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Original Article

Synthesis of 4*H*-pyrido [1,2-*a*]pyrimidin-4-one derivatives as Anti-inflammatory agents

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ABSTRACT

We have developed 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives appended to various nitrogen containing heterocycles (**3a-f**). The structures of newly synthesized compounds were confirmed by spectral as well as analytical techniques and single crystal X-ray analysis of compound **4b** is carried out. Further, the results of Osiris property explorer analysis and *in vitro* testing for the anti-inflammatory activity against hyaluronidase enzyme of these compounds are presented. Compounds **4e** and **5f** possessing *N*-methylpiperazine and piperazine ethoxy ethanol ring respectively have shown more growth inhibition than the standard drug Indomethacin at 10 µg concentration.

Key Words: Hyaluronidase, Pyrido[1,2-*a*]pyrimidin-4-one, OSIRIS property explorer, Anti-inflammatory activity

INTRODUCTION

Hybridization is concept in the development of new API (active pharmaceutical ingredients) based pharmacophoric moieties of different bioactive substances to produce new scaffold with improved affinity and efficacy when compared to the parent drugs. Hyaluronidases are the family of enzymes that destroy the hyaluronic acid (HA) backbone of cartilage matrix. HA, also known as hyluronan (or hyaluronate) is a glycosaminoglycan multifunctional protein that is involved in water and protein homeostasis of extracellular matrix, migration and cell proliferation.[1] It was reported that during chronic inflammatory condition the activity of hyaluronidase will be increased and hence the HA level in the body will be increased causing inflammatory joint diseases.[2] Therefore, efforts are to be made to develop new class of non-steroidal anti-inflammatory drugs (NSAIDS) that inhibit hyaluronidase. So far Indomethacin (Indocin) and anti-allergic agents such as sodium cromoglicate and natural product sorghum bran have been reported as inhibitors of hyaluronidase[3] and also some of the tetrahydropyrimidine derivatives have been found to show anti-inflammatory properties.[4] Pyrido[1,2-*a*]pyrimidin-4-one is a well known class of aza-bridghead fused heterocyclic compound which has miscellaneous pharmaceutical applications.[5-8] 2-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives have inhibited the carrageenan induced edema in the rats thus showing the marked anti-inflammatory property.[9] Also, pyrido[1,2-*a*]pyrimidin-4-one is a structural pattern present in well known drugs *viz.*, risperidone and paliperidone (antipsychotic agents)[10] ramastine (anti-allergic agent) and pirenperone (tranquilizer)[11-12]. Various derivatives of imidazole,[13] triazole,[14] 1,3-thiazolidine-2,4-dione,[15] piperazine, morpholine,[16] *N*-methylpiperazine[17] have exhibited potent anti-inflammatory activity. All these facts motivated us to synthesize the molecules *viz.*, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives **4-5** (**a-f**) and **8-9** (**a-f**) appended with various nitrogen containing heterocycles **3** (**a-f**) to study their anti-inflammatory activities.

MATERIALS AND METHODS

The condensation of 3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**) and 3-(2-chloroethyl)-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**) with various secondary amines **3a-f** in presence of *N*,*N*-diisopropylethylamine / an. K_2CO_3 afforded **4a-f**

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and **5a-f** respectively. Similarly, the condensation of 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6**) and 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**7**) with nitrogen containing heterocycles **3a-f** in presence of triethylamine / an.K_2CO_3 in acetonitrile afforded **8a-f** and **9a-f**. The structures of all the compounds were confirmed by IR, ^{1}H NMR, Mass spectral and CHN analyses. All the compounds have shown a sharp intense band around 1663-1688 cm^{-1} due to carbonyl functional group. The compounds **5a-f** and **9a-f** have shown a broad band around 3400-3450 cm^{-1} for OH stretching frequency. In case of ^{1}H NMR analyses, all the title compounds have shown a singlet for methyl protons at δ 1.80-2.10 ppm and two triplets at δ 2.80-4.20 ppm corresponding to the ethylene side chain. The hydroxyl proton in the compounds **5a-f** and **9a-f** resonated at δ 4.90-5.25 ppm. The aromatic protons appeared around δ 7.00-8.96 ppm. All other rings attached to the core pyrido[1,2-*a*] pyrimidine moiety have shown signals at their respective positions. Further, all the title compounds have been confirmed by their respective molecular ion peaks and possible fragmentations.

The molecular structure of 2-methyl-3-[2-(4*H*-1,2,4-triazol-4-yl)ethyl]-4*H*-pyrido[1,2-*a*] pyrimidin-4-one (**4b**) was analyzed by X-ray diffraction (XRD) studies. The asymmetric unit of the molecule is shown in **Fig. 1**. The unit cell of compound **4b** contains eight molecules. Packing of the molecule shows stacking when viewed along *c*-axis. The 4*H*-pyrido[1,2-*a*]pyrimidin-4-one ring (N5-N6-C11-C12-C13-C14-C15-C16-C17-C18) system is planar, with a maximum deviation of 0.0243(3)Å for atom C15. The dihedral angle between 4*H*-pyrido[1,2-*a*]pyrimidin-4-one ring (N5-N6-C11- C12-C13-C14–C15-C16-C17-C18) and 1,2,4-triazol ring (N2–N3-N4-C7-C8) is 47.88(16)º. The crystal structure is characterized by intermolecular C8H---N5 hydrogen bonding (**Table 1**) and π-π interactions. Also the packing of the molecules more stabilized by C10---H10B…π (N2-N3-N4-C7-C8) interactions (**Fig. 2**).

X-ray crystal structure analysis: Table 1 presents crystallographic data and X-ray structure parameters. Measurements were made using Bruker SMART CCD area-detector diffractometer with monochromatic Mo K_α radiation at room temperature. The crystalline state of crystal is characterized by a long range, well defined three dimensional orders.

Data collection, reduction and refinement: SMART; cell refinement: SAINT;[18] data reduction: SAINT; program(s) used to solve structure: SHELXS 97; program(s) used to refine structure: SHELXL97;[19] molecular graphics: ORTEP-3;[20] software used to prepare material for publication: SHELXL97. Coordinates were deposited in the Cambridge Crystallographic Data Centre vide no. CCDC-920447.

Experimental studies: Melting points were determined in open capillaries. FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer Paragon 1000 PC spectrometer. The ^{1}H and ^{13}C NMR spectral analyses were carried out in Bruker spectrometer (300 MHz) in $CDCl_3$ using TMS as internal standard and mass spectra on Shimadzu Japan QP2010 S model spectrometer. The elemental analyses data were obtained from Heraus CHN rapid analyzer. Chemicals were purchased from Aldrich and used without further purification. The calculations of c log P values of compounds were done at self consistent field theory level using PM3 (Hamiltonian Inc.) in MOPAC 6.0 PACKAGE.[21, 22]

General procedure for the preparation of pyrido[1,2-*a*]pyrimidin-4-ones appended with cyclic amines (4a-f, **5a-f**, **8a-f**, **9a-f):** A mixture of 3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**, 0.009 mole) and cyclic secondary amines (**3a-f**, 0.0108 mole) in presence of *N*,*N*-diisopropylethyamine (0.015 mol) was taken in acetonitrile (25 ml) and refluxed for about 10-12 h. The reaction was monitored by TLC. After completion, the reaction mixture was filtered and washed with acetonitrile. Acetonitrile was evaporated to get pure residue of desired compound (**5a-f**, Yield 55-70%). Similarly, hydroxy substituted pyrido[1,2-*a*]pyrimidin-4-one **5a-f** and **9a-f** derivatives were prepared. However, the derivative **8a-f** was prepared according to the above procedure using an. K_2CO_3 as base.

