17 (d, 2H, *J* = 8.0 Hz, ArH), 7.41 (dd, 1H, *J* = 5.0 Hz, 8.0 Hz, $H_{5''}$), 7.55 (dd, 1H, *J* = 7.5 Hz, 12.5 Hz, $H_{1'}$), 8.22 (d, 1H, $H_{6''}$, *J* = 8.0 Hz), 8.72 (d, 1H, $H_{4''}$, *J* = 4.5 Hz), 9.15 (s,1H, $H_{2''}$), 12.19 (d, 1H, H_{3a}, *J* = 12.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.80, 92.97, 116.67, 123.54, 130.35, 134.08, 134.59, 134.85, 137.43, 146.29, 148.75, 151.84, 188.38; ESI-MS: *m/z* 239 $[MH]^+$.

(*Z*)-3-((4-Methoxyphenyl)amino)-1-(pyridin-3-yl)prop-2-en-1-one, 3c: Yellow solid. Yield 241 mg, 95%. m.p.128-129°C. IR: 2833 (NH), 1644 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.80 (s, 3H, OCH_3), 5.95 (d, 1H, $H_{2'}$, *J* = 7.5 Hz), 6.90 (d, 2H, ArH, *J* = 9.0 Hz), 7.07 (d, 2H, ArH, *J* = 9.0 Hz), 7.38 (dd, 1H, $H_{5''}$, *J* = 5.0 Hz, 8.0 Hz), 7.48 (dd 1H, $H_{1'}$, *J* = 7.5 Hz, 12.5 Hz), 8.20 (d, 1H, $H_{6''}$, *J* = 8.0 Hz), 8.70

(d, 1H, $H_{4''}$, J = 5.0 Hz), 9.13 (s,1H, $H_{2''}$), 12.23 (d, 1H, H_{3a}, J = 12.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.58, 92.67, 115.07, 118.22, 123.44, 133.37, 134.54, 134.64, 146.76, 148.77, 151.85, 156.74, 188.25; ESI-MS: *m/z* 255 $[MH]^+$.

(*Z*)-3-((4-Chlorophenyl)amino)-1-(pyridin-3-yl)prop-2-en-1-one, 3d: Yellow solid. Yield 240 mg, 93%. m.p.160-162°C. IR: 3029 (NH), 1639 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.01 (d, 1H, $H_{2'}$, J = 7.5 Hz), 7.05 (d, 2H, ArH, J = 8.5 Hz), 7.32 (d, 2H, ArH, J = 8.5 Hz), 7.39 (dd, 1H, $H_{5''}$, J = 5.0 Hz, 8.0 Hz,), 7.49 (dd, 1H, $H_{1'}$, J = 7.5 Hz, 12.5 Hz), 8.20 (d, 1H, $H_{6''}$, J = 8.0 Hz), 8.71 (d, 1H, $H_{4''}$, J = 5.0 Hz), 9.13 (s,1H, $H_{2''}$), 12.15 (d, 1H, H_{3a}, J = 12.5 Hz, H_{3a}); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 93.91, 117.72, 123.52, 129.28, 129.87, 134.22, 134.76, 138.55, 145.49, 148.85, 152.19, 189.06; HR-MS (ESI): *m/z* Calcd for $C_{14}H_{11}ClN_2O$ $[MH]^+$ = 259.0633. Found = 259.0637.

(*Z*)-3-((4-Bromophenyl)amino)-1-(pyridin-3-yl)prop-2-en-1-one, 3e: Yellow solid. Yield 284 mg, 94%. m.p.169°C. IR: 3056 (NH), 1639 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.03 (d, 1H, $H_{2'}$, J = 8.0 Hz), 7.00 (d, 2H, J = 9.0 Hz, ArH), 7.40 (dd, 1H, $H_{1'}$, J = 8.0 Hz, 12.5 Hz), 7.47 (d, 2H, ArH, J = 9.0 Hz), 7.49–7.52 (m, 1H, $H_{5''}$), 8.20 (d, 1H, $H_{6''}$, J = 8.0 Hz), 8.72 (d, 1H, $H_{4''}$, J = 5.0 Hz), 9.14 (s,1H, $H_{2''}$), 12.14 (d, 1H, H_{3a}, J = 12.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 94.00, 116.73, 118.05, 123.52, 132.79, 134.19, 134.77, 139.03, 145.32, 148.86, 152.21, 189.10; ESI-MS: *m/z* 303 $[MH]^+$, 305 $[MH]^+$.

