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Synthesis and characterization of novel oxime analogues

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Novel oxime analogs have been synthesized from the tricyclic scaffolds. A series of iminoesters have been synthesized by reacting oximes with anti-inflammatory drugs such as Naproxen, Ibuprofen, Aspirin, Etodolac, Aceclofenac, Flurbiprofen in the presence of the coupling agent N,N′-dicyclohexylcarbodiimide.

Keywords: Tricyclic ring, Iminoesters, Anti-inflammatory drugs, N,N'-Dicyclohexylcarbodiimide

Oximes are compounds containing nitrogen that are very useful intermediaries in chemical syntheses. The most straightforward reaction of oxime formation is that of hydroxylamine with an aldehyde or ketone using a base to form an aldoxime or ketoxime.

Chemical compounds react with oximes like ketoximes and aldoximes to give analogs like iminoesters[1,2], exhibiting a range of pharmacological activity[3] which includes anti-inflammatory[4–6], anti-carcinogenic[7,8], photochemotherapeutic[9], anti-fungal[10]. Tricyclic imino esters are also evaluated as potential photo-induced DNA cleaving agents[11–13], antiproliferative agents[14], and antimicrobial agents[15].

Hybrid compound strategies to enhance the therapeutic potential by conjugating oximes with anti-inflammatory drugs like Aspirin[16], Indomethacin[17], and other NSAIDs[18] have also been studied.

The present study is aimed at synthesizing novel iminoesters by conjugating oximes of the tricyclic system such as 10,10-dimethylanthrone, dibenzo-suberenone, and dibenzosuberone with varying substrates like Naproxen, Ibuprofen, Aspirin, Etodolac, Aceclofenac, Flurbiprofen using N,N′-dicyclohexyl carbodiimide (DCC) as coupling agent at RT[19].

Experimental Details

Melting point determinations were done by the open tube capillary method and are uncorrected; JASCO,FT/IR-4100 Type A was used to record the IR spectra(using KBr pellets).^{1}H and ^{13}C NMR spectra were recorded using BRUKER, Spect PROBHD 5 mm PABBO BB400MHz, 100 MHz, respectively, using solvent $CDCl_3$ and Internal standard TMS. With Shimadzu 8040(ion source -ES+) and Waters and Synapt XS HDMS Separation Module: UPLC Acquity H class series system (ion source -ESI) LC-MS spectrometer, the mass spectra were recorded.

The general procedure for syntheses of iminoesters 1a-f, 2a-e, 3a-e

To a solution of oxime (5 mmol) in Dioxane, drug (6 mmol) and DCC (7.5 mmol) were added. The mixture was stirred at RT by keeping TLC control. The solid formed was filtered, and the filtrate was poured into acidified water. The obtained product was filtered and recrystallized from isopropyl alcohol or ethanol using decolorizing carbon.

(10,10-Dimethyl-9,10-dihydroanthracen-9-ylidene) amino (2S)-2-(6-methoxynaphthalen-2-yl)propanoate, 1a: Yield 93.3%. White solid. m. p. 124-126°C. FTIR (KBr): 3060 (C-H str, aromatic), 2932, 2854 (C-H str, aliphatic), 1761 cm^{-1} (C=O str, iminoester), ^{1}H NMR ($CDCl_3$): δ 6.70-7.95(14H,m,Ar-H), 4.05-4.08(1H,q,CH), 3.93(3H,s,OCH_3), 1.66 (6H,s,gem 2×CH_3),1.50-1.52(3H,d,CH_3); MS(ESI): *m/z* 450.45$[M+H]^+$(calculated mass M for $C_{30}H_{27}NO_3$ is 449.55).

