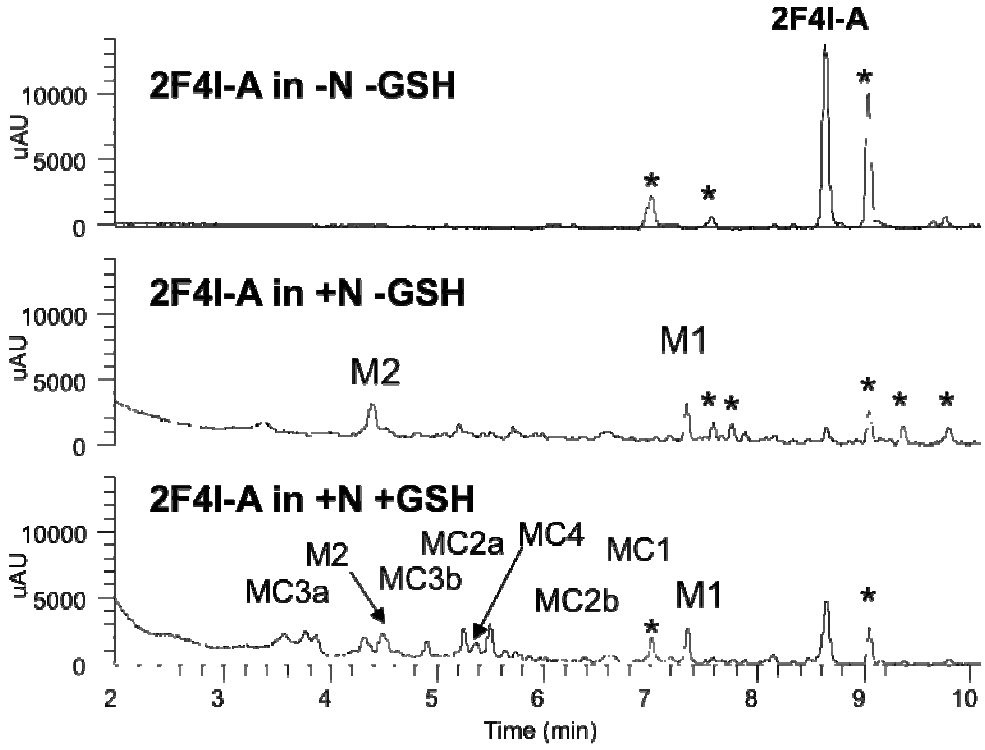
Supplemental Information

for

A Novel Mechanism for Dehalogenation and Glutathione Conjugation of Dihalogenated Anilines in Human Liver Microsomes: Evidence for *ipso* Glutathione Addition

Chenghong Zhang, Jane R. Kenny, Hoa Le, Alan Deese[†], Kevin Ford[‡], Luke K. Lightning[§], Peter W. Fan, James P. Driscoll, Jason S. Halladay, Cornelis E.C.A. Hop, S. Cyrus Khojasteh[*]

Fig. S1. UV comparison of 2-fluoro-4-iodoaniline (2F4I-A) incubated with human liver microsomes in the presence of NADPH and/or glutathione.



* is an interfering peak (not drug related).

Figure S2. Product ion scan of MC1 in the case of incubation of 2F4I-A incubated with human liver microsomes in the presence of NADPH and glutathione.

