

Synthesis and Anti-inflammatory Study of Novel N-substituted Hydroacridine-1,8-diones and Bis-hexahydroacridine-1,8-dione Derivatives

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Abstract

We report in this study the synthesis of some new N-substituted hexahydroacridine-1,8-dione compounds including some new N-2-hydroxypropylhexahydroacridine-1,8-diones and their tosylatedoctahydroacridine-1,8-dione derivatives in addition to some bis-hexahydroacridine-1,8-diones via a one pot reaction technique. Moreover, *in vivo* anti-inflammatory evaluation for some newly synthesized compounds has been investigated. The highly alkylated bis-hydroacridine-1,8-dione 5f showed a higher anti-inflammatory potency more than the non-alkylated and the standard employed indomethacin. The structure of all new products has been characterized by IR, ¹H-NMR and ¹³C-NMR.

Keywords: Acridines; Bis-acridine; Hexahydroacridinones; Anti-inflammatory agents

Introduction

Large number of natural and synthetic acridine scaffold compounds exhibit broad spectrum of biological and physical properties [1-5]. Although many researchers have devoted their studies on synthesis of acridine compounds and their pharmaceutical applications as anti-tumor [6-9], anti-bacterial [10], anti-malarial [11] and anti-inflammatory agents [12]. Acridinediones, in particular, have been identified as anti-malarial and anti-tumor agents [13-15]. Hexahydroacridine-1,8-dione derivatives are also reported to possess important properties such as high fluorescence efficiency [16]. As a consequence, the interest of organic chemists in the synthesis or structure modifications of hydroacridinone derivatives remains high. It has also been discovered that the introduction of a substituted group to the nitrogen atom of hexahydroacridine-1,8-diones leads to enhance the fluorescence activity [17,18]. Recently, Hubschwerlen et al. found that the introduction of a cyclopropyl group to the nitrogen atom of the pyridine ring results in a wide spectrum of anti-bacterial activities [19]. However, the introduction of a 2-hydroxypropyl or tosylated propyl groups to the nitrogen atom has not been reported yet.

On other hand, many studies showed that dimerization of acridine compounds enhance their biological activities. They were first developed as tumorostatic agents compared to those of the respective mono acridines [20-22]. Synthesis of such dimeric ligands, have been employed to improve the local concentration of the bioactive species and to avoid the cellular efflux mechanisms associated with multi drug resistance to the respective monomeric counter parts [23,24]. Bis-acridines have also demonstrated bioactivity in mice infected with *Plasmodium berghei* [22] and *in vitro* against *Plasmodium falciparum* and trypanosomatid parasites [25]. Such aforementioned facts inspired us to synthesis and investigate the anti-inflammatory potency of some new N-substituted hydroacridine-1,8-diones and their dimer derivatives.

Experimental

All melting points are uncorrected and were determined by Kofeler melting point apparatus. IR (cm⁻¹) spectra were recorded (KBr disc) on a Shimadzu DR-8001 spectrophotometer. ¹H-NMR and ¹³C-NMR (DMSO-d₆ or CDCl₃) spectra were recorded at 400 MHz on a Varian Mercury-300 BB at Sohag University, the chemical shift is expressed in δ value (ppm) using TMS as an internal reference Evaluation of Anti-

inflammatory effect was carried out by Faculty of Medicine, Assuite University.

Synthesis of hexahydroacridine-1,8-diones (3a-f)

General procedure: (1 mmol, 0.08 mL) of 1-aminopropan-2-ol and a catalytic amount of triethylamine were added to each of the following mixture: a mixture of (2 mmol) of the 1,3-cyclohexanedione (2a), (1 mmol) of salicylaldehyde or 5-bromosalicylaldehyde (1a,b); a mixture of (2 mmol) of the 5,5-dimethyl-1,3-cyclohexanedione (2b), (1 mmol) of salicylaldehyde or 5-bromosalicylaldehyde (1a,b) or a mixture of (2 mmol) 5-diphenyl-1,3-cyclohexane-dione (2c), (1 mmol) of 5-bromosalicylaldehyde or 3-bromo-5-chlorosalicylaldehyde (1b,c). Then each of these mixtures was refluxed in (20 mL) ethanol and monitored by TLC till completion after 5 hrs. The excess of solvent was evaporated under reduced pressure, and the obtained solid was collected by filtration and crystallized from ethanol to afford the corresponding products of hexahydroacridine-1,8-diones 3a-f respectively (Scheme 1).

9-(2-hydroxyphenyl)-10-(2-hydroxypropyl)-3, 4, 6, 7, 9, 10-hexahydroacridine-1,8-(2H,5H)-dione (3a): Yellow crystals, m.p 228°C. IR: (KBr,ν max, cm⁻¹), 3397(OH), 3062(CH aromatic), 2935-2874(CH aliphatic), 1627(C=O).¹H-NMR (DMSO-d₆):(δ_H), 10(s,1H,OH-phenolic), 9.0-6.7(m, J=4.5,6H, aromatic), 5.3-5.0 (m, J=7.2, 1H, CH₂-CHN), 5.1(s, 1H, OH alcoholic), 4.2(s,1H, ArCH), 3.8, 3.6(t, J=8.0, 4H, 2CH₂C=O cyclic),2.30-2.0(d,1H, N-CH₂-alcoholic), 2.2(t, J=8.0, 4H, 2=CH₂ cyclic), 2.0-1.9(m, J=8.0, 4H, 2CH₂-CH₂-CH₂), 1.3(d, J=7.2, 3H, CH₃).¹³C-NMR(DMSO-d₆): (δ_C), 187(2C=O), 158(2C=C hydroxyridine ring), 137(C-OH phenolic), 129.6, 129.3 (2C-CH hydroxyridine), 128.1, 127.9, 126.7, 126.1, 125.5, 123,118.9(C-Ar),109(CH-Ar), 65.9 (C-OH alc.), 58(CH₂-N), 51, 36.5,30, 27.6, 25.9, 21.6, 21.1, 20.3 (6 CH₂ + CH₃).