(*E*/*Z*)-3-((3-Hydroxyphenyl)amino)-1-(pyridin-3-yl)prop-2-en-1-one, 3f: Yellow solid. Yield 221 mg, 92%. m.p.208-210°C. IR: 3219 (NH), 3051 (OH), 1659 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.16 (d, 1H, $H_{2'}$, J = 7.5 Hz) and 6.39 (d, 1H, $H_{2'}$, J = 12.5 Hz), 6.47 (d, 1H, H_6, J = 8.5 Hz), 6.54–6.64 (m, 3H, 2H-H_2, 1H-OH) and 6.72 (s, 1H, OH), 6.78 (d, 1H, H_6, J = 8 Hz), 7.12–7.19 (m, 2H, H_5), 7.54 (dd, 2H, $H_{5''}$, J = 5 Hz, 8 Hz), 7.91 (dd 1H, $H_{1'}$, J = 7.5 Hz, 12.5 Hz) and 8. 12 (t, 1H, $H_{1'}$, 13.0 Hz), 8.20 (d, 1H, $H_{6''}$, J = 7.5 Hz) and 8.29 (d, 1H, $H_{6''}$, J = 8.0 Hz), 8.73 (d, 2H, $H_{4''}$, J = 5.0 Hz), 9.03 (d, 1H, H_4, J = 1.0 Hz, H_4) and 9.13 (d, 1H, H_4, J = 2.0 Hz), 9.63 (s, 1H, $H_{2''}$) and 9.73 (s, 1H, $H_{2''}$), 10.24 (d, 1H, H_{3a}, J = 13.0 Hz) and 12.03 (d, 1H, H_{3a}, J = 12.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 93.52 and 97.61, 103.25 and 103.87, 107.10 and 107.85, 110.69 and 111.63, 116.98, 124.22 and 124.25, 131.06, 134.21, 135.05, 135.12 and 135.27, 141.35 and 142.29, 145.59, 147.22, 148.84, 152.36 and 152.54, 157.61, 158.98 and 159.09, 186.51 and 188.18; ESI-MS: *m/z* 241 $[MH]^+$.

(*Z*)-3-(Benzylamino)-1-(pyridin-3-yl)prop-2-en-1-one, 3g: Yellow solid. Yield 226 mg, 95%, gum; IR: 3030 (NH), 1633 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.50 (d, 2H, CH_2, J = 6.0 Hz), 5.76 (d, 1H, $H_{2'}$, J = 7.5 Hz), 7.08 (dd, 1H, $H_{1'}$, J = 7.5 Hz, 13.0 Hz), 7.28 (m, 6H, 5-ArH, 1H-$H_{5''}$), 8.17 (d, 1H, $H_{6''}$, J = 7.5 Hz), 8.66 (d, 1H, $H_{4''}$, J = 4.5 Hz), 9.08 (s, 1H, $H_{2''}$), 10.67 (brs, 1H, H_{3a}); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.89, 90.72, 123.38, 127.31, 127.97, 128.95, 134.64, 134.83, 137.32, 148.64, 151.49, 154.81, 187.82; ESI-MS: *m/z* 239 $[MH]^+$.

(*Z*)-3-(Phenylethylamino)-1-(pyridin-3-yl)prop-2-en-1-one, 3h: Yellow solid. Yield 232 mg, 92%, gum; IR: 3028 (NH), 1632 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.92 (t, 2H, CH_2), 3.53-3.57 (m, 2H), 5.62 (d, 1H, $H_{2'}$, J = 7.0 Hz), 6.85 (dd, 1H, $H_{1'}$, J = 7.0 Hz, 12.5 Hz), 7.20-7.38 (m, 6H, 5-ArH, 1H-$H_{5''}$), 8.14–8.17 (m, 1H, $H_{6''}$), 8.66 (d, 1H, $H_{4''}$, J = 5.0 Hz), 9.06 (s, 1H, $H_{2''}$), 10.46 (brs, 1H, H_{3a}); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.71, 50. 99, 90.12, 123.42, 126.83, 128.77, 128.88, 134.75, 137.86, 148.48, 151.23, 154.95, 161.24, 187.43; ESI-MS: *m/z* 253 $[MH]^+$.

Synthesis of (3-((3s,5s,7s)-adamantan-1-yl)-1-aralkyl/aryl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)methanone, 5a–h

A mixture of 1-adamantanamine (1 mmol) and formaldehyde (2 mmol) in 1 mL of methanol was stirred at RT for 5–10 min. To this was added a solution of the enaminone **3** (1 mmol) in 4 mL of methanol and the resulting solution was refluxed for 4–8 h. On completion of the reaction (tlc), methanol was distilled off to give a gum which on trituration with hexane, gave a solid which was collected by filtration. The products thus obtained in 87–95% overall yields were practically pure. However, further purification was achieved by column chromatography (silica gel, 20% EtOAc-Hexane).

(3-((3s,5s,7s)-Adamantan-1-yl)-1-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)-methanone, 5a: White solid. Yield 387 mg, 97%. m.p.153–155°C; IR: 2914 (Adam), 2854 (Adam), 1578 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61–1.65 (m, 6H, Adam), 1.84 (s, 6H, Adam), 2.11 (s, 3H, Adam), 3.98 (s, 2H, CH_2-THP), 4.69 (s, 2H, CH_2-THP), 6.97–6.99 (m, 2H, ArH), 7.14 (s, 1H, CH-

THP), 7.34–7.42 (m, 4H, 3-ArH, $H_{5''}$), 7.88 (s, 1H, $H_{4''}$), 8.70-8.82 (m, 2H, $H_{2''}$, $H_{6''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.63, 36.49, 40.14, 41.17, 54.84, 62.45, 113.95, 118.63, 123.53, 124.54, 129.78, 135.70, 136.03, 143.68, 147.07, 148.94, 150.83, 190.17; MS (ESI): *m/z* = 400 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{26}H_{29}N_3O$ $[MH]^+$ = 400.2389. Found = 400.2389.