Spectral Characterization of the synthesized compounds:

3-[2-(1*H*-Imidazol-1-yl)ethyl]-2-methyl-4*H*-pyrido [1,2-*a*] pyrimidin-4-one (4a): Pale yellow solid; melting point 122-124˚C; IR (KBr, cm^{-1}): 1667 (C=O), 1631 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): *δ* (ppm) 8.96-8.94 (*d*, 1H, *J* = 6.50 Hz, C_6-H), 7.68-7.63 (*t*, 1H, *J* = 6.20 Hz, C_8-H), 7.55 (*s*, 1H, imidazole C_2-H), 7.55-7.52 (*d*, 1H, *J* = 8.88 Hz, C_9-H), 7.16-7.10 (*t*, 1H, C_7-H), 6.87 (*d*, 2H, imidazole C_4-H), 6.45 (*d*, 2H, imidazole C_5-H), 3.95-3.92 (*t*, 2H, *J* = 6.60 Hz, N-CH_2), 3.03-3.01 (*t*, 2H, *J* = 6.3 Hz, CH_2), 2.53 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 254 (M^+), 186, 173, 158, 119, 78, 55; analysis calculated for $C_{14}H_{14}N_4O$: C, 66.49%; H,

5.69%; N, 22.24%. Found: C, 66.12%; H, 5.54%; N, 22.05%.

2-Methyl-3-[2-(4*H*-1,2,4-triazol-4-yl)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (4b): White solid; melting point 138-140˚C; IR (KBr, cm^{-1}): 1667 (C=O), 1631 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.97-8.95 (*d*, 1H, *J* = 7.08 Hz, C_6-H), 8.82 (*s*, 1H, triazole C_3-H), 7.91 (*s*, 1H, triazole C_5-H), 7.70-7.65 (*t*, 1H, *J* = 7.44 Hz, C_8-H), 7.54-7.51 (*d*, 1H, *J* = 8.91 Hz, C_9-H), 7.13-7.08 (*t*, 1H, *J* = 6.72 Hz, C_7-H), 4.53-4.49 (*t*, 2H, *J* = 6.60 Hz, N-CH_2), 3.26-3.21(*t*, 2H, *J* = 6.60 Hz, CH_2), 2.21 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 162.62, 160.02, 155.01, 150.03, 144.02, 133.62, 133.20, 120.09, 119.65, 116.07, 50.06, 30.03, 16.54; MS (*m/z*, 70 eV): 255 (M^+), 173, 186, 158, 119, 78, 55; analysis calculated for $C_{13}H_{13}N_5O$: C, 61.51%; H, 5.25%; N, 27.68%. Found: C, 61.12%; H, 5.12%; N, 27.43%.

3-[2-(2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,3-thiazolidine-2,4-dione (4c): White solid; melting point 175-177˚C; IR (KBr, cm^{-1}): 1742 (S-C=O), 1688 (C=O), 1633 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.96-8.94 (*d*, 1H, *J* = 6.75 Hz, C_6-H), 7.68-7.63 (*t*, 1H, *J* = 7.62 Hz, C_8-H), 7.55-7.52 (*d*, 1H, *J* = 8.88 Hz, C_9-H), 7.10-7.05 (*t*, 1H, *J* = 6.42 Hz, C_7-H), 3.95 (*s*, 2H, thiazolidine CH_2), 3.95-3.92 (*t*, 2H, *J* = 6.57 Hz, N-CH_2), 3.05-3.01 (*t*, 2H, *J* = 6.57 Hz, CH_2), 1.93 (*s*, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 177.97, 177.68, 162.60, 160.00, 150.23, 133.67, 133.26, 120.00, 119.60, 116.97,46.99, 30.43, 30.03, 16.97; MS (*m/z*, 70 eV): 303 (M^+), 173, 186, 158, 119, 78, 55; analysis calculated for $C_{14}H_{13}N_3O_3S$: C, 55.67%; H, 4.32%; N, 13.92%. Found: C, 55.42%; H, 4.52%; N, 13.85%.

2-Methyl-3-[2-(morpholin-4-yl)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (4d): Semi solid; melting point 38-40˚C; IR (KBr, cm^{-1}): 1673 (C=O), 1630 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.90-8.88 (*d*, 1H, *J* = 7.11 Hz, C_6-H), 7.61-7.56 (*t*, 1H, *J* = 6.90 Hz, C_8-H), 7.48-7.45 (*d*, 1H, *J* = 8.91 Hz, C_9-H), 7.03-6.99 (*t*, 1H, *J* = 6.87 Hz, C_7-H), 3.68-3.66 (*t*, 4H, morpholine CH_2-O-CH_2), 2.88-2.83 (*t*, 2H, *J* = 8.22 Hz, N-CH_2), 2.51-2.48 (*t*, 4H, morpholine CH_2-N-CH_2), 2.35-2.30 (*t*, 2H, *J* = 8.22 Hz, CH_2), 1.79 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 273 (M^+), 186, 173, 119, 85, 78, 56; analysis calculated for $C_{15}H_{19}N_3O_2$: C, 65.81%; H, 7.23.%; N, 15.48%. Found: C, 65.92%; H, 7.03%; N, 15.35%.

2-Methyl-3-[2-(4-methylpiperazin-1-yl)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (4e): Brown semisolid; IR (KBr, cm^{-1}): 1662 (C=O), 1621 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.82-8.80 (*d*, 1H, *J* = 7.29 Hz, C_6-H), 7.64 (*t*, 1H, C_8-H), 7.18 (*d*, 1H, C_9-H), 6.90-6.84 (*t*, 1H, C_7-H), 3.23-3.21 (*t*, 2H, *J* = 6.00 Hz, N-CH_2), 3.14-3.10 (*t*, 2H, *J* = 6.00 Hz, CH_2), 2.93-2.88 (*m*, 8H, piperazine CH_2), 2.57 (*s*, 3H, N-CH_3), 2.29 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 286 (M^+), 187, 173, 157, 119, 113, 70, 56, 42; analysis calculated for $C_{16}H_{22}N_4O$: C, 67.31%; H, 7.74%; N 19.60%. Found: C, 67.10%; H, 7.72%; N, 19.55%.