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9-(5-bromo-2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,4,6,7,9,10-hexahydro-acridine-1,8(2H,5H)-dione (3b): Yellow crystal, m.p 218°C. IR: (KBr, ν_{\max} , cm^{-1}), 3419(OH), 3005(CH aromatic), 2966-2947(CH aliphatic), 1630(C=O), 616(C-Br); $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 10(s, 1H, OH phenolic), 7.12-7(d, $J=4.0$, 2H, aromatic), 6.66 (s, 1H, aromatic), 4.97-4.93(d, $J=4.5$, 2H, NCH₂), 3.83-3.81 (m, $J=4.5$, 1H, CH₃CH-), 3.35(s, 1H, ArCH), 3.13-3.08(t, $J=7.2$, 2H, CH₂C=O cyclic), 2.93-2.89(m, $J=7.2$, 2H, CH₂-CH₂-CH₂), 2.5(s, OH, alcoholic), 2.63-2.62(m, $J=7.2$, 2H, CH₂CH₂C=O), 2.01-1.99 (t, $J=7.2$, 4H, =CH₂CH₂), 1.15-1.16(d, $J=4.5$, 3H, CH₃); $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 198, 197.3(2 C=O), 156, 153 (2C=C hydroxyridine ring), 153(Br-C), 135.3 (CH-OH phenolic), 131, 130, 119, 114.3, 114, 111(6C Ar), 66.8(CH-OH alc), 51(CH₂-N), 36.18, 36.05(2 CH₂-CO), 26, 21 (4 CH₂ cyclic), 19(CH₃).

9-(2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3c): Yellow crystals, m.p 170°C. IR : (KBr, ν_{\max} , cm^{-1}), 3420(OH), 3055(CH aromatic), 2952, 2870(CH aliphatic), 1635(C=O), 1601(C=C), 620(C-Br). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 10.5(s, 1H, OH phenolic, D₂O exchangeable), 8.5-6.84(m, 3H, aromatic), 5.2 (s, 1H, OH-alcoholic D₂O exchangeable), 5.06 (s, 1H, CH-Ar), 3.6 (m, $J=4.0$, 1H, CH-CH₃), 2.51 (s, 4H, 2CH₂-C=O), 2.44 (d, $J=7.2$, 2H, CH₂-OH), 2.30(s, 4H, 2=CH₂), 1.19, 1.02, 0.92, 0.88 (m, 15H, 5CH₃). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 196.2 (2C=O), 164.5(2C=C hydroxyridine ring), 149.5(C-OH phenolic), 135, 133.9, 131.17, 130.6, 129.2, 120.7 (6 C-Ar), 119.6, 117.6 (2C-CH hydroxyridin ring), 66.01, 65.6(2CH₂-CO), 51.2(CH-OH alc), 40.62 (CH₂-N), 32.3, 31.9(2CH₂ cyclic), 29.68, 28.2, 26.7, 25.5, 18.77(5CH₃).

9-(5-bromo-2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3d): Yellow crystal, m.p 144°C. IR: (KBr, ν_{\max} , cm^{-1}), 3420(OH), 3055(CH aromatic), 2965(CH aliphatic), 1630(C=O), 1600(C=C). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 10.94(s, 1H, OH-phenolic, D₂O exchangeable), 7.10-6.93(m, 4H, aromatic), 5.2(s, 1H, CH-Ar), 5.06 (m, $J=8.0$, 1H, HO-CH-CH₂-N), 3.37(s, 1H, OH D₂O exchangeable), 2.56-2.51(d, $J=8.0$, 2H, N-CH₂-CHOH), 2.36(s, 2H, 2CH₂-C=O), 2.32(s, 2H, 2CH₂-C=O), 2.26 (s, 2H, =C-CH₂), 2.22 (s, 2H, =C-CH₂), 1.05(s, 3H, CH₃), 0.99(s, 6H, 2CH₃), 0.89(s, 6H, 2CH₃). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 196.2(2C=O), 165.19(C-OH aromatic), 150.1, 128.8, 127.3, 126.09, 124.62(5C aromatic + 2C(CH₃)₂), 115.7(2NC=C), 111.24 (2 NC=C), 102(CH-Ar), 50(2CH₂ for 2CH₂-C=O), 40(CH₂ for CH₂-N), 32.5(CH-OH), 32(2C=2C-CH₂), 29.6, 28.4, 26.6(5CH₃).

9-(5-bromo-2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,6-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3e): Yellow crystal, m.p 253°C. IR: (KBr, ν_{\max} , cm^{-1}), 3418(OH), 3027 (CH aromatic), 2967-2892 (CH aliphatic), 1625(C=O), 699(C-Br). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 11.2 (s, 1H, OH-phenolic), 8.3-6.8(m, 13H, 13CH aromatic), 4.54(s, 1H, Ar-CH=), 3.65 (m, $J=4.0$, H, CH₃CHCH₂N), 3.58(d, $J=4.0$, 2H, NCH₂), 3.55-3.51(m, $J=7.2$, 2H, 2PhCH), 2.5(s, 1H, OH alc.), 2.41-2.39(t, $J=7.2$, 4H, 2 CH₂C=O), 1.79-1.77(d, $J=7.2$, 4H, 2 CH₂CHPh), 1.39(d, $J=4.0$, 3H, CH₃). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 199.8, 191.8 (2 C=O), 175 (2C=CHydroxyridine ring), 170(C-OH phenolic), 156.4, 155.5(2Ph-C), 144.7, 139.9, 138.6, 132, 131, 129, 127.2, 127.1(8C, 2Ph), 121, 118, 110.9(C-Ar), 110.8(C-Br), 44(2CH-Ph), 42(CH-OH), 40(CH₂-N), 33, 15, 29.7(4CH₂ cyclic), 22 (CH₃).