(10,10-Dimethyl-9,10-dihydroanthracen-9-ylidene) amino2-(acetyloxy)benzoate, 1b: Yield 90.0%. White solid. m. p. 140-142°C. FTIR (KBr): 3072 (C-H str, aromatic), 2967(C-H str, aliphatic), 1752 cm^{-1} (C=O str, iminoester);^{1}H NMR($CDCl_3$): δ 7.16-8.19 (12H,m, Ar-H), 2.19 (3H,s,CH_3), 1.67(6H,s,gem 2×CH_3);^{13} C NMR (100 MHz, $CDCl_3$): δ 169.7, 162.1, 157.0, 151.2, 148.5, 146.2, 134.2, 131.7-131.6, 130.9-130.4, 127.8, 127.0,

126.6-126.1, 124.4-124.3, 123.6, 122.4, 77.5-76.9, 67.3, 40.1, 30.9, 20.9; MS (ESI): *m/z* 400.4 $[M+H]^+$(calculated mass M for $C_{25}H_{21}NO_4$ is 399.45).

(10,10-Dimethyl-9,10-dihydroanthracen-9-ylidene) amino 2-[(1R)-1,8-diethyl-1*H*,3*H*,4*H*-pyrano[3,4-b] indol-1-yl]acetate, 1c: Yield 90.6%. Ivory solid. m.p. 140-142°C. FTIR (KBr): 3340 (N-H str, Amine), 3064 (C-H str, aromatic), 2965 (C-H str, aliphatic), 1763 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 9.11(1H,s,NH), 7.00-8.06 (11H,m,Ar-H), 4.06 (2H, t,CH_2O), 3.11-3.21(2H,t,CH_2-CH_2O), 2.82-2.89 (2H,q,CH_2 of ethyl), 2.74-2.80(2H,s,CH_2-CO), 2.12-2.25(2H,q,CH_2), 1.62(6H,s,gem 2×CH_3), 1.32-1.38(3H,t,CH_3), 0.84-0.88(3H,t,CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 157.0,148.5,146.4, 135.9, 134.8,131.4,130.9-130.3,127.4,127.0, 126.4-126.0, 124.3,123.7,120.6, 119.8, 116.0,108.6,77.5,76.9,75.0, 61.0, 42.2, 40.1, 31.1-30.6, 24.3, 22.6, 14.0, 7.8; MS(ESI): *m/z* 507.55 $[M+H]^+$(calculated mass M for $C_{33}H_{34}N_2O_3$ is 506.65).

(10,10-Dimethyl-9,10-dihydroanthracen-9-ylidene) amino2-[(2-{2-[(2,6-dichlorophenyl)amino]phenyl} acetyl)oxy]acetate, 1d: Yield 85.2%. White solid. m. p. 120-122°C. FTIR (KBr): 3331 (N-H str, Amine), 3070 (C-H str, aromatic), 2973 (C-H str, aliphatic), 1785 (C=O str, ester), 1737 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 8.15(1H,s,NH), 6.54-8.13(15H,m, Ar-H), 5.02(2H,s,OCH_2), 3.97 (2H,s,CH_2), 1.64(6H,s,gem 2×CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ 171.7, 166.5,156.9,148.5, 146.4,143.0,138.0,131.2-131.1, 130.58-130.56, 129.7-129.0,128.4,127.1-127.0,126.3-126.2,124.3-124.0, 123.8,122.4, 118.7, 115.7, 77.5-76.9, 61.2,40.1, 38.2,30.9; MS (ES+): *m/z* 573.4 $[M]^+$(calculated mass M for $C_{32}H_{26}Cl_2N_2O_4$ is 573.48).

(10,10-Dimethyl-9,10-dihydroanthracen-9-ylidene) amino(2S)-2-{2-fluoro-[1,1'-biphenyl]-4-yl}propa-noate, 1e: Yield 84.5%. White solid. m. p. 120-122°C. FTIR (KBr): 3067 (C-H str, aromatic), 2978(C-H str, aliphatic), 1761 cm^{-1} (C=O str, iminoester); ^{1}H NMR ($CDCl_3$): δ 7.11-7.98(16H,m,Ar-H), 3.96-3.97(1H,q,CH), 1.64-1.68 (6H,s,gem 2×CH_3), 1.55-1.57(3H,d,CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ 171.5,161.2,158.7, 156.8, 148.3, 146.2,141.4,141.3, 131.5-131.2, 130.7-130.3, 129.2-129.1,128.7,127.9-127.4,126.9-126.5,125.8,124.2-124.0, 123.7, 116.0, 115.7, 77.5-76.9,44.4,40.1,32.4,29.3,18.5; MS(ESI): *m/z* 464.45 $[M+H]^+$(calculated mass M for $C_{31}H_{26}FNO_2$ is 463.55).

