Reactivity with DNA Bases and Mutagenicity toward *Salmonella typhimurium* of Methylchrysene Diol Epoxide Enantiomers

Assieh A. Melikian, Shantu Amin, Keith Huie, Stephen S. Hecht, and Ronald G. Harvey


ABSTRACT

The reactions with DNA and mutagenic activities toward *Salmonella typhimurium* TA 100 of the R,S,S,R and S,R,R,S enantiomers of anti-1,2- and anti-3,4-diol-3,4-epoxides of methylchrysenes, (anti-5-MeC-l,2-diol-3,4-epoxide, 5-MeC-7,8-diol-9,10-epoxide, and anti-6-MeC-1,2-diol-3,4-epoxide) were compared because among these compounds only the R,S,S,R enantiomer of anti-5-MeC-1,2-diol-3,4-epoxide is highly tumorigenic. The major products formed in the reaction of each racemic diol epoxide with DNA were two pairs of deoxyguanosine (dGuo) and deoxyadenosine (dAdo) adducts; one product in each pair was formed from the R,S,S,R enantiomer and the other from the S,R,R,S enantiomer of each racemic epoxide. Formation of products from R,S,S,R enantiomers exceeded formation of those from S,R,R,S enantiomers in each case. Among the R,S,S,R enantiomers, 5-MeC-1,2-diol-3,4-epoxide, which has a methyl group in the same bay region as the epoxide ring, was most reactive toward DNA, and in particular toward dGuo. The dGuo/dAdo adduct ratios were greater for the products formed from the R,S,S,R enantiomer compared to the S,R,R,S enantiomer of each diol epoxide. The dGuo/dAdo adduct ratios were also greater for the enantiomers of anti-5-MeC-l,2-diol-3,4-epoxide than for the enantiomers of anti-5-MeC-7,8-diol-9,10-epoxide or anti-6-MeC-1,2-diol-3,4-epoxide in *S. typhimurium* TA 100, the R,S,S,R enantiomer of anti-5-MeC-1,2-diol-3,4-epoxide was the most mutagenic compound (6700 revertants/µmol), followed by the R,S,S,R enantiomer of anti-5-MeC-7,8-diol-9,10-epoxide (1500 revertants/µmol). The other diol epoxide enantiomers were weakly active or inactive at the doses tested. The results of this study demonstrate that both the absolute configuration of a diol epoxide and the position of the methyl group have major effects on its reactivity with DNA. The greatest reactivity is seen in an R,S,S,R enantiomer with the methyl group and epoxide ring in the same bay region, e.g., the highly tumorigenic and mutagenic 5-MeC-1,2,5-diol-3,5,4,8-epoxide. Comparison of the dGuo/dAdo adduct ratios of the various diol epoxides with their tumorigenic and mutagenic activities suggests that dGuo adducts are important in the expression of biological activity of methylchrysenes diol epoxides.

INTRODUCTION

Previous studies have demonstrated that a major pathway of metabolic activation of the strong carcinogen 5-MeC (Fig. 1) is 5-MeC-5-5MeC-1,2-diol-5-MeC-1,2-diols (1-3). The latter is highly tumorigenic in the newborn mouse and on mouse skin but related diol epoxide isomers are either weakly active or inactive in these model systems, as illustrated in Fig. 1 (2). Racemic syn-5-MeC-1,2-diol-3,4-epoxide is also a weak tumorigen (4). The relatively high tumorigenic activity of R,S,S,R diol epoxide enantiomers has been observed in bioassays of several sets of bay region diol epoxides of unsubstituted polynuclear aromatic hydrocarbons (5-9). However, a unique feature of the structure-activity relationships summarized in Fig. 1 is the enhancing effect on tumorigenicity of a methyl group in the same bay region as the epoxide ring (methyl bay region diol epoxide). This is clearly seen by comparing the tumorigenic activities of 5-MeC-1,2,5-diol-3,5,4,8-epoxide, 5-MeC-7,8-diol-9,10-epoxide, and 6-MeC-1,2,5-diol-3,5,4,8-epoxide. Our studies indicate that this effect is responsible for the high tumorigenicity of 5-MeC among the methylchrysenes isomers. Only 5-MeC can form a methyl bay region diol epoxide; the diol epoxides formed from the other isomers such as the weak tumorigen 6-MeC do not have this structural feature. The DNA interactions of these diol epoxides are likely to be important in the expression of their tumorigenic activities. Therefore, we have compared their reactions with DNA in vitro and their mutagenic activities toward *Salmonella typhimurium*.

