

## Supporting Information

**Structure Activity Relationships and Discovery of a G Protein Biased  $\mu$  Opioid Receptor**

**Ligand, [(3-Methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro-  
[4.5]decan-9-yl]ethyl})-amine (TRV130), for the Treatment of Acute Severe Pain**

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Figure S1.  $^1\text{H}$  NMR of 2-[(2-[4-(4-Methylphenyl)oxan-4-yl]ethyl)amino]methyl]phenol (**2**)

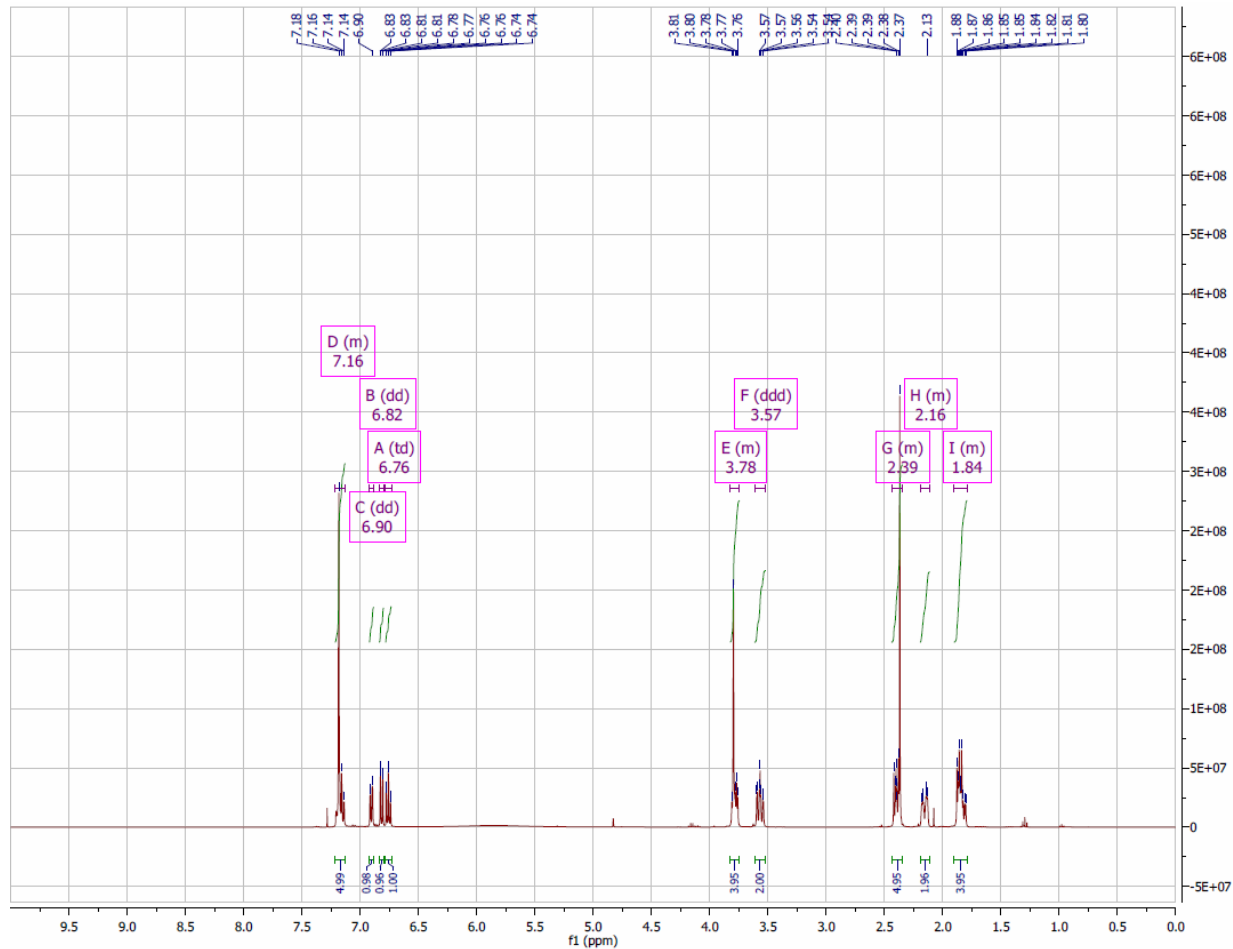


Figure S2.  $^1\text{H}$  NMR of Benzyl({2-[4-(4-fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl})amine (**4**)