(10,10-Dimethyl-9,10-dihydroanthracen-9-ylidene)-amino(2S)-2-[4-(2-methylpropyl)phenyl]propanoate, 1f: Yield 97.6%. White solid. m. p. 108-110°C. FTIR (KBr): 3046,3019 (C-H str, aromatic), 2957(C-H str, aliphatic), 1759 cm^{-1} (C=O str, iminoester); ^{1}H NMR ($CDCl_3$): δ 7.10-7.98(12H,m,Ar-H), 3.87-3.92(1H,q,CH), 2.47-2.49(2H,d,CH_2), 1.83-1.90(1H, sept,CH of isopropyl), 1.68(6H,s,gem 2×CH_3), 1.59-1.61(3H,d,CH_3), 0.89-0.91(6H,d,2×CH_3 isopropyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 156.2, 148.3, 146.2, 140.9, 137.3, 131.6, 130.6-130.2, 129.6, 127.7-127.5, 126.8-126.5, 125.8, 124.0, 123.6, 77.5-76.9, 45.3, 44.5, 40.0, 32.9, 30.4, 28.9, 22.6-22.5, 18.6; MS(ESI): *m/z* 426.5 $[M+H]^+$(calculated mass M for $C_{29}H_{31}NO_2$ is 425.57).

[(5*H*-Dibenzo[a,d][7]annulen-5-ylideneamino)oxy]-2-(6-methoxynaphthalen-2-yl)propan-1-one, 2a: Yield 93.0%. White solid. m.p.122-124°C. FTIR (KBr): 3057(C-H str, aromatic), 2942 (C-H str, aliphatic), 1751 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 7.08 -7.73(14H,m,ArH), 6.80-6.90(2H,d,benzylic protons), 3.94 (3H,s, OCH_3), 3.74-3.79 (1H,q, CH-CH_3), 1.50-1.58 (3H,d, CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ 171.5, 164.5, 157.8, 135.2, 134.4-134.0, 133.7-133.3, 130.8-130.3, 129.7-129.0, 128.7-128.3, 127.6-127.2, 126.7-126.2, 119.2-119.0, 105.8-105.7, 77.5-76.9, 55.5, 44.7-44.6, 18.2-18.1; MS (ES+): *m/z* 456.15$[M+Na]^+$ (calculated mass M for $C_{29}H_{23}NO_3$ is 433.51).

2-{[(5*H*-Dibenzo[a,d][7]annulen-5-ylideneamino) oxy]carbonyl}phenyl acetate, 2b: Yield 94.0%, off white solid. m. p. 148-150°C. FTIR (KBr): 3070, 3026 (C-H str, aromatic), 2927 (C-H str, aliphatic), 1751 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 7.09-7.82(12H,m,Ar-H), 6.97-6.99(2H,d,benzylic protons), 2.26(3H,s,CH_3);MS(ESI): *m/z* 384.3$[M+H]^+$(calculated mass M for $C_{24}H_{17}NO_4$ is 383.40).

