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# Synthesis and Structure–Activity Relationship of Dehydroxymethylepoxyquinomicin Analogues as Inhibitors of NF-κB Functions

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**Abstract**—We previously found dehydroxymethylepoxyquinomicin (DHMEQ) inhibited NF-κB activation and showed anti-inflammatory activity in vivo. Here we designed and synthesized analogues of DHMEQ and tested their biological activity as NF-κB inhibitors in human T cell leukemia Jurkat cells. The hydroxyl group at the 2-position of the benzamide moiety was found to be essential for the inhibitory activity. But etherification of this group did not diminish the activity completely. Thus, for further mechanistic studies the hydroxyl group at the 2-position may be useful for extension with a linker and biotin moiety.


## Introduction

Nuclear factor-kappa B (NF-κB) is an inducible and ubiquitous transcription factor that elicits the expression of inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α and apoptosis inhibitory proteins (IAPs). The most common form of NF-κB is a heterodimer consisting of a 50-kD protein (p50) and a 65-kD protein (p65 or RelA).[1] NF-κB is a key mediator of TNF-α responses and an attractive target for therapeutic intervention against inflammatory diseases such as rheumatoid arthritis[2] and neoplastic diseases.[3] The number of known roles of NF-κB is rapidly increasing. For instance, erythropoietin was shown to inhibit apoptosis of neuronal cells by increasing the tyrosine phosphorylation of IκB to activate NF-κB.[4] On the other hand, NF-κB was found to be often constitutively activated in breast cancer cells and in human melanoma cells.[5,6] Activation of NF-κB would provide apoptotic resistance in these neoplastic tumors.

Recently, 4 novel 5,6-epoxycyclohexenone compounds, that is, epoxyquinomicins A, B, C and D, were isolated from the culture broth of *Amycolatopsis* sp. MK 299-95F4, a microbial strain isolated from a soil sample collected in Sendai, Japan, as weak antibiotics.[7] Epoxyquinomicin C **1** is the simplest among these 4 epoxyquinomicins, and it has a 4-hydroxy-5,6-epoxycyclohexenone group that also exists in the structure of panepoxydone **2**[8] and cycloepoxydon **3**.[9] Compounds **2** and **3** were found to inhibit TNF-α-induced activation of NF-κB by inhibiting the phosphorylation and degradation of IκB.[8] Epoxyquinomicin C **1** has an additional hydroxymethyl group compared with panepoxydone **2**, and this compound did not inhibit NF-κB activation. Therefore, we designed and synthesized the 5-dehydroxymethyl derivative (DHMEQ, **4**) of **1**.[10] Compound **4** inhibited TNF-α-induced activation of NF-κB in human T cell leukemia Jurkat cells. We recently reported that compound **4** inhibited nuclear translocation of NF-κB in Jurkat and African green monkey COS-1 cells.[11] It also inhibited type II collagen-induced rheumatoid arthritis in a murine model.[10] Like epoxyquinomicin C **1**, compound **4** showed no prominent toxicity in mice. Thus we considered the possibility of developing it as a chemotherapeutic agent. In the present paper, we report the synthesis and the biological activity of DHMEQ derivatives with potential to inhibit NF-κB functions, and looked into their structure–activity relationship.

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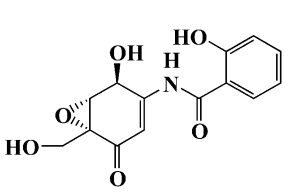
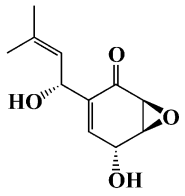

epoxyquinomicin C **1**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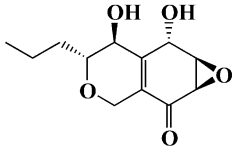
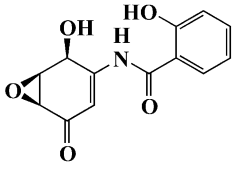

cycloepoxydon **3**


DHMEQ **4**

## Chemistry

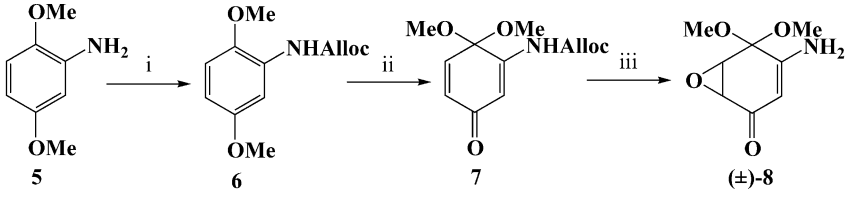
Synthesis of the target compounds **15a**–**j** was accomplished by applying a methodology different from that previously described for **4**.[10] Scheme 3 summarizes the synthetic route for **15a**–**j**. We selected racemic 3-amino-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-on (**8**) as the starting material, which could be readily obtained from commercially available 2,5-dimethoxyaniline (**5**) as shown in Scheme 1 according to the protocol of Wipf's method.[12]

As lithium *tert*-butoxide was recommended as a base for acylation of epoxyenamine **8** with various acyl chlorides,[13] compound **8** was coupled with the appropriate acyl chloride, prepared in situ from carboxylic acids **9a**–**j** by oxalyl chloride in the presence of a catalytic amount of DMF, by the aid of lithium *tert*-butoxide in THF to afford amides **10a**–**j** in 62–98% yields. Saponification of ester group of compounds **10a** and **10b** with $K_2CO_3$ in methanol gave **11a** and **11b** in 71 and 65% yields, respectively. At first, regeneration of the ketone group from acetal by hydrolysis was supposed to be troublesome. Taylar et al. reported that the direct deprotection of the acetal group of **12** was unsuccessful due to aromatization, and therefore we converted **12** into the corresponding epoxyquinone **13** via a 3-step reduction-deprotection-oxidation sequence (Scheme 2).[14]

