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Synthesis, characterization and antibacterial activity of some novel spiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran] derivatives

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Abstract:

1-(Aryl(phenylamino)methyl)naphthalen-2-ol derivatives **1a-d** were obtained by multicomponent condensation of aromatic aldehydes, 2-naphthol, and aniline in the presence of ceric ammonium nitrate (CAN) catalyst. Reaction of compounds **1a-d** with a-oxoketene dithioacetal afforded the corresponding oxazines **2a-d**. Compounds **2a-d** were reacted with malononitrile or cyclopentanone under alkaline conditions the corresponding spiro heterocycles **3a-d** and **4a-d.** Reaction of compounds **1a-d** with α-cyanoketene dithioacetal afforded naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)malononitrile derivatives **5a-d**. By the same way, the reaction of compounds **5a-d** with acetylacetone or cyclopentanone gave the corresponding spiro heterocycles **6a-d** and **7a-d** respectively. All the obtained products were identified by their elemental and spectral (IR and NMR) analyses. Gram-positive bacteria [Aureus (ATCC 25923) and S. pyogenes (ATCC 19615)] and Gram-negative bacteria [P. phaseolicola (GSPB 2828) and P. fluorescens (S 97)] were the pathogens against which the newly synthesized spiro heterocyclic compounds were tested for their antibacterial activity.

Keywords: 1-(Aryl(phenylamino)methyl)naphthalen-2-ol, ceric ammonium nitrate (CAN), oxazin-3(2H)-ylidene)pentane-2,4-dione, 3-(bis(methylthio)methylene)pentane-2,4-dione, naphthoxazin-3(2H)-ylidenemalononitrile

1 Introduction

In the world of organic synthesis, functionalized α-oxoketene dithioacetals have garnered a lot of interest as adaptable intermediates for the synthesis of different heterocyclic compounds [1-5]. Due to carbonyl or nitrile functionalities and its position in conjugation with double bond carrying bis(alkylthio) group at the □-position place them among the versatile 1,3-dielectrophilic-3-carbon equivalents [6-13]. In synthetic organic sulfur chemistry, the polarized ketene dithioacetal functional group is widely recognized as a two-carbon push-pull system. The two alkylated sulfurs quickly provide their single pair of electrons to make every part of the atomic framework highly polarized, whilst the acetyl or cyano groups function as potent centers that suck electrons away. Additionally, the α,β-unsaturated acetyl/cyano groups exhibit good Michael acceptor behavior, with one of the alkylsulfanyl groups leaving to repair the olefinic double bond following a nucleophile's attack at the P-carbon. Derivatives of amidoalkyl-2-naphthol have important medicinal implications since they can be transformed into active ingredients for hypertension and bradycardia. 1-aminoalkyl-2-naphthols through the process of amide hydrolysis [14-15].

2 Experimental Section

2.1 Materials

All melting points were determined on a Koffler melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Brukeravance 400 MHz

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spectrometer using TMS as internal reference (chemical shifts in δ, ppm), and IR spectra were obtained on a Nicolet 710 FT-IR spectrometer (KBr, ν_{max} in cm^{-1}). Elemental analyses were recorded on Vario El Fab-Nr elemental analyzer (Cairo University).

Synthesis of 1-(aryl(phenylamino)methyl)naphthalen-2-ol (1a-d):

A mixture of 2-naphthol (1.44 g, 10 mmol), aldehyde derivatives (10 mmol) and aniline (1.08 mL, 12 mmol) were treated with 10 mol% of ceric ammonium nitrate (CAN) as catalyst. The reaction mixture was heated gently (over oil bath) for 2h then left to cool, ice-cold water was then added (~50 mL) and then left for further 2h. The formed solid was collected by filtration, recrystallized from ethanol into the desired product.

1-(Phenyl(phenylamino)methyl)naphthalen-2-ol (1a):

Yield (72%), brown crystals, m.p. 206-208 ˚C, Anal. Calcd. for ($C_{23}H_{19}NO$, 325.15): C, 84.89; H, 5.89; N, 4.30. Found: C, 84.56; H, 5.62; N, 4.04. IR (υ_{max}, cm^{-1}): 3409 (OH), 3348 (NH). ^{1}H-NMR (DMSO-d_6), δ ppm: 6.54 (s, 1H, CH), 6.88-8.13 (m, 16H, CH-arom.), 9.15 (s, H, NH, exchangeable by D_2O), 10.24 (s, 1H, OH, exchangeable by D_2O). ^{13}CNMR (DMSO-d_6), δ ppm: 64.12 (CH), 113.08, 115.56, 118.34, 123.11, 123.88, 124.48, 125.09, 125.89, 126.24, 126.31, 128.12, 128.89, 129.44, 131.08, 132.35 (C-arom), 147.43 (C-NH), 153.12 (C-OH).

1-((4-Chlorophenyl)(phenylamino)methyl)naphthalen-2-ol (1b):

Yield (85%), yellow needles, m.p. 188-190 ˚C, Anal. Calcd. for ($C_{23}H_{18}ClNO$, 359.11): C, 76.77; H, 5.04; N, 3.89, Cl, 9.85. Found: C, 76.40; H, 4.88; N, 3.65, Cl, 9.60. IR (υ_{max}, cm^{-1}): 3412 (OH), 3354 (NH). ^{1}H-NMR (DMSO-d_6), δ ppm: 6.58 (s, 1H, CH), 6.92-8.10 (m, 15H, CH-arom.), 9.11 (s, H, NH, exchangeable by D_2O), 10.22 (s, 1H, OH, exchangeable by D_2O). ^{13}CNMR (DMSO-d_6), δ ppm: 64.03 (CH), 113.12, 115.50, 118.29, 123.23, 123.75, 124.40, 125.12, 125.87, 126.20, 126.35, 128.09, 128.85, 129.40, 131.12, 132.31 (C-arom), 142.63 (C-Cl), 147.50 (C-NH), 153.08 (C-OH).

