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ScienceDirect
European Journal of Medicinal Chemistry 42 (2007) 669–674
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Chemotherapy of leishmaniasis. Part V: Synthesis and *in vitro* bioevaluation of novel pyridinone derivatives☆

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Received 7 April 2006; received in revised form 16 November 2006; accepted 23 November 2006
Available online 29 November 2006

Abstract

Some novel 2-substituted pyridinone derivatives exemplified by **3** and **4** have been synthesized from 2-methyl-γ-pyrone and screened towards *in vitro* antileishmanial activity profile. Some of the compounds such as **3a**, **3b**, **4i** and **4j** displayed good antileishmanial profile.

Keywords: Pyridinone; Antileishmanial activity; γ-Pyrone; Promastigote; Amastigotes; *In vitro*

1. Introduction

Leishmaniasis is a group of tropical diseases endemic in many parts of the world [1,2]. It is considered that this ailment affect around 12 million people in 80 countries and it is estimated that there are about two to three million new cases each year. It is also considered that about 250 million people are under the risk of this infection [3].

Visceral leishmaniasis is the most severe clinical form of the disease and can be fatal when not treated. The drugs recommended for the treatment of visceral leishmaniasis like pentavalent antimonials, pentamidine, and amphotericin-B have some limitations like parenteral administration, long course of treatment, toxic side effects and high cost of treatment [4].

Newly introduced first orally active miltefosine [5] is quite effective but shows teratogenic effect and cannot be used in pregnant women. The search for new drug continues with bisphosphonates [6] and natural products [7,8]. Some biochemical targets *e.g.* trypanothione reductase [9], cysteine proteases [10], sterol biosynthesis [11], dihydrofolate reductase (DHFR) [12], ornithine decarboxylase [13] and microtubule inhibitors [14] are under investigation at various stages of drug development.

Coombs' group [15,16] investigated some 5-substituted 2,4-diamino pyrimidine derivatives that were good inhibitors of *Leishmania mexicana* DHFR in crude extracts of the enzyme (IC_{50} 0.2–2 μM) and showed activity against promastigotes (EC_{50} 12–24 μM). In view of this and our continuation of studies on chemotherapy of Leishmania [17], we synthesized some novel 5-substituted pyridinone derivatives and studied them towards *in vitro* studies and the results are reported in the present paper.

2. Chemistry

Commercially available γ-pyrone **1** on reaction with dibromopentane in the presence of dry potassium carbonate in dry DMF furnished **2** in near quantitative yield. The dimeric γ-pyrone **2** was subjected to a series of different amines to furnish monomeric and dimeric pyridinones as shown in Scheme 1.

☆ CDRI communication no. 6934.

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doi:10.1016/j.ejmech.2006.11.011

The reaction of pyrone **2** with aniline in steel bomb (120 °C, 24 h) furnished pyridinone **3e** in 58% yield. However, the reaction of pyrone **2** with electron withdrawing *p*-fluoroaniline under identical reaction conditions furnished pyridinone **4g** in 18% yield and pyridinone **3g** in 29% yield. The reaction of pyrone **2** with *p*-nitroaniline and *p*-chloroaniline under identical reaction condition furnished only monomeric substituted pyridinone derivatives **4i** and **4h** in 20% and 32% yield, respectively.

The reaction of pyrone **2** with electron donating *p*-anisidine furnished pyridinone **3d** in 40% yield and *o*-anisidine furnished pyridinone **4j** in 52% yield. The reaction of pyrone **2** with alkyl substituted aniline *i.e.* 2,6-dimethyl aniline furnished monosubstituted pyridinone **4a** in 23% yield and disubstitued pyridinone **3a** in 22% yield, while 2,3-dimethyl aniline furnished only disubstituted pyridinone **3b** in 42% yield. Apart from these aromatic amines we studied some alkyl amines as shown in Scheme 1. The reaction of pyrone **2** with cyclohexylamine furnished pyridinone **4c** in 19% yield and dipyridinone **3c** in 20% yield.