MATERIALS AND METHODS

Chemicals. For preparation of R,S,S,R and S,R,R,S diol epoxides, 5-MeC-1,2-diol, 5-MeC-7,8-diol, and 6-MeC-1,2-diol were resolved into their R,R- and S,S-enantiomers by chiral stationary phase HPLC as described previously (3), and the resulting dihydrodiols were purified further by HPLC on a 250-mm x 4-mm Lichrosorb Si60 column (EM Reagents, Cincinnati, OH), with elution by 30% tetrahydrofuran in hexane at 3 ml/min. Purified dihydrodiols were oxidized to the corresponding anti-diol epoxides by m-chloroperoxybenzoic acid as previously described (10, 11). Sodium salts of poly(dA)-poly(dT), poly(dA), dcyt, and calf thymus DNA, DNase I from bovine pancreas (EC 3.1.4.5), phosphodiesterase from *Crotilus adamanteus* venom type II (EC 3.1.4.1), and alkaline phosphatase from *Escherichia coli* type III (EC 3.1.3.1) were obtained from Sigma Chemical Co., St. Louis, MO.

Poly(dG) was purchased from P-L Biochemicals, Inc., Milwaukee, WI.

Preparation of Standard dGuo, dAdo, dCyt, and dThd Adducts of Diol Epoxides. About 8 units each of poly(dG), poly(dC), or poly(dA) were dissolved in 1 ml of 10 mM Tris-Cl buffer (pH 8.3); poly(dA)-poly(dT) was dissolved in 1.5 ml. To the above solutions about 50 µg of either racemic anti-5-MeC-1,2-diol-3,4-epoxide or anti-5-MeC-7,8-diol-9,10-epoxide or anti-6-MeC-1,2-diol-3,4-epoxide in 50 µl tetrahydrofuran and 0.4 ml acetone were added and the mixtures were incubated overnight at 37°C. Samples were extracted 10 times with equal volumes of ether (saturated with 10 mM Tris-Cl buffer, pH 7.0). The residual ether was evaporated with a stream of nitrogen and the modified polydeoxyribonucleotides were enzymatically hydrolyzed to deoxyribonucleotides as previously described for DNA (12). Modified deoxyribonucleotides were analyzed and purified by HPLC as described below and used as UV markers for identification of DNA adducts modified by various diol epoxides.

Preparation of DNA Adducts and Quantitation of Extent of Binding. Calf thymus DNA was purified as described previously (13). To solutions of DNA (5 mg) dissolved in 5 ml 10 mM Tris-Cl buffer, pH 7.0, were added about 80-150 µg either R,S,S,R or S,R,R,S, or racemic anti-diol epoxides of methylchrysenes in 0.1 ml tetrahydrofuran and 1.5 ml acetone. The mixtures were incubated at 37°C overnight. Tetracos were removed from the DNA solutions by extraction with ether (10 x 1 volume). The concentration of DNA was determined...
Fig. 1. Structures and tumorigenic activities of the diol epoxides investigated in this study.

<table>
<thead>
<tr>
<th></th>
<th>Newborn model lung tumors per mouse</th>
<th>Skin model skin tumors per mouse</th>
<th>Newborn model lung tumors per mouse</th>
<th>Skin model skin tumors per mouse</th>
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<td>5-MeC-1R,2S-diol-3S,4R-epoxide</td>
<td>13.4</td>
<td>3.2</td>
<td>0.46</td>
<td>0.4</td>
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<tr>
<td>5-MeC-1S,2R-diol-3R,4S-epoxide</td>
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<td>0.1</td>
<td>0.31</td>
<td>0.2</td>
</tr>
<tr>
<td>5-MeC-7R,8S-diol-9S,10R-epoxide</td>
<td>0.09</td>
<td>0.2</td>
<td>0.17</td>
<td>0.2</td>
</tr>
</tbody>
</table>