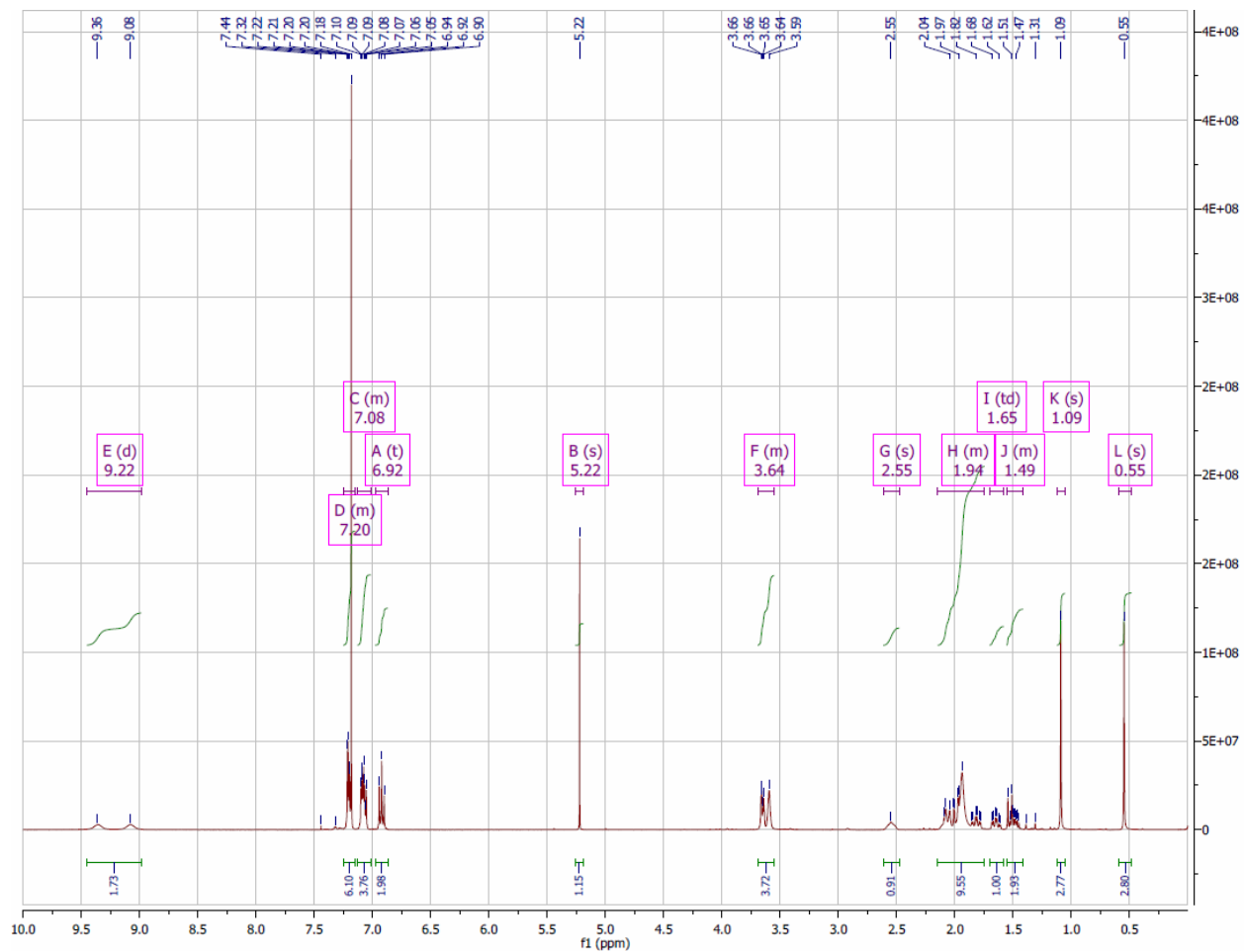


Figure S3.  $^1\text{H}$  NMR of Benzyl({2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl})amine (**5**)