(3-((3s,5s,7s)-Adamantan-1-yl)-1-(p-tolyl)-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)-methanone, 5b: White solid. Yield 388 mg, 94%, mp.: 162–163°C; IR: 2902 (Adam), 2850 (Adam), 1571 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.57-1.67 (m, 6H, Adam), 1.83 (s, 6H, Adam), 2.10 (s, 3H, Adam), 2.30 (s, 3H, CH_3), 3.96 (s, 2H, CH_2-THP), 4.65 (s, 2H, CH_2-THP), 6.88 (d, 2H, ArH, *J* = 7.2 Hz), 7.12 (d, 2H, ArH, *J* = 7.2 Hz), 7.34–7.38 (m, 2H, CH-THP, $H_{5''}$), 7.86 (d, 1H, $H_{4''}$, *J* = 5.6 Hz), 8.65 (s, 1H, $H_{6''}$), 8.76 (s, 1H, $H_{2''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.82, 29.70, 36.55, 40.15, 41.18, 55.02, 62.64, 113.40, 118.90, 123.44, 130.34, 134.57, 135.71, 136.09, 141.44, 147.45, 149.07, 150.87, 189.97; MS (ESI): *m/z* = 414 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{27}H_{31}N_3O$ $[MH]^+$ = 414.2545. Found = 414.2544.

(3-((3s,5s,7s)-Adamantan-1-yl)-1-(4-methoxy phenyl)-1,2,3,4-tetrahydropyrimidin-5-yl)-(pyridin-3-yl)methanone, 5c: Pale yellow solid. Yield 373 mg, 87%. m.p.139–141°C; IR: 2899 (Adam), 2839 (Adam), 1557 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61–1.64 (m, 6H, Adam), 1.82 (s, 6H, Adam), 2.10 (s, 3H, Adam), 3.77 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2-THP), 4.62 (s, 2H, CH_2-THP), 6.86 (brs, 2H, ArH), 6.93 (brs, 2H, ArH), 7.32 (brs, 2H, CH-THP, $H_{5''}$), 7.85 (s, 1H, $H_{4''}$), 8.64 (s, 1H, $H_{6''}$), 8.75 (s, 1H, $H_{2''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.67, 36.54, 40.15, 41.05, 54.86, 55.59, 63.15, 112.92, 114.98, 120.89, 123.44, 135.77, 136.06, 137.39, 147.93, 149.00, 150.76, 157.08, 189.71; MS (ESI): *m/z* = 430 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{27}H_{31}N_3O_2$ $[MH]^+$ = 430.2494. Found = 430.2965.

(3-((3s,5s,7s)-Adamantan-1-yl)-1-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimi din-5-yl)(pyridin-3-yl)methanone, 5d: Pale yellow solid. Yield 411 mg, 95%. m.p.169–170°C; IR: 2912 (Adam), 2856 (Adam), 1577 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.57-1.68 (m, 6H, Adam), 1.82 (s, 6H, Adam), 2.11 (s, 3H, Adam), 3.96 (s, 2H, CH_2-THP), 4.66 (s, 2H, CH_2-THP), 6.91 (d, 2H, ArH, *J* = 7.2 Hz), 7.28–7.35 (m, 4H, 2-ArH, CH-THP, $H_{5''}$), 7.88 (d, 1H, $H_{4''}$, *J* = 7.2 Hz), 8.67 (s, 1H, $H_{6''}$), 8.77 (s, 1H, $H_{2''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.63, 36.49, 40.21, 41.15, 54.90, 62.51, 114.64, 119.68, 123.53, 129.77, 129.85, 135.39, 136.11, 142.26, 146.38, 149.01, 151.09, 190.31; MS (ESI): *m/z* = 434 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{26}H_{28}ClN_3O$ $[MH]^+$ = 434.1998. Found = 434.1996.

(3-((3s,5s,7s)-Adamantan-1-yl)-1-(4-bromophenyl) -1,2,3,4-tetrahydropyrimidin-5-yl)(pyri-din-3-yl)methanone, 5e: Pale yellow solid. Yield 453 mg, 95%. m.p.194°C; IR: 2914 (Adam), 2856 (Adam), 1588 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.57–1.67 (m, 6H, Adam), 1.82 (s, 6H, Adam), 2.11 (s, 3H, Adam), 3.96 (s, 2H, CH_2-THP), 4.65 (s, 2H, CH_2-THP), 6.85 (d, 2H, ArH, J = 7.6 Hz), 7.35–7.44 (m, 4H, 2-ArH, CH-THP, $H_{5''}$), 7.88 (d, 1H, $H_{4''}$, *J* = 7.6 Hz), 8.67 (s, 1H, $H_{4''}$), 8.77 (s, 1H, $H_{2''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.60, 36.45, 40.17, 41.14, 54.91, 62.37, 114.72, 117.26, 119.93, 123.47, 132.74, 135.32, 136.04, 142.68, 146.14, 149.01, 151.10, 190.29; MS (ESI): *m/z* = 478 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{26}H_{28}BrN_3O$ $[MH]^+$ = 478.1494, 480.1473. Found = 478.1493, 480.1480.

(3-((3s,5s,7s)-Adamantan-1-yl)-1-(3-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)methanone, 5f: Yellow solid. Yield 390 mg, 94%. m.p.168–169°C; IR: 2908 (Adam), 2847 (Adam), 1566 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.60–1.64 (m, 6H, Adam), 1.82 (s, 6H, Adam), 2.10 (s, 3H, Adam), 3.93 (s, 2H, CH_2-THP), 4.64 (s, 2H, CH_2-THP), 6.45–6.62 (m, 4H, 3-ArH, OH), 7.10–7.12 (m, 1H, ArH), 7.32–7.40 (m, 2H, CH-THP, $H_{5''}$), 7.90 (d, 1H, $H_{4''}$, *J* = 6.8 Hz), 8.61 (s, 1H, $H_{6''}$), 8.72 (s, 1H, $H_{2''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.70, 36.54, 40.08, 41.19, 55.03, 62.56, 106.48, 109.93, 112.45, 113.37, 123.96, 130.67, 135.88, 136.81, 144.83, 147.94, 148.52, 150.34, 158.55, 189.90; MS (ESI): *m/z* = 416 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{26}H_{29}N_3O_2$ $[MH]^+$ = 416.2338. Found = 416.2337.