1-((4-Methoxyphenyl)(phenylamino)methyl)naphthalen-2-ol (1c):

Yield (88%), pale yellow crystals, m.p. 212-214 ˚C, Anal. Calcd. for ($C_{24}H_{21}NO_2$, 355.43): C, 81.10; H, 5.96; N, 3.94. Found: C, 80.96; H, 5.70; N, 3.66. IR (υ_{max}, cm^{-1}): 3410 (OH), 3355 (NH). ^{1}H-NMR (DMSO-d_6), δ ppm: 3.91 (s, 3H, OCH_3), 6.55 (s, 1H, CH), 6.90-8.10 (m, 15H, CH-arom.), 9.10 (s, H, NH, exchangeable by D_2O), 10.23 (s, 1H, OH, exchangeable by D_2O). ^{13}CNMR (DMSO-d_6), δ ppm: 56.22 (OCH_3), 64.10 (CH), 113.15, 115.51, 118.43, 123.18, 123.82, 124.38, 125.09, 125.91, 126.13, 126.67, 128.05, 128.78, 129.44, 131.08, 132.42 (C-arom), 142.50 (C-OCH_3), 147.37 (C-NH), 153.22 (C-OH).

1-((4-Nitrophenyl)(phenylamino)methyl)naphthalen-2-ol (1d):

Yield (82%), brown needles, m.p. 196-198 ˚C, Anal. Calcd. for ($C_{23}H_{18}N_2O_3$, 370.40): C, 74.58; H, 4.90; N, 7.56. Found: C, 74.33; H, 4.75; N, 7.60. IR (υ_{max}, cm^{-1}): 3416 (OH), 3358 (NH), 1542-1322 (NO_2). ^{1}H-NMR (DMSO-d_6), δ ppm: 6.62 (s, 1H, CH), 6.96-8.16 (m, 15H, CH-arom.), 9.13 (s, H, NH, exchangeable by D_2O), 10.25 (s, 1H, OH, exchangeable by D_2O). ^{13}CNMR (DMSO-d_6), δ ppm: 64.76 (CH), 113.23, 115.61, 118.38, 123.27, 123.88, 124.40, 125.12, 125.87, 126.20, 126.35, 128.09, 128.85, 129.47, 131.18, 132.35 (C-arom), 142.66 (C-NO_2), 147.50 (C-NH), 154.05 (C-OH).

Synthesis of 3-(1-aryl-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)-pentane-2,4-dione (2a-d):

An equimolar mixture of 3-[bis(methylthio)methylene]pentane-2,4-dione (1.02 g, 5 mmol) and 1-(aryl(phenylamino)methyl)naphthalen-2-ol **1a-d** (5 mmol) was refluxed in 50 mL of absolute ethanol for 24 h (the reaction was monitored by TLC), until a complete session of methyl mercaptan (lead acetate). On cooling the precipitated product was filtered off and recrystallized from EtOH into **2a-d**.

3-(1,2-Diphenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)pentane-2,4-dione (2a):

Yield (72%), yellow crystals, m.p. 226-228 ˚C, Anal. Calcd. for ($C_{29}H_{23}NO_3$, 433.17): C, 80.35; H, 5.35; N, 3.23. Found: C, 80.01; H, 5.11; N, 3.04. IR (υ_{max}, cm^{-1}): 1669 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.12 (s, 6H, $2CH_3$), 6.50 (s, 1H, CH), 6.88-8.08 (m, 16H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 42.04 ($2CH_3$), 66.28 (CH), 98.65 (C-C=O), 113.08, 115.56, 118.34, 123.11, 123.88, 124.48, 125.09, 125.89, 126.24, 126.31, 128.12, 128.89, 129.44, 130.55, 131.08, 132.35 (C-arom), 147.43 (=C-N), 153.12 (C-O), 171.12 (N-C=), 201.04 (C=O).

3-(1-(4-Chlorophenyl)-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)-pentane-2,4-dione (2b):

Yield (78%), yellow crystals, m.p. 205-208 ˚C, Anal. Calcd. for ($C_{29}H_{22}ClNO_3$, 467.13): C, 74.43; H, 4.74; N, 2.99; Cl, 7.58. Found: C, 74.12; H, 4.54; N, 2.71, Cl, 7.34. IR (υ_{max}, cm^{-1}): 1668 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.13 (s, 6H, $2CH_3$), 6.52 (s, 1H, CH), 6.91-8.07 (m, 15 H, CH-arom.).

^{13}CNMR (DMSO-d_6), δ ppm: 42.12 ($2CH_3$), 66.30 (CH), 98.60 (C-C=O), 113.22, 115.61, 118.55, 123.10, 123.89, 124.45, 125.11, 125.76, 126.28, 126.45, 128.12, 128.76, 129.45, 130.50, 131.12, 132.30 (C-arom), 142.55 (C-Cl), 147.48 (=C-N), 153.15 (C-O), 177.23 (=C-N), 201.02 (C=O).

3-(1-(4-Methoxyphenyl)-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)-pentane-2,4-dione (2c):

Yield (82%), pale yellow crystals, m.p. 233-235 ˚C, Anal. Calcd. for ($C_{30}H_{25}NO_4$, 463.52): C, 77.74; H, 5.44; N, 3.02. Found: C, 77.42; H, 5.22; N, 2.79. IR (υ_{max}, cm^{-1}): 1668 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.12 (s, 6H, $2CH_3$), 3.92 (s, 3H, OCH_3), 6.55 (s, 1H, CH), 6.94-8.08 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 42.10 ($2CH_3$), 61.87 (OCH_3), 66.35 (CH), 98.67 (C-C=O), 113.22, 115.66, 118.58, 123.07, 123.85, 124.41, 125.10, 125.79, 126.34, 126.43, 128.17, 128.82, 129.40, 130.56, 131.20, 132.38 (C-arom), 142.59 (C-OCH_3), 147.67 (=C-N), 153.35 (C-O), 172.02 (=C-N), 201.09 (C=O).

3-(1-(4-Nitrophenyl)-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)-pentane-2,4-dione (2d):

Yield (76%), brownish crystals, m.p. 257-259 ˚C, Anal. Calcd. for ($C_{29}H_{22}N_2O_5$, 478.50): C, 72.79; H, 4.63; N, 5.58. Found: C, 72.46; H, 4.33; N, 5.28. IR (υ_{max}, cm^{-1}): 1666 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.14 (s, 6H, $2CH_3$), 6.55 (s, 1H, CH), 6.97-8.05 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 42.18 ($2CH_3$), 66.44 (CH), 98.65 (C-C=O), 113.20, 115.63, 118.52, 123.01, 123.89, 124.40, 125.12, 125.84, 126.33, 126.40, 128.17, 128.80, 129.44, 130.57, 131.28, 132.31 (C-arom), 142.78 (C-NO_2), 147.87 (=C-N), 154.30 (C-O), 174.64 (=C-N), 201.11 (C=O).