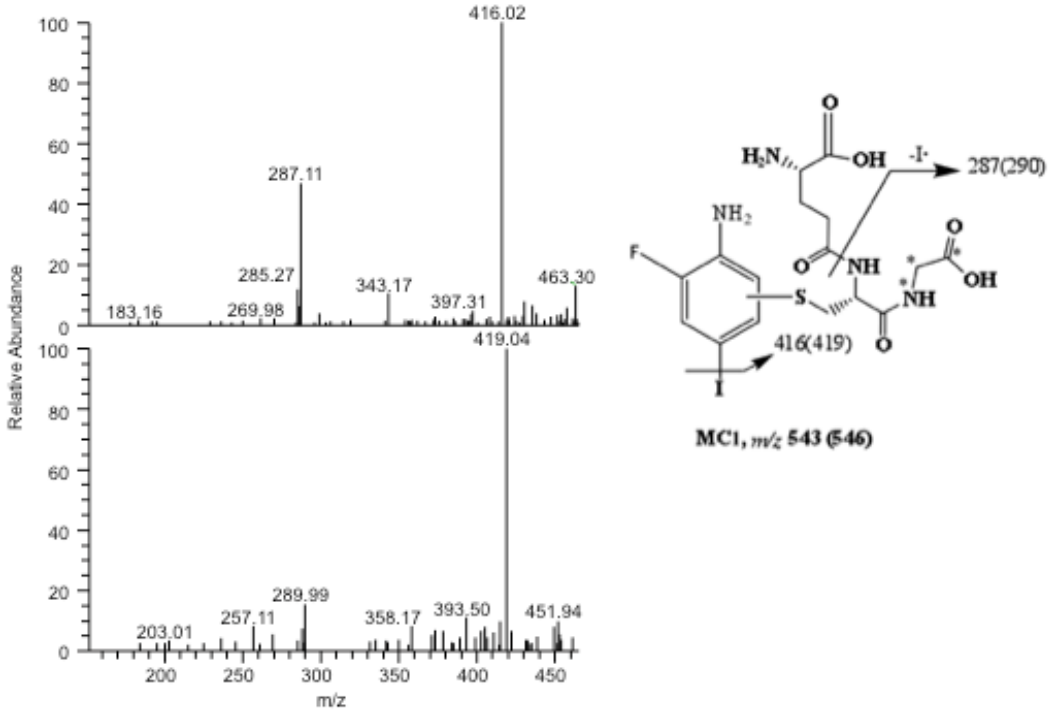


Figure S3. Product ion scan of MC2a in the case of incubation of 2F4I-A incubated with human liver microsomes in the presence of NADPH and glutathione.

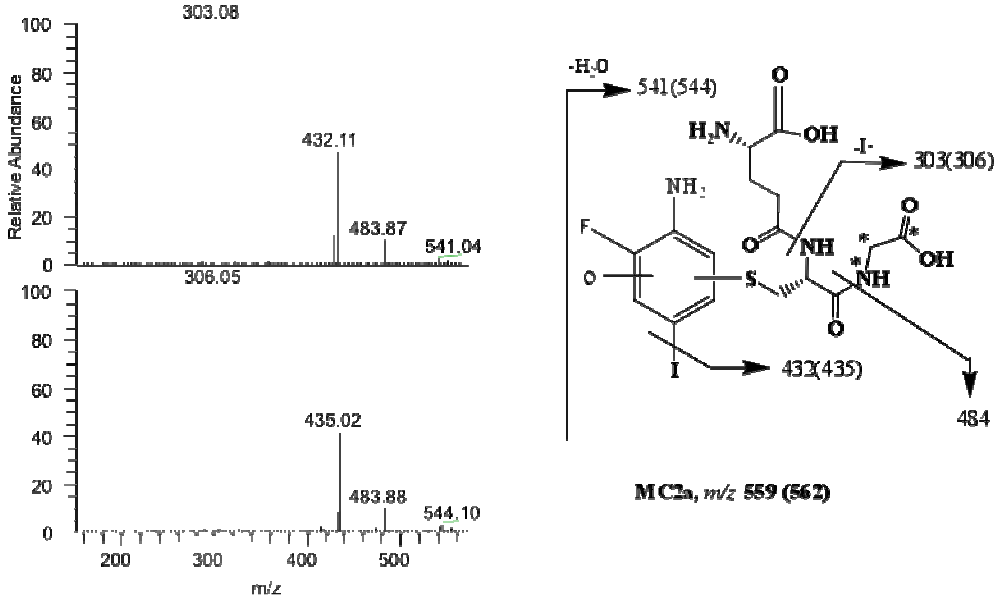


Figure S4. Product ion scan of MC2b in the case of incubation of 2F4I-A incubated with human liver microsomes in the presence of NADPH and glutathione.

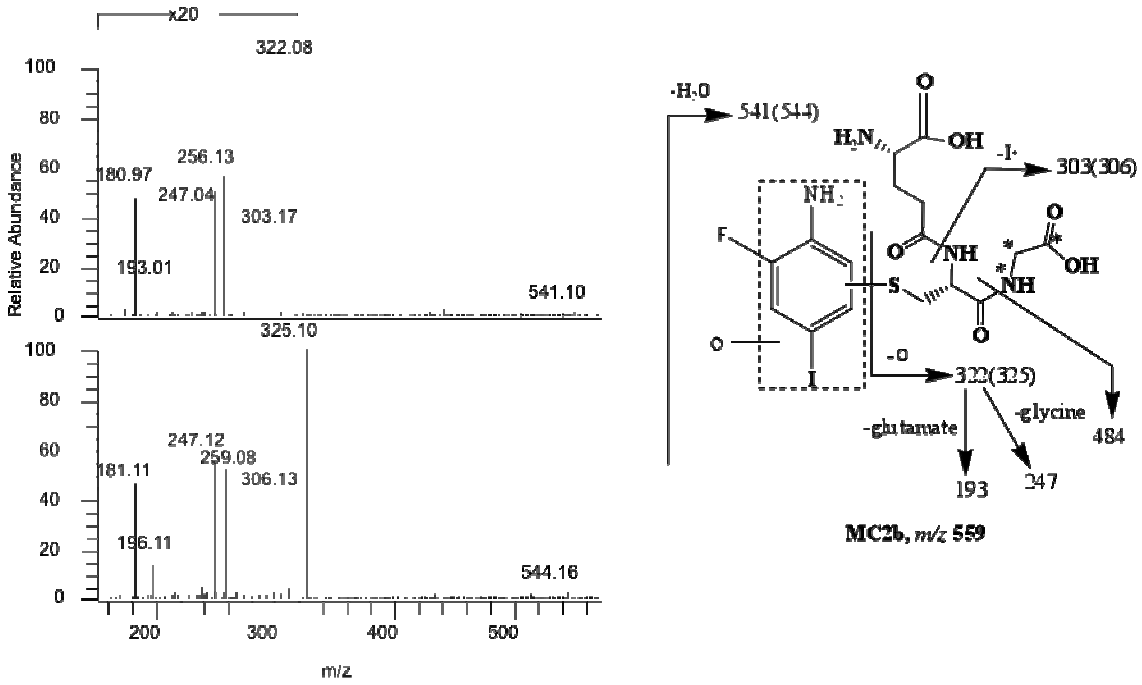


Figure S5. Product ion scan of MC3a in the case of incubation of 2F4I-A incubated with human liver microsomes in the presence of NADPH and glutathione.