(3-((3s,5s,7s)-Adamantan-1-yl)-1-benzyl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)methanone, 5g: Pale yellow solid. Yield 380 mg, 92%. m.p.124–125°C; IR: 2900 (Adam), 2852 (Adam), 1563 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.55–1.65 (m, 6H, Adam), 1.77 (s, 6H, Adam), 2.07 (s, 3H, Adam), 3.83 (s, 2H, CH_2-THP), 4.05 (s, 2H, CH_2), 4.36 (s, 2H, CH_2-THP), 7.14–7.25 (m, 3H, ArH), 7.31–7.38 (m, 4H, CH-THP, $H_{5''}$, 2-

ArH), 7.82 (d, 1H, $H_{4''}$, J = 6 Hz,), 8.63 (d, 1H, $H_{6''}$, *J* = 3.2 Hz), 8.70 (s, 1H, $H_{2''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.64, 36.56, 39.51, 40.64, 54.67, 58.28, 61.17, 109.84, 123.43, 127.67, 128.34, 129.07, 135.48, 136.04, 136.13, 148.87, 150.45, 151.63, 188.70; MS (ESI): *m/z* = 414 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{27}H_{31}N_3O$ $[MH]^+$ = 414.2545. Found = 414.2545.

(3-((3s,5s,7s)-Adamantan-1-yl)-1-phenethyl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)methanone, 5h: Pale yellow solid. Yield 389 mg, 91%. m.p.167–168°C; IR: 2903 (Adam), 2848 (Adam), 1572 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61-1.70 (m, 6H, Adam), 1.84 (s, 6H, Adam), 2.13 (s, 3H, Adam), 2.84 (s, 2H, CH_2), 3.46 (s, 2H, CH_2), 3.76 (s, 2H, CH_2-THP), 4.10 (s, 2H, CH_2-THP), 6.71 (s, 1H, ArH), 7.14–7.15 (m, 2H, CH-THP, ArH), 7.28–7.31 (m, 4H, 3-ArH, $H_{5''}$), 7.52 (d, 1H, $H_{4''}$, *J* = 6.8 Hz), 8.47 (s, 1H, $H_{6''}$), 8.60 (s, 1H, $H_{2''}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.58, 35.45, 36.58, 39.51, 40.44, 54.34, 56.32, 61.56, 108.76, 123.08, 126.92, 128.80, 128.84, 135.76, 136.04, 137.72, 148.71, 150.09, 151.51, 188.36; MS (ESI): *m/z* = 428 $[MH]^+$; HR-MS (ESI): *m/z* Calcd for $C_{28}H_{33}N_3O$ $[MH]^+$ = 428.2702. Found = 428.2701.

Biological Activity

Anti-inflammatory assay

Griess reagent system was procured from Promega (USA), Wright stain, anhydrous potassium dihydrogen phosphate, potassium chloride, disodium hydrogen phosphate, sodium-EDTA and dimethyl sulfoxide (DMSO) were purchased from (Hi-MEDIA). Methanol was purchased from Merck and Fruend's Complete Adjuvant (FCA) from Genei.

Anti-inflammatory activity of the test compounds was analysed by measuring paw diameter, NO assay in blood and in paw exudates and by performing a differential WBC count in FCA induced paw edema mice and treating them with the test compounds.

