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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 α-oxoketene dithioacetal afforded the corresponding oxazines **2a-d**. Compounds **2a-d** were allowed to react with malononitrile or cyclopentanone under alkaline conditions where the corresponding spiro heterocycles **3a-d** and **4a-d** were formed. 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. 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)*].

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

Functionalized α-oxoketene dithioacetals have attracted considerable interest as versatile intermediates for the synthesis of various heterocyclic compounds in the field of organic synthesis [1-5]. The presence of carbonyl or nitrile functionalities and its position in conjugation with double bond carrying bis(alkylthio) group at the β-position place them among the versatile 1,3-dielectrophilic 3-carbon equivalents[6-13]. The polarized ketene dithioacetal functional group is well known in synthetic organic sulfur chemistry as a two-carbon push-pull system. While the acetyl or cyano groups act as powerful electron-withdrawing centers, the two alkylated sulfurs readily donate their lone-pair of electrons to make the entire atomic framework highly polarized. Furthermore, the α,β-unsaturated acetyl/cyano groups behave as excellent Michael acceptors; subsequent to the attack of a nucleophile at the P-carbon, one of the alkylsulfanyl group leaves to regenerate the olefinic double bond.

1-Amidoalkyl-2-naphthol derivatives are of significant medical relevance since they can be converted into hypertensive and bradycardia active 1-aminoalkyl-2-naphthols by amide hydrolysis reaction [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}). Mass spectra were recorded on a GC-MSQP 1000EX Schimadzu at the Microanalytical laboratory, Cairo University, Cairo, Egypt. 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), 4-chlorobenzaldehyde (1.4 g, 10 mmol) and aniline (1.08 mL, 12 mmol) was 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, 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, 142.56, 147.43, 153.12.

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, 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, 142.63, 147.50, 153.08.

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, 64.10, 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, 142.50, 147.37, 153.22.

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). ^{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, 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, 142.66, 147.50, 154.05.

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 seasion of methyl mercaptan (lead actate). On cooling the precipitated product was filtered off and recrysallized 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, 16 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 42.04, 66.28, 98.65, 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, 142.56, 147.43, 153.12, 201.04.

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, 66.30, 98.60, 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, 142.55, 147.48, 153.15, 201.02.

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, 61.87, 66.35, 98.67, 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, 142.59, 147.67, 153.35, 201.09.

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, 66.44, 98.65, 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, 142.78, 147.87, 154.30, 201.11.

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, 66.53, 68.34, 107.33, 113.08, 115.56, 117.68, 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, 132.30, 142.51, 147.40, 153.17.

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, 66.55, 68.34, 107.55, 113.11, 115.50, 117.65, 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, 132.36, 142.56, 147.48, 154.15.

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, CH_3), 5.15 (s, 1H, =CH), 6.18, (br, 2H, NH_2), 6.50 (s, 1H, CH), 6.90-8.07 (m, 15 H, CH-arom.). ^{13}CNMR (DMSO-d_6), δ ppm: 29.10, 61.89, 66.58, 68.35, 107.55, 113.12, 115.51, 117.65, 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, 131.17, 132.30, 142.58, 147.55, 154.89.

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, 66.79, 68.67, 107.74, 113.56, 115.50, 117.68, 118.33, 123.15, 123.74, 124.20, 124.85, 125.14, 125.81, 126.16, 126.76, 127.32, 128.12, 128.73, 129.44, 130.51, 131.19, 132.32, 142.50, 147.87, 154.93.

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, 24.01, 24.46, 29.12, 66.50, 68.31, 115.50, 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, 132.31, 142.53, 147.45, 153.11.

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, 24.08, 24.50, 29.23, 66.58, 68.37, 115.55, 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, 132.34, 142.50, 147.49, 153.37.

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, 24.01, 24.46, 29.12, 61.67, 66.50, 68.31,

115.50, 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, 132.31, 142.53, 147.45, 153.24.

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, 24.08, 24.50, 29.23, 66.58, 68.37, 115.55, 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, 132.34, 142.50, 147.49, 154.46.

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 **2a-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 the left to cool. The formed solid was collected by filtration and used without further workup.

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, CH_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, 41.23, 66.58, 68.35, 107.55, 113.12, 115.51, 117.65, 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, 132.30, 142.58, 147.55, 154.89, 201.08.

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: 2.12 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.18, (br, 2H, NH_2), 6.56 (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: 2.12 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 6.22, (br, 2H, NH_2), 6.58 (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), 1678 (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.).

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.

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.

Antibacterial Screening

The newly synthesized spiro heterocyclic compounds were tested for their antimicrobial activity against Gram positive bacteria (Staphylococcus aureus *and Streptococcus pyogenes*) and Gram negative bacteria (Pseudomonas *phaseolicola* and *Pseudomonas fluorescens*).