Synthesis of 1-aryl-2-phenyl-1,2-dihydrospiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran] derivatives (3a-d) and (4a-d):

Compound **2a-d** (0.01 mol) in EtOH (40 mL) was treated with malononitrile or cyclopentanone (0.01 mol) and piperidine (1 mL) was then added. The reaction mixture was refluxed for different periods of time (30 min or 3hrs, respectively) and then left to cool. The obtained solids were collected by filtration and recrystallized from the proper solvent to afford the desired products **3a-d** and **4a-d** respectively.

2'-Amino-6'-methyl-1,2-diphenyl-1,2-dihydrospiro [naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-3'-carbonitrile (3a):

Yield (80%), pale yellow needles, m.p. 232-234 ˚C, Anal. Calcd. for ($C_{30}H_{23}N_3O_2$, 457.52): C, 78.75; H, 5.07; N, 9.18. Found: C, 78.51; H, 4.88; N, 9.04. IR (υ_{max}, cm^{-1}): 3364, 3276 (NH_2), 2206 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, CH_3), 5.16 (s, 1H, =CH), 6.15 (br, 2H, NH_2), 6.50 (s, 1H, CH), 6.88-8.08 (m, 16 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 29.12(CH_3), 66.53(CH-), 68.34(=C-CN), 107.33 (Cspiro), 113.08 (=CH), 115.56 (CN), 117.68 (=C-CH), 118.30, 123.03, 123.76, 124.21, 124.86, 125.06, 125.77, 126.03, 126.65, 127.46, 128.10, 128.83, 129.40, 130.51, 131.01 (C-arom), 132.30 (C-CH_3), 142.51(C-N), 147.40 (C-O), 153.17 (C-NH_2).

2'-Amino-1-(4-chlorophenyl)-6'-methyl-2-phenyl-1,2-dihydrospiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-3'-carbonitrile (3b):

Yield (84%), yellow needles, m.p. 244-246 ˚C, Anal. Calcd. for ($C_{30}H_{22}ClN_3O_2$, 491.14): C, 73.24; H, 4.51; N, 8.54, Cl, 7.22. Found: C, 72.96; H, 4.28; N, 8.24, Cl, 7.01. IR (υ_{max}, cm^{-1}): 3366, 3272 (NH_2), 2210 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, CH_3), 5.18 (s, 1H, =CH), 6.20, (br, 2H, NH_2), 6.52 (s, 1H, CH), 6.94-8.11 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 29.10 (CH_3), 66.55 (CH-), 68.34 (=C-CN), 107.55 (Cspiro), 113.11 (=CH), 115.50 (CN), 117.65 (=C-CH), 118.33, 123.13, 123.70, 124.20, 124.82, 125.16, 125.81, 126.16, 126.69, 127.40, 128.12, 128.80, 129.44, 130.57, 131.13 (C-CH_3), 142.36 (C-Cl), 142.56 (=C-N), 147.48 (C-O), 154.15 (C-NH_2).

2'-Amino-1-(4-methoxyphenyl)-6'-methyl-2-phenyl-1,2-dihydrospiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-3'-carbonitrile (3c):

Yield (80%), yellow needles, m.p. 258-260 ˚C, Anal. Calcd. for ($C_{31}H_{25}N_3O_3$, 487.19): C, 76.37; H, 5.17; N, 8.62. Found: C, 76.05; H, 4.88; N, 8.36. IR (υ_{max}, cm^{-1}): 3364, 3268 (NH_2), 2208 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 5.15 (s, 1H, =CH), 6.18 (br, 2H, NH_2), 6.50 (s, 1H, CH), 6.90-8.07 (m, 15H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 29.10 (CH_3), 61.89 (OCH_3), 66.58 (CH-), 68.35 (=C-CN), 107.55 (Cspiro), 113.12 (=CH), 115.51 (CN), 117.65 (=C-CH), 118.30, 123.11, 123.70, 124.23, 124.80, 125.11, 125.80, 126.15, 126.72, 127.35, 128.10, 128.75, 129.40, 130.55 (C-arom), 131.17 (C-CH_3), 142.30 (C-O), 142.58 (=C-N), 147.55 (C-OCH_3), 154.89 (C-NH_2).

2'-Amino-6'-methyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydrospiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-3'-carbonitrile (3d):

Yield (80%), yellow needles, m.p. 258-260 ˚C, Anal. Calcd. for ($C_{30}H_{22}N_4O_4$, 502.16): C, 71.70; H, 4.41; N, 11.15. Found: C, 71.38; H, 4.21; N, 10.89. IR (υ_{max}, cm^{-1}): 3382, 3277 (NH_2), 2212 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.34 (s, 3H, CH_3), 5.25 (s, 1H, =CH), 6.23, (br, 2H, NH_2), 6.58 (s, 1H, CH), 6.98-8.11 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 29.33 (CH_3), 66.79 (CH-), 68.67 (=C-CN),

107.74 (Cspiro), 113.56 (=CH), 115.50 (CN), 117.68 (=C-CH), 123.74, 124.20, 124.85, 125.14, 125.81, 126.76, 127.32, 129.44, 130.51 (C-arom), 131.19 (C-CH_3), 142.32 (C-O), 142.50 (=C-N), 147.87 (C-NO_2), 154.93 (C-NH_2).

2-Methyl-1',2'-diphenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta[b]pyran-4,3'-naphtho[1,2-e][1,3]oxazine] (4a):

Yield (70%), pale yellow needles, m.p. 245-247 ˚C, Anal. Calcd. for ($C_{32}H_{27}NO_2$, 457.20): C, 84.00; H, 5.95; N, 3.06. Found: C, 83.75; H, 5.56; N, 2.82. ^{1}H-NMR (DMSO-d_6), δ ppm: 1.90 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.32 (m, 4H $2CH_2$), 5.15 (s, 1H, =CH), 6.45 (s, 1H, CH), 6.88-8.01 (m, 16 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 18.32 (CH_2), 24.01 (CH_3), 24.46, 29.12 ($2CH_2$), 68.31(CH-), 115.50 (Cspiro), 117.66(=CH), 118.34 (=C-CH), 123.11, 123.76, 124.22, 124.81, 125.03, 125.75, 126.07, 126.69, 127.43, 128.15, 128.87, 129.43, 130.57, 131.09 (C-arom), 132.31(C-CH_3), 147.45 (C-O), 153.11 (C-O).