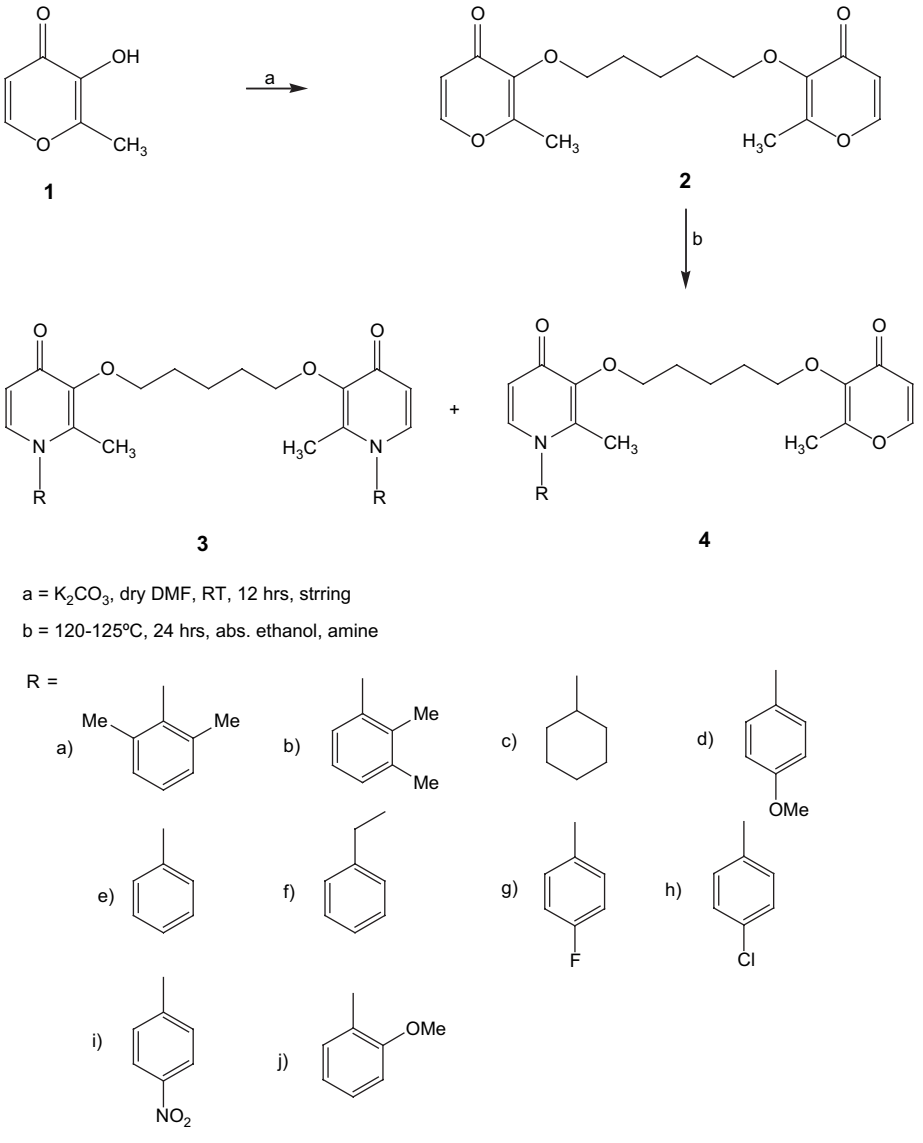
In conclusion electron donating substituents on aniline gave better yields as compared to electron withdrawing substituents on aniline.