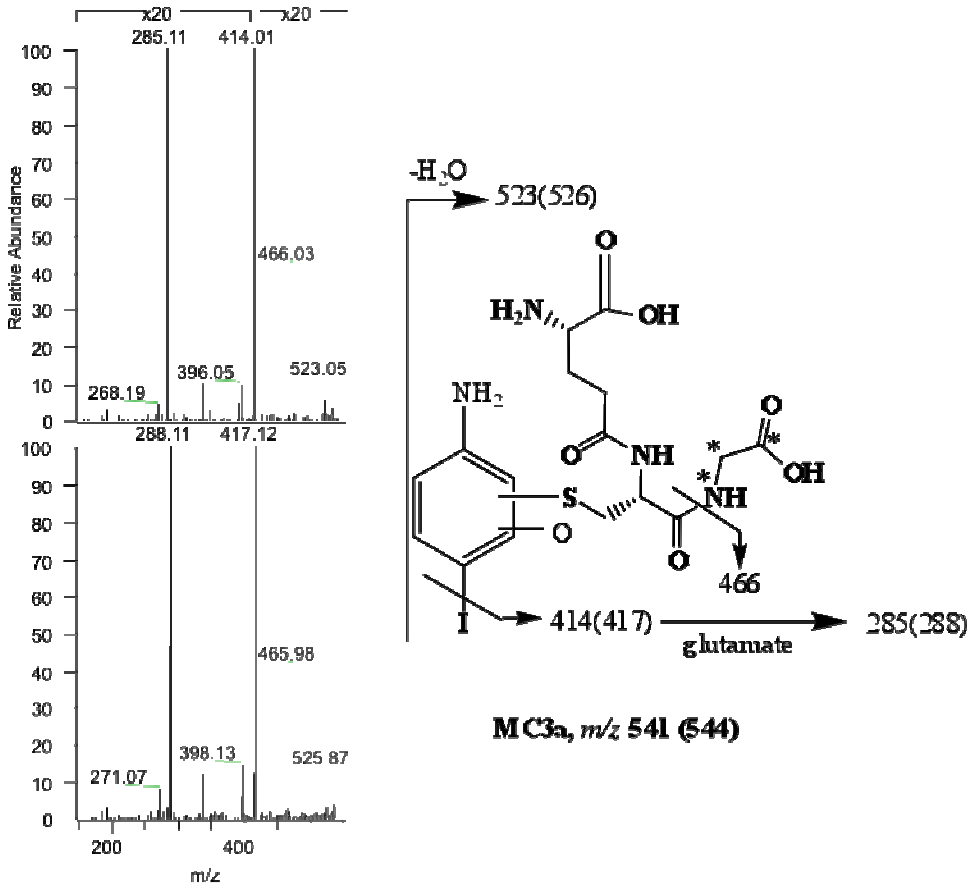
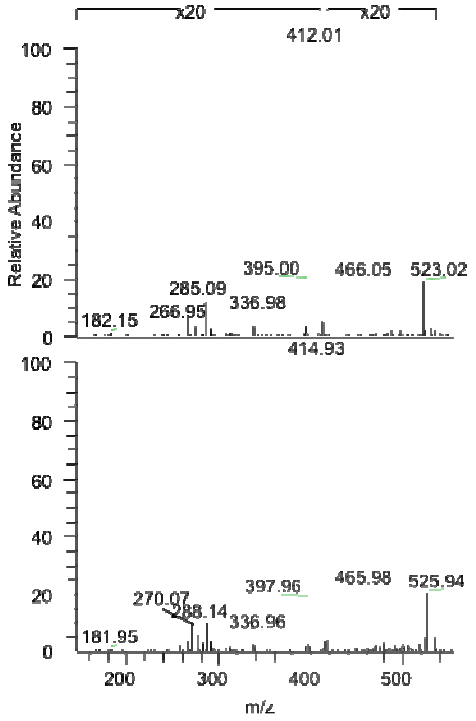
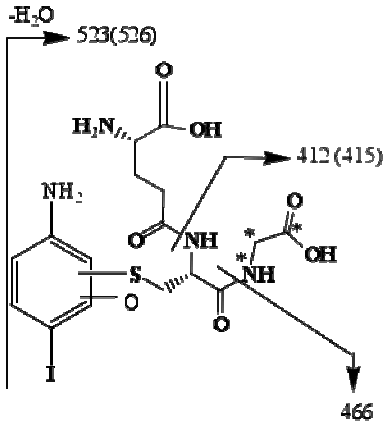


Figure S6. Product ion scan of MC3b in the case of incubation of 2F4I-A incubated with human liver microsomes in the presence of NADPH and glutathione.