1'-(4-Chlorophenyl)-2-methyl-2'-phenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta-[b]pyran-4,3'-naphtho[1,2-e][1,3]oxazine] (4b):

Yield (75%), pale yellow powder, m.p. 233-235 ˚C, Anal. Calcd. for ($C_{32}H_{26}ClNO_2$, 492.01): C, 78.12; H, 5.33; N, 2.85, Cl, 7.21. Found: C, 77.78; H, 5.06; N, 2.62, Cl, 6.98. ^{1}H-NMR (DMSO-d_6), δ ppm: 1.91 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.32 (m, 4H $2CH_2$), 5.14 (s, 1H, =CH), 6.48 (s, 1H, CH), 6.94-8.05 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 18.30 (CH_2), 24.08 (CH_3), 24.50, 29.23 ($2CH_2$), 66.58 (CH-), 111.55 (Cspiro), 115.66 (=CH), 118.35 (=C-CH), 123.17, 123.75, 124.23, 124.85, 125.07, 125.73, 126.09, 126.67,127.01, 127.43, 128.11, 128.85, 129.43, (C-arom), 130.55 (C-Cl), 132.50(C-CH_3), 147.49(C-O), 153.37(C-O).

1'-(4-Methoxyphenyl)-2-methyl-2'-phenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta-[b]pyran-4,3'-naphtho[1,2-e][1,3]oxazine] (4c):

Yield (78%), pale yellow needles, m.p. 245-247 ˚C, Anal. Calcd. for ($C_{33}H_{29}NO_3$, 487.21): C, 81.29; H, 5.99; N, 2.87. Found: C, 82.87; H, 5.59; N, 2.62. ^{1}H-NMR (DMSO-d_6), δ ppm: 1.90 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.32 (m, 4H $2CH_2$), 3.91 (s, 3H, CH_3), 5.15 (s, 1H, =CH), 6.45 (s, 1H, CH), 6.88-8.01 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 18.31(CH_2), 24.01(CH_3), 24.46, 29.12 ($2CH_2$), 61.67 (OCH_3), 68.31(CH-), 113.50 (Cspiro), 117.66 (=CH), 118.34 (=C-CH), 123.11, 123.76, 124.22, 124.81, 125.03, 125.75, 126.07, 126.69, 127.43, 128.15, 128.87, 129.43, 130.57 (C-arom), 135.09 (C-CH_3), 137.31 (C-OCH_3), 147.45(C-O), 153.24 (C-O).

2-Methyl-1'-(4-nitrophenyl)-2'-phenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta-[b]pyran-4,3'-naphtho[1,2-e][1,3]oxazine] (4d):

Yield (82%), dark brown powder, m.p. 263-266 ˚C, Anal. Calcd. for ($C_{32}H_{26}N_2O_4$, 502.19): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.20; H, 5.03; N, 5.44. ^{1}H-NMR (DMSO-d_6), δ ppm: 1.92 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.32 (m, 4H, $2CH_2$), 5.15 (s, 1H, =CH), 6.55 (s, 1H, CH), 6.95-8.05 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 18.45(CH_2), 24.08(CH_3), 24.50, 29.23($2CH_2$), 66.58(CH-), 112.55 (Cspiro), 117.66(=CH), 118.35 (=C-CH), , 123.17, 123.75, 124.23, 124.85, 125.07, 125.73, 126.09, 126.67, 127.43, 128.11, 128.85, 129.43, 130.55, 131.09 (C-arom), 132.34 (C-CH_3), 142.50 (C-NO_2), 147.49 (C-O), 154.46 (C-O).

Synthesis of 2-(1-aryl-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)-malononitrile (5a-d):

An equimolar mixture of compound **1a-d** (0.01 mol) and 2-(bis(methylthio)methylene)malononitrile (1.70 g, 0.01 mol) was dissolved in absolute ethanol (75 mL). The reaction mixture was heated under reflux for 24 hrs and left to cool. The formed solid was collected by filtration and used without further workup.

Synthesis of 2-(1,2-diphenyl-1,2-dihydro-3H-naphtho[1,2-e][1,3]oxazin-3-ylidene)malononitrile (5a):

Yield (70%), pale yellow needles, m.p. 245-247 ˚C, Anal. Calcd. for ($C_{27}H_{17}N_3O$, 399.14): C, 84.00; H, 5.95; N, 3.06. Found: C, 83.75; H, 5.56; N, 2.82. ^{1}H-NMR (DMSO-d_6), δ ppm: 6.45 (s, 1H, CH), 6.88-8.01 (m, 16 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 41.02 (C-CN), 68.31(CH-), 115.50 (CN), 117.66, 118.34, 123.11, 123.76, 124.22, 124.81, 125.03, 125.75, 126.07, 126.69, 127.43, 128.15, 128.87, 129.43, 130.57, 131.09, 137.44 (C-arom), 142.31(C-N), 147.45 (C-O), 153.11 (C-O).

Synthesis of 2-(1-(4-chlorophenyl)-2-phenyl-1,2-dihydro-3H-naphtho[1,2-e][1,3]oxazin-3-ylidene)malononitrile (5b):

Yield (75%), pale yellow powder, m.p. 233-235 ˚C, Anal. Calcd. for ($C_{27}H_{16}ClN_3O$, 433.10): C, 78.12; H, 5.33; N, 2.85, Cl, 7.21. Found: C, 77.78; H, 5.06; N, 2.62, Cl, 6.98. ^{1}H-NMR (DMSO-d_6), δ ppm: 6.22 (s, 1H, CH), 6.94-8.05 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 39.11 (C-CN), 66.58 (CH-), 111.55 (CN), 115.66, 118.35, 123.17, 123.75, 124.23, 124.85, 125.07, 125.73, 126.09, 126.67,127.01, 127.43, 128.11, 128.85, 129.43130.55, 132.50, (C-arom), 147.49 (C-Cl), 153.37 (C-N), 155.22 (C-O), 157.44 (C-O).

Synthesis of 2-(1-(4-methoxyphenyl)-2-phenyl-1,2-dihydro-3H-naphtho[1,2-e][1,3]oxazin-3 ylidene)malononitrile (5c):

Yield (78%), pale yellow needles, m.p. 265-267 ˚C, Anal. Calcd. for ($C_{28}H_{19}N_3O_2$, 429.15): C, 81.29; H, 5.99; N, 2.87. Found: C, 82.87; H, 5.59; N, 2.62. ^{1}H-NMR (DMSO-d_6), δ ppm: 3.91 (s, 3H, OCH_3), 6.45 (s, 1H, CH), 6.88-8.01 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 58.67 (OCH_3), 68.31(CH-), 113.50 (CN), 117.66, 118.34, 123.11, 123.76, 124.22, 124.81, 125.03, 125.75, 126.07, 126.69, 127.43, 128.15, 128.87, 129.43, 130.57 (C-arom), 137.31 (C-OCH_3), 147.45(C-N), 153.24 (C-O), 158.14 (C-O).