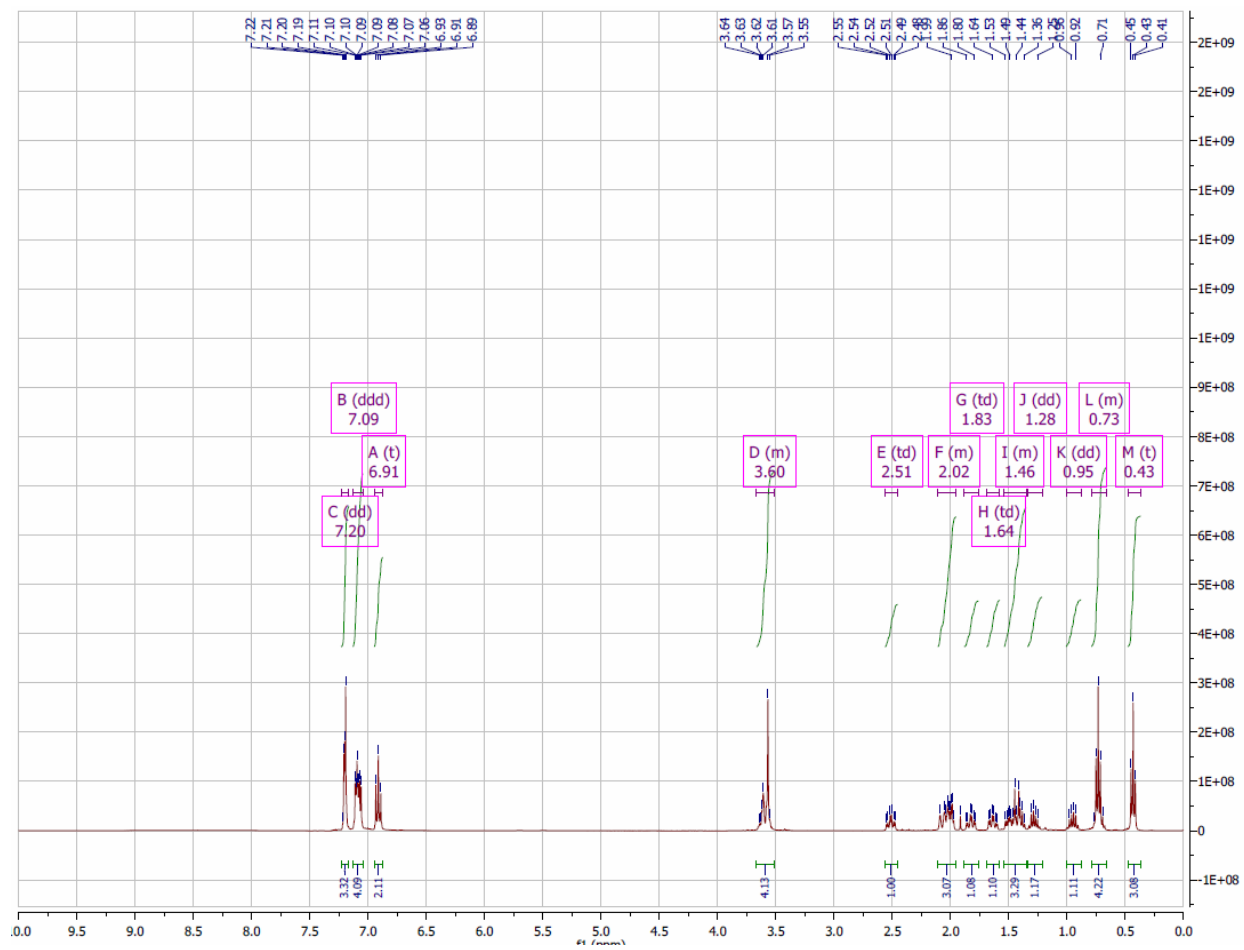


Figure S4. <sup>1</sup>H NMR of Benzyl({2-[9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine  
**(6)**

