INTRODUCTION
Valproic acid, chemically known as 2-propylpentanoic acid, is an anticonvulsant drug widely used in the treatment of epilepsy and bipolar disorder. The quantitation of valproic acid in plasma utilizing LC/MS techniques traditionally has been challenging due to weak retention in chromatography and lack of sensitivity and specificity in detection by directly monitoring unfavorable ion transition pair under negative ion mode. Here, we explore the derivatization method that changed the detection polarity of the analyte from negative to positive mode and also chromatographic properties to improve robustness of the method. The signal-to-noise ratio and thus the specificity of detection were significantly improved by monitoring the different ion transition pair under positive ion mode.

METHOD
Following a protein precipitation procedure, the extract was subjected to a derivatization reaction using N-(3-Dimethylaminopropyl)-N-ethylcarbodiimide (EDC) and 2,2,2-trifluoro ethylamine (TFEA) in phosphate buffer. The resulting solution was diluted and chromatographed on a Betasil Phenyl column using a valve switching system preventing the introduction of reaction salts into the LC/MS system. Derivatized valproic acid and its internal standard (valproic acid-d$_4$) were detected by an API 3000 LC/MS system under positive MRM mode.

RESULTS
The method showed a linear range of 0.500 to 150 µg/mL with weighted linear regression (1/x$^2$). The correlation coefficients for three validation batches were 0.997 or better (Figure 3).

CONCLUSION
The method was fully validated over a range of 0.500 to 150 µg/mL with weighted (1/x$^2$) linear regression. The effect of hemolysis and lipemic plasma was also evaluated with no significant effect observed. This method showed acceptable accuracy, precision, selectivity, stability, and reproducibility.

ACKNOWLEDGMENTS
The authors would like to thank Kim Tuyen Nguyen and Kim Jackson for assistance with extraction and data processing.