Synthesis of 2-(1-(4-nitrophenyl)-2-phenyl-1,2-dihydro-3H-naphtho[1,2-e][1,3]oxazin-3-ylidene)malononitrile (5d):

Yield (82%), dark brown powder, m.p. 272-274 ˚C, Anal. Calcd. for ($C_{27}H_{16}N_4O_3$, 444.12): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.20; H, 5.03; N, 5.44. ^{1}H-NMR (DMSO-d_6), δ ppm: 6.55 (s, 1H, CH), 6.95-8.05 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 66.58(CH-), 112.55 (CN), 117.66, 118.35, , 123.17, 123.75, 124.23, 124.85, 125.07, 125.73, 126.09, 126.67, 127.43, 128.11, 128.85, 129.43, 130.55, 131.09 (C-arom), 142.50 (C-NO_2), 146.50 (C-NO_2), 148.49 (C-O), 154.46 (C-O).

Synthesis of 1,2-dihydrospiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-5'-carbonitrile (6a-d) and (7a-b):

Compound **5a-d** (0.01 mol) in EtOH (40 mL) was treated with acetylacetone or cyclopentanone (0.01 mol) and piperidine (1 mL) was then added. The reaction mixture was refluxed for different periods of time (30 min or 3hrs, respectively) and then left to cool. The obtained solids were collected by filtration and recrystallized from the proper solvent to afford the desired products **6a-d** and **7a-d** respectively.

3'-Acetyl-6'-amino-2'-methyl-1,2-diphenyl-1,2-dihydrospiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-5'-carbonitrile (6a):

Yield (75%), pale yellow crystal, m.p. 224-226 ˚C, Anal. Calcd. for ($C_{32}H_{25}N_3O_3$, 499.19): C, 76.94; H, 5.04; N, 8.41. Found: C, 76.65; H, 4.88; N, 8.16. IR (υ_{max}, cm^{-1}): 3361, 3274 (NH_2), 2202 (CN), 1678 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.12 (s, 3H, CH_3), 2.32 (s, 3H, $COCH_3$), 6.15, (br, 2H, NH_2), 6.52 (s, 1H, CH), 6.90-8.07 (m, 16 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 29.10 (CH_3), 41.23 ($COCH_3$), 66.58 (CH-), 68.35 (=C-CN), 107.55 (Cspiro), 113.12 (=CH), 115.51(CN), 117.65 (=C-CH), 118.30, 122.43, 123.11, 123.70, 124.23, 124.80, 125.11, 125.80, 126.15, 126.72, 127.35, 128.10, 128.75, 129.40, 130.55, 131.17 (C-arom), 132.30 (C-CH_3), 142.58 (C-N), 147.55 (C-O), 154.89 (C-NH_2), 201.08 (C=O).

3'-Acetyl-6'-amino-1-(4-chlorophenyl)-2'-methyl-2-phenyl-1,2-dihydrospiro-[naphtha[1,2-e][1,3]oxazine-3,4'-pyran]-5'-carbonitrile (6b):

Yield (82%), yellow needles, m.p. 240-242 ˚C, Anal. Calcd. for ($C_{32}H_{24}ClN_3O_3$, 533.15): C, 71.97; H, 4.53; N, 7.87, Cl, 6.64. Found: C, 71.62; H, 4.38; N, 7.55, Cl, 6.33. IR (υ_{max}, cm^{-1}): 3366, 3275 (NH_2), 2205 (CN), 1675 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.41 (s, 3H, CH_3), 2.72 (s, 3H, $COCH_3$), 6.47, (br, 2H, NH_2), 6.85 (s, 1H, CH), 6.94-8.08 (m, 15 H, CH-arom.).

3'-Acetyl-6'-amino-1-(4-methoxyphenyl)-2'-methyl-2-phenyl-1,2-dihydrospiro-[naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-5'-carbonitrile (6c):

Yield (80%), yellow crystals, m.p. 205-207 ˚C, Anal. Calcd. for ($C_{33}H_{27}N_3O_4$, 529.20): C, 74.84; H, 5.14; N, 7.93. Found: C, 74.60; H, 4.88; N, 7.65. IR (υ_{max}, cm^{-1}): 3360, 3272 (NH_2), 2203 (CN), 1678 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.28 (s, 3H, CH_3), 2.65 (s, 3H, $COCH_3$), 3.94 (s, 3H, OCH_3), 6.42, (br, 2H, NH_2), 6.74 (s, 1H, CH), 6.92-8.05 (m, 15 H, CH-arom.).

3'-Acetyl-6'-amino-2'-methyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydrospiro[naphtho[1,2-e][1,3]oxazine-3,4'-pyran]-5'-carbonitrile (6d):

Yield (78%), brown crystals, m.p. 196-192 ˚C, Anal. Calcd. for ($C_{32}H_{24}N_4O_5$, 544.17): C, 70.58; H, 4.44; N, 10.29. Found: C, 70.41; H, 4.19; N, 10.04. IR (υ_{max}, cm^{-1}): 3368, 3276 (NH_2), 2208 (CN), 1677 (CO). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.12 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.22, (br, 2H, NH_2), 6.58 (s, 1H, CH), 6.96-8.06 (m, 15 H, CH-arom.).

2-Amino-1',2'-diphenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta[b]pyran-4,3'-naphtho[1,2-e][1,3] oxazine]-3-carbonitrile (7a):

Yield (75%), pale yellow crystals, m.p. 230-232 ˚C, Anal. Calcd. for ($C_{32}H_{25}N_3O_2$, 483.19): C, 79.48; H, 5.21; N, 8.69. Found: C, 79.27; H, 4.98; N, 8.40. IR (υ_{max}, cm^{-1}): 3360, 3268 (NH_2), 2202 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 1.90 (m, 2H, CH_2), 2.32 (t, 4H, $2CH_2$), 6.18, (br, 2H, NH_2), 6.52 (s, 1H, CH), 6.90-8.02 (m, 16 H, CH-arom.), ^{13}CNMR (DMSO-d_6), δ ppm: 18.32 (CH_2), 24.46, 29.12 ($2CH_2$), 68.31(CH-), 78.44(C-CN), 115.50 (Cspiro), 117.66(=CH), 118.34 (=C-CH), 120.11, 120.96, 123.11, 123.76, 124.22, 124.81, 125.03, 125.75, 126.07, 126.69, 127.43, 128.15, 128.87, 129.43, 130.57, 131.09 (C-arom), 142.31(C-NH_2), 147.45 (C-O), 153.11 (C-O).