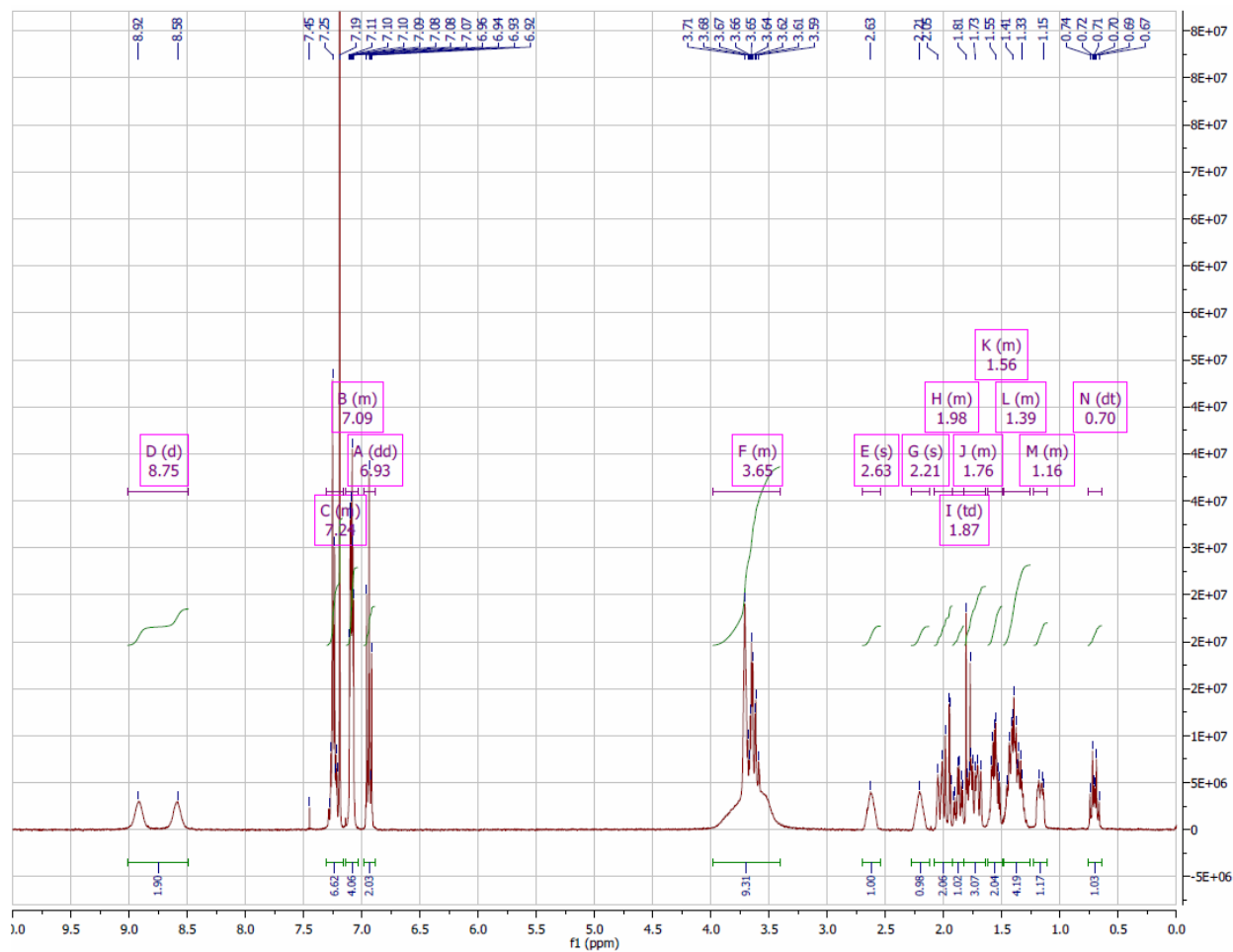


Figure S5.  $^1\text{H}$  NMR of Benzyl({2-[(9*R*)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**6**)