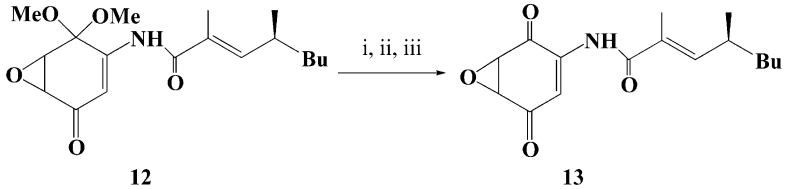
Fortunately, however, treatment of **10c**–**j** and **11a**–**b** with boron trifluoride etherate in $CH_2Cl_2$ at $-20\,^{\circ}C$ furnished epoxyquinone compounds **14a**–**j** in 57–85% yields without any difficulty. Then, regioselective reduction of **14a**–**j** was carried out by treatment with sodium triacetoxyborohydride in methanol to provide the target compounds **15a**–**j** in 54–89% yields. No epimer was detected in TLC after the reduction by sodium triacetoxyborohydride for preparation of **15a**–**j**. The relative stereochemistry of **15a**–**j** was determined based on the physical data by comparison with those of DHMEQ, whose stereochemistry was established unambiguously by X-ray crystallography.[10]

## Biological Activity

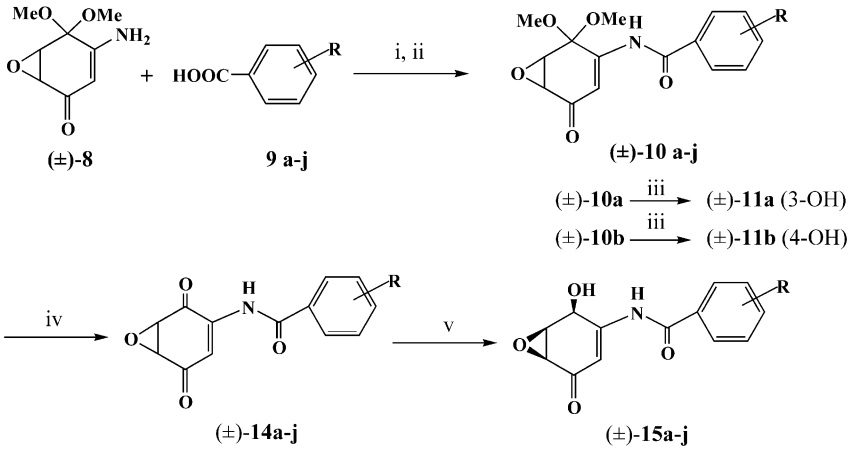
The newly synthesized analogues **15a**–**j** were assayed for their inhibitory activity toward TNF-α-induced NF-κB activation in Jurkat cells, with DHMEQ **4** adopted as a reference standard. The cells were transfected with κB-luciferase DNA by the DEAE-dextran method. The activity of NF-κB can be detected by transient transfection of Jurkat cells with the reporter DNA having the binding sequence for NF-κB and the luciferase gene. Figure 1 shows inhibition of TNF-α-induced NF-κB activation by all of the synthesized compounds. The hydroxyl group at the 2-position of the benzamide ring system was found to be essential for the inhibitory activity, since the regional isomers **15a** and **15b**, possessing a respective hydroxyl group at the 3- and 4-positions, and the deoxy compound **15c** all completely lost the activity. The methylated compound **15h** and halogenated compounds such as **15i** and **15j** at the 2-position also showed no activity. Interestingly, etherification of the hydroxyl group at the 2-position did not diminish the inhibitory activity. The presence of a hexyl group (**15f**) or phenyl group (**15g**) weakened the activity, but lower alkyl groups such as the methyl and ethyl of **15d** and **15e**, respectively, did not affect the inhibitory activity. For the detection of molecular target for DHMEQ **4**, the biotin-labeled derivative of **4** must be useful. Thus, based on the results of the structure–activity relationship, we found that the hydroxyl functional




**Scheme 1.** Reagents and conditions: (i) Alloc-Cl, $Et_3N$, THF; (ii) $PhI(OAc)_2$, MeOH; (iii) TBHP, DBU, $CH_2Cl_2$.




**Scheme 2.** Reagents and conditions: (i) $LiEt_3BH$, THF; (ii) montmorillonite K10, $CH_2Cl_2$; (iii) PDC, $CH_2Cl_2$.




| Cpds. **9** and **10** | R |
|---|---|
| a | 3-OAc |
| b | 4-OAc |
| c | H |
| d | 2-OMe |
| e | 2-OEt |
| f | 2-$OC_6H_{13}$ |
| g | 2-OPh |
| h | 2-Me |
| i | 2-F |
| j | 2-Cl |

| Cpds. **14** and **15** | R |
|---|---|
| a | 3-OH |
| b | 4-OH |
| c | H |
| d | 2-OMe |
| e | 2-OEt |
| f | 2-$OC_6H_{13}$ |
| g | 2-OPh |
| h | 2-Me |
| i | 2-F |
| j | 2-Cl |

**Scheme 3.** Reagents and conditions: (i) $(COCl)_2$, cat. DMF, $CH_2Cl_2$, rt, 0 °C, 1.5 h; (ii) *t*-BuOLi, THF, −78 °C, 30 min; (iii) $K_2CO_3$, MeOH, rt, 30 min; (iv) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −20 °C, 30 min; (v) NaBH $(OAc)_3$, MeOH, 0 °C, 30 min.