from the absorbance at 260 nm. It was hydrolyzed enzymatically to deoxyribonucleosides as described (12) except that the amount of phosphodiesterase was increased 4-fold to assure that all modified deoxyadenosine adducts were released from DNA (14). Aliquots of hydrolyzed DNA were either analyzed directly by HPLC as described below or unmodified deoxyribonucleosides were separated from modified deoxyribonucleosides by chromatography on Sephadex LH-20 or on Sep-pak C18 cartridges (15), then analyzed by HPLC. The extent of modification of each DNA sample was calculated based on the assumption that all methylchrysene diol epoxide-deoxyribonucleoside adducts have a similar extinction coefficient at 254 nm. The total binding of diol epoxides to DNA as well as the relative extents of formation of each diol epoxide-deoxyribonucleoside adduct were measured by comparison of the peak areas of the modified deoxyribonucleosides formed from each diol epoxide and separated by HPLC. Similar results for total binding were obtained from comparison of the UV absorption of total modified deoxyribonucleosides separated from unmodified deoxyribonucleosides by chromatography on Sephadex LH-20 (15).

Fig. 2. HPLC chromatograms obtained upon analysis of enzymatic hydrolysates of reactions with DNA of A, racemic anti-5-MeC-1,2-diol-3,4-epoxide, B, 5-MeC-1R,2S-diol-3S, 4R-epoxide, and C, 5-MeC-1S,2R-diol-3R,4S-epoxide. Only the portions of the chromatograms containing major modified deoxyribonucleoside peaks are shown. Earlier eluting major peaks corresponded only to unmodified deoxyribonucleosides. Darkened peaks, R,S,S,R adducts; open peaks, S,R,R,S adducts; hatched peak, unassigned.
mm; Beckman Instruments, Berkeley, CA). The following solvent system was used for separation of modified and unmodified deoxyribonucleosides: 15% MeOH in H2O for 35 min, then 15 to 45% MeOH in H2O (linear gradient) over 10 min, then 45% MeOH in H2O for 35 min, then 45 to 55% MeOH in H2O (linear gradient) over 10 min, then 55% MeOH in H2O for 20 min, and then 55–100% MeOH over 10 min. The flow rate was 1 ml/min.

Mutagenicity Assays. *E. coli* strains TA 98 and TA 100 were kindly provided by Dr. Bruce N. Ames, University of California, Berkeley, CA. Diol epoxides were dissolved in dimethyl sulfoxide and the assays were performed as described with preincubation (16, 17). Cytotoxicity was determined by reduction in colonies in nutrient agar plates. 5-MeC-1R,2S-diol-3S,4R-epoxide was toxic above 0.2 nmol/plate. For the other compounds, no significant cytotoxicity was observed at doses up to 0.8 nmol/plate. Reported mutagenicity values are the means of triplicate assays. Background revertants (154/plate for TA 100) have not been subtracted. Revertants/nmol were determined from the slopes of the linear portions of the dose-response curves.

RESULTS

Fig 2A is a chromatogram obtained upon analysis of the deoxyribonucleosides formed in the reaction of racemic *anti*-5-Mc-1,2-diol-3,4-epoxide with DNA. Peak 1 was identified as the tetraol resulting from trans- ring opening of the diol epoxide. The major deoxyribonucleoside adducts were peaks 4, 6, 10, and 12. Among these, peak 6 predominated; we have previously identified this peak as arising from trans- ring opening by attack of N2 of deoxyguanosine at carbon 4 of the diol epoxide (18). Reactions of the racemic diol epoxide with poly(dG) or poly(dA) indicated that peak 4 was a deoxyguanosine adduct and that peaks 10 and 12 were deoxyadenosine adducts (Fig. 3, A and C). Reardon et al. have recently characterized these peaks. Peak 4 is a diastereomer of peak 6, resulting from trans- ring opening of the diol epoxide by attack of N2 of deoxyguanosine at carbon 4 of the opposite enantiomer to that which gave peak 6. Peaks 10 and 12 result from trans- ring opening of the diol epoxide enantiomers by attack of N8 of deoxyadenosine at carbon 4 of the diol epoxide (19). The minor adducts have not been investigated thoroughly. However, comparison of retention times of the peaks shown in Figs. 2A and 3, A–D suggests that peak 2 is formed by reaction with dGuo or dCyt and peak 11 by reaction with dAdo.