MC3b, *m/z* 541 (544)

Figure S7a. MC4 was isolated when 2F4I-A was incubated in human liver microsomes fortified with NADPH and GSH. Three proton resonances were observed (figure 7a); a broad singlet at 7.73 ppm, a doublet at 7.50 ppm (8.64 Hz splitting) and a doublet at 6.70 ppm (8.64 Hz splitting).

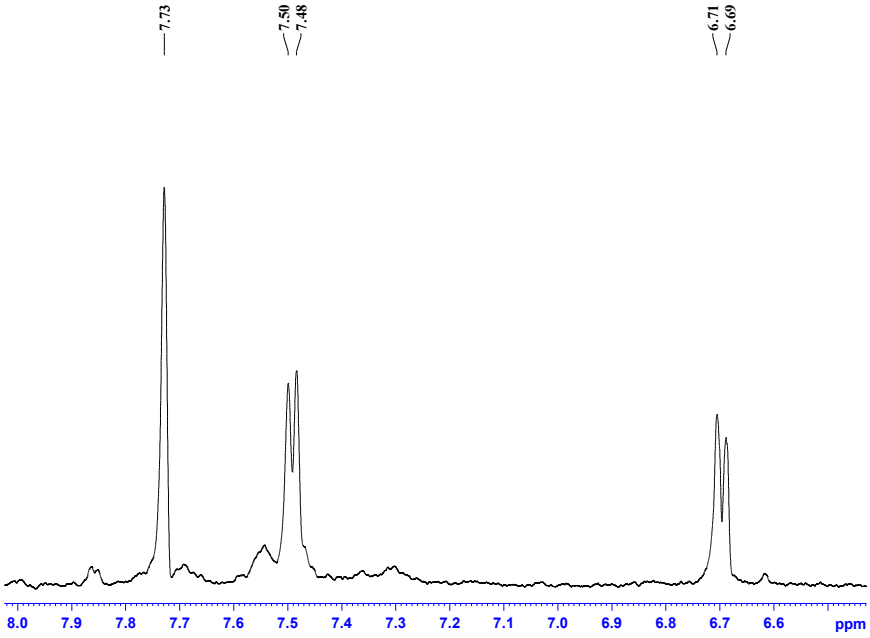


Figure S7b. Additionally, a nOe is observed between H-6 and the methylene protons attached to C-8.