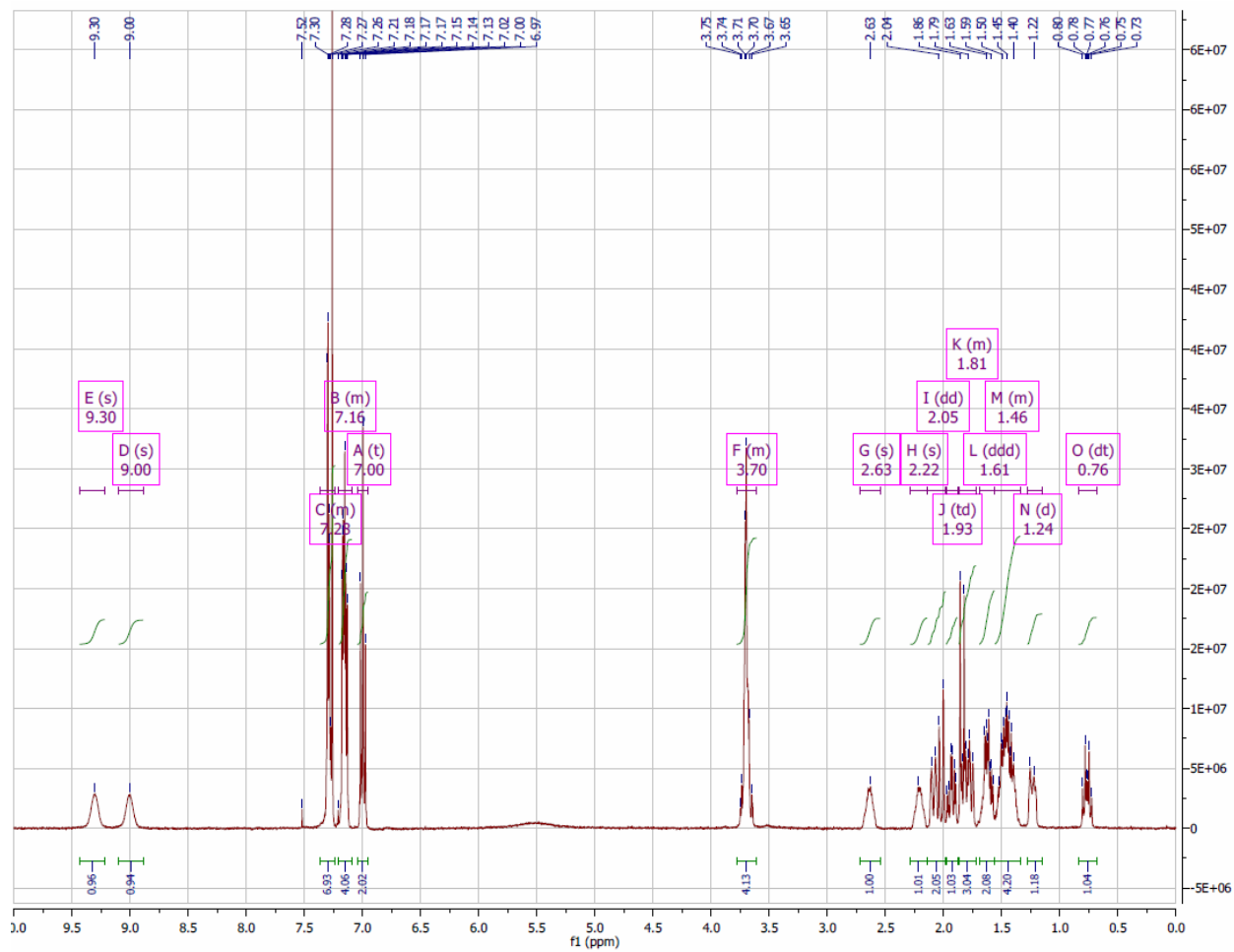




Figure S6.  $^1\text{H}$  NMR of Benzyl({2-[(9*S*)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*S*)-**6**)