3-[2-(4-(2-(2-Hydroxyethoxy)ethyl)piperazin-1-yl)ethy])-2-methyl-4*H*-pyrido[1,2-*a*] pyrimidin-4-one (4f): Pale yellow solid; melting point: 55-57˚C; IR (KBr, cm^{-1}): 3253 (OH), 1649 (C=O), 1620 C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.89-8.83 (*d*, 1H, *J* = 7.32 Hz, C_6-H), 7.65-7.61 (*t*, 1H, *J* = 6.82 Hz, C_8-H), 7.44-7.41 (*d*, 1H, *J* = 8.92 Hz, C_9-H), 7.12-7.09 (*t*, 1H, *J* = 6.38 Hz, C_7-H), 3.83-3.81 (*t*, 2H, *J* = 7.26 Hz, N-CH_2), 3.75 (*t*, 2H, -CH_2-C$\underline{H_2}$-OH), 3.58 (*t*, 2H, -C$\underline{H_2}$-CH_2-OH), 3.42 (*t*, 2H, -CH_2-C$\underline{H_2}$-O-), 2.75 (*t*, 2H, -C$\underline{H_2}$-CH_2-O-), 2.61 (*s*, 1H, OH), 2.61-2.58 (*t*, 2H, *J* = 6.38 Hz, CH_2), 2.46-2.38 (*m*, 8H, piperazine CH_2), 1.88 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 360 (M^+), 329, 299, 187, 173, 157, 111, 97, 78; analysis calculated for $C_{19}H_{28}N_4O_3$: C, 63.36%; H, 7.91%; N, 15.61%. Found: C, 63.30%; H, 7.82%; N, 15.55%.

9-Hydroxy-3-[2-(1*H*-imidazol-1-yl)ethyl]-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (5a): Pale yellow solid; melting point 148-150˚C; IR (KBr, cm^{-1}): 3473 (OH), 1672 (C=O), 1603 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.96-8.94 (*d*, 1H, *J* = 6.75 Hz, C_6-H), 7.68-7.66 (*d*, 1H, *J* = 7.86 Hz, C_8-H), 7.55-7.52 (*t*, 1H, *J* = 8.88 Hz, C_7-H), 6.87 (*s*, 2H, imidazole-H), 6.45 (*d*, 1H, imidazole-H), 5.23 (*s*, 1H, OH), 3.95-3.92 (*t*, 2H, *J* = 6.63 Hz, N-CH_2), 3.05-3.01 (*t*, 2H, *J* = 6.56 Hz, CH_2), 2.53 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 270 (M^+), 230, 187, 173, 113, 70, 42; analysis calculated for $C_{14}H_{14}N_4O_2$: C, 62.30%; H, 5.29%; N, 20.76%. Found: C, 62.20%; H, 5.21%; N, 20.72%.

3-(2-(1*H*-1,2,4-triazol-1-yl)ethyl)-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (5b): Pale yellow solid; melting point 158-160˚C; IR (KBr, cm^{-1}): 3407 (OH), 1688 (C=O), 1623, (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.95-8.92 (*d*, 1H, *J* = 7.62 Hz, C_6-H), 7.91 (*s*, 1H, triazole C_3-H), 7.87 (*s*, 1H, triazole C_5-H), 7.68-7.65 (*d*, 1H, *J* = 8.13 Hz, C_8-H), 7.13-7.11 (*t*, 1H, *J* = 7.29 Hz, 6.72, C_7-H), 5.21 (*s*, 1H, OH), 4.53-4.49 (*t*, 2H, *J* = 6.60 Hz, N-CH_2), 3.26-3.21 (*t*, 2H, *J* = 6.60 Hz, CH_2), 2.21 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 271 (M^+), 230, 173, 187, 157, 113, 70, 56; analysis calculated for $C_{13}H_{13}N_5O_2$: C, 57.66%; H, 4.86%; N, 25.89%. Found: C, 57.54%; H, 4.82%; N 25.82%.

3-[2-(9-Hydroxy-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,3-thiazolidine-2,4-dione (5c): White solid; melting point 154-156˚C; IR (KBr, cm^{-1}): 3404 (OH), 1742 (S-C=O), 1688 (C=O), 1613 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.53-8.50 (*d*, 1H, *J* = 6.84 Hz, C_6-H), 8.44-8.33 (*d*, 1H, *J* = 6.66 Hz, C_8-H), 6.98-6.96 (*t*, 1H, *J* = 6.42 Hz, C_7-H), 5.28 (*s*, 1H, OH), 3.96 (*s*, 2H, thiazolidin-CH_2), 3.96-3.94 (*t*, 2H, *J* = 6.62 Hz, N-CH_2), 2.50-2.47 (t, 2H, *J* = 6.61 Hz, CH_2), 1.96 (s, 3H, CH_3); MS (*m/z*, 70 eV): 319 (M^+), 249, 206, 187, 177, 165, 117, 74, 63; analysis calculated for $C_{14}H_{13}N_3O_4S$: C, 52.68%; H, 4.19%; N, 13.22%. Found: C, 52.65%; H, 4.09%; N, 13.15%.

9-Hydroxy-2-methyl-3-[2-(morpholin-4-yl)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (5d): Brown solid; melting point 111-113˚C; IR (KBr, cm^{-1}): 3531 (OH), 1667 (C=O), 1603 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.90-8.88 (*d*, 1H, *J* = 7.11 Hz, C_6-H), 7.61-7.56 (*d*, 1H, *J* = 6.69 Hz, C_8-H), 7.03-6.99 (*t*, 1H, *J* = 6.87 Hz, C_7-H), 5.22 (*s*, 1H, OH), 3.68-3.66 (*t*, 4H, morpholine CH_2-O-CH_2), 2.88-2.85 (*t*, 2H, *J* = 7.47 Hz, N-CH_2), 2.51-2.48 (*t*, 4H, morpholine CH_2-N-CH_2) 2.33-2.30 (*t*, 2H, *J* = 7.45 Hz, CH_2), 1.99 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 161.89, 161.19, 158.42, 142.32, 123.25, 120.85, 120.59, 113.45, 66.87, 54.89, 53.55, 30.50, 17.00; MS (*m/z*, 70 eV): 289 (M^+), 273, 222, 187, 173, 119, 111, 78, 42; analysis calculated for $C_{15}H_{19}N_3O_3$: C, 62.31%; H, 6.71%; N, 14.58%. Found: C, 62.26%; H, 6.63%; N, 14.53%.

9-Hydroxy-2-methyl-3-[2-(4-methylpiperazin-1-yl)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (5e): Pale brown solid; melting point 112-114˚C; IR (KBr, cm^{-1}): 3453 (OH), 1668 (C=O), 1615 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.43-8.41 (*d*, 1H, *J* = 6.66 Hz, C_6-H), 7.68-7.65 (*d*, 1H, *J* = 6.84 Hz, C_8-H), 6.89-6.86 (*t*, 1H, *J* = 7.95 Hz, C_7-H), 5.19 (*s*, 1H, OH), 4.27-4.25 (*t*, 2H, *J* = 6.69 Hz, N-CH_2), 3.22-3.19 (*t*, 2H, *J* = 6.84 Hz, CH_2), 2.87-2.65 (*m*, 8H, piperazine CH_2), 2.53 (*s*, 3H, N-CH_3), 1.98 (*s*, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 160.09, 160. 09, 158.40, 142.28, 123.20, 120.82, 120.59, 113.42, 54.99, 54.55, 45.49, 30.52, 17.14; MS (*m/z*, 70 eV): 302 (M^+), 222, 209, 187, 173, 157, 144, 119, 111, 97, 78, 56, 42; analysis calculated for $C_{16}H_{22}N_4O_2$: C, 63.46%; H, 7.36%; N, 18.66%. Found: C, 63.53%; H, 7.32%; N, 18.51%.