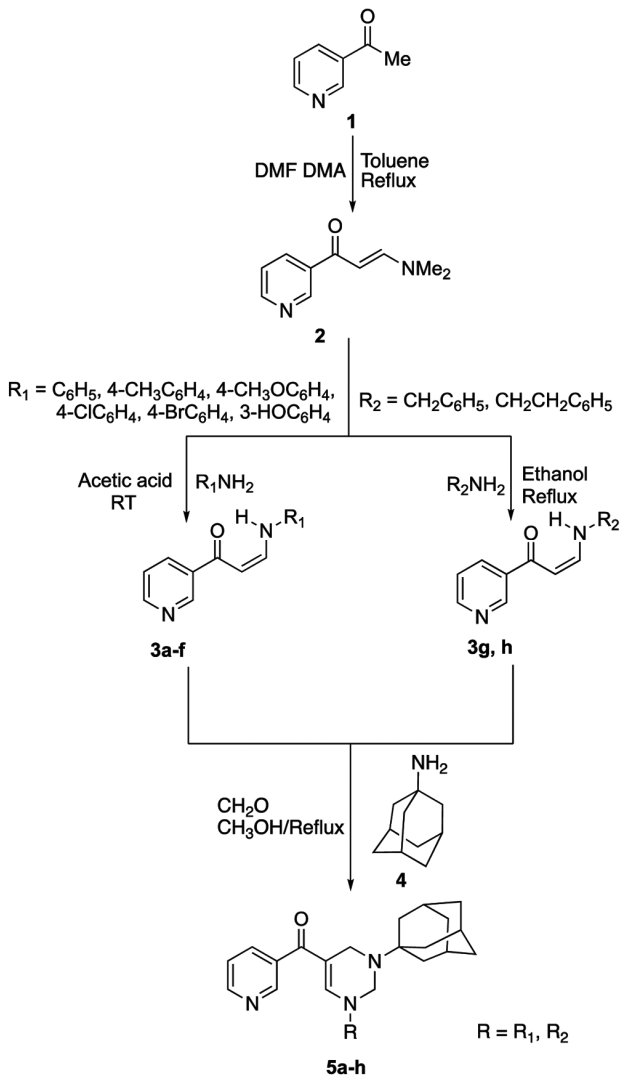
Initiation of paw edema: Lai *et al.*[14] method with slight modification has been incorporated to determine the anti-inflammatory activity of all the synthesized compounds. Swiss Albino mice were used in all the experiments. The mice aged between 8 and 10 weeks of either sex (3 per group) were fed with standard mice feed and common tap drinking water and was maintained at a controlled temperature in 12 h light/12 h dark conditions. About 50 µL of the Fruend's complete adjuvant (FCA) was injected into the plantar side of left hind paws of the mice[15]. Paw diameter of the FCA-induced edema of mice was measured at 0, 1, 3, and 24 h after the administration of the FCA by using a calliper. Test compound (dissolved in 10% DMSO) was administered 1 h after FCA injection. The percentage increase/decrease of the paw edema is calculated by the formula $\frac{b-a}{a}\times 100$, where 'a' is the paw diameter at 0 h and 'b' is the paw diameter at different time interval. The mice were sacrificed by cervical dislocation after 24 h and blood was collected by retro-orbital bleeding, used for determining the NO level. Ice-cold normal saline was used to rinse the left hind paw tissue which was then immediately placed in 1 mL of cold normal saline and homogenized. The homogenate was then centrifuged at 12,000 rpm for 5 min and the supernatant was collected for NO assay.

NO assay NO^{2-}

Greiss reaction was used to measure NO^{2-}. The assay of NO^{2-} was performed according to the manufacturer's instruction. In short, 1 mL of 100 µM nitrite solution was prepared by diluting the 0.1 M nitrite standard (1:1000) in distilled water. A nitrite standard reference curve was established using three chosen columns of the 96-wells plate. To generate the standard curve, dilution of 100 μM nitrite solution (50 μL/well) in six-serial twofold in triplicate was executed. Experimental sample (50 μL) was taken in triplicate in test wells. Sulphanilamide solution 50 μL was added to all the wells and incubated for 5–10 min at RT protected from light. This was followed by the dispensation of 50 μ of the *N*-1 naphthyl ethylenediamine dihydrochloride (NED) to all the wells. The plate was incubated at RT for 5–10 min in the dark. A purple/magenta colour begins to form immediately. The absorbance was measured within 30 min in a plate reader with a filter between 520 and 550 nm. The NO concentration was calculated from the standard curve obtained for all the experimental samples.

Differential WBC count

The differential WBC count was performed according to the method described by Houwen[16]. Blood film was prepared on glass slides by wedge method and air dried. This was then fixed for 30 s in absolute methanol. The slides were stained with



Scheme 1 — Synthesis of 3-adamantyl-5-nicotinoyl-1,2,3,4-tetrahydropyrimidine hybrids

Wright's stain for 2 min and an aliquot of Sorensen's buffer was added, mixed and allowed to stand for 3 min. The slides were rinsed with distilled water and air dried. The prepared slides were observed under microscope and WBCs were counted.

Results and Discussion

Chemistry

The enaminones required for the synthesis of target adamantane-tetrahydropyrimidine hybrids were achieved by first reacting 3-acetylpyridine with DMF-DMA[17] to obtain the formylated product **2** which then was converted to **3** by a procedure[6] developed in our laboratory (Scheme 1). Thus, when compound **2** was stirred with an equimolar amount of aniline in acetic acid at RT, work up of the resulting reaction mixture afforded a yellow solid in 87% yield, which was characterized as 3-anilino-1-(pyridin-3-yl)prop-2-en-1-one **3a** with the help of physical and spectral data. The reaction proved to be general between **2** and various primary aromatic amines affording the corresponding enaminones **3b–f** in overall yields of 92–95%. However, the reaction of compound **2** with aralkyl amines failed to give 3-aralkylamino-enaminones **3g**, **3h** under similar reaction conditions. Remarkably, the reaction of compound **2** with aralkyl amines in refluxing ethanol took place smoothly forming the desired enaminones **3g**, **3h** in 92–95% overall yields. It is noteworthy that reaction of **2** with primary aromatic amines failed in refluxing ethanol. The enaminones **3b**–**h** were further taken forward for the synthetic construction of the proposed molecular hybrids.

The structure elucidation of **3a** was done with the help of IR, NMR and MS data. IR spectrum of the compound showed peaks at 3219, 1649 cm^{-1} attributed to the NH and CO stretching respectively. The ^{1}H NMR spectrum revealed a doublet and a double-doublet signals at 6.00 ppm (J = 8 Hz) and 7.57 ppm (J = 8, 12.8 Hz) for the α-vinylic proton $H_{2'}$ and β-vinylic proton $H_{1'}$ respectively. The coupling constant of α, β-vinylic proton ($H_{2'}$ and $H_{1'}$) at 8 Hz supports the existence of the compound as *Z*-isomer. In the ^{1}H NMR spectrum a multiplet in the range 7.33–7.41 ppm was observed due to $H_{5''}$ proton of pyridine and two protons of phenyl group. Also, two doublets for $H_{4''}$ and $H_{6''}$ protons were found resonating at δ 8.22 and 8.71 ppm with a coupling constant of 7.6 and 6.0 Hz respectively and a singlet due to $H_{2''}$ proton was observed at δ 9.14 ppm. The NH (H_{3a}) proton showed a singlet at 12.17 ppm indicating hydrogen bonded state with the adjacent carbonyl oxygen. In the ^{13}C NMR spectrum, the expected signals were observed with the most de-shielded carbonyl carbon found at 188.7 ppm. Additionally, the MS of compound **3a** with the molecular ion peak at 224 was in support of the assigned structure.