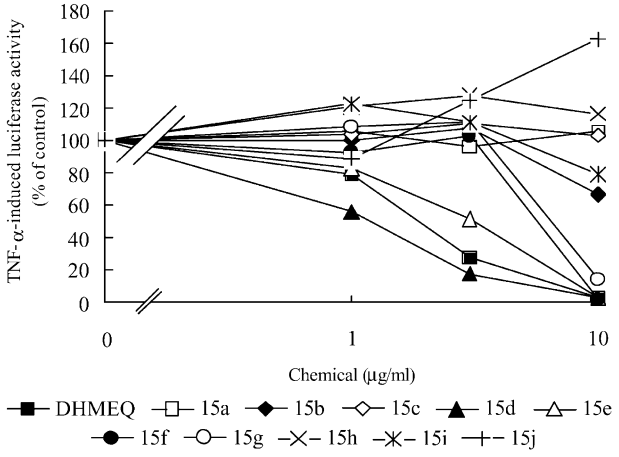



**Figure 1.** Effect of DHMEQ and its analogues on TNF-α-induced activation of NF-κB in Jurkat cells. The cells were treated with each compound with or without 20 ng/mL of TNF-α.

group at the 2-position of the benzamide ring is a suitable candidate for extension with a linker and biotin moiety.

## Experimental

All reactions requiring anhydrous and oxygen-free conditions were conducted in an argon atmosphere. *t*-BuOLi (0.1 M in THF) was obtained from Aldrich Chemical Co. Analytical TLC was performed on Merck pre-coated silica gel 60 $F_{254}$ plates. Column chromatography was performed by using silica gel 60 (particle size 0.063–0.200 mm, Merck). Melting points were obtained with a Yanaco micro melting point apparatus and left uncorrected. $^1H$ NMR (300 MHz) and $^{13}C$ NMR (75.4 MHz) spectral data were obtained on a Jeol JNM-LA300 spectrometer, and chemical shifts were reported as parts per million (ppm) downfield from tetramethylsilane as an internal standard. High-resolution mass spectra were recorded on a Jeol JMS-GCmate mass spectrometer.

### General method for preparation of *N*-(2,2,-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide derivatives

Dry DMF (10 μL) was added to a cold solution of appropriate carboxylic acid (1 equiv) from **9a–j** and oxalyl chloride (2 equiv) in dry $CH_2Cl_2$. The clear solution was stirred at 0 °C for 1.5 h and allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure; and after the addition of dry toluene, the mixture was concentrated in vacuo. Dry THF was added, and the solution was cannulated under Ar to a flask containing epoxyenamine **8** (1 equiv). To this stirred solution was added *t*-BuOLi (0.1 M THF solution, 1 equiv) at −78 °C. The reaction was allowed to proceed with stirring at 0 °C for 30 min. On completion, the reaction mixture was extracted with ethyl acetate; and the organic layers were washed with brine, dried over anhydrous sodium sulphate, and evaporated to yield a

residue. Purification of this residue by using column chromatography over silica gel with *n*-hexane/ethyl acetate (2:1, v/v) as eluent yielded the benzamide derivatives **10a–j**.

**3-Acetoxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10a).** (96%, mp 128–130 °C): $^1$H NMR ($CDCl_3$) δ 2.30 (s, 3H), 3.30 (s, 3H), 3.53 (dd, 1H, $J$ = 4.2, 2.1 Hz), 3.67 (s, 3H), 3.84 (d, 1H, $J$ = 3.9 Hz), 7.23 (d, 1H, $J$ = 2.1 Hz), 7.30 (t, 1H, $J$ = 5.6 Hz), 7.45 (d, 1H, $J$ = 8.1 Hz), 7.51 (t, 1H, $J$ = 1.8 Hz), 7.55 (t, 1H, $J$ = 8.1 Hz), 8.39 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 21.0, 50.9, 51.3, 51.4, 52.1, 95.6, 109.1, 120.8, 124.0, 126.1, 130.0, 135.2, 145.1, 150.6, 164.8, 169.2, 192.8. HRMS (EI) $m/z$ calcd for $C_{17}H_{17}NO_7$, 347.1005; found, 347.1011.

**4-Acetoxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10b).** (92%, mp 145–147 °C): $^1$H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.33 (s, 3H), 3.56 (dd, 1H, $J$ = 3.6, 1.8 Hz), 3.70 (s, 3H), 3.87 (d, 1H, $J$ = 3.9 Hz), 7.26 (t, 3H, $J$ = 7.8 Hz), 7.80 (d, 2H, $J$ = 8.4 Hz), 8.42 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 21.1, 50.8, 51.3, 51.4, 52.1, 95.6, 108.9, 122.2, 128.6, 131.2, 145.3, 154.0, 164.9, 168.8, 171.1, 192.8. HRMS (EI) $m/z$ calcd for $C_{17}H_{17}NO_7$, 347.1005; found, 347.1006.

***N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10c).** (95%, mp 117–118 °C): $^1$H NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.56 (dd, 1H, $J$ = 4.2, 2.1 Hz), 3.72 (s, 3H), 3.88 (d, 1H, $J$ = 4.3 Hz), 7.31 (d, 1H, $J$ = 2.0 Hz), 7.54 (d, 2H, $J$ = 7.6 Hz), 7.57 (t, 1H, $J$ = 1.5 Hz), 7.77 (d, 2H, $J$ = 6.8 Hz), 8.48 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 50.9, 51.3, 51.4, 52.2, 95.6, 108.8, 126.9, 128.9, 132.7, 133.5, 145.2, 165.6, 192.6. HRMS (EI) $m/z$ calcd for $C_{15}H_{15}NO_5$, 289.0950; found, 289.0958.

**2-Methoxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10d).** (77%, mp 125–127 °C): $^1$H NMR ($CDCl_3$) δ 3.29 (s, 3H), 3.47 (dd, 1H, $J$ = 4.3, 2.1 Hz), 3.67 (s, 3H), 3.83 (d, 1H, $J$ = 4.4 Hz), 4.00 (s, 3H), 6.97 (d, 1H, $J$ = 8.4 Hz), 7.05 (t, 1H, $J$ = 7.4 Hz), 7.31 (d, 1H, $J$ = 2.2 Hz), 7.49 (td, 1H, $J$ = 7.8, 1.8 Hz), 8.10 (dd, 1H, $J$ = 8.1, 1.8 Hz), 10.58 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 50.6, 51.1, 51.5, 51.9, 56.0, 95.6, 108.8, 111.7, 120.6, 121.6, 132.4, 134.3, 146.3, 157.3, 164.0, 193.3. HRMS (EI) $m/z$ calcd for $C_{16}H_{17}NO_6$, 319.1056; found, 319.1054.