9-Hydroxy-3-(2-{4-[(hydroxyethoxy) ethyl] piperazin-1-yl}ethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (5f): Pale yellow solid; melting point 118-120˚C; IR (KBr, cm^{-1}): 3376 (OH), 1680 (C=O), 1603 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.95-8.93 (*d*, 1H, *J* = 6.68 Hz, C_6-H), 7.64-7.62 (*d*, 1H, *J* = 7.01 Hz, C_8-H), 6.97-6.94 (*t*, 1H, *J* = 7.13 Hz, C_7-H), 5.22 (*s*, 1H, OH), 3.95-3.92 (*t*, 2H, *J* = 6.66 Hz, N-CH_2), 3.72 (*t*, 2H, -CH_2-C<u>H</u>$_2$-OH), 3.61 (*t*, 2H, -C<u>H</u>$_2$-CH_2-OH), 3.45 (*t*, 2H, -CH_2-C<u>H</u>$_2$-O-), 2.88 (*t*, 2H, *J* = 6.72 Hz, CH_2), 2.69 (*t*, 2H, -C<u>H</u>$_2$-CH_2-O-), 2.58 (*s*, 1H, OH), 2.45-2.23 (*m*, 8H, piperazine CH_2), 1.88 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 376 (M^+), 329, 299, 285, 190, 187, 173, 119, 111, 97, 78; analysis calculated for $C_{19}H_{28}N_4O_4$: C, 60.72%; H, 7.55%; N, 14.90%. Found: C, 60.63%; H, 7.49%; N, 14.86%.

3-[2-(1*H*-Imidazol-1-yl)ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8a): White solid; melting point 105-107˚C; IR (KBr, cm^{-1}): 1652 (C=O), 1612 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 7.66 (*s*, 1H, imidazole C_2-H), 6.90 (*d*, 1H, imidazole C_4-H), 6.49 (*d*, 1H, imidazole C_5-H), 4.08-4.03 (*t*, 2H, *J* = 6.72 Hz, N-CH_2), 3.84-3.80 (*t*, 2H, *J* = 6.09 Hz, CH_2), 2.84-2.79 (*t*, 2H, *J* = 6.78 Hz, C_6-CH_2), 2.77-2.73 (*t*, 2H, *J* = 6.33 Hz, C_9-CH_2), 2.06 (*s*, 3H, CH_3), 1.77-1.64 (*m*, 4H, $C_{7,8}$-CH_2); MS (*m/z*, 70 eV): 258 (M^+), 232, 205, 192, 177, 165, 117, 77, 44; analysis calculated for $C_{14}H_{18}N_4O$: C, 65.14%; H, 7.12%; N, 21.69%. Found: C, 65.08%; H, 7.01%; N, 21.65%.

3-(2-(1*H*-1,2,4-triazol-1-yl)ethyl)-6,7,8,9-tetrahydro-2-methylpyrido[1,2-*a*]pyrimidin-4-one (8b): White solid; melting point 135-137˚C; IR (KBr, cm^{-1}): 1649 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.20 (*s*, 1H, triazole C_3-H), 7.95 (*s*, 1H, triazole C_5-H), 4.32-4.29 (*t*, 2H, *J* = 6.68 Hz, N-CH_2), 3.80-3.77 (*t*, 2H, *J* = 6.68 Hz, CH_2), 2.91-2.89 (*t*, 2H, *J* = 6.65 Hz, C_6-CH_2), 2.78-2.75 (*t*, 2H, *J* = 6.71 Hz, C_9-CH_2), 1.98 (*s*, 3H, CH_3), 1.95-1.80 (*m*, 4H, $C_{7,8}$-CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.54, 161.01, 154.05, 152.01, 142.39, 120.09, 49.96, 46.60, 34.03, 26.79, 26.36, 23.54, 17.54; MS (*m/z*, 70 eV): 259 (M^+), 177, 235, 207, 190, 165, 117, 91, 82, 55; analysis calculated for $C_{13}H_{17}N_5O$: C, 60.21%; H, 6.69%; N, 27.22%. Found: C, 60.19%; H, 6.61%; N, 27.01%.

3-[2-(2-Methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,3-thiazolidine-2,4-dione (8c): White solid; melting point 235-237˚C; IR (KBr, cm^{-1}): 1740 (S-C=O), 1645 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 4.40 (*s*, 2H, thiazolidin-CH_2), 3.80-3.78 (*t*, 2H, *J* = 6.81 Hz, N-CH_2), 3.60-3.57 (t, 2H, *J* = 6.80 Hz, CH_2), 3.01-2.92 (*t*, 2H, *J* = 6.72 Hz, C_6-CH_2), 2.71-2.68 (*t*, 2H, *J* = 6.70 Hz, C_9-CH_2), 2.10 (*s*, 3H, CH_3), 1.92-1.86 (*m*, 4H, $C_{7,8}$-CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 178.87, 178.44, 163.77, 161.03, 152.03, 119.03, 46.96, 46.00, 33.98, 30.99, 30.03, 26.36, 23.54, 17.76; MS (*m/z*,

70 eV): 307 (M^+), 177, 289, 234, 191, 163, 82, 53; analysis calculated for $C_{14}H_{17}N_3O_3S$: C, 54.76%; H, 5.66%; N, 13.73%. Found: C, 54.68%; H, 5.54%; N, 13.66%.

2-Methyl-3-[2-(morpholin-4-yl)ethyl]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8d): Pale yellow solid; melting point 123-125˚C; IR (KBr, cm^{-1}): 1649 (C=O), 1609 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 4.25-4.22 (*t*, 2H, *J* = 7.04 Hz, N-CH_2), 3.90-3.87 (*t*, 2H, *J* = 7.06 Hz, CH_2), 3.71-3.67 (*m*, 4H, morpholine CH_2-O-CH_2), 2.86-2.81 (*t*, 2H, *J* = 6.82 Hz, C_6-CH_2), 2.74-2.72 (*t*, 2H, *J* = 6.78 Hz, C_9-CH_2), 2.69-2.65 (*m*, 4H, morpholine CH_2-N-CH_2), 2.05-2.03 (*m*, 4H, $C_{7,8}$-CH_2), 1.93 (*s*, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.88, 161.00, 152.29, 119.80, 66.72, 54.84, 53.65, 46.44, 33.82, 30.22, 25.47, 23.00, 16.50; MS (*m/z*, 70 eV): 277 (M^+), 177, 209, 190, 163, 149, 97, 82, 53; analysis calculated for $C_{15}H_{23}N_3O_2$: C, 64.95%; H, 8.36%; N, 5.25%. Found: C, 64.89%; H, 8.34%; N, 15.13%.