3. Biological activities

3.1. Material and method

3.1.1. Antipromastigote activity

The *Leishmania donovani* promastigotes (MHOM IN/Dd_8; originally obtained from Imperial college, London) were transfected with firefly luciferase gene, and the transfectants were maintained in medium 199 (Sigma chemical Co., USA) supplemented with 10% foetal calf serum (GIBCO), 1% penicillin (50 μg/ml), and streptomycin (50 μg/ml) solution (Sigma) under pressure of G418 (Sigma) [18]. The *in vitro* effect of the



Scheme 1.

compounds on the growth of promastigotes was assessed by monitoring the luciferase activity of viable cells after the treatment. The transgenic promastigotes of late log phase were seeded at 5×10^5/100 μl medium 199 per well in 96-well flat bottomed microtitre (MT) plates (CELLSTAR) and incubated for 72 h in medium alone or in the presence of serial dilutions of drugs (2.5–50 μg/ml) in DMSO. Parallel dilutions of DMSO were used as controls. After incubation, an aliquot (50 μl) of promastigote suspension was aspirated from each well of a 96-well plate and mixed with an equal volume of steady Glo® reagent (Promega) and luminescence was measured by a luminometer. The values were expressed as relative luminescence unit (RLU). The inhibition of parasitic growth was determined by comparing the luciferase activity of drug treated parasites with that of untreated controls by the general formula:

$$\text{Percentage Inhibition} = \frac{N - n}{N} \times 100$$

where N is average relative luminescence unit (RLU) of control wells and n is average RLU of treated wells.

3.1.2. Antiamastigote activity

For assessing the activity of compounds against the amastigote stage of the parasite, mouse macrophage cell line (J-774A.1) infected with promastigotes expressing luciferase firefly reporter gene was used [18]. Cells were seeded in a 96-well plate (5×10^4cell/100 μl/well) in RPMI-1640 containing 10% foetal calf serum and the plates were incubated at 37 °C in a CO_2 incubator. After 24 h, the medium was replaced with fresh medium containing stationary-phase promastigotes (2.5×10^5/100 μl/well). Promastigotes invade the macrophage and are transformed into amastigotes. The test material in appropriate concentrations (2.5–50 μg/ml) in complete medium was added after replacing the previous medium and the plates were incubated at 37 °C in a CO_2 incubator for 72 h. After incubation, the drug-containing medium was decanted and 50 μl PBS was added in each well and mixed with an equal volume of steady Glo® reagent. After gentle shaking for 1–2 min, the reading was taken in a luminometer. The inhibition of parasitic growth was determined as described above.

3.1.3. Data analysis

IC_{50} and IC_{90} were calculated by Probit analysis [19]. Compounds with more than 15 μg/ml IC_{50} were considered as inactive while compounds with IC_{50} between 15 and 5 μg/ml were considered as moderately active and less than 5 μg/ml IC_{50} as highly active compounds.

4. Results and discussion

The dimeric pyridinone **3** and monomeric pyridinone **4** were subjected to *in vitro* antileishmanial screening against promastigote and amastigote model. The dimeric pyrone **2** has shown good leishmanicidal activity and the potency of compounds was greatly enhanced by the N-substitution of oxygenated function of pyrone **2**. But the N-substituted pyrone *i.e.* pyridinones **3** and **4** showed very little differentiation in leishmanicidal activity. Amongst the 15 compounds tested for *in vitro* antipromastigote activity, several compounds (**3a**, **3b**, **3c**, **3f**, **4c**, **4i** and **4j**) have shown significant activity (IC_{50}, IC_{90} and C.I. values, Table 1).

These compounds were also evaluated against amastigote stage in macrophages. Of these, four compounds (**3a**, **3b**, **4i**,

Table 1
In vitro antileishmanial activity profile of substituted pyridinone derivatives against promastigotes and amastigotes