9-(3-bromo-5-chloro-2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,6-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3f): Yellow crystal, m.p 235°C. IR: (KBr, ν_{\max} , cm^{-1}), 3437(OH), 3014(CH aromatic), 2987-2990 (CH aliphatic), 1645(C=O), 750(C-Cl), 640(C-Br). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 11(s, 1H, OH-phenolic),

8.3-7.0 (m, 12H, aromatic), 6.86-6.83(m, $J=8.0$, 2H, 2PhCH), 4.5(s, 1H, CH-Ar), 3.6(m, $J=7.6$, 1H, CH₃CHOH), 3.4(s, 1H, OH-alcoholic), 2.3(t, $J=8.0$, 4H, 2 CH₂C=O in cyclohexanone), 1.7(d, $J=7.6$, 2H, NCH₂), 1.3(d, $J=8.0$, 4H, 2 CH₂CH in cyclohexanone), 0.8(d, $J=7.6$, 3H, CH₃). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 175, 170(2C=O), 157.8, 156(2Ph-C), 147 (C=C hydroxyridine ring), 140 (C-OH phenolic), 139.1, 131.7(C-Cl, C-Br respectively), 129.8, 129.5, 127.7, 127.5, 119.9, 119.7, 119.1 (ArCH cyclic), 116.8 (2C-CH hydroxyridine ring), 44(CHOH), 30.1 (CH₂-N), 22.6(NCH₂), 19.2(2CH₂ cyclic), 18.3(CH₃).

Preparation of (3a) from the corresponding xanthenone (7) (see Scheme 2)

To a solution of 9-(2-hydroxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthen-1,8(2H)-dione(7)[26](0.248 g, 0.0008 mol) in (20 ml) ethanol, 1-aminopropan-2-ol (0.0625 ml, 0.0008 mol) and catalytic amount of triethylamine were added. The reaction mixture was refluxed for 3 hrs and allowed to cool at room temperature. The solid product was collected by filtration and crystallized from ethanol as yellow crystals, m.p. 228°C.

Synthesis of tosylated hexahydroacridinediones (4a-d)

General procedure: A solution of (1 mmol) of the hexahydroacridine-1,8-dione derivatives 3a-d, (1 mmol) of tosyl chloride and a catalytic amount of triethylamine in (20 mL) ethanol was refluxed and monitored by TLC till completion after 3 hrs. The reaction mixture was allowed to cool down to room temperature and the obtained solid product was collected by filtration, dried under vacuum and crystallized from the appropriate solvent to afford the corresponding tosylated acridinediones 4a-d respectively.

1-(9-(2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)propan-2-yl 4-methylbenzenesulfonate (4a): Yellow fine powder, m.p. 154°C. IR: (KBr, ν_{\max} , cm^{-1}), 3008(CH aromatic), 2950-2924(CH aliphatic), 1639(C=O), 1183(O=S=O). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 7.5(m, 9H, Ar), 5.01 (m, $J=4.4$, 1H, CH-O tosylate), 3.5(s, 1H, CH-Ar), 3.1(t, $J=4.4$, 4H, 2CH₂-Otosyl), 2.7, 2.5 (t, $J=8.0$, 4H, 2CH₂C=O), 2.29-2.27(t, $J=8.0$, 4H, 2=C-CH₂), 1.82, 1.81(m, $J=8.0$, 4H, 2 CH₂CH₂CH₂C=O), 1.21, 1.19(s, 6H, 2CH₃ of tosyl), 1.18(d, m, $J=4.4$, 3H, CH₃). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 197.3, 196.4(4C=O), 166.9 (2C=C cyclic hydroxyridine ring), 149.2 (C-OH phenolic), 146.4 (C-SO₂ tosyl), 133.7(C-CH₃ tolyl), 130.8, 128.7, 128.4, 128.2, 127.8, 125.9, 125.1(C-CAr), 123(CH-N), 116 (CH-Ar), 56.4(CH₂-O alc.), 46, 36.8(2CH₂-C=O cyclic), 28, 27.6(2CH₂=C), 21.6, 20.9 (2C-C), 20.4, 19.9(2 CH₃).

1-(9-(5-bromo-2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)propan-2-yl 4-methylbenzenesulfonate (4b): Yellow fine powder, mp. 192°C. IR: (KBr, ν_{\max} , cm^{-1}), 3402(OH), 3005(CH aromatic), 2950-2881(CH aliphatic), 1638(C=O), 1180(O=S=O). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 9.5(s, 1H, OH-phenolic), 7.6-6.9(m, 6H, Ar), 5.0(m, m, $J=4.2$, 1H, CH-O tosylate), 3.0 (s, 3H, CH₃ of tosyl), 2.9-2.8(m, $J=4.2$, 1H, CH-tosylate), 2.3-2.2(t, 2H, CH₂C=O), 2.0-1.9(t, $J=7.2$, 2H, CH₂CH₂CH₂), 1.84, 8(t, $J=7.2$, 4H, =C-CH₂), 1.9-1.8(d, d, $J=4.2$, 2H, NCH₂CH), 1.2-1.0(d, $J=4.2$, 3H, CH₃). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 207, 197.3(2C=O), 167.9(2=C-N cyclic), 150 (C-OH phenolic), 146.4(C-SO₂ tosyl), 139, 130, 129.7, 128.5, 125, 122.1, 120, 115(C-C Ar), 111(C-Br), 100, 58(CH-O alc.), 45.8(2CH₂-C=O), 32(CH₂-N), 28, 25.6 (2CH₂=C), 21.1, 23(2 CH₂-CH₂-CH₂), 23, 19.01(CH₃ alc., CH₃ tolyl respectively).

1-(9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)propan-2-yl 4-methylbenzenesulfonate (4c): Yellow fine powder, m.p 100°C. IR:

(KBr, ν max, cm^{-1}), 3300(OH arm), 3008(CH arm), 2975, 2870(CH aliphatic), 1696(C=O), 1177(O=S=O). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 10(s, 1H, OH aromatic), 7.78-6.93(m, 8H, CH aromatic), 5.26 (s, 1H, CHAr), 5.04(m, d, $J=2.6$, 1H, CH-O tosylate), 2.42-2.32(t, $J=2.6$, 2H, $\text{CH}_2\text{-O}$ tosyl), 2.27 (t, $J=4.8$, 4H, $2\text{CH}_2\text{C=O}$), 2.24-2.23(t, $J=4.8$, 4H, 2-C-CH_2), 2.1 (s, 3H, CH_3 of tosyl) 1.1, 0.93, 0.85 (s, 15H, 5CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 197.3, 188.3 (2C=O), 166, 149.9, 136.5, 133.1, 130.8, 129.4, 128.7, 127.6, 125.8, 125.6, 124.8, 118.6, 116.8, 31, 29.4(12C aromatic + 2C=C + 2C-(CH_2) $_2$ respectively), 115.9(CH-N), 111(CH-Ar), 50.6 ($\text{CH}_2\text{-O}$), 50.4, 46.7, 41, 40.8, 28 (4 CH_2), 26.9, 26.4, 25.4, 21.5, 21, 20.9(6 CH_3).