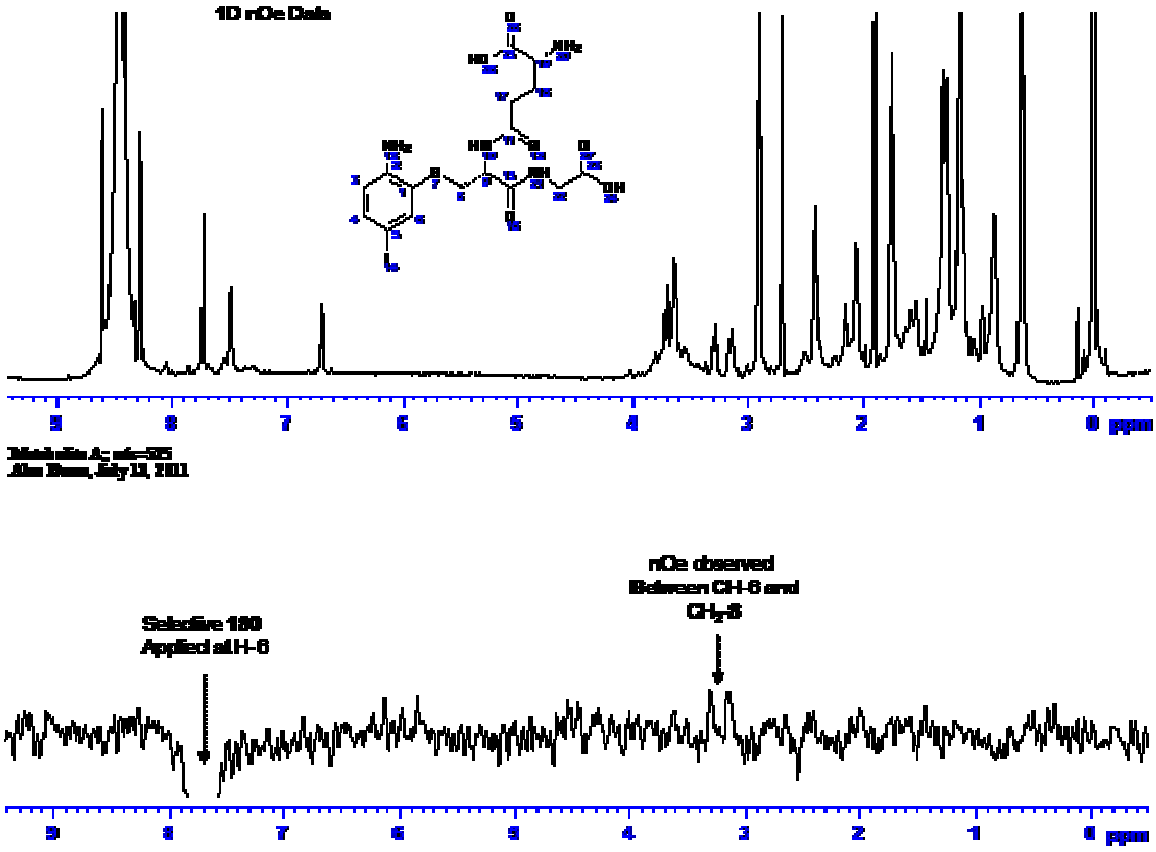


Figure S7c. 2D-COSY data shows spin-spin coupling between protons 3, 4 and 6. Also observed is a coupling between CH_2-8 and CH-9 in the GSH moiety.

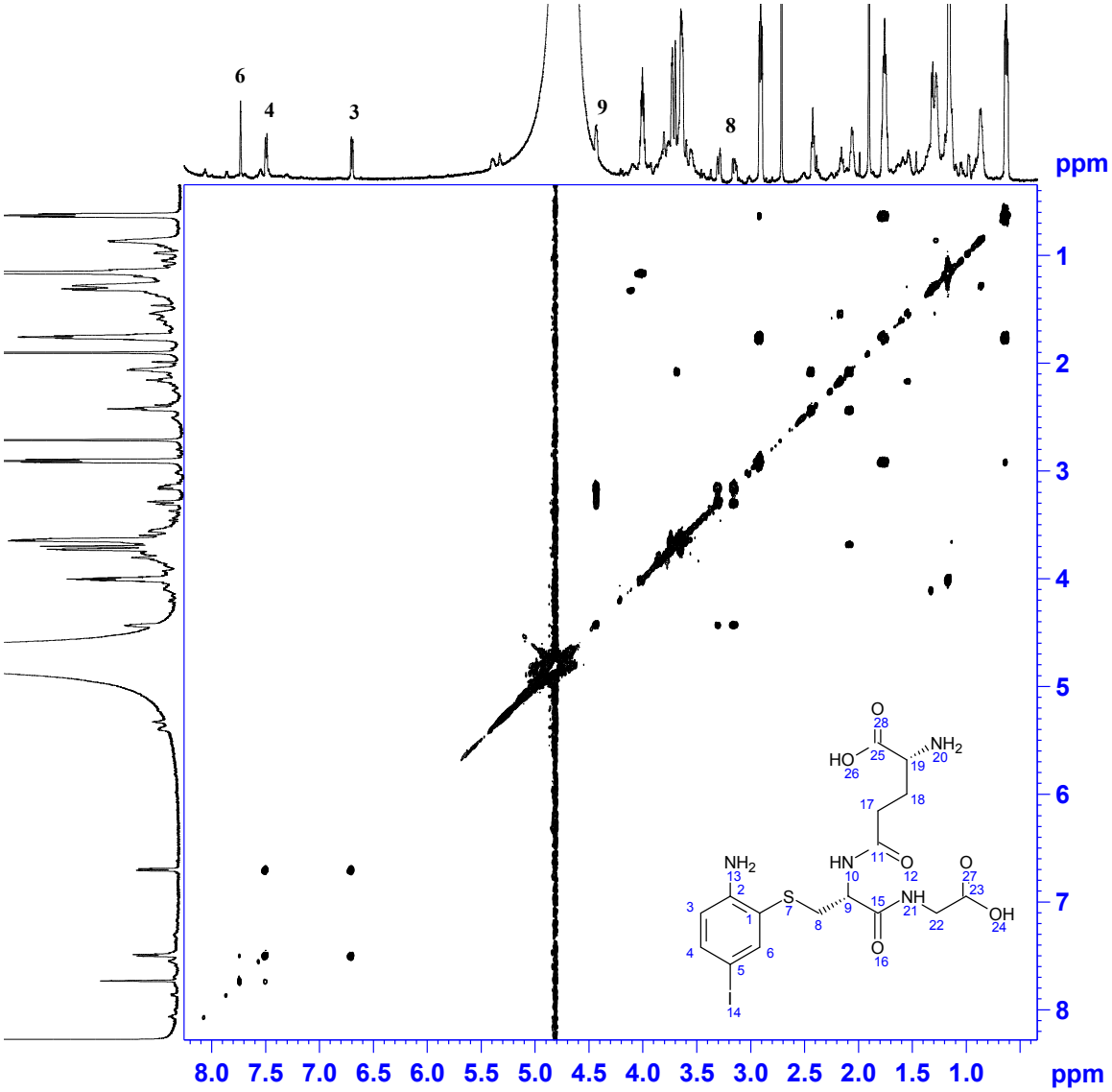


Figure S8. Charges of each atom in the in the molecular structure of the 2-fluoro-4-haloanilines.