S. no.	Compound	Antipromastigote activity (μg/ml)		Antiamastigote activity (μg/ml)	
		IC_{50} (C.I.)	IC_{90} (C.I.)	IC_{50} (C.I.)	IC_{90} (C.I.)
1	**2**	18.68 (14.90–23.43)	122.95 (67.17–225.04)	12.89 (9.32–17.83)	112.99 (57.19–223.22)
2	**3a**	6.91[a] (6.33–7.55)	12.49 (10.73–14.52)	9.64[a] (7.97–11.65)	48.43 (29.72–78.93)
3	**3b**	7.37[a] (6.48–8.38)	19.07 (15.43–23.57)	8.57[a] (7.07–10.39)	42.30 (31.19–57.37)
4	**3c**	4.57[b] (3.86–5.35)	18.65 (14.74–23.57)	22.80 (20.11–25.87)	62.23 (49.20–78.71)
5	**3d**	12.59[a] (15.56–19.90)	43.75 (36.19–52.90)	ND	ND
6	**3e**	22.68 (20.40–25.22)	49.79 (41.96–59.08)	ND	ND
7	**3f**	9.98[a] (8.77–11.37)	29.29 (23.96–35.80)	13.16[a] (9.77–17.73)	99.48 (54.68–180.98)
8	**3g**	Inactive	Inactive	ND	ND
9	**4a**	17.89 (15.39–20.81)	57.92 (44.42–75.53	ND	ND
10	**4c**	4.59[b] (4.13–5.10)	10.70 (9.01–12.71)	24.01 (20.23–28.49)	102.89 (66.95–138.13)
11	**4f**	13.55[a] (11.78–15.57)	47.93 (37.40–61.42)	ND	ND
12	**4g**	43.56 (28.05–67.66)	855.52 (210.89–3470.5)	ND	ND
13	**4h**	15.71 (13.84–17.83)	38.73 (32.20–46.58)	ND	ND
14	**4i**	5.75[a] (4.75–6.97)	20.21 (16.19–25.20)	6.15[a] (5.24–7.22)	28.58 (22.05–37.05)
15	**4j**	4.04[b] (3.49–4.69)	13.32 (10.83–16.41)	5.32[a] (4.31–6.56)	38.08 (27.09–53.53)
16	Pentamidine	0.58 (0.55–0.60)	0.88 (0.82–0.96)	–	–
17	Amphotericin-B	–	–	6.46×10^{-3} ($3.44–12.09) \times 10^{-3}$	157.13×10^{-3} ($91.2–270.8) \times 10^{-3}$
18	Miltefosine	–	–	33.90 (29.90–38.44)	107.51 (88.68–130.35)

NI = no inhibition; ND = not done.
[a] Moderately active.
[b] Highly active.

and **4j**) have shown encouraging results (Table 1). The activity of these compounds was superior to miltefosine but inferior to amphotericin-B, treated as reference drug. These compounds are new lead in antileishmanial chemotherapy and may be very useful for further optimization work in the area of drug development against leishmaniasis.

5. Experimental

The reported melting points (°C) are the uncorrected ones. The infrared spectra were recorded using KBr on a Perkin–Elmer model 881. NMR spectra were obtained in $CDCl_3$ (with Me_4Si as internal standard, Aldrich) and are reported in parts per million downfield from Me_4Si. Proton, and carbon NMR spectra were recorded on Bruker Advance DRX 2000 instrument. FAB mass spectra were recorded on a FAB mass spectrometer model SX-102 (Jeol make). Elemental analysis was carried out on a Carlo-Erba EA1108 instrument.

5.1. 1,5-Bis(2-methyl-4-1H-pyrone)pentane **2**

A mixture of 2-methyl-γ-pyrone (6.3 g, 50 mmol), dry potassium carbonate (34 g, 2.5 mol) and dibromopentane (5.75 g, 25 mmol) in dry DMF was stirred at room temperature for 24 h. After completion of the reaction (TLC monitoring) the reaction mixture was poured in ice water (500 ml). It was extracted with dichloromethane (2 × 100 ml). The combined organic extract was washed with cold water (5 × 100 ml) and brine solution (2 × 100 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, 60–120 mesh). Elution with 2% methanol in chloroform furnished cream coloured thick liquid (7 g, 43.75%). IR (Neat, cm^{-1}) 2947, 1635, 1573, 1432, 1253, 1192; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 2H), 1.80 (m, 4H), 2.32 (s, 6H), 4.00 (m, 4H), 6.35 (d, 2H), 7.62 (d, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2 × 14.88 (q), 22.50 (t), 2 × 29.92 (t), 2 × 72.20 (t), 2 × 117.19 (d), 2 × 144.94 (s), 2 × 153.97 (d), 2 × 159.32(s), 2 × 175.24 (s); MS (*m/e*) 343 (M^+ + Na), 322 ($M^+ + 1$).