1-(9-(5-bromo-2-hydroxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)propan-2-yl 4-methylbenzenesulfonate (4d): Yellow fine powder, m.p 160°C. IR: (KBr, ν max, cm^{-1}), 3008(CH aromatic), 2950, 2924, 2886, 2856(CH aliphatic), 1638 (C=O), 1178 (O=S=O), 660(C-Br). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 8.03-6.88(m, 11H, CH-Ar), 5.06 (m, $J=6.8$, 1H, CH-O tosylate), 2.83(s, 2H, $\text{CH}_2\text{-C=O}$), 2.51 (s, 6H, CH_3 of alc., CH_3 of tosyl), 2.38-2.33(m, $J=6.8$, 1H, CH-N), 2.25 (d, $J=6.8$, 2H, $\text{CH}_2\text{-O}$ tosyl), 2.08(s, 4H, 2-C-CH_2), 1.03, 0.96 (s, 12H, 4 CH_3), 0.87(s, 3H, CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 197.3, 196.2(2C=O), 165.7, 164.6 (2=C-N dihydropyridine ring), 163(C-OH phenolic), 149.4, 148.4, 146.6, 133.4, 131.1, 130.9, 129.8, 128.07, 126.2, 119.3 (C-C Ar), 118.9(C-Br), 108.8(2=C-CH dihydropyridine ring), 56.4($\text{CH}_2\text{-O}$ propyl), 51.1, 50.5(2C-CO), 42.1, 41.3(2C-C), 29.4, 28.8, 28.3, 27.6 (4 CH_3 cyclic), 25.8(CH_3 -tosyl), 19.9 (CH_3 -propyl).

Synthesis of bis-hexahydroacridine-1,8-diones (5a,b,e,f) and bis-Schiff bases (6a,b)

General procedure: A mixture of (4 mmol) of the 1,3-cyclohexanedione derivatives 2a-c (448 mg of 2a, 560 mg of 2b or 752 mg of 2c), (2 mmol) of salicylaldehyde 1a (244 mg) or its derivative 1b (402 mg) and a catalytic amount of triethylamine was refluxed for 3 hrs. Ethylenediamine (60 mg, 1mmol) was added to the reaction mixture with further reflux for another 3 hours. The mixture was allowed to cool down to the ambient temperature, and the resulting solid product was collected by filtration, dried under vacuum and crystallized from ethanol to afford the pure products of the corresponding bis-hexahydroacridine-1,8-diones 5a,b,e,f (Scheme 1). In some cases, when we tried to repeat the reaction but at a shorter time with cyclohexane-1,3-dione 2a and also with the dimedone 2b, we isolated the corresponding bis-Schiff bases 6a,b instead.

10,10'-(ethane-1,2-diyl)bis(9-(2-hydroxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione) (5a): Yellow fine powder, m.p 213°C. IR: (KBr, ν max, cm^{-1}), 3387(OH), 3035(CH aromatic), 2911-2863 (CH aliphatic), 1640(C=O). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 9.93(s, 2H, 2OH-phenolic), 7.8-6.90(m, 8H, 8CH aromatic), 5.4(s, 2H, 2Ar-CH), 3.27-2.95(t, $J=7.4$, 8H, 4 $\text{CH}_2\text{C=O}$), 2.10-2.00(t, $J=8.0$, 4H, $\text{NCH}_2\text{CH}_2\text{N}$), 1.89-1.83(t, $J=7.4$, 8H, 4C=C- CH_2), 1.76-1.70(m, $J=7.4$, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{C=O}$). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 200.08, 195.01(4C=O), 163 (4 C=C- CH_2), 153 (2C-OH phenolic), 126.5, 125.9, 124.4, 123.5, 122.2, 121.4, 119.1(C-C Ar), 113(4=C-N), 100 (2CH cyclic), 59.2 (2 CH_2 , $\text{NCH}_2\text{CH}_2\text{N}$), 51, 39, 37, 35(4 CH_2 , 4 $\text{CH}_2\text{C=O}$), 29.2, 28.3, 26.7, 25.2(4 CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2\text{C=O}$ cyclic), 19.9, 18.5, 17.2, 16.8(4 CH_2 , $\text{CH}_2\text{CH}_2\text{C=O}$ cyclic).

10,10'-(ethane-1,2-diyl)bis(9-(5-bromo-2-hydroxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione) (5b): Yellow fine powder, m.p 223°C. IR: (KBr, ν max, cm^{-1}), 3437(OH), 3076(CH aromatic), 2941-2885(CH aliphatic), 1639 (C=O), 725(C-Br). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 10.3(s, 2H, 2OH-phenolic), 7.1-6.93(m, 8H, 8CH

aromatic), 5.1(s, 2H, 2Ar-CH), 2.57-2.51(t, $J=7.8$, 8H, 4 $\text{CH}_2\text{C=O}$), 2.15-2.24(t, $J=4.6$, 4H, $\text{NCH}_2\text{CH}_2\text{N}$), 1.92-1.86 (t, $J=7.8$, 8H, 4C=C CH_2), 1.85-1.73 (m, $J=7.8$, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{C=O}$). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 204.6, 196.4(4C=O), 167, 150(4C aromatic), 128.8, 128.3, 127.4, 127.2, 126, 121.8(8CH aromatic), 119.8(4NC=C), 115(4NC=C), 101(2CH cyclic), 56.4 (2 CH_2 , $\text{NCH}_2\text{CH}_2\text{N}$), 48, 37, 36, 34 (4 CH_2 , 4 $\text{CH}_2\text{C=O}$), 27.7, 27, 25.8, 24(4 CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2\text{C=O}$ cyclic), 20.8, 20.7, 20.2, 19(4 CH_2 , $\text{CH}_2\text{CH}_2\text{C=O}$ cyclic).