**2-Ethoxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10e).** (98%, mp 157–159 °C): $^1$H NMR ($CDCl_3$) δ 1.55 (t, 3H, $J$ = 6.9 Hz), 3.32 (s, 3H), 3.51 (dd, 1H, $J$ = 4.3, 2.1 Hz), 3.66 (s, 3H), 3.83 (d, 1H, $J$ = 4.2 Hz), 4.29 (q, 2H, $J$ = 6.9 Hz), 7.00 (d, 1H, $J$ = 7.8 Hz), 7.06 (t, 1H, $J$ = 7.5 Hz), 7.47 (m, 2H), 8.17 (d, 1H, $J$ = 7.8 Hz), 10.35 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 14.7, 51.4, 52.0, 65.1, 95.9, 109.9, 112.5, 121.5, 122.1, 132.8, 134.2, 146.2, 156.7, 164.6, 193.1. HRMS (EI) $m/z$ calcd for $C_{17}H_{19}NO_6$, 333.1212; found, 333.1206.

**2-Hexyloxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10f).** (62%, mp 58–60 °C): $^1$H NMR ($CDCl_3$) δ 0.89 (t, 3H, $J$ = 6.9 Hz), 1.35 (m, 6H), 1.91 (m, 2H), 3.31 (s, 3H), 3.52 (dd, 1H, $J$ = 3.9, 1.8 Hz), 3.66 (s, 3H), 3.83 (d, 1H, $J$ = 4.5 Hz), 4.20 (t, 2H, $J$ = 7.2 Hz), 7.00 (d, 1H, $J$ = 8.4 Hz), 7.07 (t, 1H, $J$ = 7.2 Hz), 7.43 (d, 1H, $J$ = 1.8, Hz), 7.45 (td, 1H, $J$ = 8.1, 1.2 Hz), 8.15 (dd, 1H, $J$ = 7.8, 1.8 Hz), 10.30 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 13.9, 22.6, 25.5, 28.9, 31.5, 50.9, 51.4, 52.0, 69.8, 95.8, 110.0, 112.6, 121.0, 121.5, 132.8, 134.1, 146.1, 156.8, 164.6, 193.1. HRMS (EI) $m/z$ calcd for $C_{21}H_{27}NO_6$, 389.1838; found, 389.1860.

**2-Phenoxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10g).** (64%, mp 69–71 °C): $^1$H NMR ($CDCl_3$) δ 3.21 (s, 3H), 3.25 (s, 3H), 3.48 (dd, 1H, $J$ = 3.9, 2.1 Hz), 3.76 (d, 1H, $J$ = 4.4 Hz), 6.80 (d, 1H, $J$ = 8.1 Hz), 7.12 (d, 2H, $J$ = 7.6 Hz), 7.20 (t, 1H, $J$ = 7.2 Hz), 7.26 (t, 1H, $J$ = 7.8 Hz), 7.34 (d, 1H, $J$ = 2.4 Hz), 7.44 (m, 3H), 8.24 (dd, 1H, $J$ = 6.0, 1.8 Hz), 10.54 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 50.0, 51.0, 51.4, 52.1, 95.5, 109.0, 117.5, 120.2, 122.5, 123.7, 125.5, 130.3, 132.5, 134.1, 146.2, 154.6, 156.1, 163.4, 193.4. HRMS (EI) $m/z$ calcd for $C_{21}H_{19}NO_6$, 381.1212; found, 381.1206.

**2-Methyl-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10h).** (85%, mp 102–103 °C): $^1$H NMR ($CDCl_3$) δ 2.41 (s, 3H), 3.28 (s, 3H), 3.50 (dd, 1H, $J$ = 4.2, 2.1 Hz), 3.59 (s, 3H), 3.80 (d, 1H, $J$ = 3.9 Hz), 7.21 (m, 3H), 7.34 (t, 2H, $J$ = 8.4 Hz), 8.00 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 20.0, 50.7, 51.3, 51.5, 52.1, 95.5, 108.8, 126.1, 126.7, 131.1, 131.7, 134.8, 137.0, 145.3, 168.3, 192.8. HRMS (EI) $m/z$ calcd for $C_{16}H_{17}NO_5$, 303.1107; found, 303.1083.

**2-Fluoro-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10i).** (72%, mp 126–128 °C): $^1$H NMR ($CDCl_3$) δ 3.32 (s, 3H), 3.52 (dd, 1H, $J$ = 3.9, 2.1 Hz), 3.66 (s, 3H), 3.85 (d, 1H, $J$ = 1.8 Hz), 7.16 (t, 1H, $J$ = 8.1 Hz), 7.28 (m, 2H), 7.53 (d, 1H, $J$ = 3.9 Hz), 8.05 (td, 1H, $J$ = 7.8, 1.5 Hz), 9.20 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 50.7, 51.2, 51.5, 52.1, 95.4, 109.5, 116.2, 116.6, 125.3, 132.4, 134.8, 145.6, 158.8, 162.0, 193.3. HRMS (EI) $m/z$ calcd for $C_{15}H_{14}NO_5F$, 307.0856; found, 307.0853.