{Tricyclo[9.4.0.0^{3,8}]pentadeca-1(15),3,5,7,9,11,13-heptaen-2-ylidene}amino2-[(1R)-1,8-diethyl-1*H*, 3*H*,4*H*-pyrano[3,4-b]indol-1-yl]acetate, 2c: Yield 87.3%. White solid. m. p. 138-140°C. FTIR (KBr): 3345 (N-H str, Amine), 3054 (C-H str, aromatic), 2968,2932 (C-H str, aliphatic), 1743 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 9.05(1H,s,NH), 7.01-7.49 (11H,m,Ar-H), 6.91-6.96(2H,d,benzylic H), 3.97 (2H,t,CH_2O), 3.0-3.07(2H,t,CH_2-CH_2-O), 2.96(2H,s, CH_2-CO); 2.80-2.88(2H, q,CH_2 of ethyl), 1.88-1.91 (2H,q,CH_2), 1.34-1.37(3H,t,CH_3), 0.82-0.92 (3H,t,CH_3);

MS(ESI): *m/z* 491.5 $[M+H]^+$(calculated mass M for $C_{32}H_{30}N_2O_3$ is 490.60).

{Tricyclo[9.4.0.0^{3},^{8}]pentadeca-1(15),3,5,7,9,11,13-heptaen-2-ylidene}amino 2-[(2-{2-[(2,6-dichlorophenyl)amino]phenyl}acetyl)oxy]acetate, 2d: Yield 87.5%. White solid. m. p. 130-132°C. FTIR (KBr): 3371 (N-H str, Amine), 3064 (C-H str, aromatic), 2932 (C-H str, aliphatic), 1769 (C=O str, ester), 1746 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 7.72 (1H,s,NH), 6.84-7.51 (15H,m,Ar-H), 6.53-6.59(2H,d, benzylic protons), 4.72-4.84 (2H,s,OCH_2), 3.76-3.85 (2H,s,CH_2); ^{13}C NMR (100MHz, $CDCl_3$): δ 171.5, 165.8, 164.8,142.9,138.0,134.5,133.4-133.2,131.1,130. 7-130.0, 129.7-129.1, 128.5-128.1, 124.2-124.0, 122.3, 118.7, 77.5-76.9,60.9,38.1; MS (ES+): *m/z* 557.10 $[M]^+$(calculated mass M for $C_{31}H_{22}Cl_2N_2O_4$ is 557.42).

{Tricyclo[9.4.0.0^{3},^{8}]pentadeca-1(11),3(8),4,6,9,12,14-heptaen-2-ylidene}amino (2S)-2-{2-fluoro-[1,1'-biphenyl]-4-yl}propanoate, 2e: Yield 88.3%, white solid. m. p. 124-126°C. FTIR (KBr): 3067 (C-H str, Aromatic), 2941(C-H str, aliphatic), 1769 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 7.09-7.70(16H,m,Ar-H), 6.91-6.98(2H,d,benzylic protons), 3.77-3.82(1H,q,CH), 1.49-1.54(3H,d,CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ 171.0, 165.0, 158.6, 141.3, 134.4, 133.6, 133.4, 131.0, 130.8-130.3, 129.9-129.0, 128.7-128.3, 127.9-127.7, 123.8, 115.9-115.4, 77.5-76.9, 44.2, 18.0; MS(ESI): *m/z* 448.4 $[M+H]^+$(calculated mass M for $C_{30}H_{22}FNO_2$ is 447.51).