10,10'-(ethane-1,2-diyl)bis(9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione) (5e): Yellow fine powder, m.p 250°C. IR: (KBr, ν max, cm^{-1}), 3443 (OH-phenolic), 3100 (CH aromatic), 2951-2883(CH aliphatic), 1630(C=O). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 9.4 (2OH phenolic), 7.3-6.8 (m, 6H, aromatic), 5(s, 2H, 2CHAr), 4.9(HO-C=, D_2O exchangeable), 2.5(s, 4H, 2CH=C-OH), 2.25-2.15 (t, $J=8.0$, 4H, $\text{NCH}_2\text{CH}_2\text{N}$), 2.1(s, 8H, 4C=C CH_2), 1.0(s, 24H, 8 CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 196.1(4 C=O), 164.9 (2C-Br, aromatic), 149.4 (2C-OH, aromatic), 131, 130, 128 (6CH, aromatic), 118(4 NC=C), 115(4NC=C), 110(2CH-C, aromatic), 56(4C, C- CH_3), 50.8(2 CH_2 , $\text{NCH}_2\text{CH}_2\text{N}$), 40.6 (4 CH_2 , 4 $\text{CH}_2\text{C=O}$ cyclic), 32(=C- CH_2), 29, 28, 26, 25 (8 CH_3).

10,10'-(ethane-1,2-diyl)bis(9-(5-bromo-2-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione) (5f): Yellow fine powder, m.p 225°C. IR: (KBr, ν max, cm^{-1}), 3443 (OH-phenolic), 3100 (CH arm), 2951-2883(CH aliphatic), 1630(C=O). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 9.4 (2 OH phenolic), 7.3-6.8 (m, 6H, aromatic), 5 (s, 2H, 2CHAr), 4.9(HO-C=, D_2O exchangeable), 2.5(s, 4H, 2CH=C-OH), 2.25-2.15 (t, $J=8.0$, 4H, $\text{NCH}_2\text{CH}_2\text{N}$), 2.1 (s, 8H, 4C=C CH_2), 1.0 (s, 24H, 8 CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 196.1(4C=O), 164.9 (2C-Br, arm), 149.4(2C-OH, aromatic), 131, 130, 128 (6CH, aromatic), 118(4NC=C), 115(4NC=C), 110 (2CH-C, aromatic), 56(4C, C- CH_3), 50.8(2 CH_2 , $\text{NCH}_2\text{CH}_2\text{N}$), 40.6 (4 CH_2 , 4 $\text{CH}_2\text{C=O}$ cyclic), 32(=C- CH_2), 29, 28, 26, 25 (8 CH_3).

(3Z,3'E)-3,3'-(ethane-1,2-diyl)bis(azanylylidene)dicyclohexanone (6a): IR: 2889-2818(CH_2 aliphatic), 1638(C=O), 1602(C=N). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 3.45(s, 4H, $2\text{-C-CH}_2\text{C=O}$), 3.3(t, $J=6.4$, 4H, $2\text{CH}_2\text{-C=N}$ cyclic) 2.70-2.73(t, $J=8.0$, 4H, $\text{N-CH}_2\text{-CH}_2\text{-N}$), 2.26-2.4 (m, $J=6.4$, 8H, 4 CH_2 cyclic). $^{13}\text{C-NMR}$ (DMSO- d_6): (δ_{C}), 210 (2C=O), 165 (2C=N), 65(2N- CH_2), 40, 43(2 $\text{CH}_2\text{-CO-CH}_2$), 35(2 $\text{CH}_2\text{-C=N}$), 20 (2 CH_2 cyclic).

(5Z, 5'E)-5, 5'-(ethane-1,2-diyl)bis(azanylylidene)bis(3,3-dimethylcyclohexanone) (6b):

IR: 2900-2828(CH_2 aliphatic), 1640(C=O), 1610(C=N). $^1\text{H-NMR}$ (DMSO- d_6): (δ_{H}), 3.15 (s, 4H, $2\text{-C-CH}_2\text{C=O}$), 1.38-1.34(t, $J=8.0$, 4H, $\text{N-CH}_2\text{-CH}_2\text{-N}$), 2.16(s, 2H, $\text{C-CH}_2\text{-C}(\text{CH}_3)_2$), 1.97 (s, 4H, $2\text{O=C-CH}_2\text{-C}(\text{CH}_3)_2$), 0.99-0.97 (s, 12H, 4 CH_3).

Results and Discussion

Heating a solution of cyclohexane-1,3-dione 2a, 5,5-dimethylcyclohexane-1,3-dione 2b or 5-phenylcyclohexane-1,3-dione 2c with salicylaldehyde 1a, 5-bromo-salicylaldehyde 1b, or 5-bromo-3-chlorosalicylaldehyde 1c and 1-amiopropan-2-ol afforded the corresponding six derivatives of hexahydroacridinones 3a-f (Scheme 1).