**2-Chloro-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (10j).** (94%, mp 114–116 °C): $^1$H NMR ($CDCl_3$) δ 3.32 (s, 3H), 3.55 (dd, 1H, $J$ = 4.2, 1.8 Hz), 3.62 (s, 3H), 3.85 (d, 1H, $J$ = 3.9 Hz, 1H), 7.23 (d, 1H, $J$ = 1.8 Hz), 7.35 (m, 1H), 7.45 (d, 2H, $J$ = 3.6 Hz, 2H), 7.72 (d, 1H, $J$ = 7.8 Hz), 8.66 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 50.6, 50.7, 51.4, 52.0, 95.5, 109.5, 126.7, 130.6, 131.4, 132.4, 133.5, 145.2, 165.0, 170.5, 193.2. HRMS (EI) $m/z$ calcd for $C_{15}H_{14}NO_5Cl$, 323.0561; found, 323.0566.

**3-Hydroxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (11a).** A solution of **10a** (66.2 mg, 0.19 mmol) and $K_2CO_3$ (26.4 mg, 0.19 mmol) in MeOH (4 mL) and water (0.5 mL) was stirred for 30 min at room temperature. The reaction mixture was diluted with water (2 mL), acidified, and then extracted with EtOAc (10 mL). The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and then concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (*n*-hexane:EtOAc = 2:1) to afford **11a** (41.1 mg, 71%) as a white solid. Mp 152–154 °C; $^1$H

NMR ($CDCl_3$) δ 3.30 (s, 3H), 3.52 (dd, 1H, $J=3.9$, 2.1 Hz), 3.66 (s, 3H), 3.85 (d, 1H, $J=3.9$ Hz), 7.04 (dd, 1H, $J=8.1$, 1.8 Hz), 7.21 (t, 1H, $J=7.8$ Hz), 7.23 (d, 1H, $J=2.1$ Hz), 7.28 (m, 2H), 7.54 (br s, 1H), 8.46 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 50.8, 51.2, 51.4, 52.1, 95.6, 108.6, 114.3, 118.3, 120.2, 130.2, 134.9, 145.8, 157.0, 165.9, 193.4. HRMS (EI) $m/z$ calcd for $C_{15}H_{15}NO_6$, 305.0899; found, 305.0910.

**4-Hydroxy-*N*-(2,2-dimethoxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (11b).** The same procedure as for **11a**, starting from **10b**, was employed for the synthesis of **11b**. Compound **11b** was obtained as a white solid (65%). Mp 170–172 °C; $^1H$ NMR (acetone-$d_6$) δ 3.36 (s, 3H), 3.46 (dd, 1H, $J=4.2$, 2.1 Hz), 3.66 (s, 3H), 4.08 (d, 1H, $J=3.9$ Hz), 6.91 (dd, 2H, $J=6.9$, 1.8 Hz), 7.10 (d, 1H, $J=2.1$ Hz), 7.75 (dd, 2H, $J=6.9$, 2.1 Hz), 8.71 (br s, 1H), 9.23 (br s, 1H); $^{13}C$ NMR (acetone-$d_6$) δ 50.9, 51.5, 52.2, 52.7, 96.6, 108.0, 116.4, 125.8, 130.4, 147.6, 162.5, 166.1, 193.6. HRMS (EI) $m/z$ calcd for $C_{15}H_{15}NO_6$, 305.0899; found, 305.0898.

### General method for preparation of *N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide derivatives

To a stirred solution of appropriate compound (1 equiv) from **10c**–**j** and **11a**–**b** in $CH_2Cl_2$ was added boron trifluoride etherate (2.5 equiv) at −20 °C. The reaction mixture was stirred for 30 min and then warmed up to room temperature. On completion the reaction mixture was extracted with ethyl acetate; and the organic layers were washed with brine, dried over anhydrous sodium sulphate, and evaporated to yield a residue, which upon purification by column chromatography over silica gel using *n*-hexane/ethyl acetate (2:1, v/v) as eluent yielded the epoxyquinone derivatives **14a**–**j**.

**3-Hydroxy-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14a).** (67%, mp 156–158 °C) $^1H$ NMR (acetone-$d_6$) δ 3.91 (dd, 1H, $J=4.0$, 2.1 Hz), 4.12 (d, 1H, $J=3.9$ Hz), 7.10 (m, 1H), 7.37–7.40 (m, 3H), 7.50 (d, 1H, $J=2.1$ Hz), 8.96 (br s, 1H); $^{13}C$ NMR (acetone-$d_6$) δ 53.8, 54.8, 115.1, 115.2, 119.2, 120.8, 131.0, 135.6, 140.5, 158.7, 166.8, 189.0, 192.4. HRMS (EI) $m/z$ calcd for $C_{13}H_9NO_5$, 259.0481; found, 259.0486.

**4-Hydroxy-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14b).** (75%, mp 193–194 °C) $^1H$ NMR (acetone-$d_6$) δ 3.78 (dd, 1H, $J=3.6$, 1.8 Hz), 3.98 (d, 1H, $J=3.6$ Hz), 6.85 (d, 2H, $J=7.8$ Hz), 7.38 (d, 1H, $J=2.1$ Hz), 7.72 (d, 2H, $J=9.0$ Hz), 8.78 (br s, 1H), 9.18 (br s, 1H); $^{13}C$ NMR (acetone-$d_6$) δ 53.7, 54.8, 114.7, 116.4, 125.2, 130.7, 140.7, 156.6, 166.3, 189.1, 192.4. HRMS (EI) $m/z$ calcd for $C_{13}H_9NO_5$, 259.0481; found, 259.0488.

***N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14c).** (78%, mp 101–103 °C): $^1H$ NMR ($CDCl_3$) δ 3.87 (dd, 1H, $J=3.6$, 2.3 Hz), 3.98 (d, 1H, $J=3.8$ Hz), 7.52 (d, 2H, $J=7.7$ Hz), 7.62 (t, 1H, $J=7.2$ Hz), 7.70 (d, 1H, $J=2.3$ Hz), 7.83 (d, 2H, $J=7.3$ Hz), 8.65 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 52.5, 53.9, 115.5, 127.2, 128.9, 132.7, 133.1, 165.6, 188.0, 190.8. HRMS (EI) $m/z$ calcd for $C_{13}H_9NO_4$, 243.0532; found, 243.0522.

