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FACILE AND EFFICIENT SYNTHESIS OF NOVEL OXAZINE, OXAZEPINE AND PHENOXAZINE OF CHROMENONES FUSED WITH 1,4-NAPHTHOQUINONE

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Dedicated to Professor Emeritus Keiichiro Fukumoto on occasion of his 75th birthday.

Abstract— A series of novel mono ethers **5, 7**, diethers **6, 8, 9**, oxazine **10**, oxazepine **11** and phenoxazines **12** of chromenones fused with 1,4-naphthoquinone have been synthesized.

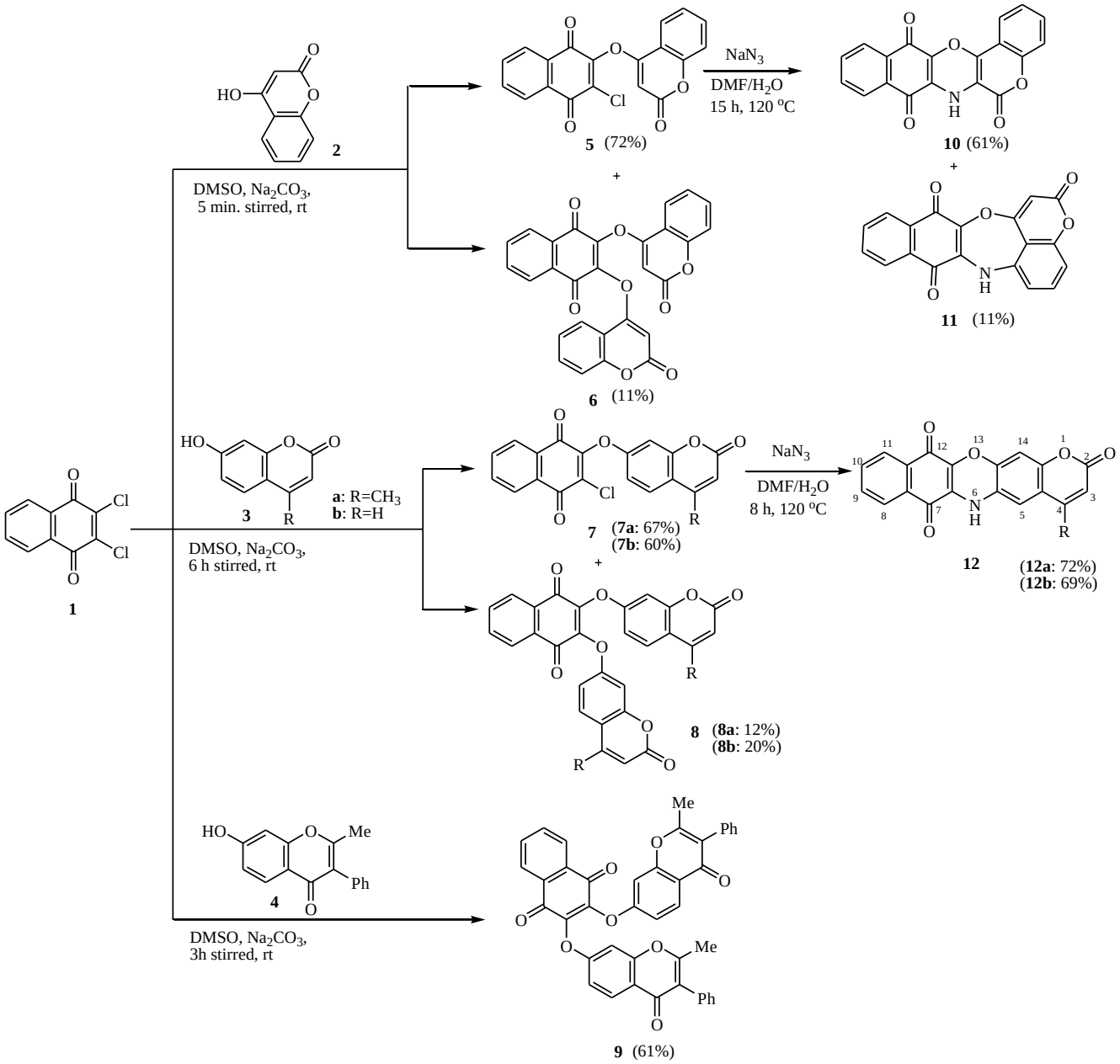
The quinone group forms the basis of biological activity of number of clinical and experimental drugs that are associated with antitumor, antimalarial, antifungal and antibacterial studies.[1] In addition chromenones have been reported to possess antimicrobial, anti-inflammatory and antitumor activity.[2-4] The clinical significance of these two class of compounds has stimulated the synthesis of novel ring systems agents retaining the core quinone and chromenone moiety.