2-Amino-1'-(4-chlorophenyl)-2'-phenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta-[b]pyran-4,3'-naphtho [1,2-e][1,3]oxazine]-3-carbonitrile (7b):

Yield (78%), pale yellow crystals, m.p. 240-242 ˚C, Anal. Calcd. for ($C_{32}H_{24}ClN_3O_2$, 517.16): C, 74.20; H, 4.67; N, 8.11, Cl, 6.84. Found: C, 73.97; H, 4.38; N, 7.94. IR (υ_{max}, cm^{-1}): 3366, 3270 (NH_2), 2210 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 1.92 (m, 2H, CH_2), 2.32 (t, 4H, $2CH_2$), 6.20, (br, 2H, NH_2), 6.55 (s, 1H, CH), 6.96-8.06 (m, 15 H, CH-arom.).

2-Amino-1'-(4-methoxyphenyl)-2'-phenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta-[b]pyran-4,3'-naphtho[1,2-e][1,3]oxazine]-3-carbonitrile (7c):

Yield (75%), pale yellow crystals, m.p. 265-267 ˚C, Anal. Calcd. for ($C_{33}H_{27}N_3O_3$, 513.21): C, 77.17; H, 5.30; N, 8.18. Found: C, 78.95; H, 5.05; N, 7.90. IR (υ_{max}, cm^{-1}): 3362, 3266 (NH_2), 2206 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 1.92 (m, 2H, CH_2), 2.30 (t, 4H, $2CH_2$), 3.91 (s, 3H, CH_3), 6.22, (br, 2H, NH_2), 6.58 (s, 1H, CH), 6.96-8.02 (m, 15 H, CH-arom.).

2-Amino-1'-(4-nitrophenyl)-2'-phenyl-1',2',6,7-tetrahydro-5H-spiro[cyclopenta-[b]pyran-4,3'-naphtho [1,2-e][1,3]oxazine]-3-carbonitrile (7d):

Yield (78%), pale yellow crystals, m.p. 268-270 ˚C, Anal. Calcd. for ($C_{32}H_{24}N_4O_4$, 528.18): C, 72.72; H, 4.58; N, 10.60. Found: C, 72.55; H, 4.22; N, 10.35. IR (υ_{max}, cm^{-1}): 3374, 3275 (NH_2), 2212 (CN). ^{1}H-NMR (DMSO-d_6), δ ppm: 1.93 (m, 2H, CH_2), 2.32 (t, 4H, $2CH_2$), 6.25, (br, 2H, NH_2), 6.62 (s, 1H, CH), 6.98-8.09 (m, 15 H, CH-arom.).

2. 2 Biological Evaluation:

The antimicrobial activity of the newly synthesized spiro heterocyclic compounds were tested against the following microorganisms: Gram-positive bacteria [*aureus (ATCC 25923)* and *S. pyogenes (ATCC 19615)*] and Gram-negative bacteria [*P. phaseolicola (GSPB 2828)* and *P. fluorescens (S 97)*]. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. Compounds **3c**, **3d, 4c**, **4d**, **7c** and **7d** were found to be active against Gram-positive bacteria, where compounds **3a**, **3b**, **4a**, **4b**, **6a**, **6b**, **7a** and **7b** are active against Gram-negative bacteria. The rested of the tested compounds were showed week to moderate sensitivity towards the tested micro-organisms, results were summarized in Table 1.

S. aureus *(ATCC 25923)* = Staphylococcus aureus *(ATCC 25923)*; *S. pyogenes (ATCC 19615)* = *Streptococcus pyogenes (ATCC 19615)*; *P. phaseolicola (GSPB 2828)* = Pseudomonas *phaseolicola* (*GSPB 2828*); *P. fluorescens (S 97)* = *Pseudomonas fluorescens (S 97)*. The sensitivity of microorganisms to the tested compounds is identified in the following manner: Highly sensitive = Inhibition zone 15-20 mm; Moderately sensitive = Inhibition zone: 10-15 mm; Slightly sensitive = Inhibition zone: 5-10 mm; Not sensitive = Inhibition zone: 0 mm;* Each result represents the average of triplicate readings. The newly synthesized compounds were screened for their antimicrobial activities and they showed moderate to potent activity against their corresponding pathogens.

Antibacterial Screening

The antibacterial activity of the recently synthesized spiro heterocyclic compounds was evaluated against both Gram negative (Pseudomonas phaseolicola and Pseudomonas fluorescens) and Gram positive (Staphylococcus aureus and Streptococcus pyogenes) bacteria.

Medium:

All media went through sterilization at 121 °C for 20 minutes. The nutrient medium for all bacteria contained (g/L distilled water): peptone, 5 and meat extract, 3. The pH was adjusted to 7.0.

Table 1. *In vitro* antibacterial activities of the synthesized compounds.

Comp. No	Diameter of zone inhibition in mm							
	Gram-positive bacteria				Gram-negative bacteria			
	S. aureus (ATCC 25923)		*S. pyogenes (ATCC 19615)*		*P. phaseolicola (GSPB 2828)*		*P. fluorescens (S 97)*	
	10 mg/mL	15 mg/mL	10 mg/mL	15 mg/mL	10 mg/mL	15 mg/mL	10 mg/mL	15 mg/mL
3a	10	16	12	17	18	28	16	25
3b	12	17	10	18	16	32	15	29
3c	19	32	18	30	11	23	12	22
3d	20	33	20	32	12	22	14	21
4a	11	20	12	22	18	32	16	30

4b	12	25	14	24	19	33	18	30
4c	19	33	18	32	10	21	8	23
4d	18	30	17	31	11	23	10	19
6a	10	24	8	22	7	18	12	25
6b	14	26	11	25	17	30	15	28
6c	15	25	10	24	18	29	19	33
6d	15	23	12	20	19	33	18	32
7a	13	20	12	21	18	30	17	29
7b	12	22	16	26	19	34	18	32
7c	18	30	19	33	14	24	13	23
7d	16	29	17	31	14	24	12	22
Cephalothin	28		30		NT		NT	
Chloramphenicol	NT		NT		25		30	

*Less active: 6–12 mm; moderately active: 13–19 mm; highly active: 20–30m m; –: No inhibition or inhibition less than 5 mm; NT not tested.