**2-Methoxy-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14d).** (57%, mp 105–107 °C): $^1H$ NMR ($CDCl_3$) δ 3.76 (dd, 1H, $J=3.7$, 2.2 Hz), 3.86 (d, 1H, $J=3.7$ Hz), 4.04 (s, 3H), 6.95 (d, 1H, $J=8.4$ Hz), 7.04 (t, 1H, $J=7.3$ Hz), 7.47 (td, 1H, $J=8.1$, 1.8 Hz), 7.64 (d, 1H, $J=2.2$ Hz), 8.08 (dd, 1H, $J=7.7$, 1.5 Hz), 10.74 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 52.6, 53.8, 56.2, 111.7, 115.5, 120.1, 121.7, 132.5, 134.7, 139.9, 157.6, 164.4, 188.3, 191.5. HRMS (EI) $m/z$ calcd for $C_{14}H_{11}NO_5$, 273.0637; found, 273.0639.

**2-Ethoxy-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14e).** (69%, mp 172–174 °C): $^1H$ NMR ($CDCl_3$) δ1.63 (t, 3H, $J=6.9$ Hz), 3.78 (dd, 1H, $J=3.6$, 2.1 Hz), 3.86 (d, 1H, $J=3.6$ Hz), 4.22 (q, 2H, $J=6.9$ Hz), 6.95 (d, 1H, $J=8.4$ Hz), 7.03 (t, 1H, $J=7.5$ Hz), 7.45 (t, 1H, $J=6.9$ Hz), 7.72 (d, 1H, $J=1.8$ Hz), 8.11 (dd, 1H, $J=6.3$, 1.8 Hz), 10.66 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 14.7, 52.6, 53.9, 65.4, 112.4, 115.8, 120.1, 121.5, 140.0, 157.2, 164.7, 188.4. HRMS (EI) $m/z$ calcd for $C_{15}H_{13}NO_5$, 287.0794; found, 287.0797.

**2-Hexyloxy-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14f).** (71%, mp 65–67 °C): $^1H$ NMR ($CDCl_3$) δ 0.89 (t, 3H, $J=7.2$ Hz), 1.39 (m, 6H), 2.06 (m, 2H), 3.82 (dd, 1H, $J=4.1$, 1.8 Hz), 3.91 (d, 1H, $J=3.9$ Hz), 4.20 (td, 2H, $J=6.9$, 1.8 Hz), 7.00 (d, 1H, $J=8.4$ Hz), 7.07 (t, 1H, $J=8.1$ Hz), 7.49 (td, 1H, $J=8.4$, 1.8 Hz), 7.76 (d, 1H, $J=1.8$ Hz), 8.14 (dd, 1H, $J=8.1$, 1.8 Hz, 1H), 10.65 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 14.0, 22.6, 25.8, 28.7, 31.4, 52.6, 53.8, 69.9, 112.4, 115.8, 120.1, 121.4, 132.7, 140.0, 157.3, 164.7, 188.3, 191.6. HRMS (EI) $m/z$ calcd for $C_{19}H_{21}NO_5$, 343.1420; found, 343.1418.

**2-Phenoxy-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14g).** (77%, mp 128–130 °C): $^1H$ NMR ($CDCl_3$) δ 3.75 (dd, 1H, $J=3.6$, 2.1 Hz), 3.80 (d, 1H, $J=3.6$ Hz), 6.86 (dd, 1H, $J=8.4$, 2.1 Hz), 7.11 (d, 2H, $J=7.8$ Hz), 7.17 (m, 2H), 7.38 (t, 3H, $J=7.6$ Hz), 7.68 (d, 1H, $J=2.4$ Hz), 8.15 (dd, 1H, $J=8.1$, 1.8 Hz), 10.55 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 52.5, 53.8, 115.8, 118.0, 119.7, 122.3, 123.8, 125.2, 130.3, 132.8, 134.4, 139.7, 154.6, 155.7, 164.0, 188.1, 192.4. HRMS (EI) $m/z$ calcd for $C_{19}H_{13}NO_5$, 335.0794; found, 335.0807.

**3-Methyl-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14h).** (85%, mp 134–136 °C): $^1H$ NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.84 (dd, 1H, $J=3.8$, 2.1 Hz), 3.92 (d, 1H, $J=3.6$ Hz), 7.27 (d, 2H, $J=5.7$ Hz), 7.43 (m, 2H), 7.67 (d, 1H, $J=2.1$ Hz), 8.24 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 20.1, 52.5, 53.8, 115.4, 126.2, 126.9, 131.6, 131.9, 133.9, 137.4, 138.3, 168.2, 188.1, 191.1. HRMS (EI) $m/z$ calcd for $C_{14}H_{11}NO_4$, 257.0688; found, 257.0674.

**2-Fluoro-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14i).** (68%, mp 136–137 °C): $^1H$ NMR ($CDCl_3$) δ 3.85 (dd, 1H, $J=3.6$, 2.1 Hz), 3.95 (d, 1H, $J=3.9$ Hz), 7.21 (dd, 1H, $J=8.4$, 3.6 Hz), 7.30 (t, 1H, $J=7.5$ Hz), 7.56 (d, 1H, $J=7.8$ Hz), 7.69 (d, 1H, $J=2.1$ Hz), 8.06 (td, 1H, $J=7.8$, 1.8 Hz), 9.30 (br s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 52.7, 54.0, 116.4, 116.8, 125.5, 132.4, 135.3, 135.5, 139.2, 159.1, 162.4, 188.0, 191.4. HRMS (EI) $m/z$ calcd for $C_{13}H_8NO_4F$, 261.0437; found, 261.0436.