2-Methyl-3-[2-(4-methylpiperazin-1-yl)ethyl]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8e): Pale yellow semisolid; melting point 35-37˚C; IR (KBr, cm^{-1}): 1648 (C=O), 1601 C=N; ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 4.20-4.18 (*t*, 2H, *J* = 7.12 Hz, N-CH_2), 3.91-3.89 (*t*, 2H, *J* = 7.08 Hz, CH_2), 2.89-2.86 (*t*, 2H, *J* = 6.70 Hz, C_6-CH_2), 2.72-2.69 (*t*, 2H, *J* = 6.73 Hz, C_9-CH_2), 2.61-2.56 (*m*, 8H, piperazine CH_2), 2.24 (*s*, 3H, N-CH_3), 2.01-1.97 (*m*, 4H, $C_{7,8}$-CH_2), 1.96 (*s*, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 164.09, 159.06, 158.03, 119.88, 72.29, 53.60, 52.55, 46.54, 45.56, 30.27, 27.67, 24.29, 16.28; MS (*m/z*, 70 eV): 290 (M^+), 189, 275, 191, 177, 163, 149, 82, 55; analysis calculated for $C_{16}H_{26}N_4O$: C, 66.28%; H, 9.12%; N, 19.38%. Found: C, 66.17%; H, 9.20%; N, 19.29%.

3-{2-[4-(Hydroxyethoxyethyl)piperazin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8f): Pale yellow solid; melting point 190-192˚C; IR (KBr, cm^{-1}): 3453 (OH), 1662 (C=O), 1604 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 4.19-4.17 (*t*, 2H, *J* = 6.86 Hz, N-CH_2), 3.88-3.86 (*t*, 2H, *J* = 6.82 Hz, CH_2), 3.69 (*t*, 2H, -CH_2-C<u>H</u>$_2$-OH), 3.63 (*t*, 2H, -C<u>H</u>$_2$-CH_2-OH), 3.41 (*t*, 2H, -CH_2-C<u>H</u>$_2$-O-), 2.90 (*t*, 2H, C_6-CH_2), 2.73 (*t*, 2H, C_9-CH_2), 2.69 (*t*, 2H, -CH_2-C<u>H</u>$_2$-O-), 2.62 (*t*, 2H, -C<u>H</u>$_2$-CH_2-O-), 2.52 (*s*, 1H, OH), 2.48-2.43 (*m*, 8H, piperazine CH_2), 2.03-1.99 (*m*, 4H, $C_{7,8}$-CH_2), 1.97 (*s*, 3H, CH_3). MS (*m/z*, 70 eV): 364 (M^+), 190, 339, 209, 173, 163, 149, 97, 82, 53; analysis calculated for $C_{19}H_{32}N_4O_3$: C, 62.67%; H, 8.95%; N, 15.39%. Found: C, 62.59%; H, 8.83%; N, 15.35%.

9-Hydroxy-3-[2-(1*H*-imidazol-1-yl)ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2 *a*]pyrimidin-4-one (9a): Pale brown solid; melting point 142-144˚C; IR (KBr, cm^{-1}): 3340 (OH), 1659 (C=O), 1615 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 7.66 (*s*, 1H, imidazole C_2-H), 6.90 (*d*, 1H, imidazole C_4-H), 6.79 (*d*, 1H, imidazole C_5-H), 4.08-4.03 (*t*, 2H, *J* = 6.72 Hz, N-CH_2), 3.84-3.80 (*t*, 2H, *J* = 6.80 Hz, CH_2), 3.23 (*s*, 1H, OH), 2.84-2.81 (*t*, 2H, *J* = 6.93 Hz, C_6-H), 2.77-2.73 (*t*, 1H, *J* = 6.87 Hz, C_9-H), 2.06 (*s*, 3H, CH_3), 1.98-1.93 (*m*, 4H, $C_{7,8}$-CH_2); MS (*m/z*, 70 eV): 274 (M^+), 206, 222, 193, 177, 165, 150, 96, 55; analysis calculated for $C_{14}H_{18}N_4O_2$: C, 61.41%; H, 6.46%; N, 20.54%. Found: C, 61.28%; H, 6.58%; N, 20.41%.

9-Hydroxy-2-methyl-3-[2-(4*H*-1,2,4-triazol-4-yl)ethyl]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9b): Pale brown solid; melting point 122-124˚C; IR (KBr, cm^{-1}): 3440 (OH), 1649 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 8.33 (*s*, 1H, triazole C_3-H), 7.91 (*s*, 1H, triazole C_5-H), 4.30-4.28 (*t*, 2H, *J* = 7.68 Hz, N-CH_2), 3.80-3.78 (*t*, 2H, *J* = 7.72 Hz, CH_2), 3.27 (*s*, 1H, OH), 2.90-2.87 (*t*, 2H, *J* = 6.86 Hz, C_6-CH_2), 2.72-2.70 (*t*, 1H, *J* = 7.02 Hz, C_9-H), 2.06-2.02 (*s*, 4H, $C_{7,8}$-H), 1.99 (*s*, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.25, 158.68, 154.44, 152.21, 144.20, 120.00, 71.66, 52.35, 46.40, 27.68, 27.25, 24.02, 16.83; MS (*m/z*, 70 eV) 275 (M^+), 206, 247, 193, 177, 165, 150, 96, 70, 55; analysis calculated for $C_{13}H_{17}N_5O_2$: C, 56.78%; H, 6.34%; N, 25.58%. Found: C, 56.68%; H, 6.21%; N 25.42%.

3-[2-(9-Hydroxy-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,3-thiazolidine-2,4-dione (9c): Pale brown solid; melting point 150-152˚C; IR (KBr, cm^{-1}): 3449 (OH), 1738 (S-C=O), 1645 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 4.17-4.15 (*t*, 2H, *J* = 6.22 Hz, N-CH_2), 3.61-3.58 (*t*, 2H, *J* = 6.24 Hz, CH_2), 3.21 (*s*, 1H, OH), 2.90 (*s*, 2H, thiazolidine CH_2), 2.86-2.84 (*t*, 2H, *J* = 7.11 Hz, C_6-CH_2), 2.70-2.68 (*t*, 1H, *J* = 6.68 Hz, C_9-H), 2.11 (*s*, 3H, CH_3), 2.03-1.98 (*m*, 4H, $C_{7,8}$-H); MS (*m/z*, 70 eV): 323 (M^+), 249, 187, 165, 117, 96, 74, 63; analysis calculated for $C_{14}H_{17}N_3O_4S$: C, 52.23%; H, 5.35%; N, 13.12%. Found: C, 52.01%; H, 5.27%; N, 12.96%.