Likewise, the structures of enaminones **3b**–**h** were well established without ambiguity giving exclusively the *Z*-form except in compound **3f**. The ^{1}H and ^{13}C NMR of compound **3f** showed the existence of the compound in *Z*- and *E*-isomer, based on the analysis of their coupling patterns. In the spectra of **3f** in DMSO–d_6, the doublet due to N–H resonated at 12.03 ppm for *Z*-isomer and at 10.24 ppm for E isomer. A well-defined double-doublet for β-vinylic proton $H_{1'}$

Table 1 — Synthesis of (3-((3s,5s,7s)-adamantan-1-yl)-1-aralkyl/aryl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)methanone **5a–h**

Entry	Compd	R	Reaction Time (h)	Yield (%)	m.p. (°C)
1	**5a**	C_6H_5	4	87	153–155
2	**5b**	4-$CH_3C_6H_4$	6	94	162–163
3	**5c**	4-$CH_3OC_6H_4$	7.5	94	139–141
4	**5d**	4-ClC_6H_4	5	95	169–170
5	**5e**	4-BrC_6H_4	4	95	194
6	**5f**	3-HOC_6H_4	8	94	168–169
7	**5g**	$C_6H_5CH_2$	6.5	92	124–125
8	**5h**	$C_6H_5CH_2CH_2$	4	91	167–168

resonated at 7.91 ppm with the coupling constants 7.5 and 12.5 Hz for the *Z*-isomer and at 8.12 ppm with coupling constants 13.0 and 12.5 Hz for the *E*-isomer. The proportion of the two isomers (*Z/E*) was calculated by their ratio of integrations of $H_{2'}$ signals which are well differentiated and were found to be about 55%/45%.

The desired adamantane-tetrahydropyrimidine hybrids (**5a**–**h**) synthesis was undertaken by employing the enaminone **3** (Scheme 1). Thus, when enaminone **3a**, 1-adamantanamine **4** and formaldehyde in methanol was heated at reflux for 4 h, the resulting mixture gave **5a** in 87% yield, which was proposed to be (3-((3s,5s,7s)-adamantan-1-yl)-1-(4-phenyl)-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridin-3-yl)methanone through spectral and analytical data. The reaction conditions was effectively employed for the synthesis of **5b**–**h** in 4–8 h with an overall yields of 87–95% (Table 1).

The structures of the products were clearly affirmed with the help of spectral and analytical data. Thus, the IR spectrum of **5a** showed bands at 1578 cm^{-1} owing to the carbonyl group. The characteristic bands at 2914 and 2854 cm^{-1} due to C–H stretching of adamantane was noticed. In the ^1H NMR spectrum, a singlet due to the C_6–H proton resonated at 7.14 ppm. The CH_2 protons at C–2 and C–4 of the tetrahydropyrimidine ring appeared as a singlet at 4.69 ppm and 3.98 ppm respectively. The adamantyl group presence is confirmed by the presence of the three distinct signals at 1.61–1.65, 1.84 and 2.11 ppm for six, six and three protons respectively. In the ^{13}C NMR spectrum of **5a**, the most noticeable signal was due to the CO carbon at 190.17 ppm and those due to adamantyl group carbons appeared at 29.63, 36.49, 40.14 and 41.17 ppm. The absence of NH signal and the vinylic C–H signal at about 12.00 ppm and 6.00 ppm respectively further supports the proposed cyclic

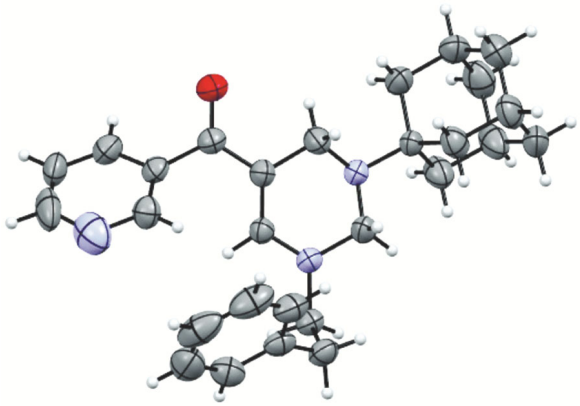


Fig. 2 — Crystal structure of compound **5h**

structure for **5a** due their involvement in cyclisation. The peak at 400.2389 in the HR-MS of **5a** for $[MH]^+$ (calculated value 400.2389) further supported the proposed structure.