5.2. Representative procedure for **3** and **4**

To a solution of dipyrone **2** (0.97 g, 3 mmol) in absolute ethanol (25 ml) was added corresponding amine (10 mmol) and resulting reaction mixture was heated in a steel bomb at 120–125 °C for 12 h. Solvent was then removed *in vacuo*. It was extracted in dichloromethane (2 × 50 ml). The combined organic extract was washed with water (2 × 50 ml) and brine solution (50 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, 60–120 mesh). Elution with 2% methanol in chloroform furnished monomeric substituted pyridinone derivative **4** while 3% methanol in chloroform furnished dimeric pyridinone **3** derivatives.

5.2.1. 1,5-Bis[1-(2,6-dimethyl phenyl)-2-methyl-4-pyridone-3-yloxy]pentane (**3a**)

Yield 22%; IR (Neat, cm^{-1}) 2943, 1622, 1561, 1479, 1282, 1247, 1188; ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.80 (m, 4H), 1.90 (s, 6H), 2.00 (s, 2H), 4.20 (m, 4H), 6.50 (d, 2H), 7.20 (m, 8H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 2 × 14.00 (q), 4 × 18.00 (q), 24.00 (t), 2 × 30 (t), 2 × 72 (t), 2 × 119 (s), 6 × 129 (d), 2 × 130 (d), 2 × 135 (s), 2 × 138 (d), 4 × 140 (s), 2 × 141 (s), 2 × 174 (s); MS (*m/e*) 527 ($M^+ + 1$).

5.2.2. 1,5-Bis[1-(2,3-dimethyl phenyl)-2-methyl-4-1H-pyridone-3-yloxy]pentane (**3b**)

Yield 30%; IR (Neat, cm^{-1}) 2946, 1624, 1582, 1471, 1353, 1289, 1201; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90 (m, 12H), 2.10 (m, 6H), 2.40 (s), 4.30 (m, 4H), 7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2 × 18.01 (q), 2 × 18.75 (q), 2 × 24.55 (q), 26.45 (t), 2 × 34.01 (t), 2 × 80.87 (t), 2 × 118.99 (s), 2 × 127.98 (d), 3 × 131.83(d), 2 × 136.46 (s), 3 × 136.79 (d), 2 × 144.18 (s), 2 × 144.36 (d), 2 × 144.93 (d), 2 × 151.81 (s), 176 (s), 177 (s); MS (*m/e*) 527 ($M^+ + 1$).

5.2.3. 1,5-Bis[1-(cyclohexane)-2-methyl-4H-pyridone-3-yloxy]pentane (**3c**)

Yield 19%; IR (Neat, cm^{-1}) 2936, 1622, 1554, 1505, 1228; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1–1.90 (m, 28H), 2.32 (s, 6H), 4.00 (m, 4H), 6.35 (d, 2H), 7.30 (d, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2 × 12.508 (q), 2 × 25.35 (t), 5 × 26.10 (t), 30.25 (t), 5 × 33.69 (t), 2 × 60.56 (d), 2 × 71.96 (t), 2 × 117.41(d), 2 × 134.02 (d), 2 × 140.72 (s), 2 × 147.24 (s), 2 × 173.40 (s); MS (*m/e*) 483 ($M^+ + 1$).

5.2.4. 1,5-Bis[1-(4-methoxy phenyl)-2-methyl-4-1H-pyridone-3-yloxy]pentane (**3d**)

Yield 56%; IR (Neat, cm^{-1}) 2937, 1621, 1553, 1507, 1286, 1244, 1182; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 2H), 1.80 (m, 4H), 2.05 (s, 6H), 3.90 (s, 6H), 4.20 (m, 2H), 6.40 (d, 2H), 7.00 (d, 2H), 7.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2 × 14.59 (q), 22.50 (t), 2 × 30.36 (t), 2 × 56.03 (q), 2 × 71.91 (t), 4 × 115.28 (d), 2 × 117.00 (d), 4 × 128.25 (d), 2 × 135.06 (s), 2 × 139.21 (d), 2 × 141.34 (s), 2 × 146.94 (s), 2 × 160.41 (s), 2 × 174.17 (s); MS (*m/e*) 531 ($M^+ + 1$); Anal. Calcd. for $C_{31}H_{34}O_6N_2$: C, 66.10; H, 6.45; N, 4.60. Found: C, 65.52; H, 6.32; N, 4.11%.

