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단 신

NADH-Ubiquinone Oxidoreductase의 새로운 저해제 합성

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Synthesis of New Inhibitors on NADH-Ubiquinone Oxidoreductase

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Recently myxalamid[2] and benzimidazole derivatives[3] have been found as new classes of NADH-ubiquinone oxidoreductase inhibitors in the respiratory electron transport (RET) system. All these compounds are similar to ubiquinones (UQ) in the structural distribution of hydrophilic and hydrophobic moieties, and a suitable size of those lipophilic parts could be estimated between ten to fourteen carbon-bond length. Structural similarity between inhibitors and UQ suggests that a very special situation arises at their binding sites of NADH-UQ oxidoreductase, namely the inhibiors may occupy the UQ niche to interrupt the electron flow in the RET system.

Quinoline system is an attractive nucleus for a new type of inhibitors because it may be biomimetic to menaquinones (MQ) which are widely distributed in both respiratory[4] and photosynthetic mechanisms[5,6], and perform the function of UQ.

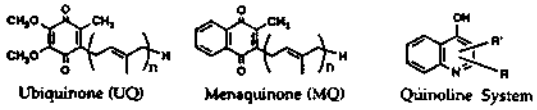
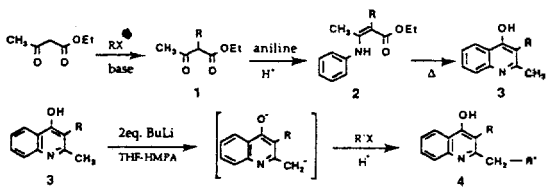


Fig. 1

For consequent works to design inhibitors tremendous effort will be required to complete all combination of possible nucleus and sidechains,



Scheme

however this seems to be reduced by usage of suitable intermediates which are readily synthesized from simple reagents (Scheme).

Compounds **3** were synthesized by condensation between ethyl 2-alkylacetoacetate (**1**)[7] and aniline followed by cyclization to give various derivatives of 4-hydroxyquinoline[8,9]. Then, treatment of compound **3** (R: small alkyl groups) with 2 eq. of BuLi in THF-HMPA followed by the coupling of the resulting carbanion with various halides gave the new compounds **4** holding a lipophilic sidechain at α-position[10,11]. This simple and easy preparation of **3** and **4** suggests its wide applicability for variation of the 4-hydroxyquinoline moiety.

Preliminary biological test showed that compounds **3** and **4** were highly active against NADH-ubiquinone oxidoreductase[12].

EXPERIMENTAL

Ethyl 2-alkylacetoacetates (**1**) were prepared by using method[8] in 65~92% yields.

Ethyl 2-methylacetoacetate (1-a). 87%; bp. 184~185℃; IR (neat): 3000, 2950, 1740, 1715, 1200, 1150 cm^{-1}; NMR ($CDCl_3$): δ 1.29 (t, 3H), 1.34 (d, 3H), 2.18 (s, 3H), 3.52 (q, 1H), 4.2 (q, 3H); MS m/e (rel. int.): 144 (M^+, 100).

Ethyl 3-phenylamino-2-alkylcrotonates (2). A mixture of aniline (0.1 mol, 9.3 g), ethyl 2-alkylacetoacetate (**1**; 0.10 mol), and 0.5 g of toluenesulfonic acid as a catalyst in 100 m*l* of toluene was refuxed for 3 h with Dean-Stark trap. The reaction mixture was washed with 5% HCl, 5% $NaHCO_3$ and water. Solvent was removed and the yellowish oil product was used in the next step directly. All enamines were obtained in 72~91% yields.

Ethyl 3-phenylamino-2-methylcrotonate (2-a). 87%; oil; IR (neat): 3350, 2970, 1725, 1640, 1570, 1500, 1250, 1100 cm^{-1}; NMR ($CDCl_3$): δ 1.28 (t, 3H), 1.83 (s, 3H), 2.01 (s, 3H), 4.14 (q, 2H), 6.90~7.33 (m, 5H).

3-Alkyl-2-methyl-4-hydroxyquinolines (3). To 200 m*l* of refluxing diphenyl ether was added compound **2** in 50 m*l* xylene dropwise for 30 minutes. After refluxing for one hour, the mixture was cooled, filtered, washed with petroleum ether, and dried to give soid products in 67~76% yields.

2,3-Dimethyl-4-hydroxyquinoline (3-a). 76%; mp. 240℃; IR (KBr): 3400, 3050, 2980, 1640, 1590, 1540 cm^{-1}; NMR ($CDCl_3$-CD_3OD): δ 2.11 (s, 3H), 2.42 (s, 3H), 7.28~8.26 (m, 4H); MS m/e (rel. int.): 173 (M^+, 90), 144 (100), 130 (50), 118 (15), 103 (20); HRMS. Calcd. for $C_{11}H_{11}NO$: 173.0841. Found: 173.0821.

Synthesis of compound 4. Compound **3** (1.0 mmol) in 4 m*l* of THF and 1 m*l* of HMPA was treated with 1.5 m*l* of 1.6 *M* butyllithium in hexane under nitrogen at room temperature. Then a halide (1.0 mmol) in 1 m*l* THF was added, and the mixture was stirred for 30 minutes. After neutralization with 2 N HCl the solvent was removed. The residue was purified by column chromatography with ethyl acetate to give pure products in 60~70% yields.

3-Methyl-2-(6′-phenylhexyl)-4-quinolinol (4-a). 67%; mp. 192~195℃; IR (KBr): 3500, 3050, 2920, 2850, 1640, 1600, 1590, 1550, 1490, 1360, 1250, 1100 cm^{-1}; NMR ($CDCl_3$-DMSO-d_6): δ 1.33~1.52 (m, 4H), 1.54~1.73 (m, 4H), 2.03 (s, 3H), 2.53~2.71 (m, 4H), 7.10~8.14 (9H, aromatic). MS m/z (rel. int.): 319 (M^+, 75), 228 (42), 200 (45), 186 (73), 173 (100), 145 (15). HRMS. Found: 319.1939. Calcd. for $C_{22}H_{25}NO$: 319.1936.

Supplementary Material Available. Spectral data for compounds prepared including IR, ^1H NMR, and MS (6 pages). Ordering information is given on masterhead page.

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