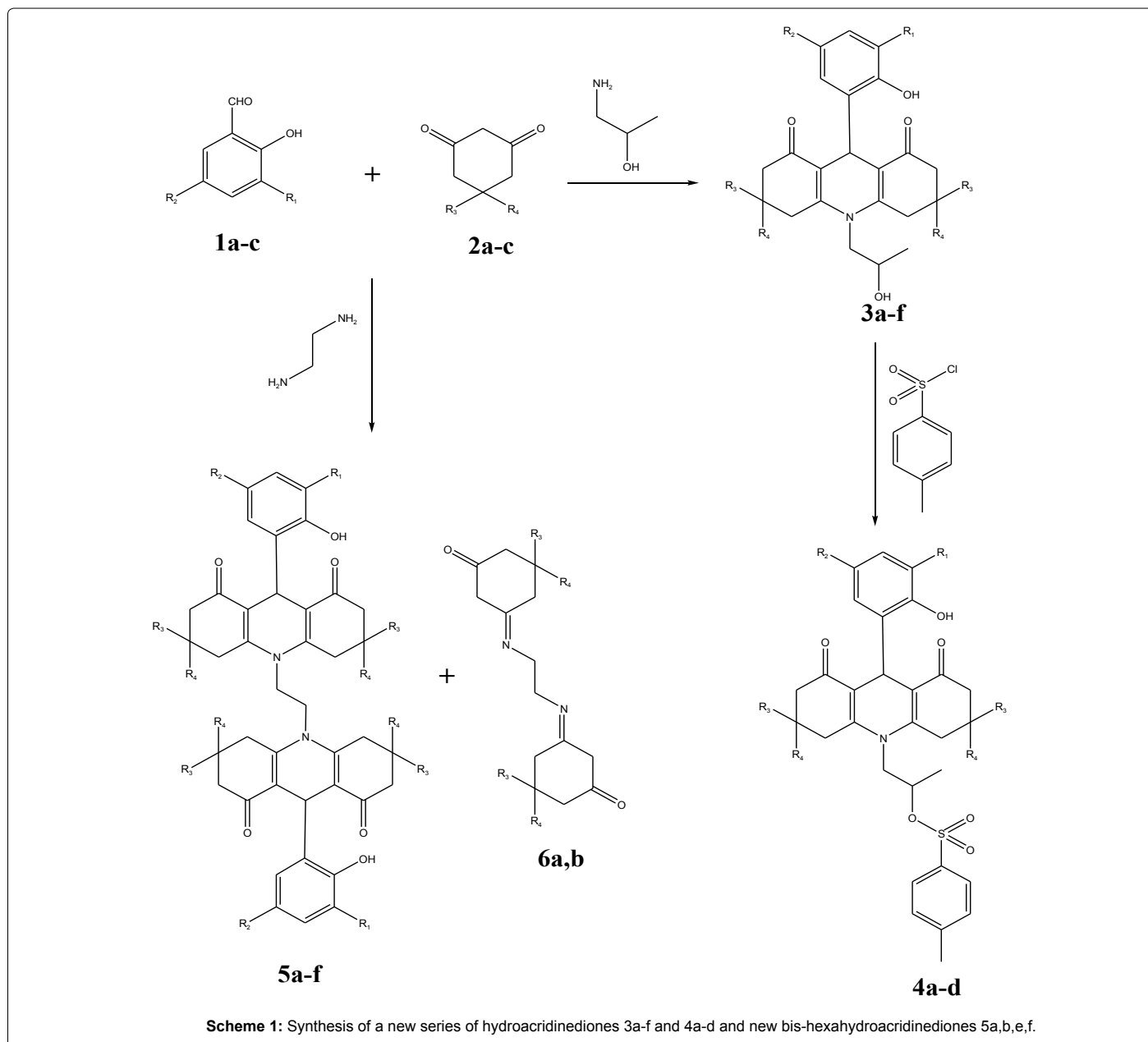
The molecular structure of the products 3a-f was elucidated from their IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra. The IR spectrum of these products in KBr showed broad bands at 3397-3421 cm^{-1} assigned for both of phenolic and alcoholic OH groups, and strong bands ranged from 1630-1648 cm^{-1} related to carbonyl groups. Broad bands characteristic of stretching the aliphatic CH_3 and CH_2 groups have

been also observed at $2874\text{--}2965\text{ cm}^{-1}$. The $^1\text{H-NMR}$ spectrum of 3a-f showed clearly the presence of phenolic OH at $\delta=10\text{--}10.9\text{ ppm}$ and alcoholic OH at $\delta=3.2\text{--}3.5\text{ ppm}$. Singlet sharp peaks at $\delta=1.05, 0.99, 0.89\text{ ppm}$ were attributed to the alcoholic CH_3 and the four methyl groups of dimedone scaffold respectively in 3d. The other two clear singlet peaks were observed at $\delta=3.6$ and 5.06 ppm assigned for the CH of the hydro pyridine ring and the CH of the isopropanol group respectively. The $^{13}\text{C-NMR}$ spectrum of 3a-f supported the presence of carbonyl at the range $\delta=199\text{--}196\text{ ppm}$, and aliphatic carbon signals appeared in the regular region (see experimental). Moreover, compound 3a has been further confirmed by refluxing the corresponding xanthenone 7 [26] with amino-iso-propanol (Scheme 2). The spectral data of the authentic product was identical with 3a.

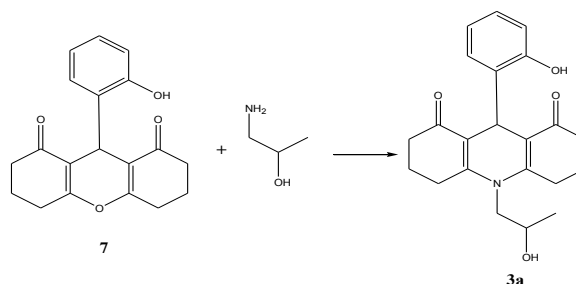
The alcoholic group in 3a-d has been tosylated by tosyl chloride in TEA to afford the corresponding tosylatedoctahydro-acridine-1,8-diones 4a-d via elimination of HCl. IR spectra showed a clear characteristic peak at 1177 (in 4c), 1178 (in 4d), 1180 (in 4b) and

1183 cm^{-1} (in 4a) for $(\text{O}=\text{S}=\text{O})$ group. The $^1\text{H-NMR}$ supported the presence of a multiplet peaks at $\delta=5\text{--}5.06\text{ ppm}$ assigned for the CH-O tosylate and a singlet peak for the CH_3 tolyl has been observed at the range $\delta=2.5\text{--}2.9\text{ ppm}$. Furthermore $^{13}\text{C-NMR}$ confirmed the existence carbonyl at average $\delta=197\text{ ppm}$. Two clear peaks have been also observed at $\delta=19$ and 22 ppm attributed to the CH_3 tolyl and CH_3 propyl groups respectively.

Gratifyingly, the symmetry function in the structures of the new products 5a,b,e,f (Scheme 1) has been unambiguously confirmed by both $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra. The ^{13}C resonance of the two carbon atoms of the ethyl linkage have been observed in all compounds 5a,b,e,f at the average $\delta=50\text{--}56\text{ ppm}$ and the $^1\text{H-NMR}$ confirmed the four proton resonance of the ethyl linkage as a symmetrical triplet peak between $\delta=2.0\text{--}2.5\text{ ppm}$. Moreover $^{13}\text{C-NMR}$ confirmed the existence of the peaks of four carbonyl groups between $\delta=204\text{--}196\text{ ppm}$ for all compounds 5a,b,e,f.