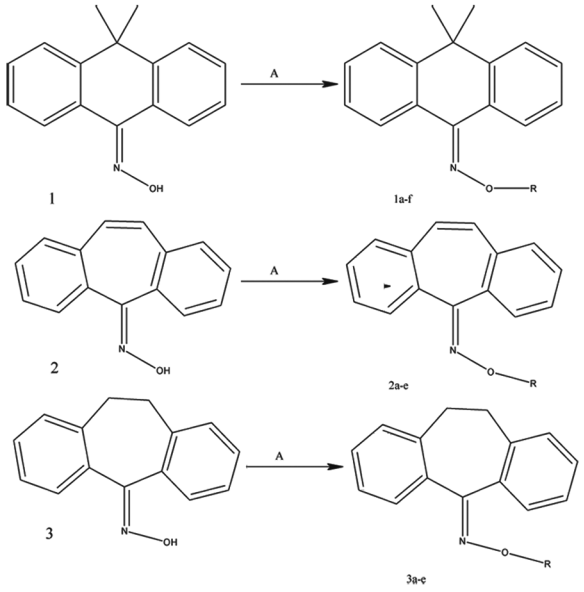
[(10,11-Dihydro-5*H*-dibenzo[a,d][7]annulen-5-ylideneamino)oxy]-2-(6-methoxynaphthalen-2-yl)propan-1-one, 3a: Yield 97.7%. White solid. m. p. 116-118°C. FTIR (KBr): 3054(C-H str, aromatic), 2946, 2879 (C-H str, aliphatic), 1774 cm^{-1} (C=O str, iminoester). ^{1}H NMR($CDCl_3$): δ 7.08 -7.64(14H, m, ArH); 3.93 (3H,s,OCH_3); 3.8-3.86 (1H,q,CH), 2.99-3.10(4H,t, 10,11-H), 1.54(3H,d,CH_3); MS (ES+): *m/z* 458.17 $[M+Na]^+$(calculated mass M for $C_{29}H_{25}NO_3$ is 435.52).

2-{[(10,11-Dihydro-5*H*-dibenzo[a,d][7]annulen-5-ylideneamino)oxy]carbonyl}phenyl acetate, 3b: Yield 97.4%. Cream coloured solid. m.p.126-128°C. FTIR (KBr): 3070, 3025(C-H str, aromatic), 2927 (C-H str, aliphatic), 1752 cm^{-1} (C=O str, iminoester); ^{1}H NMR ($CDCl_3$): δ 7.09-7.76(12H,m,Ar-H), 3.00-3.20(4H,t,10,11- H), 2.31 (3H,s,CH_3); MS(ESI): *m/z* 386.4 $[M+H]^+$(calculated mass M for $C_{24}H_{19}NO_4$ is 385.42).

{Tricyclo[9.4.0.0^{3},^{8}]pentadeca-1(15),3,5,7,11,13-hexaen-2-ylidene}amino2-[(1R)-1,8-diethyl-1*H*,3*H*,4*H*-pyrano[3,4-b]indol-1-yl]acetate, 3c: Yield 87.0%, Off white solid. m.p.124-126°C. FTIR (KBr): 3342 (N-H str, Amine), 3054 (C-H str, aromatic),2962 (C-H str, aliphatic), 1766 cm^{-1} (C=O str, iminoester); ^{1}H NMR ($CDCl_3$): δ 9.07(1H,s,NH), 7.00-7.70(11H, m, Ar-H), 3.98(2H,t,CH_2O), 3.03-3.17(4H,t,10,11-H), 2.99(2H, s, CH_2-CO), 2.84-2.89(2H, t, CH_2-CH_2-O), 2.68-2.82(2H,q,CH_2 of ethyl), 1.97-2.16(2H,q, CH_2), 1.33-1.36(3H, t, CH_3), 0.78(3H, t, CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ 170.5, 139.4, 137.9, 135.9, 134.7, 133.8, 132.9, 130.8-130.1,129.5, 128.5,127.6, 127.0, 126.6,126.0, 120.6, 119.8, 116.0, 108.6, 77.5, 76.9, 75.0, 60.9, 41.9, 33.5, 31.9,30.7, 24.3, 22.6, 14.0,7.7; MS(ESI): *m/z* 494.65 $[M+H]^+$(calculated mass M for $C_{32}H_{32}N_2O_3$ is 492.62).