5.2.5. 1,5-Bis[1-phenyl)-2-methyl-4-1H-pyridone-3-yloxy]pentane (**3e**)

Yield 57%; IR (KBr, cm^{-1}) 2933, 1626, 1562, 1485, 1287, 1193; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.75 (m, 2H), 1.85 (m, 4H), 2.06 (s, 6H), 4.20 (t, 4H), 6.45 (d, 2H), 7.30 (m, 7H), 7.55 (m, 5H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2 × 14.63 (q), 22.86 (t), 2 × 30.35 (t), 2 × 71.92 (t), 2 × 117.11 (d), 4 × 127.16 (d), 2 × 129.86 (d), 4 × 130.29 (d), 2 × 128.82 (d), 2 × 140.85 (s), 2 × 142.17 (s), 2 × 147.01 (s), 2 × 174.18 (s); MS (*m/e*) 472 ($M^+ + 2$), 471 ($M^+ + 1$); Anal. Calcd. for $C_{29}H_{30}O_4N_2$: C, 70.76; H, 6.42; N, 5.95. Found: C, 70.06; H, 6.32; N, 5.12%.

*5.2.6. 1,5-Bis[1-benzyl)-2-methyl-4-1H-pyridone-3-yloxy]pentane (**3f**)*

Yield 42%; IR (KBr, cm^{-1}) 2946, 1625, 1567, 1457, 1250; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 2H), 1.80 (m, 4H), 2.24 (s, 6H), 4.10 (m, 4H), 5.05 (s, 4H), 6.40 (d, 2H), 7.00 (d, 2H), 7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2×12.94 (q), 22.51 (t), 2×30.28 (t), 2×57.51 (t), 2×71.94 (t), 2×117.54 (d), 4×126.28 (d), 2×126.67(d), 4×129.63 (d), 2×135.83 (s), 2×139.48 (d), 2×141.28 (s), 2×147.69 (s), 2×173.97 (s); MS (*m/e*) 500 ($M^+ + 2$); Anal. Calcd. for $C_{31}H_{34}O_4N_2$: C, 72.18; H, 6.87; N, 5.61. Found: C, 71.38; H, 7.34; N, 5.07%.

*5.2.7. 1,5-Bis[1-fluorophenyl)-2-methyl-4-1H-pyridone-3-yloxy]pentane (**3g**)*

Yield 29%; IR (KBr, cm^{-1}) 2936, 1627, 1578, 1502, 1291, 1219, 1189; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 2H), 1.85 (m, 4H), 2.05 (s, 6H), 4.17 (m, 4H), 6.40 (d, 2H), 7.25 (m, 10H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2×21.60 (q), 26.20 (t), 52.61 (t), 57.37 (t), 58.79 (t), 70.91 (t), 2×109.19 (s), 2×111.37 (d), 118.59 (d), 120.00 (d), 122.29 (d), 2×129.61 (s), 4×128.95 (d), 4×130.03 (d), 135.36 (s), 136.60 (s), 138.21 (s), 138.78 (s), 2×173.67 (s); MS (*m/e*) 507 ($M^+ + 1$); Anal. Calcd. for $C_{29}H_{28}O_4N_2F_2$: C, 68.16; H, 5.57; N, 5.13. Found: C, 67.54; H, 5.33; N, 4.61%.