1-6	1			2			3						4				5				6			
	a	b	c	a	b	c	a	b	c	d	e	f	a	b	c	d	a	b	c	e	f	a	b	
R ¹	H	H	Br	-	-	-	H	H	H	H	H	Br	H	H	H	H	H	H	H	H	H	H	H	H
R ²	H	Br	Cl	-	-	-	H	Br	H	Br	Br	Cl	H	Br	H	Br	H	Br	H	Br	Br	H	H	H
R ³	-	-	-	H	Me	H	H	H	Me	Me	H	H	H	H	Me	Me	H	H	Me	Me	Me	Me	H	Me
R ⁴	-	-	-	H	Me	Ph	H	H	Me	Me	Ph	Ph	H	H	Me	Me	H	H	Me	Me	Me	Me	H	Me



Scheme 2: Synthesis of 3a via direct reaction of the corresponding xanthenone 7 with isopropanol amine.

The formation of N-hydroxypropyl-hexahydroacridine-1,8-diones 3a-f and the bis-hexahydroacridine-1,8-dione derivatives 5a,b,e,f can be rationalized as depicted in Scheme 3. An initial nucleophilic attack by the unstable imine 9 on the electrophilic C=C of the arylidene 8, where the two electron withdrawing carbonyl groups facilitate this reaction to form the intermediate 10 which undergoes an intramolecular arrangement to form the corresponding hydroxyl-octahydroacridinediones 10. Elimination a molecule of water from 10 affords the formation of 3a-f. As a result, this synthesis allows much wider substrate scope and provides a general and practical access to 3a-j. Similarly bis-hexahydroacridine-1,8-diones 5a,b,e,f can be justified by formation of the stable bis-imines 6 which we have succeeded to isolate two of these isomers 6a,b and characterized their structures (see experimental). The two nucleophilic centers labeled by the pair of electrons of the bis-imine nitrogen atoms could attack two folds of the arylidenes 8 to form the intermediate 12 which in turn could be stabilized to give the corresponding bis-hydroxy-octahydroacridine-1,8-diones 13. Elimination of two water molecules from 13 gives ultimately the corresponding bis-hexahydroacridine-1,8-diones 5a,b,e,f (Scheme 3).

Anti-inflammatory activity

Carrageenan-induced paw oedema standard method in rats: Anti-inflammatory activity screening for the chosen compounds 3c, 5a, 5b and 5f was determined *in vivo* by the acute carrageenan-induced paw oedema standard method in rats [27]. Adult albino rats of either sex (pregnant female animals were excluded) weighing 160-190 g were divided into 6 groups of 6 animals each. To reduce the variability of oedema response, rats were fasted overnight, then on the next day (day of experiment), animals were uniformly hydrated by giving 3 ml of water per rat orally. Indomethacin (reference standard) and the tested compounds (20 mg/kg body weight) were suspended in saline solution by the aid of few drops of Tween 80 (to improve wettability of particles) and given orally one hour before induction of inflammation. The control group was given saline solution containing few drops of Tween 80.

Carrageenan paw oedema was induced according to a modified method of Winter et al. [27,28] by subcutaneous injection of 1% solution of carrageenan in saline (0.1 ml/rat) into the subplanter region

of the right hind paw of rats. The thickness of rat paw was measured by mercury digital micrometer at different time intervals, at zero time and after one, two three, four and five hours of carrageenan injection. The oedema was determined from the difference between the thickness of injected and non-injected paws.

Data were collected, checked, revised and analyzed. Quantitative variables from normal distribution were expressed as means \pm SE "standard error". The significant difference between groups was tested by using one-way ANOVA followed by post hoc test [29] at $p < 0.05$ and $p < 0.01$.

The results of the anti-inflammatory activity were expressed as percentage inhibition of oedema thickness in treated animals in comparison with the control group according to the following equation (Table 1, Figure 1).

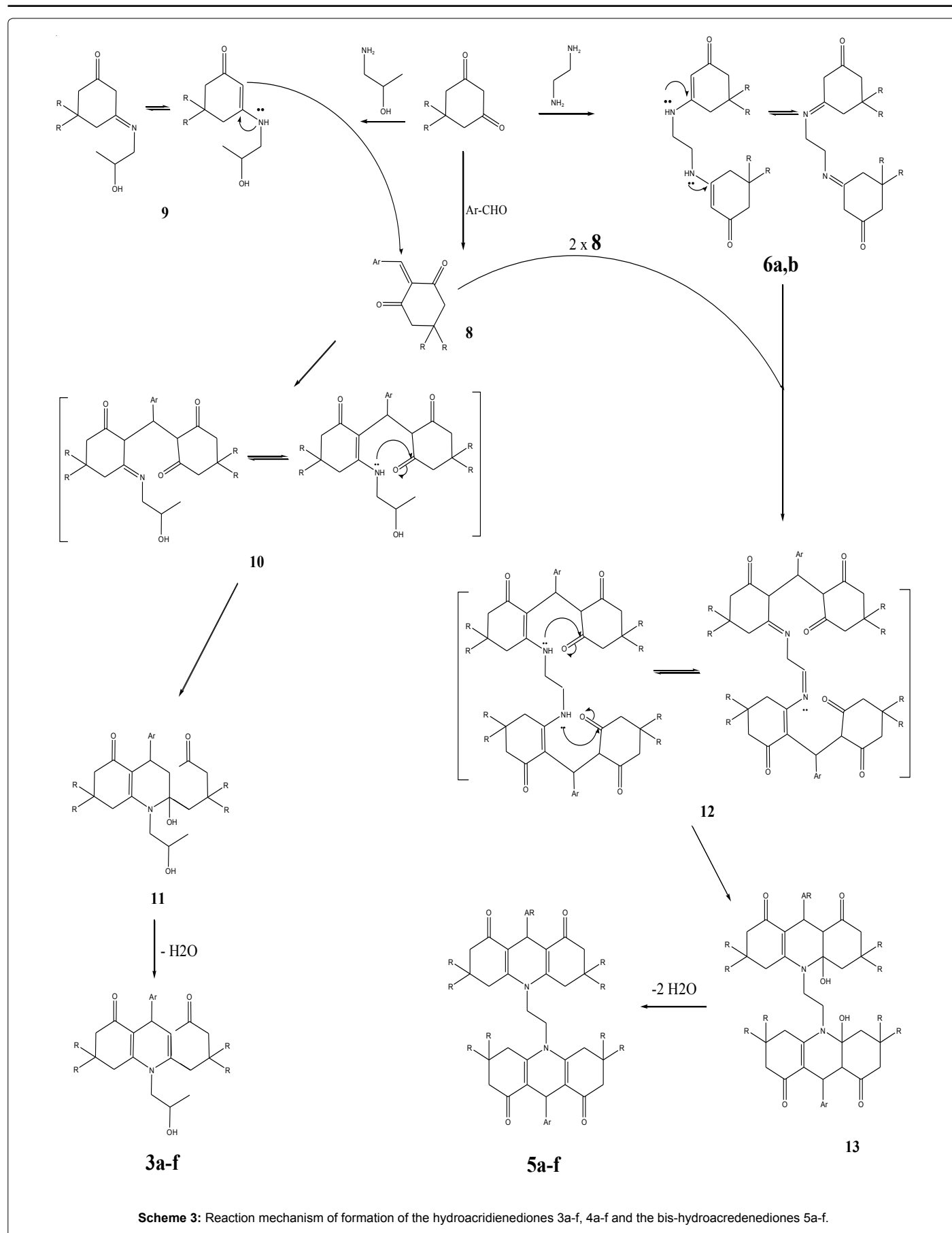
$$\% \text{Oedema inhibition} = \frac{(V_R - V_L)_{\text{treated}} \times 100}{(V_R - V_L)_{\text{control}}}$$