Additionally, the final confirmation of the structure was done with the help of X–ray crystallography of a representative candidate **5h**. The proposed structure of (3-((3s,5s,7s)-adamantan-1-yl)-1-phenethyl-1,2,3,4-tetrahydropyrimidin-5-yl)(pyridine-3-yl)methanone (**5h**) was substantiated by single X-ray crystallography (Fig. 2) with CCDC no. 996553. The crystals required for the X-ray analysis were acquired by the slow crystallisation of compound **5h** in ethyl acetate. The crystal belongs to triclinic, space group P1 with a = 9.4324 (3) Å, b = 9.8497 (4) Å, c = 14.6954 (4) Å, β = 76.025 (1)°, V = 1174.06 (7) $Å^3$ and Z = 2.

Biological Studies

Anti-inflammatory test of the synthesized molecular hybrids **5a–h** was assessed. In our earlier investigations, we have discussed the parameters that we took for evaluating the anti-inflammatory effects of the synthesized compounds[18]. Paw thickness, NO level in paw exudates and whole blood were taken as the physical parameters for anti-inflammatory investigation. The NO level is used to determine the inflammation in many tissues of mammals. Elevated levels of NO indicate inflammatory reaction and thus test compounds that can bring about the reduction of NO levels are regarded as potential anti-inflammatory agents. To determine any alteration in the number of different leukocytes to the test compounds and Ibuprofen in mice bearing paw-edema, a differential leucocyte count in peripheral blood was performed. Leukocytes such as basophils and eosinophils are indicative of inflammation and hence a decrease in their counts in blood suggests a reduction in inflammation.

Table 2 — Paw thickness measured at different time intervals in FCA-induced mice of the test compounds **5a–h** (50 mg/kg), Ibuprofen (30 mg/kg) and an untreated control

Treatment groups	Time (h)	Paw edema	Increase in paw thickness from 0 (h)	Percentage increase/decrease in paw thickness (%)
Control	0	3.08 ±0.07	0	0.00
	1	3.27 ±0.28	0.19	6.17
	3	3.42 ±0.29	0.35	11.04
	24	3.69 ±0.27	0.62	19.81
Ibuprofen	0	3.83 ±0.06	0.00	0.00
	1	3.53 ±0.06	0.00	0.00
	3	3.60 ±0.12	–0.84	–21.16
	24	3.97 ±0.17	–0.17	–4.28
5a	0	4.00 ±0.00	0	0.00
	1	4.00 ±0.00	0	0.00
	3	3.83 ±0.06	–0.17	–4.25
	24	3.97 ±0.06	–0.03	–0.75
5b	0	3.97 ±0.06	0	0.00
	1	4.00 ±0.00	0.03	0.76
	3	3.97 ±0.06	0	0.00
	24	4.03 ±0.06	0.03	1.51
5c	0	3.50 ±0.00	0	0.00
	1	3.80 ±0.00	0.3	8.57
	3	3.50 ±0.00	0	0.00
	24	3.60 ±0.17	0.10	2.86
5d	0	3.90 ±0.10	0	0.00
	1	3.83 ±0.29	–0.07	–1.79
	3	3.77 ±0.25	–0.13	–3.33
	24	4.00 ±0.10	0.10	2.56
5e	0	3.60 ±0.17	0	00
	1	3.73 ±0.21	0.13	3.61
	3	3.80 ±0.00	0.2	5.56
	24	3.83 ±0.06	0.23	6.39
5f	0	3.83 ±0.06	0	0.00
	1	3.83 ±0.06	0	0.00
	3	3.27 ±0.21	–0.57	–14.62
	24	3.80 ±0.26	–0.03	–0.78
5g	0	3.73 ±0.21	0	0.00
	1	3.87 ±0.06	0.14	3.75
	3	3.50 ±0.00	–0.23	–6.17
	24	3.63 ±0.55	–0.10	–2.68
5h	0	3.83 ±0.06	0	0.00
	1	3.70 ±0.17	–0.13	–3.39
	3	3.70 ±0.17	–0.13	–3.39
	24	3.67 ±0.42	–0.16	–4.18

For our study, FCA-induced paw edema mice were treated with an intra-peritoneal injection of the test compounds at a dose of 50 mg/kg of the body weight, used as test subjects after 1 h. Mice bearing paw edema without subsequent treatment with the compounds and mice treated with Ibuprofen (a NSAID) served as controls and positive controls respectively.

Inhibition of FCA-induced paw edema

On measuring the paw diameter at different intervals of 0, 1, 3 and 24 h, it was found that some of the test compounds indicated a decrease in the paw diameter. The investigation of the molecular hybrids **5a**–**h** for their ability to decrease FCA-induced paw edema is shown in Table 2, where all the compounds demonstrated potential to reduce paw thickness. Compounds **5h** and **5g** exhibited the highest reduction after 24 h accompanied by compounds **5f** and **5a**.

NO level in paw exudates

When the sored mice were subjected to treatment with synthesized molecular hybrids **5a**–**h**, NO measurements in paw exudates displayed highest reduction with compound **5e** followed by compounds **5d**, **5h**, **5a**, **5g** and **5f** (Fig. 3), while compounds **5b** and **5c** showed no reduction in NO level.

NO concentration in whole blood

NO concentration in blood against the test compounds and Ibuprofen is given in Fig. 4. The molecular hybrids **5f**, **5g** and **5h** demonstrated the highest NO level reduction in blood, while **5d** showed equal potential as that of Ibuprofen.