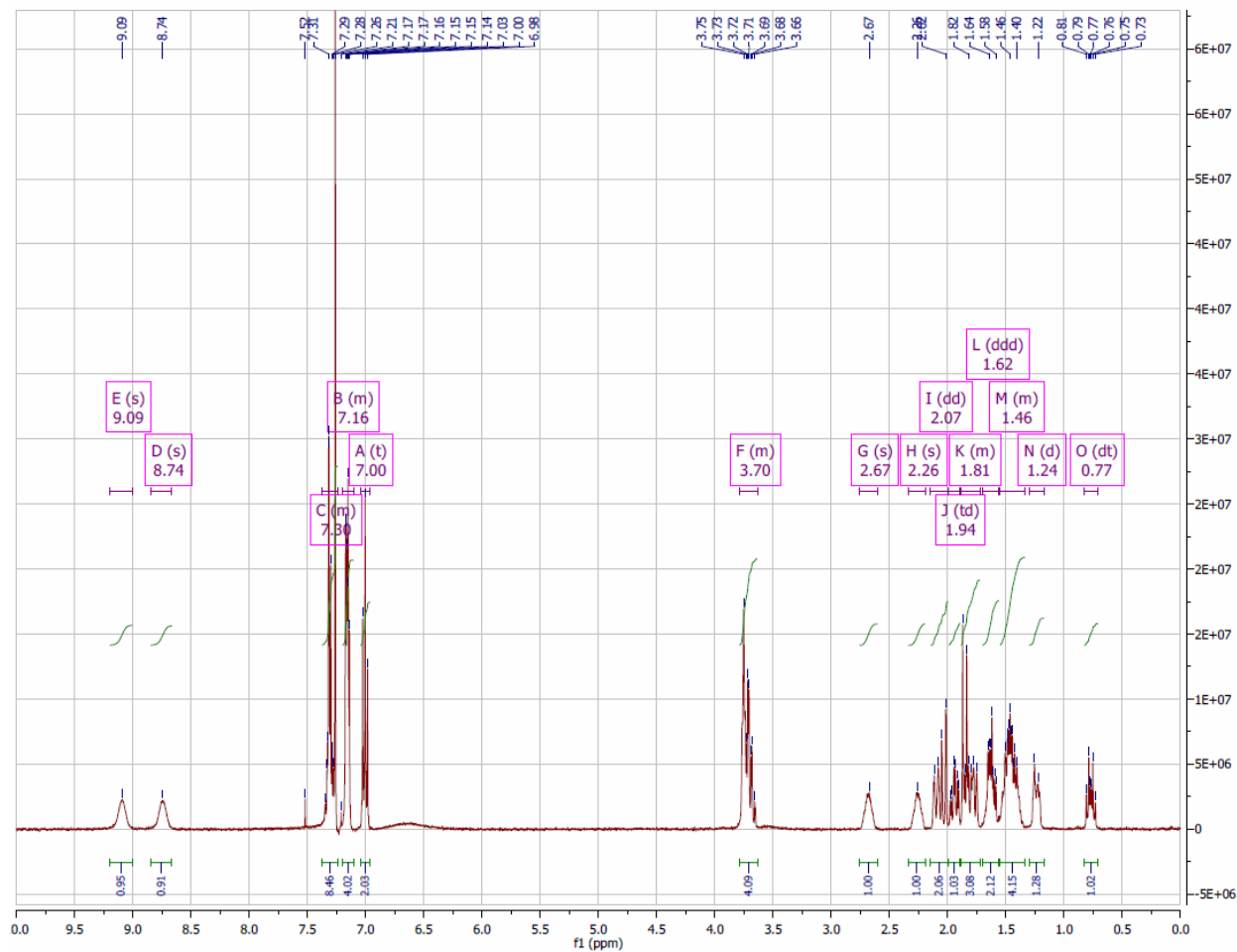


Figure S7. <sup>1</sup>H NMR of Benzyl({2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl})amine (7)