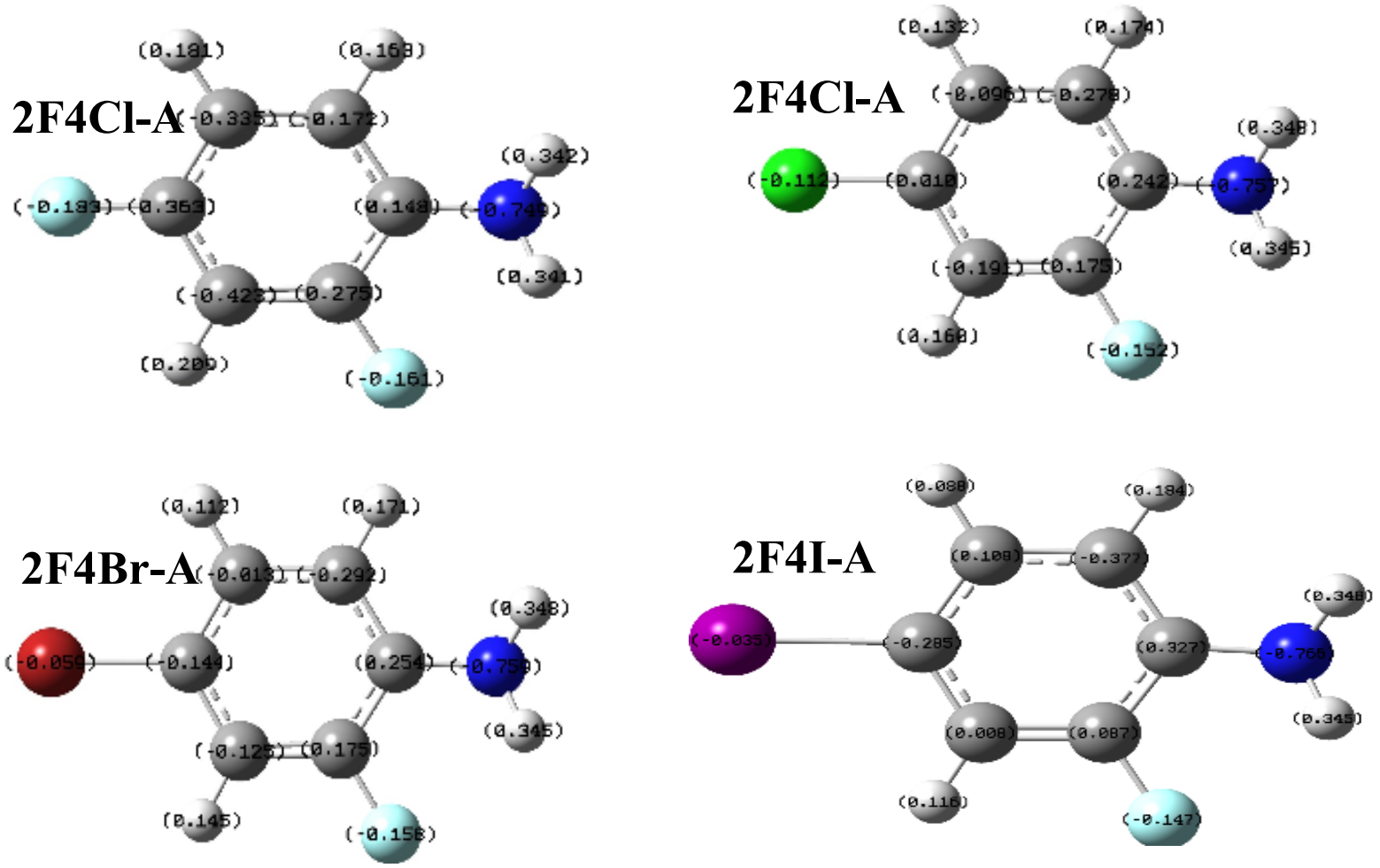
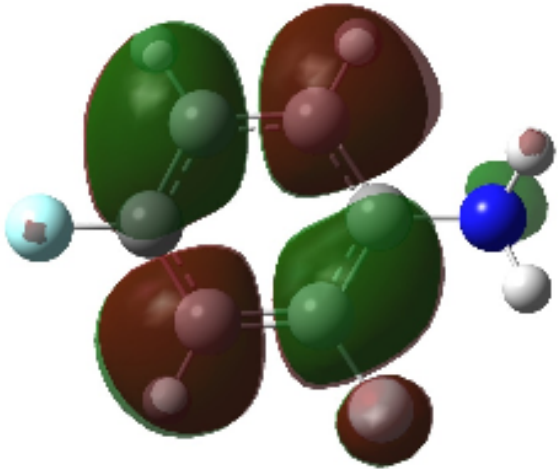
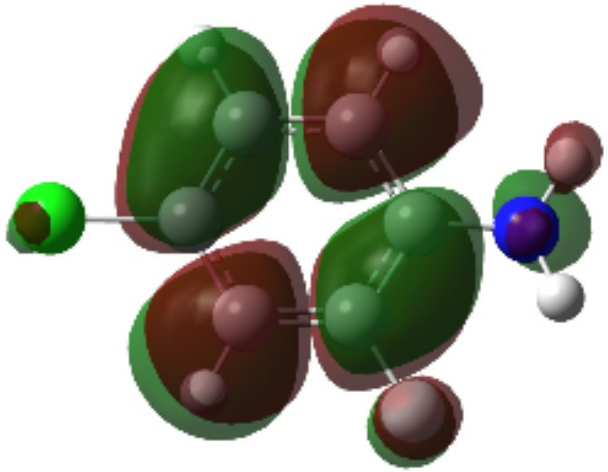


Figure S9. Lowest unoccupied molecular orbital (LUMO) energies of the 2-fluoro-4-haloanilines.