9-Hydroxy-2-methyl-3-[2-(morpholin-4-yl)ethyl]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9d): Pale yellow solid; melting point 85-87˚C; IR (KBr, cm^{-1}): 3478 (OH), 1652 (C=O), 1611 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): δ (ppm) 3.91-3.87 (*t*, 2H, *J* = 8.13 Hz, N-CH_2), 3.71-3.69 (*t*, 4H, morpholine CH_2-O-CH_2), 3.67-3.66 (*t*, 2H, *J* = 8.09 Hz, CH_2), 2.86-2.81 (*t*, 2H, *J* = 6.87 Hz, C_6-CH_2), 2.74-2.71 (*t*, 1H, *J* =

6.67 Hz, C_9-H), 2.55 (*m*, 4H, morpholine CH_2-N-CH_2), 2.03-1.93 (*m*, 4H, $C_{7,8}$-CH_2), 1.90 (*s*, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 164.03, 161.06, 152.27, 119.87, 72.00, 66.60, 54.85, 53.55, 46.54, 30.30, 27.47, 24.00, 16.46; MS (*m/z*, 70 eV): 293 (M^+), 206, 173, 144, 144, 119, 111, 97, 78; analysis calculated for $C_{15}H_{23}N_3O_3$: C, 61.55%; H, 7.90%; N, 14.39%. Found: C, 61.41%; H, 7.87%; N 14.30%.

9-Hydroxy-2-methyl-3-[2-(4-methylpiperazin-1-yl)ethyl]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9e): Pale brown solid; melting point 98-100˚C; IR (KBr, cm^{-1}): 3452 (OH), 1659 (C=O), 1611 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): *δ* (ppm) 3.91-3.87 (*t*, 2H, *J* = 7.78 Hz, N-CH_2), 3.71-3.67 (*t*, 2H, *J* = 7.56 Hz, CH_2), 3.26 (*s*, 1H, OH), 2.86-2.84 (*t*, 2H, *J* = 7.04 Hz, C_6-CH_2), 2.74-2.71 (*t*, 1H, *J* = 7.12 Hz, C_9-H), 2.69-2.65 (*m*, 8H, piperazine CH_2), 2.05-2.03 (*m*, 4H, $C_{7,8}$-CH_2), 2.01 (*s*, 3H, N-CH_3), 1.99 (*s*, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 164.09, 159.06, 158.03, 119.88, 72.29, 53.060, 52.55, 46.54, 45.56, 30.27, 27.67, 24.29, 16.28; MS (*m/z*, 70 eV): 306 (M^+), 187 285, 222, 209, 173, 157, 144, 119, 111, 78; analysis calculated for $C_{16}H_{26}N_4O_2$: C, 62.82%; H, 8.75%; N, 18.39%. Found: C, 62.70%; H, 8.55%; N, 18.25%.

9-Hydroxy-3-{2-[4-(Hydroxyethoxyethyl) piperazin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9f): Pale brown solid; melting point 124-126˚C; IR (KBr, cm^{-1}): 3453 (OH), 1649 (C=O), 1609 (C=N); ^{1}H NMR ($CDCl_3$,300 MHz): *δ* (ppm) 3.80-3.77 (*t*, 2H, *J* = 7.43 Hz, N-CH_2), 3.67 (*t*, 2H, -CH_2-C<u>H</u>$_2$-OH), 3.59 (*t*, 2H, -C<u>H</u>$_2$-CH_2-OH), 3.44 (*t*, 2H, -CH_2-C<u>H</u>$_2$-O-), 3.31-3.28 (*t*, 2H, *J* = 7.38 Hz, CH_2), 3.27 (*s*, 1H, OH), 2.82-2.78 (*t*, 2H, *J* = 6.78 Hz, C_6-H), 2.66 (*t*, 1H, C_9-H), 2.62 (*t*, 2H, -C<u>H</u>$_2$-CH_2-O-), 2.51 (*s*, 1H, OH), 2.45-2.41 (*m*, 8H, piperazine CH_2), 2.03-1.93 (*m*, 4H, $C_{7,8}$-H), 2.01 (*s*, 3H, CH_3); MS (*m/z*, 70 eV): 380 (M^+), 187, 361, 329, 285, 209, 173, 119, 111, 78, 56; analysis calculated for $C_{19}H_{32}N_4O_4$: C, 60.08%; H, 8.57%; N, 14.83%. Found: C, 59.97%; H, 8.47%; N, 14.72%.

Pharmacological assay:

Molecular OSIRIS property explorer: For a new molecule to emerge as drug molecule, initially it has to be evaluated for the parameters set by Lipinski's rule of five.[23] All the title compounds have shown promising drug score value in the range 0.51-0.96 without any mutagenic, tumorogenic, irritability and reproductive effect (**Table 2**).

Anti-inflammatory assay: All the newly synthesized compounds were screened for *in vitro* anti-inflammatory activity against hyaluronidase enzyme. At 10 µg concentration, compounds **4e** and **5f** possessing *N*-methylpiperazine and piperazine ethoxy ethanol ring respectively have shown more growth inhibition than the standard drug indomethacin. Derivatives **5a** bearing imidazole ring and **8f**, **9f** containing piperazine ethoxy ethanol ring have shown inhibition comparable to the standard drug. All other derivatives have shown moderate to least activity at this concentration. At 50 µg concentration, compounds **5a** bearing imidazole ring, **8f** and **9f** containing piperazine ethoxy ethanol ring have shown good activity. Only the compound **9e** containing *N*-methylpiperazine ring has shown promising activity at 100 µg concentration (Table 3).

RESULTS AND DISCUSSION

Methodology for *in vitro* anti-inflammatory activity: The assay was performed according to Ling et al and Sigma Protocol.[24] The assay medium consisting of 3-5U hyaluronidase (from Sigma – Aldrich, Bangalore) in 100µl of 20mM sodium phosphate buffer (pH 7.0) with 77mM sodium chloride, 0.01% BSA was pre-incubated with different concentrations of the test compound for 15 min at 37 °C. The assay commenced by adding 100µl hyaluronic acid (from Sigma–Aldrich, Bangalore; 0.03% in 300mM sodium phosphate, pH 5.35) to the incubation mixture and incubated for a further 45 min at 37 °C. The undigested hyaluronic acid was precipitated with acid albumin solution (1.00 ml) made up of 0.1% bovine serum albumin in 24mM sodium acetate and 79mM acetic acid, (pH 3.75). After standing at room temperature for 10 min, the absorbance of the reaction mixture was measured at 600 nm. The absorbance in absence of enzyme was used as the reference value for maximum inhibition. The inhibitory activity of test compound was calculated as the percentage ratio of the absorbance in the presence of test compound *vs.* absorbance in the absence of enzyme. The enzyme activity was checked by control experiment run simultaneously, in which the enzyme was pre-incubated with DMSO (5µl) instead, and followed by the assay procedures described above. Compound was tested in a range of 10µg - 100µg in the reaction mixture. Indomethacin (Indo) was used as reference standard.