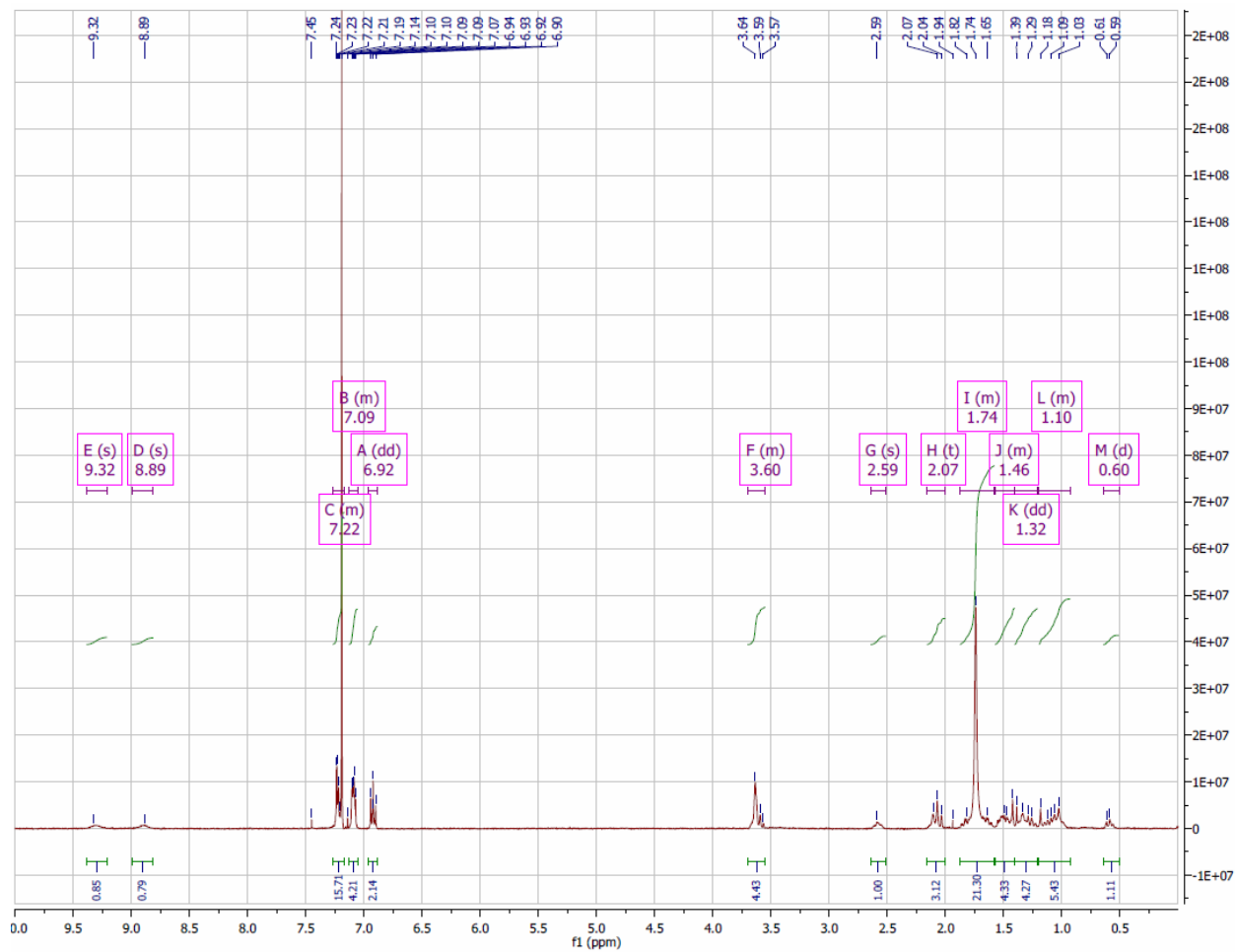


Figure S8.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(4-Fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(1*S*)-1-phenylethyl]amine ((*R*)-**8**)