Fig. 3. HPLC chromatograms of the products formed upon reaction with polydeoxyribonucleosides of *anti*-5-Mc-1,2-diol-3,4-epoxide (A–D), *anti*-5-Mc-7,8-diol-9,10-epoxide (E–H), and *anti*-6-Mc-1,2-diol-3,4-epoxide (I–L). Only the portions of the chromatograms containing major modified deoxyribonucleoside peaks are shown. Earlier eluting major peaks corresponded only to unmodified deoxyribonucleosides. The peak heights in different panels do not reflect extents of reactivity.
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Fig. 4. HPLC chromatograms obtained upon analysis of enzymatic hydrolysates of reactions with DNA of A, anti-5-MeC-7,8-diol-9,10-epoxide, B, anti-5-MeC-7R,8S-diol-9S,10R-epoxide, and C, 5-MeC-7S,8R-diol-9R,10S-epoxide. Only the portions of the chromatograms containing major modified deoxyribonucleoside peaks are shown. Earlier eluting major peaks corresponded only to unmodified deoxyribonucleosides.

The availability of 5-MeC-1R,2S-diol-3S,4R-epoxide and 5-MeC-1S,2R-diol-3R,4S-epoxide, the enantiomers of anti-5-MeC-1,2-diol-3,4-epoxide, allowed us to determine the origins of the major diastereomeric adducts 4, 6, 10, and 12. Fig. 2, B and C, illustrates the chromatograms obtained upon reaction of each enantiomer with DNA. Comparison of these chromatograms with that shown in Fig. 2A demonstrates that peaks 6 and 10 are formed from 5-MeC-1R,2S-diol-3S,4R-epoxide and that peaks 4 and 12 are formed from 5-MeC-1S,2R-diol-3R,4S-epoxide.

Fig. 4A illustrates the products obtained upon reaction of racemic anti-5-MeC-7,8-diol-9,10-epoxide with DNA. We have previously characterized peak 6 as having arisen from trans-ring opening of the diol epoxide by attack of N2 of deoxyguanosine at carbon 10 (18). Peak 5 was assigned as a dGuo adduct and peaks 10 and 12 as dAdo adducts by reactions with poly(dG) or poly(dA) (Fig. 3, E and G). Comparisons of retention times suggested that the other peaks may be formed by reactions as follows: peak 3, dCyt or dGuo; peak 4, dCyt. Reactions of DNA with 5-MeC-7R,8S-diol-9S,10R-epoxide

Fig. 5. HPLC chromatograms obtained upon analysis of enzymatic hydrolysates of reactions with DNA of A, anti-6-MeC-1,2-diol-3,4-epoxide, B, anti-6-MeC-1R,2S-diol-3S,4R-epoxide, and C, 6-MeC-1S,2R-diol-3R,4S-epoxide. Only the portions of the chromatograms containing major modified deoxyribonucleoside peaks are shown. Earlier eluting major peaks corresponded only to unmodified deoxyribonucleosides.
Other three diol epoxide enantiomers were inactive at the doses tested. The racemic diol epoxides were inactive in S. typhimurium TA 98 at doses up to 0.6 nmol/plate.

**DISCUSSION**

In a previous study, we compared the extents of reaction with DNA of racemic anti-5-MeC-1,2-diol-3,4-epoxide and anti-5-MeC-7,8-diol-9,10-epoxide (20). The availability of the enantiomeric diol epoxides for the present study allowed us to separate the effects on reactivity of absolute configuration and position of the methyl group, and to extend our investigation to the enantiomers of anti-6-MeC-1,2-diol-3,4-epoxide. The results clearly demonstrate that both the absolute configuration of the diol epoxide and the position of the methyl group have major effects on diol epoxide reactivity with DNA.