As part of our research program of the synthesis of biologically active quinones,[1] we became interested in the synthesis of novel oxazine, oxazepine, phenoxazine and ether derivatives of chromenones fused with 1,4-naphthoquinone.

2,3-Dichloro-1,4-naphthoquinone **1** reacts readily with nucleophiles leading to substitution of one or both chlorine atoms.[5] Based on the reactivity of **1**, we have studied its reaction with chromenones **2-4** (one equivalents) in the presence of Na_2CO_3 using DMSO as solvent at room temperature.[8] Quinone **1** was reacted with 4-hydroxy-2*H*-chromen-2-one **2** to give a mixture of the 2-chloro-3-(2-oxo-2*H*-chromen-4-yloxy)naphthalene-1,4-dione **5** and 2,3-bis(2-oxo-2*H*-chromen-4-yloxy)naphthalene-1,4-dione **6** in 72% and 11% yields respectively (Scheme 1) whereas reaction with 7-hydroxy-4-methyl-2*H*-chromen-2-one **3a** and 7-hydroxy-2*H*-chromen-2-one **3b** gave ethers, 2-chloro-3-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)naphthalene-1,4-dione **7a** and 2-chloro-3-(2-oxo-2*H*-chromen-7-yloxy)naphthalene-1,4-dione **7b**

in 67% and 60% yields respectively. In addition to formation of **7a** and **7b**, diethers, 2,3-bis(4-methyl-2-oxo-2*H*-chromen-7-yloxy)naphthalene-1,4-dione **8a** and 2,3-bis(2-oxo-2*H*-chromen-7-yloxy)-naphthalene-1,4-dione **8b** were obtained in 12% and 20% yields, respectively.

In separate experiments quinone **1** was reacted with two equivalents of chromenones **2, 3a** and **3b** at 100 ^{o}C resulting in the formation of diethers **6, 8a** and **8b** in 84%, 81% and 79% yield, respectively.



Scheme 1

We then studied the reaction of quinone **1** with 7-hydroxy-2-metnyl-3-phenyl-4*H*-chromen-4-one **4** (one equivalents) at room temperature and 100 ^{o}C exclusively, monitoring TLC at regular interval, the reaction produced only disubstituted product, 2,3-bis(2-methyl-4-oxo-3-phenyl-4*H*-chromen-7-yloxy)naphthalene-

1,4-dione **9** in 61% yield. It is believed[9] that the chromenone **4** increased the reactivity of second substitution, therefore mono derivative was converted into disubstituted as soon as it formed.

In order to synthesize novel oxazine, oxazepine and phenoxazine, we studied the reaction of mono ethers[7] **5, 7a** and **7b** with sodium azide using DMF/H_2O as solvent at 120 ^oC using methods as reported Kim et al.[10] The reaction led to formation of chromeno[3,4-*e*]naphtho[2,3-*b*][1,4]oxazine-6,8,13(7*H*)-trione **10**

Table 1. Physical spectral and micro analytical data of **5-12**[6,7]