**2-Chloro-*N*-(2,5-dioxo-3,4-epoxy-cyclohex-6-enyl)benzamide (14j).** (62%, mp 125–127 °C): $^1$H NMR ($CDCl_3$) δ 3.84 (dd, 1H, $J$ = 3.6, 2.1 Hz), 3.93 (d, 1H, $J$ = 3.6 Hz), 7.35 (m, 1H), 7.44 (d, 2H, $J$ = 3.9 Hz), 7.66 (d, 1H, $J$ = 1.5 Hz), 7.73 (d, 1H, $J$ = 7.8 Hz), 8.84 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 52.6, 53.8, 116.0, 116.1, 127.5, 130.8, 130.9, 132.9, 133.0, 138.6, 165.1, 187.8, 191.1. HRMS (EI) $m/z$ calcd for $C_{13}H_8NO_4Cl$, 277.0142; found, 277.0132.

### General method for preparation of *N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide derivatives

To a stirred solution of the appropriate compound (1 equiv) from **14a–j** in MeOH was added $NaBH(OAc)_3$ (1 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature over 30 min. On completion the reaction mixture was diluted with ethyl acetate; and the organic layers were washed with brine, dried over anhydrous sodium sulphate, and evaporated to yield a residue, which upon purification by column chromatography over silica gel using chloroform/MeOH (20:1, v/v) as eluent yielded the derivatives **15a–j** of DHMEQ.

**3-Hydroxy-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15a).** (60%, mp. 185–187 °C): $^1$H NMR (acetone-$d_6$) δ 3.76 (dd, 1H, $J$ = 3.9, 1.5 Hz), 3.84 (dd, 1H, $J$ = 4.2, 2.4 Hz), 4.94 (s, 1H), 6.79 (d, 1H, $J$ = 1.8 Hz), 6.89 (t, 1H, $J$ = 1.8 Hz), 7.05 (m, 3H), 8.99 (br s, 1H); $^{13}$C NMR (acetone-$d_6$) δ 52.6, 56.0, 64.7, 108.7, 115.4, 119.5, 120.3, 130.6, 136.3, 152.6, 158.4, 167.9, 194.2. HRMS (EI) $m/z$ calcd for $C_{13}H_{11}NO_5$, 261.0637; found, 261.0647.

**4-Hydroxy-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15b).** (75%, mp. 197–199 °C): $^1$H NMR (acetone-$d_6$) δ 3.33 (dd, 1H, $J$ = 4.2, 2.1 Hz), 3.74 (dd, 1H, $J$ = 4.2, 2.4 Hz), 4.93 (s, 1H), 6.72 (d, 1H, $J$ = 2.1 Hz), 6.90 (d, 2H, $J$ = 8.7 Hz), 7.80 (dd, 2H, $J$ = 9.6, 2.4 Hz), 9.45 (br s, 1H); $^{13}$C NMR (acetone-$d_6$) δ 52.7, 56.0, 108.2, 116.1, 125.8, 130.9, 151.1, 153.1, 162.4, 167.4, 194.1. HRMS (EI) $m/z$ calcd for $C_{13}H_{11}NO_5$, 261.0637; found, 261.0630.

***N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15c).** (78%, mp. 155–157 °C): $^1$H NMR ($CDCl_3$) δ 3.47 (dd, 1H, $J$ = 4.0, 2.0 Hz), 3.92 (t, 1H, $J$ = 3.5 Hz), 4.97 (s, 1H), 6.07 (d, 1H, $J$ = 2.5 Hz), 7.51 (t, 2H, $J$ = 7.6 Hz), 7.66 (t, 1H, $J$ = 7.4 Hz), 8.16 (d, 2H, $J$ = 7.4 Hz). $^{13}$C NMR ($CDCl_3$) δ 51.3, 53.3, 67.7, 96.9, 128.2, 128.7, 130.0, 134.2, 156.0, 166.0, 190.1. HRMS (EI) $m/z$ calcd for $C_{13}H_{11}NO_4$, 245.0688; found, 245.0689.

**2-Methoxy-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15d).** (54%, mp. 114–116 °C): $^1$H NMR (acetone-$d_6$) δ 3.25 (dd, 1H, $J$ = 4.0, 2.2 Hz), 3.80 (dd, 1H, $J$ = 4.0, 2.6 Hz), 3.96 (s, 3H), 4.79 (s, 1H), 6.91 (d, 1H, $J$ = 1.5 Hz), 7.01 (t, 1H, $J$ = 7.7 Hz), 7.11 (d, 1H, $J$ = 8.4 Hz), 7.47 (td, 1H, $J$ = 7.7, 1.8 Hz), 7.96 (dd, 1H, $J$ = 8.1, 1.8 Hz), 10.73 (br s, 1H); $^{13}$C NMR (acetone-$d_6$) δ 54.0, 54.3, 56.8, 66.1, 106.9, 113.2, 121.6, 122.2, 132.8, 135.2, 151.1, 158.6, 165.1, 194.4. HRMS (EI) $m/z$ calcd for $C_{14}H_{13}NO_5$, 275.0794; found, 275.0798.

**2-Ethoxy-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15e).** (64%, mp 187–189 °C): $^1$H NMR ($CDCl_3$) δ 1.52 (t, 3H, $J$ = 6.9 Hz), 3.49 (dd, 1H, $J$ = 3.9, 1.8 Hz), 3.85 (t, 1H, $J$ = 3.9 Hz), 4.20 (t, 2H, $J$ = 6.9 Hz), 4.67 (s, 1H), 6.87 (s, 1H), 6.95 (d, 2H, $J$ = 8.4 Hz), 7.03 (t, 1H, $J$ = 7.8 Hz), 7.44 (td, 1H, $J$ = 8.1, 1.8 Hz), 8.10 (dd, 1H, $J$ = 8.1, 1.5 Hz), 10.44 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 14.7, 53.6, 53.8, 65.5, 107.7, 112.3, 120.3, 121.6, 132.8, 134.4, 189.5. HRMS (EI) $m/z$ calcd for $C_{15}H_{15}NO_5$, 289.0950; found, 289.0956.