Medium:

For all bacteria (Nutrient Medium), consisting of (g/L distilled water): peptone, 5 and meat extract, 3. pH was adjusted to 7.0. For solid media, 2% agar was added. All media were sterilized at 121 °C for 20 min. 3.2.1.

Agar Diffusion Method [16]

One mg of each of the newly synthesized spiro compounds was dissolved in dimethyl sulphoxide (DMSO, 1 mL) then made up to 10 mL with sterile water to give a concentration of 100 µg/mL. A solution of the tested compounds was placed separately in the agar medium. The inhibition zones were measured after 24 h incubation.

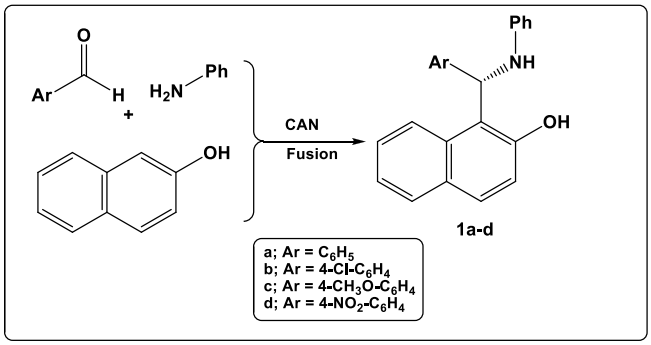
Filter Paper Disc-Diffusion Method [17]

Proper concentrations of microbial suspensions were prepared from one-day-old liquid stock cultures incubated on a rotary shaker (100 rpm). The mycelia were then subdivided by mechanical stirring at speed No. 1 for 30 min. Turbidity of bacteria was adjusted with a spectrophotometer at 350 nm to give an optical density of 1.0. Appropriate agar plates were aseptically surface inoculated uniformly by a standard volume (ca. 1 mL) of the microbial broth culture of the tested bacteria. Whatman No. 3 filter paper discs of 10 mm diameter were sterilized by autoclaving for 15 min at 121 °C. Test compounds were dissolved in 80% ethyl alcohol to give final concentration of 5 µg/mL. The sterile discs were impregnated with the test compounds (5 µg/disc). After the impregnated discs have been air dried, they were placed on the agar surface previously seeded with the organism to be tested. Discs were gently pressed with forceps to insure thorough contact with the media. Each test compound was conducted in triplicate. Plates were kept in the refrigerator at 5 °C for 1 h to permit good diffusion before transferring them to an incubator at 37 °C for 24 h.

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.



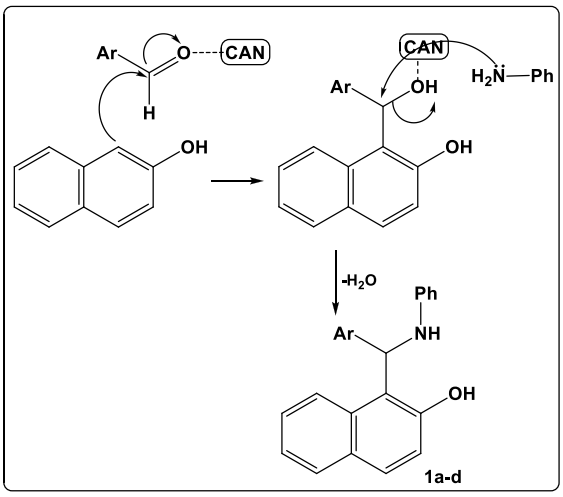
Scheme 1. Synthesis of 1-(Aryl(phenylamino)methyl)naphthalen-2-ol derivatives **1a-d**.

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

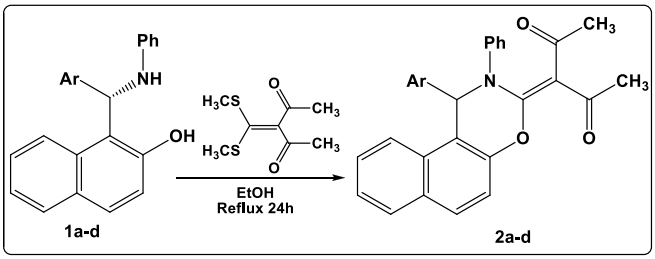
The proposed mechanism for the ceric ammonium nitrate (CAN) catalyzed synthesis of 1-(Aryl(phenylamino)methyl)naphthalen-2-ol derivatives **1a-d** from the reaction of 2-naphthol, aromatic aldehydes, and aniline is shown in Scheme 2.



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.