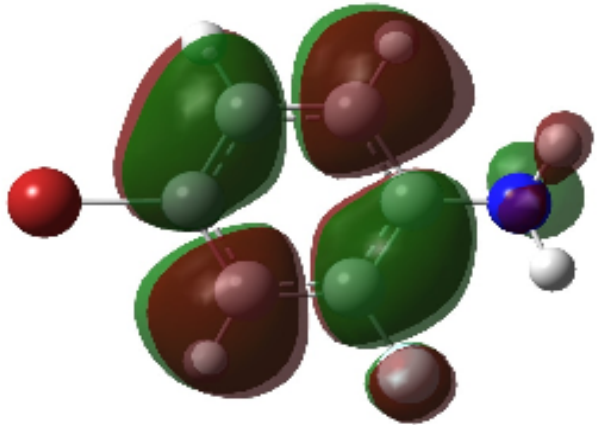
2F4F-A

E=-4.782 kcal/mol



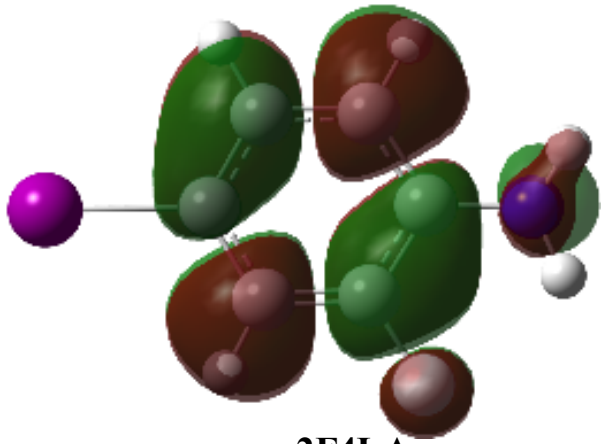
2F4Cl-A

E=-6.846 kcal/mol



2F4Br-A

E=-6.821 kcal/mol



2F4I-A

E=-20.080 kcal/mol

Figure S10. Charges of each atom in the molecular structure of the 3-fluoro-4-haloanilines.