**2-Hexyloxy-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15f).** (89%, mp 88–90 °C): $^1$H NMR ($CDCl_3$) δ 0.85 (t, 3H, $J$ = 7.2 Hz), 1.36 (m, 6H), 1.89 (m, 2H), 3.48 (dd, 1H, $J$ = 3.9, 2.1 Hz), 3.85 (t, 1H, $J$ = 3.9 Hz), 4.15 (m, 2H), 4.65 (s, 1H), 6.82 (d, 1H, $J$ = 1.9 Hz), 6.94 (d, 1H, $J$ = 8.0 Hz), 7.02 (t, 1H, $J$ = 7.8 Hz), 7.44 (td, 1H, $J$ = 7.5, 2.1 Hz), 8.10 (dd, 1H, $J$ = 8.0, 1.8 Hz), 10.39 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 14.0, 22.6, 25.7, 28.7, 31.4, 53.6, 53.8, 65.5, 69.7, 107.7, 112.4, 120.3, 121.4, 132.7, 134.4, 149.7, 157.0, 164.9, 193.2. HRMS (EI) $m/z$ calcd for $C_{19}H_{23}NO_5$, 345.1576; found, 345.1563.

**2-Phenoxy-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15g).** (75%, mp 138–140 °C): $^1$H NMR ($CDCl_3$) δ 3.44 (dd, 1H, $J$ = 4.2, 2.1 Hz), 3.76 (t, 1H, $J$ = 4.2 Hz), 4.85 (s, 1H), 6.82 (d, 1H, $J$ = 8.1 Hz), 6.96 (s, 1H), 7.03 (d, 2H, $J$ = 8.1 Hz), 7.16 (m, 2H), 7.36 (t, 3H, $J$ = 7.8 Hz), 8.14 (dd, 1H, $J$ = 7.8, 1.8 Hz), 10.33 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 53.3, 53.8, 65.6, 107.6, 118.0, 119.7, 122.6, 123.8, 125.2, 130.3, 132.6, 134.2, 149.1, 154.7, 155.5, 164.1, 193.2. HRMS (EI) $m/z$ calcd for $C_{19}H_{15}NO_5$, 337.0950; found, 337.0947.

**2-Methyl-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15h).** (63%, mp 168–169 °C): $^1$H NMR ($CDCl_3$) δ 2.66 (s, 3H), 3.46 (dd, 1H, $J$ = 3.8, 2.1 Hz), 3.91 (t, 1H, $J$ = 4.2 Hz), 5.19 (s, 1H), 6.03 (d, 1H, $J$ = 1.8 Hz), 7.30 (d, 2H, $J$ = 7.8 Hz) 7.48 (t, 1H, $J$ = 6.6 Hz), 8.08 (d, 1H, $J$ = 7.8 Hz); $^{13}$C NMR ($CDCl_3$) δ 21.7, 50.9, 52.9, 66.9, 96.6, 125.7, 126.8, 130.8, 131.8, 133.0, 141.1, 155.8, 166.3, 189.9. HRMS (EI) $m/z$ calcd for $C_{14}H_{13}NO_4$, 259.0845; found, 259.0870.

**3-Fluoro-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15i).** (61%, mp 141–142 °C): $^1$H NMR (acetone-$d_6$) δ 3.27 (dd, 1H, $J$ = 3.9, 2.1 Hz), 3.81 (t, 1H, $J$ = 3.9 Hz), 4.82 (s, 1H), 6.86 (d, 1H, $J$ = 1.8 Hz), 7.17–7.30 (m, 2H), 7.55 (d, 1H, $J$ = 6.3 Hz), 7.88 (td, 1H, $J$ = 8.1, 1.8 Hz), 9.29 (br s, 1H); $^{13}$C NMR (acetone-$d_6$) δ 54.0, 54.2, 65.8, 107.5, 117.1, 117.4, 126.1, 132.5, 135.6, 135.7, 150.3, 159.5, 162.8, 194.3. HRMS (EI) $m/z$ calcd for $C_{13}H_{10}NO_4F$, 263.0594; found, 263.0610.

**3-Chloro-*N*-(2-hydroxy-3,4-epoxy-5-oxo-cyclohex-6-enyl)benzamide (15j).** (70%, mp 139–141 °C): $^1$H NMR (acetone-$d_6$) δ 3.41 (dd, 1H, $J$ = 3.9, 2.1 Hz), 3.83 (t, 1H, $J$ = 3.9 Hz), 4.66 (s, 1H), 6.92 (d, 1H, $J$ = 1.5 Hz), 7.33 (m, 1H), 7.39 (d, 2H, $J$ = 4.2 Hz), 7.60 (d, 1H, $J$ = 8.1 Hz), 8.72 (br s, 1H); $^{13}$C NMR (acetone-$d_6$) δ 53.6, 55.5, 65.2, 107.5, 109.1, 127.4, 130.6, 132.6, 133.5, 148.7, 151.1, 165.7, 193.8. HRMS (EI) $m/z$ calcd for $C_{13}H_{10}NO_4Cl$, 279.0298; found, 279.0304.

**κB/Luciferase reporter gene assay.** Jurkat cells ($2\times10^6$ cells) were transfected with 2 μg of DNA consisting of 3 tandem κB repeats and the luciferase gene by the DEAE-dextran method. The transfected cells were seeded into 12-well plates at $1\times10^6$ cells/well. Chemicals dissolved in DMSO and TNF-α were added at 14 and 16 h, respectively. Six hours after the TNF-α addition, the cells were harvested and lysed, and the lysate was used for the luciferase assay with luciferin substrate buffer (20 mM Tricin-NaOH [pH 8.0], 1.07 mM magnesium carbonate hydroxide, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 33.3 mM DTT, 270 M CoA, 470 M luciferin, and 530 μM ATP). Luminescence was measured with a Lumat 9501 (Berthold). Each value was normalized by the transfection efficiency obtained from the β-actin promoter/β-galactosidase assay.

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