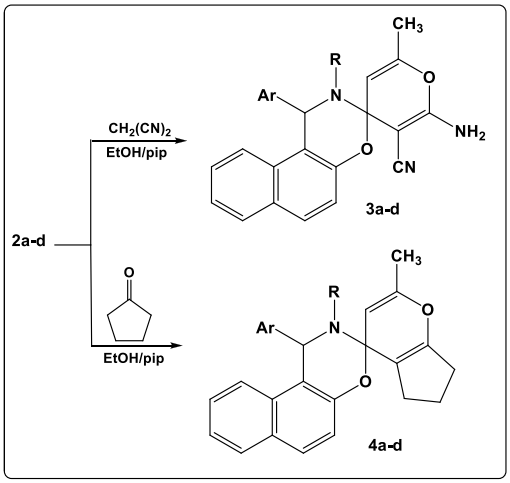
Reaction of compounds **1a-d** with a-oxoketene dithioacetal namely: 3-(bis(methylthio)methylene)pentane-2,4-dione in ethanol afforded the corresponding oxazine products namely: 3-(1-aryl-2-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-ylidene)pentane-2,4-dione **2a-d**, Scheme 3.



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**.

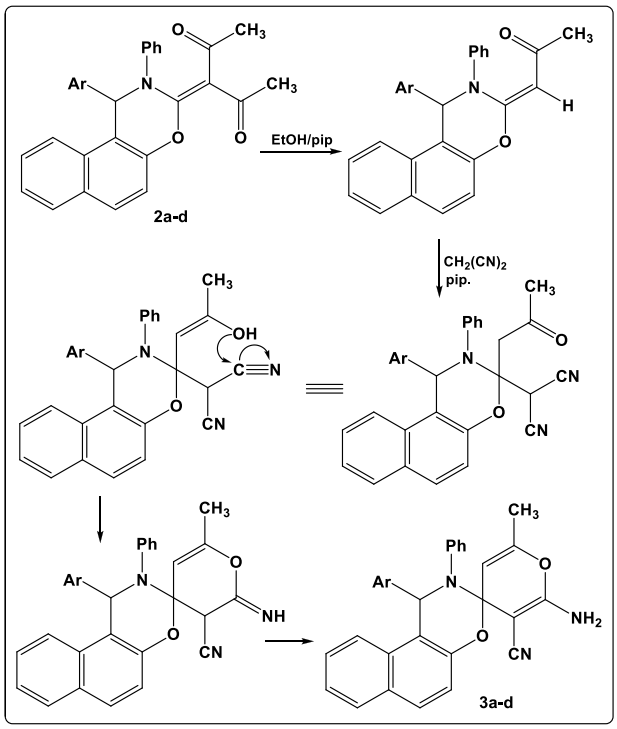
Compounds **2a-d** were allowed to react with malononitrile or cyclopentanone under alkaline conditions (ethanol/piperidine), where the corresponding spiro

heterocycles **3a-d** and **4a-d** were obtained respectively, Scheme 4.



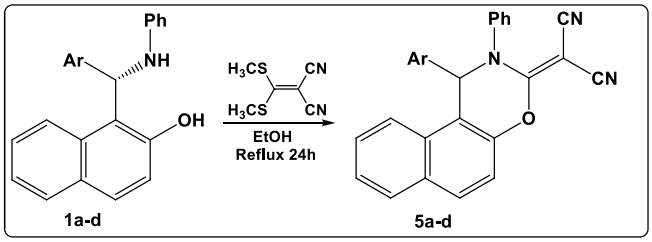
Scheme 4. Synthesis of spiro heterocycles **3a-d** and **4a-d**.

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.



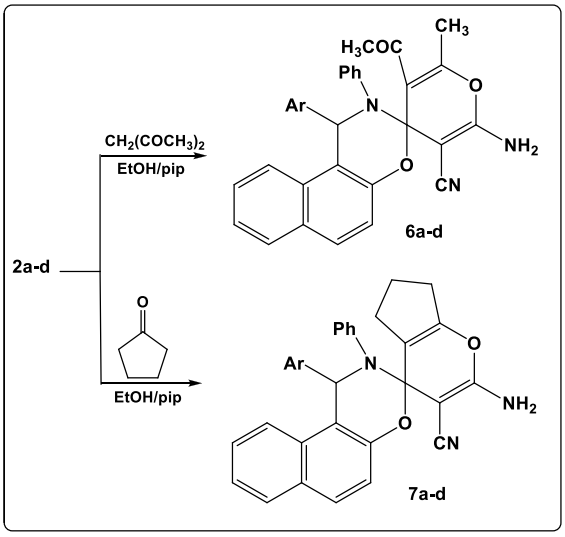
Scheme 5. Mechanism of formation of compounds **3a-d**.

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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