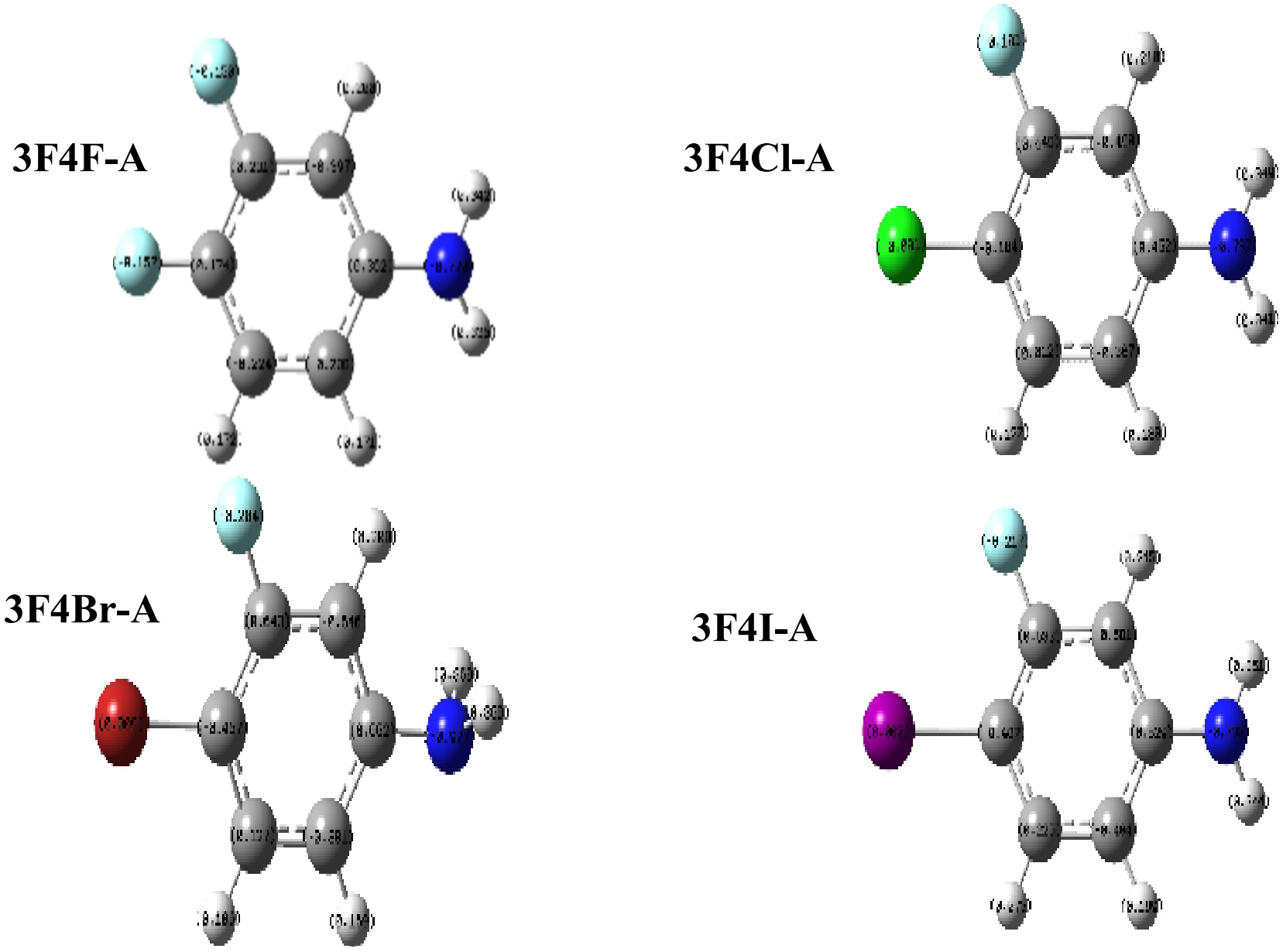
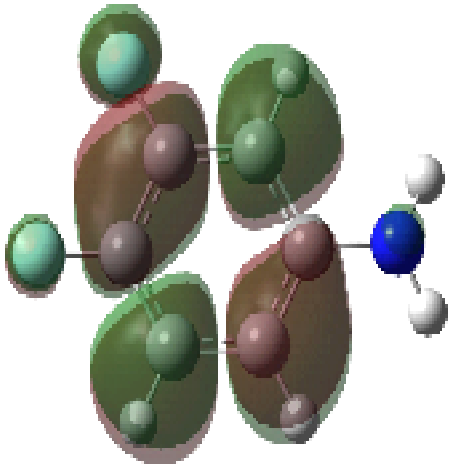
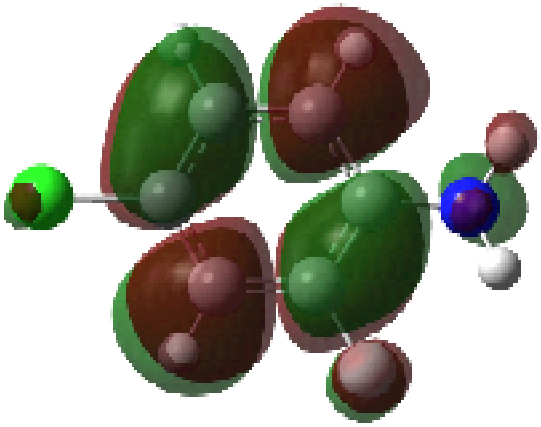


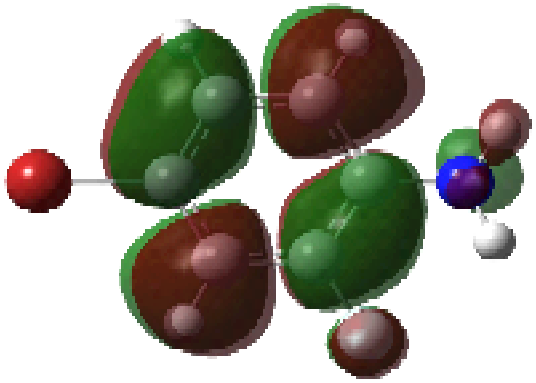
Figure S11. Lowest unoccupied molecular orbital (LUMO) energies of the 3-fluoro-4-haloanilines.



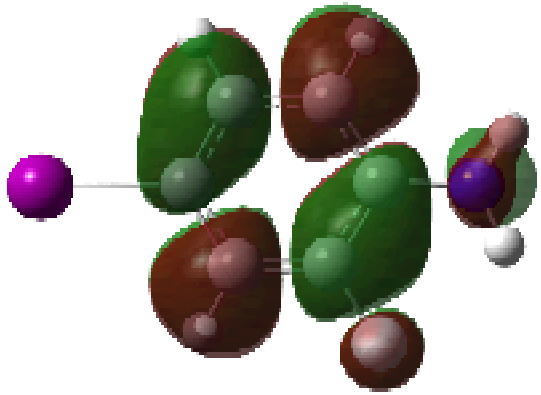
3F4F-A: LUMO
E=-4.782 kcal/mol



3F4Cl-A: LUMO
E=-6.846 kcal/mol



3F4Br-A: LUMO
E=-6.821 kcal/mol



3F4I-A: LUMO
E=-20.080 kcal/mol