Fig. 7A shows that formation of products from reaction of each R,S,S,R diol epoxide enantiomer with DNA exceeds that from reaction of the corresponding S,R,R,S enantiomer. The effect is most pronounced for the enantiomers of the 5-MeC diol epoxides. As illustrated in Table 1 and Fig. 7B, the stereoselectivity was most apparent for reaction with deoxyguanosine of DNA. The formation of dGuo adducts was 5.5, 6.7, and 3.1 times greater for the R,S,S,R than the S,R,R,S enantiomers of anti-5-MeC-1,2-diol-3,4-epoxide, anti-5-MeC-7,8-diol-9,10-epoxide, and anti-6-MeC-1,2-diol-3,4-epoxide, respectively. In contrast, the reactions with deoxyadenosine of DNA were not highly stereoselective, as illustrated in Fig. 7C. The formation of dAdo adducts was only 1.6–1.9 times greater for the R,S,S,R than the S,R,R,S enantiomers of the 5-MeC diol epoxides. In the case of anti-6-MeC-1,2-diol-3,4-epoxide, the S,R,R,S enantiomer reacted 1.6 times more extensively with dAdo than did the R,S,S,R enantiomer. The higher reactivity with DNA and stereoselective binding with deoxyguanosine of R,S,S,R diol epoxide enantiomers compared to S,R,R,S enantiomers are parallel to results obtained with the enantiomers of benzo[a]pyrene-7,8-diol-9,10-epoxide (21).

Fig. 7A also demonstrates the enhanced reactivity with DNA of methyl bay region diol epoxide enantiomers. The products of reaction of the R,S,S,R enantiomers with DNA were formed 1.9 and 3.8 times more extensively from anti-5-MeC-1,2-diol-3,4-epoxide than from anti-5-MeC-7,8-diol-9,10-epoxide and anti-6-MeC-1,2-diol-3,4-epoxide, respectively. The corresponding figures for the S,R,R,S enantiomers were 1.7 and 1.3. The methyl group in the bay region had a major effect on the

and 5-MeC-7,8R-diol-9R,10S-epoxide demonstrated that peaks 6 and 10 were produced from the former and peaks 5 and 12 from the latter (Fig. 4, B and C).Fig. 5 summarizes the results obtained upon reaction of racemic anti-6-MeC-1,2-diol-3,4-epoxide and its R,S,S,R and S,R,R,S enantiomers with DNA. Peaks 8 and 9 were assigned as dGuo adducts and peaks 12 and 14 as dAdo adducts by comparison of their retention times and UV spectra to the products of reaction with poly(dG) and poly(dA), respectively (Fig. 3, I and K). Peaks 8 and 12 were formed from 6-MeC-1R,2S-diol-3,4-epoxide and peaks 9 and 14 from 6-MeC-1S,2R-diol-3,4-epoxide, respectively (Fig. 5, B and C). Minor peaks corresponded in retention time to products of the reactions with polydeoxyribonucleotides as follows: peak 3, dCyt; peak 4, dGuo; peaks 13 and 15, dAdo (Fig. 3, I–L).

Table 1 summarizes the relative amounts of the major dGuo and dAdo adducts formed in the reaction of each racemic or enantiomeric diol epoxide with DNA. The data for each modified deoxyribonucleoside are expressed as the percentage of total modified deoxyribonucleosides eluting from HPLC in each reaction mixture (Figs. 2, 4, and 5). These data were used to calculate dGuo/dAdo adduct ratios, which are illustrated for the six enantiomeric diol epoxides in Fig. 6.

Table 1 summarizes the relative extents of formation of total adducts, dGuo adducts, and dAdo adducts from the reactions of the diol epoxides with DNA.

Fig. 8, A and B, illustrates the results of mutagenicity assays of the enantiomeric diol epoxides in Salmonella typhimurium TA 100. 5-MeC-1R,2S-diol-3S,4R-epoxide (6700 revertants/nmol) was the most mutagenic compound, followed by 5-MeC-7R,8S-diol-9S,10R-epoxide (1500 revertants/nmol) and 5-MeC-1S,2R-diol-3R,4S-epoxide (540 revertants/nmol). The other three diol epoxide enantiomers were inactive at the doses tested.