Entry	Mp	Spectra
5	>280	IR (KBr):1680,1632,1601 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.40 (m, 2H), 7.71 (s, 1H), 7.95 (m, 2H), 8.07 (m, 2H), 8.14 (m, 2H); M^+: 353; Anal. Calcd ($C_{19}H_9ClO_5$): C, 64.70; H, 2.57. Found: C, 64.94; H, 2.68.
6	>280	IR (KBr): 1679, 1632, 1594 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.42 (m, 3H), 7.72 (m, 2H), 7.96 (m, 5H), 8.09 (d, 2H, J=6), 8.18 (d, 2H, J=6); M^+: 479; Anal. Calcd ($C_{28}H_{14}O_8$): C, 70.30; H, 2.95. Found: C, 70.52; H, 3.10.
7a	215	IR (KBr): 2985, 1675,1591, 1539 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H), 6.31 (s, 1H), 7.28 (d, 1H), 7.30 (d,1H, J=6) 7.40 (s, 1H, J=6), 7.96 (m, 2H), 8.01 (m, 2H); M^+: 367; Anal. Calcd ($C_{20}H_{11}ClO_5$): C, 65.50; H, 3.02. Found: C, 65.36; H, 3.20
7b	207	IR (KBr): 1657, 1586, 1542 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.17 (d, 1H, J=6), 6.75 (m, 2H), 7.50 (m, 2H) 7.90 (m, 2H), 8.01 (m, 2H); M^+: 353; Anal. Calcd ($C_{19}H_9ClO_5$): C, 64.70; H, 2.57. Found: C,64.88; H, 2.46.
8a	220	IR (KBr): 2925, 1733,1655,1607 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 6H), 6.25 (s, 2H), 7.15 (m, 4H), 7.70 (m, 2H), 7.95 (m, 2H), 8.05 (d, 2H, J=6); ^{13}CNMR (300 MHz, DMSO-d_6): 18.03, 18.19, 103.78, 103.33, 112.56, 113.09, 115.55, 126.47, 126.65, 126.99, 130.62, 131.56, 134.45, 134.63, 151.76, 152.37, 152.83, 153.11, 153.65, 153.86, 154.36, 156.19, 158.65, 159.04, 159.53, 159.75, 166.73, 176.90, 177.59, 178.05; M^+: 508; Anal. Calcd ($C_{30}H_{18}O_8$): C, 71.15; H, 3.58. Found: C, 71.28; H, 3.70.
8b	214	IR (KBr): 1722, 1650, 1601 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.19 (m, 2H), 6.72 (m, 4H), 7.49 (m, 4H), 7.88 (m, 2H), 8.02 (m, 2H); M^+: 479; Anal. Calcd ($C_{28}H_{14}O_8$): C, 70.30; H, 2.95. Found: C, 70.42; H, 3.14.
9	187	IR (KBr): 2928, 1627, 1591, 1543 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 6H), 6.89 (m, 4H), 7.28 (m, 1H),7.40 (m, 2H), 7.75 (m, 6H), 7.95 (m, 7H); M^+: 659; Anal. Calcd ($C_{42}H_{26}O_8$): C, 76.59; H, 3.98. Found: C, 76.72; H, 4.18.
10	118	IR (KBr): 3447, 1652, 1605, 1543 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.5 (bs, 1H), 7.25 (m, 2H), 7.60 (m, 2H), 7.90 (m, 2H), 8.05 (m, 2H); ^{13}CNMR (300 MHz, DMSO-d_6): 79.19,101.75, 115.49, 115.91, 116.71, 116.96, 119.49, 123.04, 124.54, 126.13, 130.29, 135.24, 135.24, 135.24, 135.67, 159.14, 161.26, 167.80, 168.67, 172.09; M^+ (M^++1): 332; Anal. Calcd ($C_{19}H_9NO_5$): C, 68.89; H, 2.74; N, 4.23. Found: C, 68.66; H, 2.82; N, 4.40.
11	>280	IR (KBr): 3444, 1767, 1635, 1621 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.69 (bs, 1H), 5.82 (s, 1H), 6.87 (m, 1H), 7.09 (m, 1H), 7.26 (m, 1H), 7.53 (m, 2H), 7.90 (m, 2H); M^+ (M^++1): 332; Anal. Calcd ($C_{19}H_9NO_5$): C, 68.89; H, 2.74; N, 4.23. Found: C, 68.68; H, 2.64; N, 4.32
12a	>280	IR (KBr): 3430, 1670, 1593, 1541 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 4.20 (bs, 1H, NH), 6.25 (s, 1H, C_3-H), 6.70 (m, 2H, C_5-H & C_{14}-H), 7.63 (m, 2H, C_8-H & C_{11}-H), 7.91 (m, 2H, C_9-H & C_{10}-H); M^+ (M^++1): 346; Anal. Calcd ($C_{20}H_{11}NO_5$): C, 69.57; H,3.21; N, 4.06. Found: C, 69.70; H, 3.30; N, 4.14.
12b	>280	IR (KBr): 3433, 1668, 1592, 1535 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.19 (bs, 1H, NH), 6.18 (m, 1H, C_3-H), 6.74 (m, 2H, C_5-H & C_{14}-H), 7.65 (m, 3H), 7.96 (m, 2H) M^+ (M^++1): 332; Anal. Calcd ($C_{19}H_9NO_5$): C, 68.89; H, 2.74; N, 4.23. Found: C, 68.64; H, 2.82; N, 4.44.