{Tricyclo[9.4.0.0^{3},^{8}]pentadeca-1(11),3(8),4,6,12,14-hexaen-2-ylidene}amino 2-[(2-{2-[(2,6-dichloro phenyl)amino]phenyl}acetyl)oxy]acetate, 3d: Yield 87.5%. Cream coloured solid. m. p. 112-114°C. FTIR (KBr): 3373 (N-H str, Amine), 3068 (C-H str, aromatic), 2928(C-H str, aliphatic), 1765 (C=O str, ester), 1752 cm^{-1} (C=O str, iminoester); ^{1}H NMR ($CDCl_3$): δ 7.67 (1H,s,NH), 6.52-7.65(15H,m, Ar-H), 4.79(2H,s,0CH_2), 3.77(2H,s,CH_2), 3.02-3.14(4H,t,10,11-H); ^{13}C NMR (100MHz, $CDCl_3$): δ 171.4, 168.0, 165.7, 142.8, 146.4, 143.0, 139.4, 138.0- 137.9, 133.6, 132.7, 131.2-131.1, 130.8-130.6, 130.2, 129.7-129.0,128.6-128.3,127.6,126.5-126.1,124.3-124.2,124.0,122.4-122.3, 118.8-118.6, 77.5-76.9, 63.2,61.0-60.9, 56.2, 38.3-38.0, 33.9-33.5, 32.8, 32.2, 31.8, 30.9; MS (ES+): *m/z* 559.30$[M]^+$(calculated mass M for $C_{31}H_{24}Cl_2N_2O_4$ is 559.44).

[(10,11-Dihydro-5*H*-dibenzo[a,d][7]annulen-5-ylideneamino)oxy]-2-[4-(2-methylpropyl)phenyl] propan-1-one, 3e: Yield 97.0%. Off white solid. m. p. 140-142°C. FTIR (KBr): 3055, 3027 (C-H str, aromatic), 2945, 2863 (C-H str, aliphatic), 1759 cm^{-1} (C=O str, iminoester); ^{1}H NMR($CDCl_3$): δ 7.02 -7.67 (12H, m, ArH), 3.64-3.69 (1H,q,CH); 3.01-3.12(4H,t, 10,11-H), 2.43-2.45(2H,d,CH_2), 1.80-1.88(1H, sept, CH of isopropyl), 1.43-1.47 (3H,d,CH_3), 0.87-0.91 (6H,d, 2×CH_3 of isopropyl); ^{13}C NMR (100MHz, $CDCl_3$): δ 171.9 , 140.7, 139.3, 137.9,137.1, 133.9, 133.1, 130.6, 129.8, 128.3, 127.9, 127.5, 126.4,125.8, 45.27, 44.27, 33.6, 32.9, 31.9, 31.2, 30.6, 30.4, 26.4, 25.7, 24.9, 22.6, 21.2, 18.2; MS (ES+): *m/z* 413.6 $[M+H]^+$(calculated mass M for $C_{28}H_{29}NO_2$ is 411.55).



Scheme 1 — Syntheses of Iminoesters with tricyclic systems (**1a-f**, **2a-e**, **3a-e**); A = RCOOH, DCC, RT (1a, 2a, 3a: R =Naproxen; 1b, 2b, 3b: R= Aspirin,; 1c, 2c, 3c: R = Etodolac; 1d, 2d, 3d: R = Aceclofenac; 1e, 2e: R = Flubiprofen; 1f, 3e: R = Ibuprofen)

Results and Discussion

The current synthesis of iminoester derivatives is depicted in Scheme 1. The oximes 1-3, the critical starting materials, were prepared using pyridine from respective ketone and hydroxylamine. The designed iminoesters (1a-f, 2a-e, 3a-e) in 84-98% yield were synthesized by conjugating oximes 1-3 with selected anti-inflammatory drugs using DCC as a coupling agent at RT.

The structures of all conjugates were confirmed and authenticated by IR, ^{1}H and ^{13}C NMR, and Mass data. In all the spectral studies of the title compound, carbonyl of iminoester was seen in the range of 1737-1774 cm^{-1}; each of the title compounds exhibited a δ value for corresponding protons in the respective NMR spectrum. In the Mass spectral study, all molecular ion peaks M^{+}/M^{-} were obtained corresponding to the mass of the compound, clearly indicating the formation of iminoester.

Conclusion

The study involves syntheses of 16 novel iminoesters in the presence of DCC. These iminoesters may have potential pharmacological activity.

Supplementary Information

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

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