CONCLUSION

In this communication, we herein report the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives appended to various heterocyclic secondary amines **3a-f**. All the newly synthesized

molecules were evaluated for their drug likeliness and drug score, and screened for *in vitro* anti-inflammatory activity against hyaluronidase enzyme. Compounds **4e** and **5f** bearing *N*-methylpiperazine and piperazine ethoxy ethanol ring respectively have shown more growth inhibition than the standard drug indomethacin at 10 µg concentration. Compounds **8f** and **9f** containing piperazine ethoxy ethanol ring have shown promising activity at 10 µg and 50 µg concentrations.

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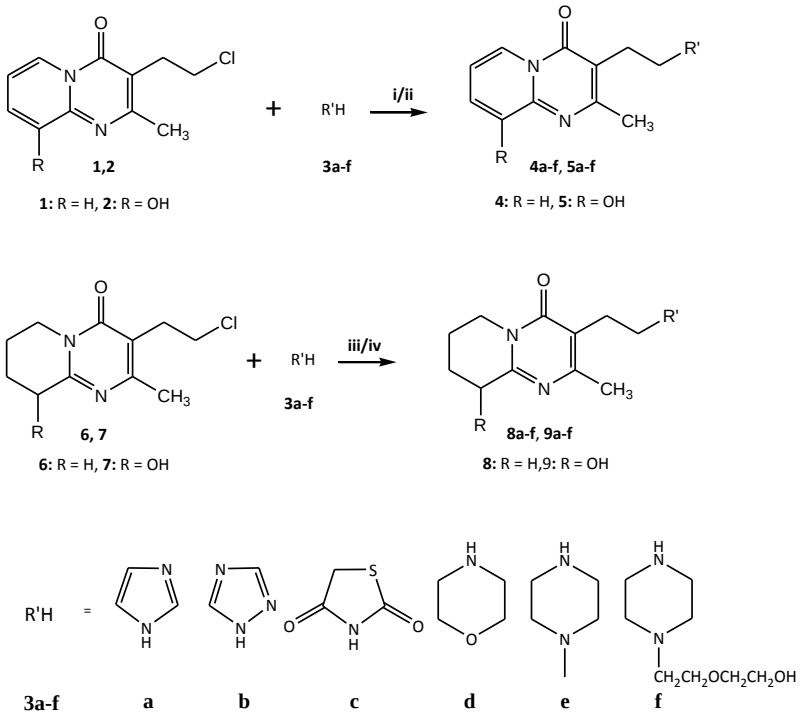
Disclosure: The authors report no conflicts of interest in this work.



Reaction Conditions: i) Diisopropylethylamine, CH_3CN, reflux, 10-12 h (for **4a-f**), ii) Diisopropylethylamine, CH_3CN, reflux, 14-20 h (for **5**a-**f**), iii) K_2CO_3, CH_3CN, reflux, 12-16 h (for **8a-f**), iv) Diisopropylethylamine, CH_3CN, reflux, 15-18 h (for **9a-f**)

Scheme 1 Synthetic route for target molecules **4a-f**, **5a-f**, **8a-f**, **9a-f**

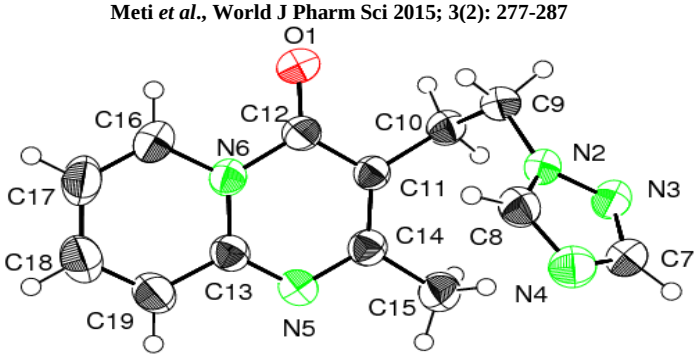


Fig. 1. ORTEP diagram of compound 4b

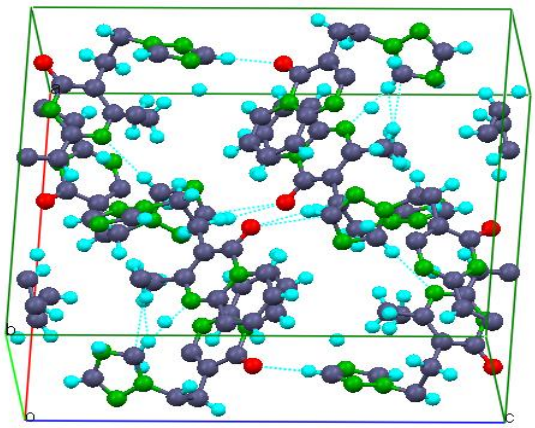


Fig. 2. Molecular packing diagram of compound 4b

Table 1: Crystal data of compound (**4b)**

$C_{13}H_{13}N_5O$	Z = 8
M_r = 255.28	D_x = 1.349 Mg m^{-3}
Orthorhombic, *Pbca*	Mo *K*α
a = 17.0018 (8) Å	μ = 0.09 mm^{-1}
b = 7.9091 (4) Å	T = 296 (2) K
c = 18.6958 (9) Å	Needles, colorless
V = 2514.0 (2) Å^3	0.29 × 0.25 × 0.21mm
Data collection	
Bruker SMART CCD area-detector diffractometer	1510 independent reflections
ω and φ scans	1341 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan SADABS (Sheldrick, 2007)	R_{int} = 0.022
T_{min} = 0.975, T_{max} = 0.982	θ_{max} = 21.8°
9919 measured reflections	
Refinement	
Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.099P)^2 + 2.6397P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.057	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.175	$\Delta\rho_{max}$ = 0.47 e Å^{-3}
S = 1.07	$\Delta\rho_{min}$ = −0.51 e Å^{-3}
1510 reflections	Extinction correction: SHELXL, $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
173 parameters	Extinction coefficient: 0.0072 (16)
H-atom parameters constrained	

Table 2: Pharmacological parameters for bioavailability of compounds **4a-f**, **5a-f**, **7a-f and 9a-f**

Comp	*C*logP	Drug likeness	Drug score	Compd	*C*logP	Drug likeness	Drug score	Compd	*C*logP	Drug likeness	Drug score
4a	0.11	5.12	0.96	**5c**	-0.45	4.49	0.55	**8e**	1.02	8.22	0.95
4b	0.11	4.18	0.76	**5d**	-0.14	4.83	0.95	**8f**	0.44	3.49	0.90
4c	0.14	4.32	0.55	**5e**	-0.31	5.91	0.95	**9a**	-0.27	5.26	0.96
4d	0.45	4.67	0.95	**5f**	-0.02	10.74	0.95	**9b**	-0.27	4.39	0.76
4e	0.57	10.64	0.95	**8a**	0.56	3.36	0.94	**9c**	-0.24	3.72	0.55
4f	-0.01	5.93	0.91	**8b**	0.56	2.48	0.73	**9d**	0.07	4.22	0.94
5a	-0.48	5.29	0.96	**8c**	0.59	1.78	0.51	**9e**	0.19	10.02	0.95
5b	-0.48	4.37	0.75	**8d**	0.90	2.27	0.90	**9f**	-0.39	5.39	0.90