*5.2.8. 1-(2,6-Dimethyl-phenyl)-2-methyl-3-[5-(2-methyl-4-oxo-4H-pyran-3-yloxy)pentyloxy]-1H-pyridin-4-one (**4a**)*

Yield 22%; IR (Neat, cm^{-1}) 3006, 1624, 1575, 1475, 1434, 1281, 1250, 1216, 1189; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.65 (m, 2H), 1.80 (m, 4H), 2.00 (s, 3H), 2.10 (s, 6H), 2.35 (s, 3H), 4.10 (m, 2H), 4.20 (m, 2H), 6.35 (d, 1H), 6.55 (d, 1H), 7.10 (d, 1H), 7.20 (d, 1H), 7.30 (m, 2H), 7.60 (d, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 13.20 (q), 15.11 (q), 2×17.68 (q), 22.79 (t), 30.24 (t), 30.31 (t), 71.88 (t), 72.54 (t), 2×117.49 (d), 118.39 (s), 2×129.40 (d), 130.02 (d), 2×135.52 (s), 137.81 (d), 140.23 (s), 140.69 (s), 145.22 (s), 153.74 (d), 159.41 (s), 140.69 (s), 145.22 (s), 153.74 (d), 159.41 (s), 175.23 (s), 175.44 (s); MS (*m/e*) 424 ($M^+ + 1$).

*5.2.9. 1-(Cyclohexane)-2-methyl-3-[5-(2-methyl-4-oxo-4H-pyran-3-yloxy)pentyloxy]-1H-pyridin-4-one (**4c**)*

Yield 18%; IR (Neat, cm^{-1}) 2941, 1645, 1624, 1568, 1434, 1220; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20–2.00 (m, 10H), 2.32 (s, 3H), 2.39 (s, 3H), 4.00 (m, 4H), 6.30 (d, 1H), 6.40 (d, 1H), 7.35 (d, 1H), 7.60 (d, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 12.50 (q), 15.11 (q), 22.79 (t), 25.41 (t), 2×26.16 (t), 2×30.23 (t), 2×33.75 (t), 60.54 (d), 71.87 (t), 2×117.48 (d), 133.91 (d), 140.47 (s), 145.23 (s), 147.29 (s), 153.76 (d), 159.50 (s), 173.46 (s), 175.49 (s); MS (*m/e*) 402 ($M^+ + 1$).

*5.2.10. 1-(Benzyl)-2-methyl-3-[5-(2-methyl-4-oxo-4H-pyran-3-yloxy)pentyloxy]-1H-pyridin-4-one (**4f**)*

Yield 15%; IR (Neat, cm^{-1}) 2948, 1636, 1572, 1251; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 (m, 2H), 1.70 (m, 4H), 2.18 (s, 3H), 2.34 (s, 3H), 4.00 (t, 2H), 4.10 (t, 2H), 5.00 (s, 2H), 6.30 (d, 1H), 6.40 (d, 1H), 6.90 (d, 1H), 7.20 (m, 5H), 7.50 (d, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 12.60 (q), 14.80 (q), 22.5 (t), 2×29.9 (t), 57.2 (t), 71.6 (t), 72.2 (t), 117.2 (d), 117.3 (d), 2×125.9 (d), 128.40 (d), 2×129.4 (d), 135.5 (s), 139.1 (d), 140.8 (s), 144.9 (s), 147.4 (s), 153.5 (d), 159.2 (s), 173.7 (s), 175.2 (s); MS (*m/e*) 410 ($M^+ + 1$).

*5.2.11. 1-(4-Fluoro-phenyl)-3[5-(2-methyl-4-oxo-4H-pyran-3yloxy)pentyloxy]-1H-pyridin-4-one (**4g**)*

Yield 18%; IR (Neat, cm^{-1}) 2953, 1644, 1626, 1577, 1507, 1293, 1254, 1221, 1189; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.70 (m, 2H), 1.80 (m, 4H), 2.05 (s, 3H), 2.31 (s, 3H), 4.10 (t, 2H), 4.20 (t, 2H), 6.30 (d, $J = 6.0$ Hz, 1H), 6.40 (d, $J = 8$ Hz, 1H), 7.20 (m, 5H), 7.60 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.59 (q), 15.07 (q), 22.72 (t), 30.14 (t), 30.24 (t), 71.80 (t), 72.47 (t), 117.04 (d), 117.16 (d), 117.39 (d), 117.50 (d), 129.09 (d), 129.26 (d), 138.15 (s), 138.92 (d), 140.82 (s), 145.13 (s), 146.95 (s), 153.86 (s), 159.48 (s), 165.44 (s), 174.13 (s), 175.42 (s); MS (*m/e*) 414 ($M^+ + 1$).