and chromeno[5,4-*ef*]naphtha[2,3-*b*][1,4]oxazepine-2,8,13(*7H*)-trione (**11**) from mono ether **5**, 4-methylbenzo[*b*]pyrano[2,3-*i*]naphthoxazine-2,7,12(*6H*)-trione (**12a**) and benzo[*b*]pyrano[2,3-*i*]-naphthoxazine-2,7,12(*6H*)-trione (**12b**) from mono ethers **7a** and **7b** in 61%, 11%, 72% and 69% yields respectively.

Compounds **5-12** synthesized were evaluated for their antibacterial activities against various strains of the bacteria, for example, *Staphylococcus aureus*, *Streptococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli* and antifungal activity against various strains of pathogenic fungi, for example, *Candida albicans*, *Candida parapsilosis* (ATCC 22019), *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Sporothrix schenckii* and *Trichophyton mentagraphytes* and carried out according to the broth microdilution technique described by NCCLS[1] of minimum inhibitory concentration(MIC) assay at 50 µg/mL or lower concentration. Compound **7a** exhibited *in vitro* antifungal activity against *Candida albicans*, *Cryptococcus neoformans*, and *Sporothrix schenckii* at 25 µg/mL whereas compounds **7a** also showed *in vitro* antibacterial activity against *Klebsiella pneumoniae* and *Escherichia coli*.

In conclusion, we have synthesized novel oxazine, oxazepine, phenoxazines and ethers of different chromenones **2-4** fused with 1,4-naphtnoquinone **1**. Further work to evaluate other biological effects is in progress.

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6. *General procedure* (**5-9**): To a solution of 2,3-dichloro-1,4-napthoquinone **1** (2 mmol) in DMSO (4 mL), chromenone **2-4** (2.2 mmol) was added followed by Sodium carbonate (2.2 mmol). The reaction mixture was stirred at rt as shown in Scheme 1. The reaction mixture was poured in crushed

ice and extracted with EtOAc followed to wash with brine and dried *in vacuo*. The mixture of mono and diethers **5-9** was separated by column chromatography(SiO_2) using EtOAc in hexane (30-100%).

7. *General Procedure* (**10-12**): To a solution of mono ether **5, 7** (1 mmol) and NaN_3 (3 mmol) in DMF (3 mL) and H_2O (1 mL) was stirred at 120 ^oC. The reaction mixture was poured into crushed ice. The precipited solid was collected by filtration, washed with water, dried and purified by column chromatography (SiO_2) using EtOAc in hexane (20-80%).

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