Table 3: Percentage inhibition of hyaluronidase enzyme by the samples **(4a-f, 5a-f, 8a-f, 9a-f)**

Sample	**Test concentration (µg)**	**O.D. at 600nm**	**% Inhibition**
	10	0.281	24.67
4a	50	0.413	35.34
	100	0.712	52.50
	10	0.128	11.12
4b	50	0.232	20.33
	100	0.398	34.95
	10	0.315	27.67
4c	50	0.620	54.40
	100	0.781	68.54
	10	0.255	22.36
4d	50	0.540	47.32
	100	0.702	61.65
	10	0.923	81.00
4e	50	1.432	*
	100	1.436	*
	10	0.394	34.54
4f	50	0.551	48.34
	100	0.787	69.06
	10	0.709	62.24
5a	50	0.809	71.00
	100	1.620	*
	10	0.582	51.05
5b	50	0718	63.00
	100	1.007	88.34
	10	0.016	14.50
5c	50	0.102	09.00
	100	0.176	15.44
	10	0.140	12.30
5d	50	0.516	45.28
	100	0.766	67.23
	10	0.239	21.00
5e	50	0.498	43.71
	100	0.628	55.06
	10	0.889	78.05
5f	50	1.450	*
	100	1.670	*

	10	0.194	17.00
8a	50	0.342	30.00
	100	0.775	68.00
	10	0.106	09.30
8b	50	0.396	34.00
	100	0.602	52.81
	10	0.091	08.00
8c	50	0.502	44.00
	100	0.695	61.00
	10	0.085	07.50
8d	50	0.136	11.30
	100	0.228	20.00
	10	0.196	17.20
8e	50	0.330	29.00
	100	0.520	45.60
	10	0.772	67.70
8f	50	0.923	81.00
	100	1.413	*
	10	0.105	09.25
9a	50	0.163	14.30
	100	0.240	21.05
	10	0.027	02.35
9b	50	0.062	05.40
	100	0.105	09.18
	10	0.017	01.51
9c	50	0.057	05.00
	100	0.103	09.00
	10	0.057	05.00
9d	50	0.138	12.98
	100	0.388	34.00
	10	0.244	21.43
9e	50	0.581	51.00
	100	0.923	81.00
	10	0.740	64.72
9f	50	0.967	84.30
	100	1.418	*
	10	0.886	77.72
Indomethacin	50	1.390	*
	100	1.530	*

* Beyond measurable range: much higher activity

REFERENCES

1. Toole B P, Wight TN, Tammi MI. Hyaluronan-Cell interactions in cancer and vascular disease. J Biol Chem 2002; 277: 4593-4596.
2. Foschi D, et al. Hyaluronic-acid prevents oxygen free-radical damage to granulation-tissue - A study in rats. Int J Tiss React 1990; 12: 333-339.
3. Shen TY, Winter CA, Chemical and biological studies on indomethacin, sulindac and their analogs. Adv Drug Res 1977; 12: 90-245.
4. Motta CL, et al. Pyrido[1,2-*a*]pyrimidin-4-one derivatives as a novel class of selective aldose reductase inhibitors exhibiting antioxidant activity. J Med Chem 2007; 50: 4917-4927.
5. Youssouf MS, et al. Anti-histaminic, anti-inflammatory and bronchorelaxant activities of 2,7-dimethyl-3-nitro-4*H* pyrido [1,2-*a*] pyrimidine-4-one. Int Immunopharmacol 2008; 8: 1049-1055.
6. Roma G, et al. Synthesis, antiplatelet activity and comparative molecular field analysis of substituted 2-amino-4H-pyrido[1,2-a]pyrimidin-4-ones, their congeners and isosteric analogues. Bioorg Med Chem 2000; 8: 751-768.
7. Mane UR, et al. Pyrido[1,2-*a*]pyrimidin-4-ones as antiplasmodial falcipain-2 inhibitors. Bioorg Med Chem 2012; 20: 6296-6304.

8. Mallesha L, Mohana KN, Veeresh B, Alvala R, Mallika A. Synthesis and *in vitro* antiproliferative activity of 2-methyl-3-(2-piperazin-1-yl-ethyl)-pyrido [1, 2-a] pyrimidin-4-one derivatives against human cancer cell lines. Arch Pharm Res 2012; 35: 51-57.
9. Braccio DM, et al. Derivatives of pyrimidine 1,2-condensate. IV. Synthesis and pharmacological properties of the N,N-disubstituted 4-amino-2*H*-pyrido(1,2-*a*)pyrimidin-2-ones and 2-amino-4*H*-pyrido(1,2-*a*)pyrmidin-4-ones. Farmaco Sci 1988; 43: 705-723.
10. Leysen JE, Janssen PM, Megens AA, Schotte A. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. J Clin Psychiatry 1994; 55: 5-12.
11. Awouters F, et al. Oral antiallergic activity in ascaris hypersensitive dogs: A study of known antihistamines and of the new compounds ramastine (R 57 959) and levocabastine (R 50 547). Drug Dev Res 1986; 8: 95-102.
12. Smith RL, Barrett RJ, Sanders-Bush E. Neurochemical and behavioral evidence that quipazine-ketanserin discrimination is mediated by serotonin2A receptor. J. Pharmacol Exp Ther 1995; 275: 1050-1057.
13. Steel HC, Tintinger GR, Anderson R. Comparison of the anti-inflammatory activities of imidazole antimycotics in relation to molecular structure. Chem Biol Drug Des 2008; 72: 225-228.
14. Mullican MD, et al. Design of 5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-l,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally-active, non-ulcerogenic anti-inflammatory agents. J Med Chem 1993; 36: 1090-1099.
15. Ali AM, et al. Synthesis and three-dimensional qualitative structure selectivity relationship of 3,5-disubstituted-2,4-thiazolidinedione derivatives as COX2 inhibitors. Arch Pharm Res 2007; 30: 1186-1204.
16. Bandgar BP, et al. Synthesis and biological evaluation of nitrogen-containing chalcones as possible anti-inflammatory and antioxidant agents. Bioorg Med Chem Lett 2010; 20: 730–733.
17. Wang L, Brown JR, Varki A, Esko JD, Heparin's anti-inflammatory effects require glucosamine 6-O-sulfation and are mediated by blockade of L- and P-selectins. J Clin Invest 2002; 110: 127–136.
18. Bruker. SMART and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA, 2001.
19. Sheldrick GM SHELXS97, University of Göttingen, Germany, 1997.
20. Farrugia, LJ, WinGX and ORTEP for Windows: an update J. Appl. Cryst 2012; 45: 849-854.
21. Stewart JP. Optimization of parameters for semi empirical methods I. Method J Comput Chem 1989; 10: 209–220.
22. Stewart JP. MOPAC 6.0 QCPE 455. Indiana University, Bloomington (IN 47405). 1990.
23. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997; 23: 3-25.
24. Ling SK, Tanaka T, Kouno I. Effects of iridoids on lipoxygenase and hyaluronidase activities and their activation by β-glucosidase in the presence of amino acids. Biol Pharm Bull 2003; 26: 352-356.