Agar Diffusion Method [16]

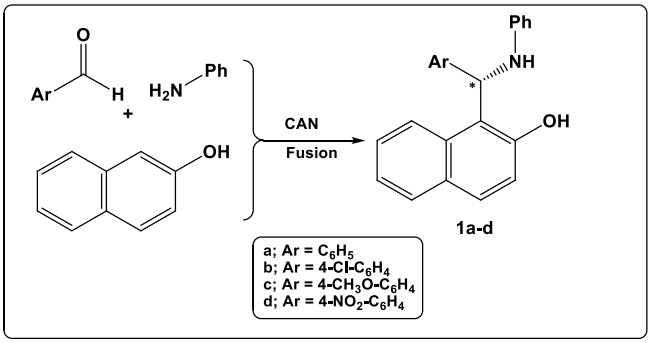
To get a concentration of 100 µg/mL, one milligram of each of the recently created spiro compounds was suspended in one milliliter of dimethyl sulphoxide (DMSO) and then topped off with ten milliliters of distilled water. Each tested compound's solution was added to the agar medium individually. After inoculation for 24 hours, the inhibition zones were assessed.

Filter Paper Disc-Diffusion Method [17]

Bacterial preparations at the appropriate concentrations were made from liquid stock cultures that had been cultured for one day at 100 rpm on a rotary shaker. After that, the mycelia were separated by 30 minutes of mechanical stirring at speed No. 1. Using a spectrophotometer set to 350 nm, the turbidity of the bacteria was adjusted to yield an optical density of 1.0. The tested bacteria were aseptically cultured in a microbial broth culture, using a standard volume of approximately 1 milliliter to evenly inoculate the appropriate agar plates. Discs of 10 mm in diameter Whatman No. 3 filter paper were autoclaved for 15 minutes at 121 °C to sanitize them. Ethanol alcohol was dissolved in test compounds to yield a final concentration of 5 µg/mL. The test chemicals (5 µg/disc) were applied to the sterile discs. The impregnated discs were placed on the agar surface that had previously been seeded with the organism to be evaluated after they had air dried. To ensure complete contact with the medium, discs were carefully compressed using forceps. For every test chemical, three trials were carried out. To allow for adequate diffusion, plates were refrigerated at 5 °C for one hour before being placed in an incubator at 37 °C for twenty-four hours.

3 Results and Discussion

1-(Aryl(phenylamino)methyl)naphthalen-2-ol derivatives **1a-d** were obtained by multicomponent condensation of aromatic aldehydes, 2-naphthol, and aniline in the presence of ceric ammonium nitrate (CAN) catalyst under solvent free conditions, Scheme 1.



Scheme 1. Synthesis of 1-(Aryl(phenylamino)methyl)naphthalen-2-ol derivatives **1a-d**.

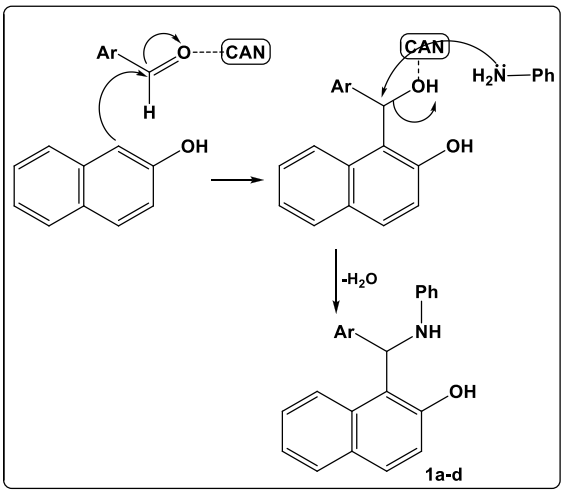
To optimize the reaction conditions, the reaction of 2-naphthol (1 mmol), 4-chlorobenzaldehyde (1 mmol) and aniline (1.2 mmol) was selected as a model reaction and carried out in various solvents and under solvent-free condition in the presence of 5, 10 and 15 mol% of ceric ammonium nitrate (CAN) as catalyst. As shown in Table 2, higher yield and shorter reaction time was obtained under solvent-free condition in the presence of 10 mol% of ceric ammonium nitrate (CAN).

Table 2. Three-Component Reaction of 2-naphthol, 4-chlorobenzaldehyde and aniline.

Entry	Solvent	Catalyst	Cat. mol%	Yield (%)
1	CH_3COOH	CH_3COOH	-	50
2	EtOH	HCl	-	72

3	EtOH	$FeCl_3$	10	45
4	-	CAN	5	82
5	-	CAN	10	94
	-	CAN	15	90

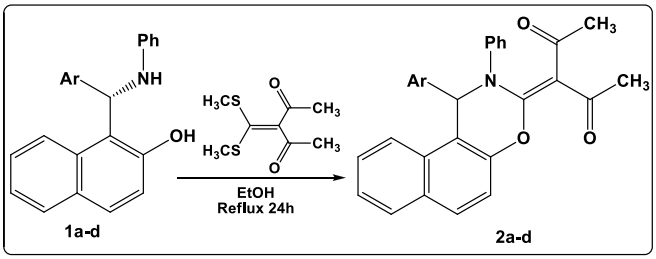
The proposed mechanism for the ceric ammonium nitrate (CAN) catalyzed synthesis of 1-(Aryl(phenylamino)methyl)naphthalen-2-ol derivatives **1a-d** from the reaction of 2-naphthol, aromatic aldehydes, and aniline is shown in Scheme 2.



Scheme 2. The proposed mechanism for the synthesis of compounds **1a-d**.