*5.2.12. 1-(4-Chloro-phenyl)-2-methyl-3-[5-(2-methyl-4-oxo-4H-pyran-3-yloxy)pentyloxy]-1H-pyridin-4-one (**4h**)*

Yield 32%; IR (Neat, cm^{-1}) 2938, 1630, 1573, 1487, 1287, 1254, 1187, 1091; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.70 (m, 2H), 1.80 (m, 4H), 2.06 (s, 3H), 2.31 (s, 3H), 4.10 (t, 2H), 4.20 (t, 2H), 6.30 (d, $J = 6.0$ Hz, 1H), 6.45 (d, $J = 8.00$ Hz, 1H), 7.30 (m, 4H), 7.55 (d, $J = 8.00$ Hz, 1H), 7.70 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.69 (q), 15.14 (q), 22.79 (t), 30.23 (t), 30.32 (t), 71.89 (t), 72.56 (t), 2×117.53 (d), 2×128.64 (d), 2×130.56 (d), 136.01 (s), 138.62 (d), 2×145.25 (s), 153.75 (d), 2×159.48 (s), 174.23 (s), 175.44 (s); MS (*m/e*) 429 ($M^+ + 1$).

*5.2.13. 1-(4-Nitro-phenyl)-2-methyl-3-[5-(2-methyl-4-oxo-4H-pyran-3-yloxy)pentyloxy]-1H-pyridin-4-one (**4i**)*

Yield 20%; IR (Neat, cm^{-1}) 2942, 2361, 1628, 1578, 1526, 1291, 1189; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 2H), 1.80 (m, 4H), 2.10 (s, 3H), 2.35 (s, 3H), 4.10 (t, 2H), 6.35 (d, 1H), 6.50 (d, 1H), 7.20 (d, 1H), 7.50 (d, 1H), 7.60 (d, 1H), 8.40 (d, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.80 (q), 15.11 (q), 22.76 (t), 30.28 (t), 71.95 (t), 72.49 (t), 117.48 (d), 117.78 (d), 2×125.72 (d), 2×128.67 (d), 138.12 (d), 139.69 (s), 145.21 (s), 147.08 (s), 147.34 (s), 148.29 (s), 153.83 (d), 159.52 (s), 174.29 (s), 175.46 (s); MS (*m/e*) 441 ($M^+ + 1$).

*5.2.14. 1-(2-Methoxy-phenyl)-2-methyl-4-oxo-4H-pyran-3-yloxy)pentyloxy]-1H-pyridin-4-one (**4j**)*

Yield 52%; IR (Neat, cm^{-1}) 2946, 1625, 1560, 1499, 1284, 1252, 1192; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 2H), 1.80 (m, 4H), 2.00 (s, 3H), 2.30 (s, 3H), 3.80 (s, 3H), 4.00 (m, 2H), 4.15 (m, 2H), 6.30 (d, 1H), 6.40 (d, 1H), 7.00 (d, 1H), 7.20 (m, 3H), 7.40 (m, 1H), 7.60 (d, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 13.73 (q), 15.16 (q), 29.66 (t), 2×30.29 (t), 56.83 (q), 71.05 (t), 71.68 (t), 2×112.61 (d), 117.55 (d), 121.54 (d), 128.69, 130.87 (s), 131.52 (s), 139.25 (d), 141.85 (s), 145.28 (s), 147.33 (s), 153.70 (d), 154.94 (s), 159.49 (s), 173.0 (s), 175.52 (s); MS (*m/e*) 426 ($M^+ + 1$).

Acknowledgements

Financial support to SP by MOH, New Delhi, technical support by Mrs. Manju are gratefully acknowledged. Thanks are also due to Mr. M.P.S. Negi., Div. Of Biometry for data analysis.

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