### Table 1: Relative yields of major dGuo and dAdo adducts formed in the reaction of methylchrysene diol epoxides with DNA

<table>
<thead>
<tr>
<th>Adducts formed</th>
<th>Racemic anti-5-MeC-1,2-diol-3,4-epoxide</th>
<th>5-MeC-1R,2S-diol-3S,4R-epoxide</th>
<th>5-MeC-1S,2R-diol-3R,4S-epoxide</th>
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<tr>
<td>dGuo-peak 6 of Fig. 2</td>
<td>72</td>
<td>82.5</td>
<td>61.2</td>
</tr>
<tr>
<td>dGuo-peak 4 of Fig. 2</td>
<td>13</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>dAdo-peak 10 of Fig. 2</td>
<td>6.5</td>
<td>6</td>
<td>16.5</td>
</tr>
<tr>
<td>dAdo-peak 12 of Fig. 2</td>
<td>4</td>
<td></td>
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</tr>
</tbody>
</table>

*Mean of at least five HPLC runs.*
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Fig. 7. Relative extents of formation of total adducts, dGuo adducts, and dAdo adducts in the reactions of methylchrysene diol epoxides with DNA.

Fig. 8. Mutagenicity toward S. typhimurium TA 100 of A, 5-methylchrysene and B, 6-methylchrysene diol epoxide enantiomers.

As illustrated in Fig. 6, both the absolute configuration of the diol epoxide and the position of the methyl group affected the dGuo/dAdo adduct ratios. In each case, the dGuo/dAdo adduct ratio was greater for the products formed from the $R,S,S,R$ enantiomer compared to the $S,R,R,S$ enantiomer. The dGuo/dAdo adduct ratios were also greater for the enantiomers of $anti$-$5$-$MeC-1,2$-diole-3,4$-epoxide than for those of either $anti$-$5$-$MeC-7,8$-diole-9,10$-epoxide or $anti$-$6$-$MeC-1,2$-diole-3,4$-epoxide. The greatest effect was observed in comparing the reactions with DNA of $5$-$MeC-1R,2S$-diole-3,4$R$-epoxide and $6$-$MeC-1R,2S$-diole-3,4$S$-epoxide; the dGuo/dAdo adduct ratio was 13.8 for the former and 4.2 for the latter.

Based on their studies of diol epoxide reactivity in the 7,12-dimethylbenz[a]anthracene and benzo[c]phenanthrene series, Bigger et al. and Dipple et al. have developed the hypothesis that reactions with deoxyadenosine are important in the expres-
tion of tumorigenicity (26, 27). This hypothesis is supported by the observation that deoxyadenosine is a target of mutagenicity in the Ha-ras gene, which is expressed in 7,12-dimethylbenz[a]anthracene-induced mouse skin tumors (28, 29). Although this hypothesis is attractive, it does not appear to be consistent with the results obtained in the binding studies and tumorigenicity assays of methylchrysenes diol epoxides. The greatest relative extents of reaction with dAdo were seen with the enantiomers of the inactive anti-6-MeC-1,2-diol-3,4-epoxide. In the present study, reactivity with dGuo was more closely related to tumorigenicity than was reactivity with dAdo, suggesting that the major deoxyguanosine adduct formed from 5-MeC-1,2S-diol-3S,4*R-epoxide may be important in the initiation of tumorigenesis.

The two most reactive diol epoxides with DNA, 5-MeC-1R,2S-diol-3S,4R-epoxide and 5-MeC-7R,8S-diol-9S,10R-epoxide, were also the two most mutagenic in S. typhimurium TA 100. The other diol epoxide enantiomers were either weakly active or inactive at the doses tested. These results suggest that the extent of reaction with DNA is one important determinant of mutagenicity for these compounds. However, the differences in mutagenicity seem to be greater than the differences in reactivity, suggesting that factors such as sequence specificity in reaction, adduct conformation, or adduct processing could also play an important role in the expression of mutagenicity.

The differences in tumorigenicity among the various diol epoxides are greater than observed in the mutagenicity experiments. Only 5-MeC-1R,2S-diol-3S,4R-epoxide was highly tumorigenic in both systems examined. The high reactivity of this diol epoxide with DNA, due to its bay region methyl group and R,S,S,R configuration, is certainly one determinant of the tumorigenic response, but as in the mutagenicity experiments, other factors are likely to be involved. Experiments are currently in progress to delineate the effects of sequence specificity and adduct conformation in the expression of methyl bay region diol epoxide mutagenicity and tumorigenicity.

ACKNOWLEDGMENTS

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