Where V_R represents the mean right paw thickness, V_L represents the mean left paw thickness, $(V_R - V_L)_{\text{control}}$ represents the mean increase in paw thickness in the control group of rats and $(V_R - V_L)_{\text{treated}}$ represents the mean increase in paw thickness in rats treated with the tested compounds [30,31].

Discussion

The anti-inflammatory activity of four representative synthesized compounds (5a,b,f and 3c) was determined by the carrageenan induced paw oedema standard method in rats [27,28]. Generally, it has been observed from the obtained results, (Table 1, Figure 1), that all the tested compounds show considerable anti-inflammatory activity. In addition, compounds 5f exhibit better anti-inflammatory properties (57.53 % inhibition of oedema) than that of the used reference standard indomethacin (54.9 % inhibition of oedema).

The effect of substituents on the anti-inflammatory potency has been considered by comparing the activity of the bis-hydroacridine derivatives 5a,b and 5f. The compound 5b showed higher anti-inflammatory potency (39.72) compared to 5a. This might attributed to the existence of the halogen atom. On other hand, we found the bis-hydroacridinedione 5f bearing 8 alkyl groups exhibits even better anti-inflammatory potency than 5b. The N-substituted



Compound	% of Oedema Inhibition				
	1 hours	2 hours	3 hours	4 hours	5 hours
Control	0.00	0.00	0.00	0.00	0.00
Indomethacin	15.06 ± 2.1	27.39 ± 0.39	28.76 ± 0.2	41.09 ± 3.2	54.79 ± 1.4
5a	12.33 ± 1**	23.28 ± 1.2**	26.02 ± 1.2**	8.22 ± 2.7**	5.47 ± 0.91**
5b	6.85 ± 0.79**	12.33 ± 1.2**	26.03 ± 3.2	30.13 ± 0.8**	39.72 ± 2.8**
5f	15.06 ± 0.85**	24.66 ± 0.85**	28.76 ± 0.61**	41.09 ± 1.2**	57.53 ± 2.1**
3c	2.74 ± 1.6**	13.7 ± 1.4	20.55 ± 1.2**	20.37 ± 0.83**	36.73 ± 1.7**

All values are represented as means of 6 experiments ± SE. Statistical analysis was carried out by one-way ANOVA test. ** Significant difference from the control value at $p < 0.01$

Table 1: Anti-inflammatory activity of the tested compounds using carrageenan-induced paw oedema in rats.

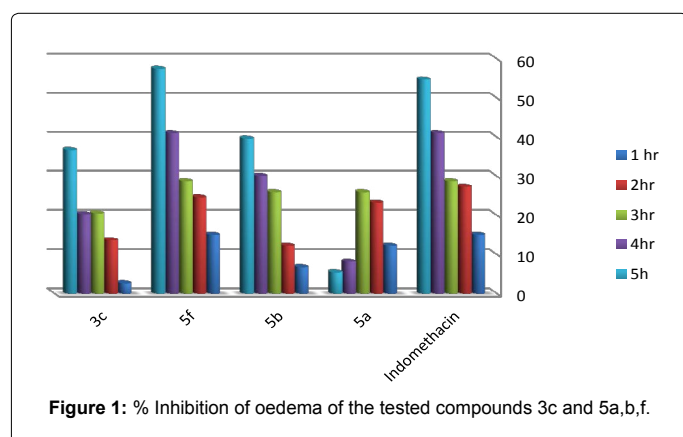


Figure 1: % Inhibition of oedema of the tested compounds 3c and 5a,b,f.

alcohol of the mono-hydroacridinedione 3c showed more effectiveness as an anti-inflammatory agent compare to the bis-hydroacridine-dione 5a. In general, we concluded that bis-hydroacridinediones bearing more electron donating alkyl groups showed high anti-inflammatory effect than the standard indomethacin. This means that the electron donating alkyl groups in hydroacridines could enhance their anti-inflammatory activity.

Conclusion

Synthesis of 9-(2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,4,6,7,9,10-hexahydro-acridine-1,8(2H,5H)-diones 3a-f and 10,10'-(ethane-1,2-diyl)bis-(9-(2-hydroxy phenyl)-3,4,6,7,9,10-hexahydro-acridine-1,8(2H,5H)-diones 5a,b,e,f are performed efficiently in a one pot reaction technique and described as a new class of anti-inflammatory agents. These agents showed (particularly 5f) an anti-inflammatory potency higher than the standard drug indomethacin.

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