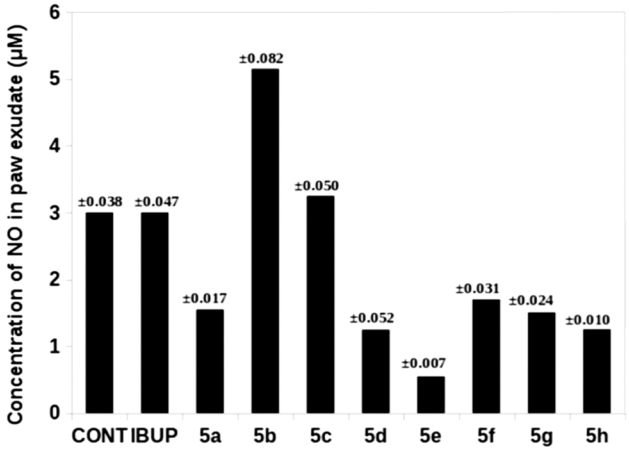


Fig. 3 — NO concentration (µM) in paw exudates of different treatment groups. Mice from each group (3 mice each) were sacrificed (after 24 h) from FCA injection, and the hind paw was excised and homogenised in 1 mL normal saline. Griess reaction with standard nitrite reference curve used for NO level measurement. Each group represents the mean ± S.E.M (n=3). *P < 0.05 statistical significance compared to control (unpaired Student's t-test)

Differential leucocyte counts in blood

The results of the total leucocytes count in percentage are depicted in Fig. 5. The test compounds resulted in the reduction of basophil percentages. It was observed that the basophils counts were lower in mice treated with hybrids **5e** and **5h**.

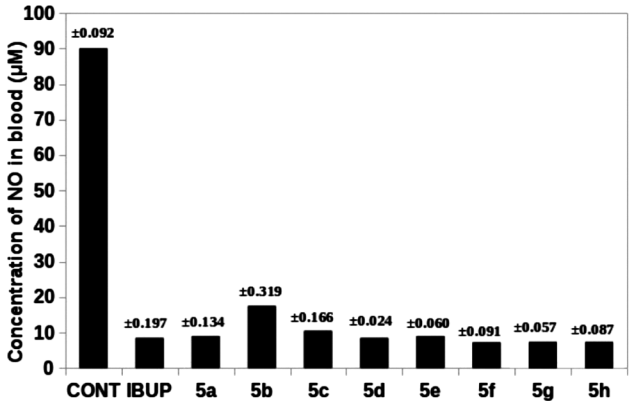


Fig. 4 — NO concentration (µM) in whole blood of different treatment groups. Paw edema induced by injecting FCA and intra-peritoneal injections of test compounds (50 mg/kg bw) and Ibuprofen (30 mg/kg bw) injected 1 h later. Blood was collected by retro-orbital bleeding from mice of different group (3 mice each) and used for the measurement of NO level. Each group represents the mean ± S.E.M (n=3). *P < 0.05 statistical significance compared to control (unpaired Student's t-test)

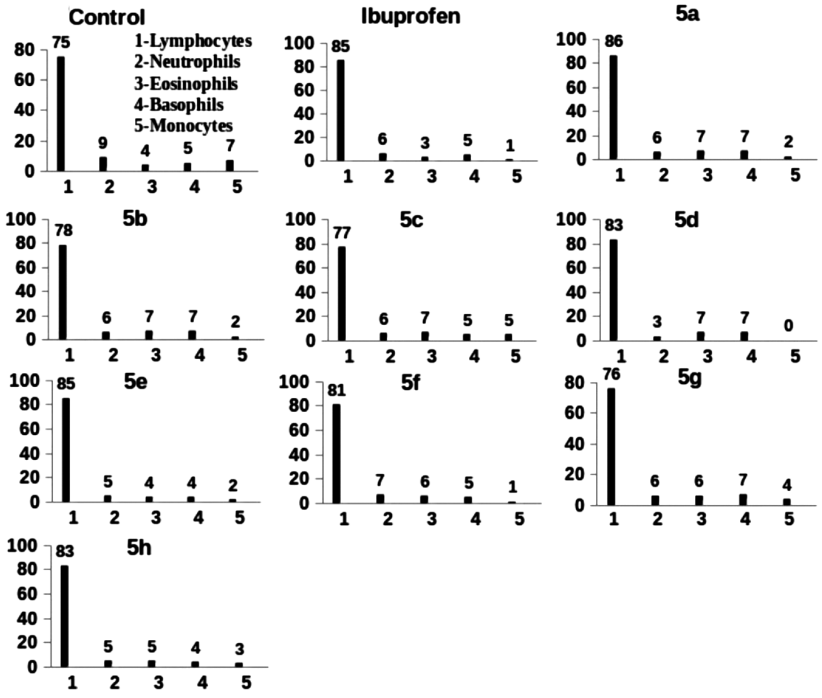


Fig. 5 — Percentage of different types of leucocytes for different treatment groups and untreated control carrying inflammation only. After 24 h from FCA injection blood was collected by retro-orbital bleeding and blood smear prepared and the slides stained with Wright stain and cells were counted under a microscope

Conclusion

Novel 3-aralkyl/arylamino-1-pyridin-3-ylpro-penones and 3-adamantyl-5-nicotinoyl-1,2,3,4-tetrahydropyrimidine hybrids were successfully synthesised in good to excellent yields. Anti-inflammatory study of the hybrids **5a–h** revealed that compound **5h** possess excellent anti-inflammatory activities as revealed across all tested parameters while compounds **5a**, **5d**, **5e**, **5f** and **5g** displayed varying levels of activity across the different parameters. Further investigation of tetrahydropyrimidine derivatives amalgamated with different biologically active heterocyclic cores are in progress.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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