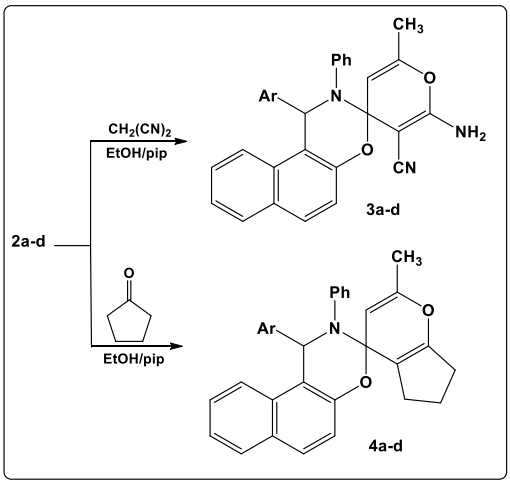
The IR spectra of compound **1a** exhibited the absorption band of 3409 cm^{-1} (OH) and 3348 cm^{-1}(NH). The ^{1}H-NMR spectra of compound **1a** showed sharp signals at δ 6.54 ppm arising from CH proton, δ 6.88-8.13 ppm from aromatic protons, δ 9.15 for NH proton and a signal at δ 10.24 ppm from OH proton. 19 Signals corresponding to all C-atoms in compound **1a** were observed in the ^{13}C-NMR spectra.

Reaction of compounds **1a-d** with a-oxoketene dithioacetal namely: 3-(bis(methylthio)methylene)pentane-2,4-dione in ethanol afforded the corresponding oxazine products namely: 3-(1-aryl-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)pentane-2,4-dione **2a-d**, Scheme 3.



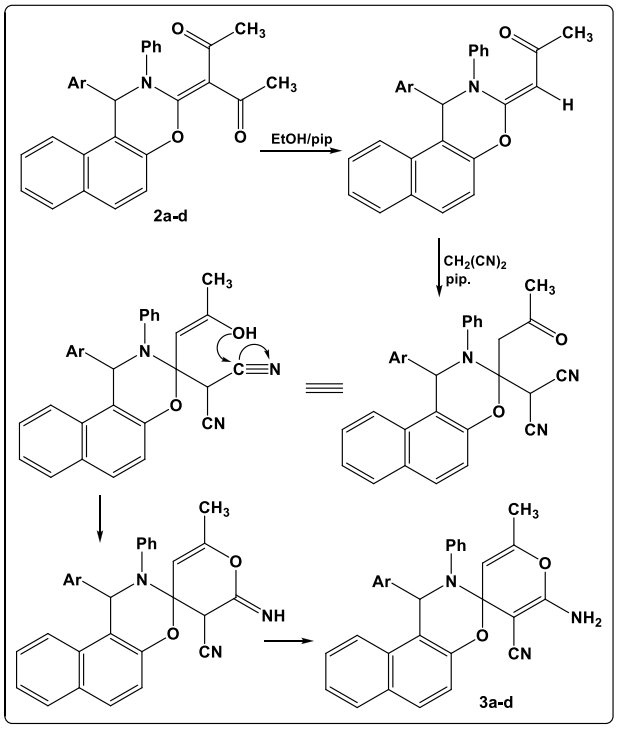
Scheme 3. Synthesis of 3-(1-aryl-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)pentane-2,4-dione **2a-d**.

Compounds **2a-d** were allowed to react with malononitrile or cyclopentanone under alkaline conditions (ethanol/piperidine), where the corresponding spiro heterocycles **3a-d** and **4a-d** were obtained respectively, Scheme 4.



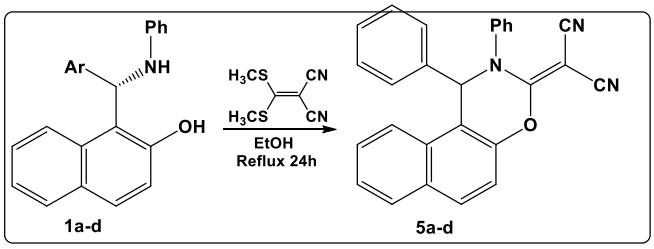
Scheme 4. Synthesis of spiro heterocycles **3a-d** and **4a-d**.

Formation of spiro heterocycles **3a-d** and **4a-d** was assumed to proceed via a preliminary elimination of one acetyl group followed by Michael addition of malononitrile or cyclopentanone onto the activated ethylenic bond and subsequent cyclization, Scheme 5.



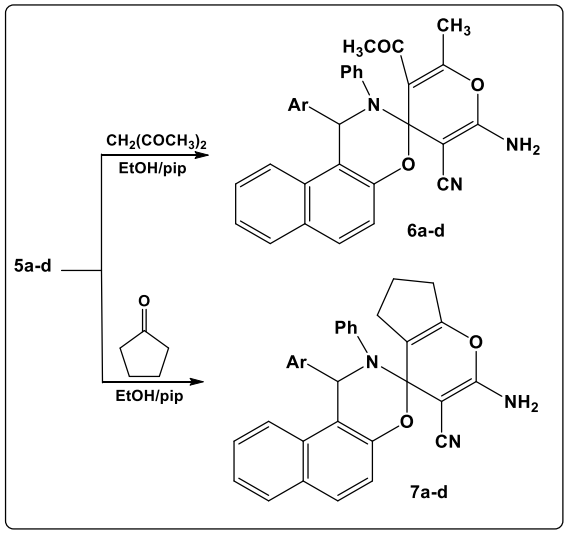
Scheme 5. Mechanism of formation of compounds **3a-d**.

Similarly, the reaction of compounds **1a-d** with a-cyanoketene dithioacetal namely: 2-(bis(methylthio)methylene)malononitrile afforded 2-(1-aryl-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)malononitrile **5a-d**, Scheme 6.



Scheme 6. Synthesis of 2-(1-aryl-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)malononitrile **5a-d**.

By the same way, the reaction of compounds **5a-d** with acetylacetone or cyclopentanone under alkaline conditions (ethanol/piperidine) gave the corresponding spiro heterocycles **6a-d** and **7a-d** respectively, Scheme 7.



Scheme 7. Synthesis of spiro heterocycles **6a-d** and **7a-d**.

All the obtained products were identified by their elemental and spectral (IR and NMR) analyses, see experimental section.

Acknowledgments

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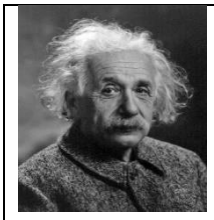

Albert Einstein, the most influential physicist of the 20th century, with his work also having a major impact on the development of atomic energy. With a focus on unified field theory. Einstein took on a position at the Institute for Advanced Study at Princeton, New Jersey and never went back to his native land.

Marie Curie, her work focused on radioactivity. With first female to win a Nobel Prize, Curie developed an international reputation for her scientific efforts, and she used her prize money to continue her research. Curie received another great honor in 1911, winning her second Nobel Prize, this time in chemistry. She was selected for her discovery of radium and polonium, and became the first scientist to win two Nobel Prizes.