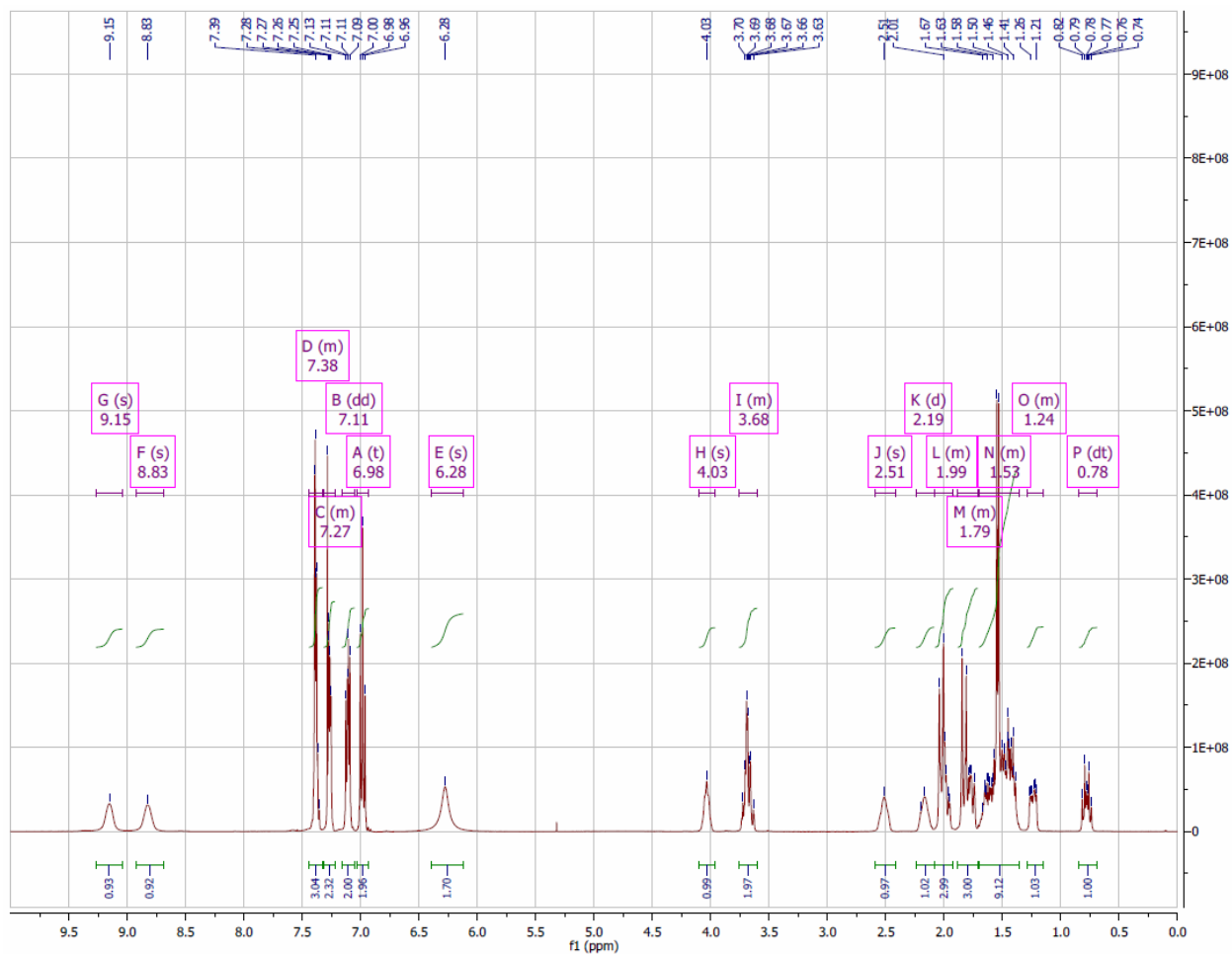


Figure S9.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(4-Fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(1*R*)-1-phenylethyl]amine ((*R*)-**9**)

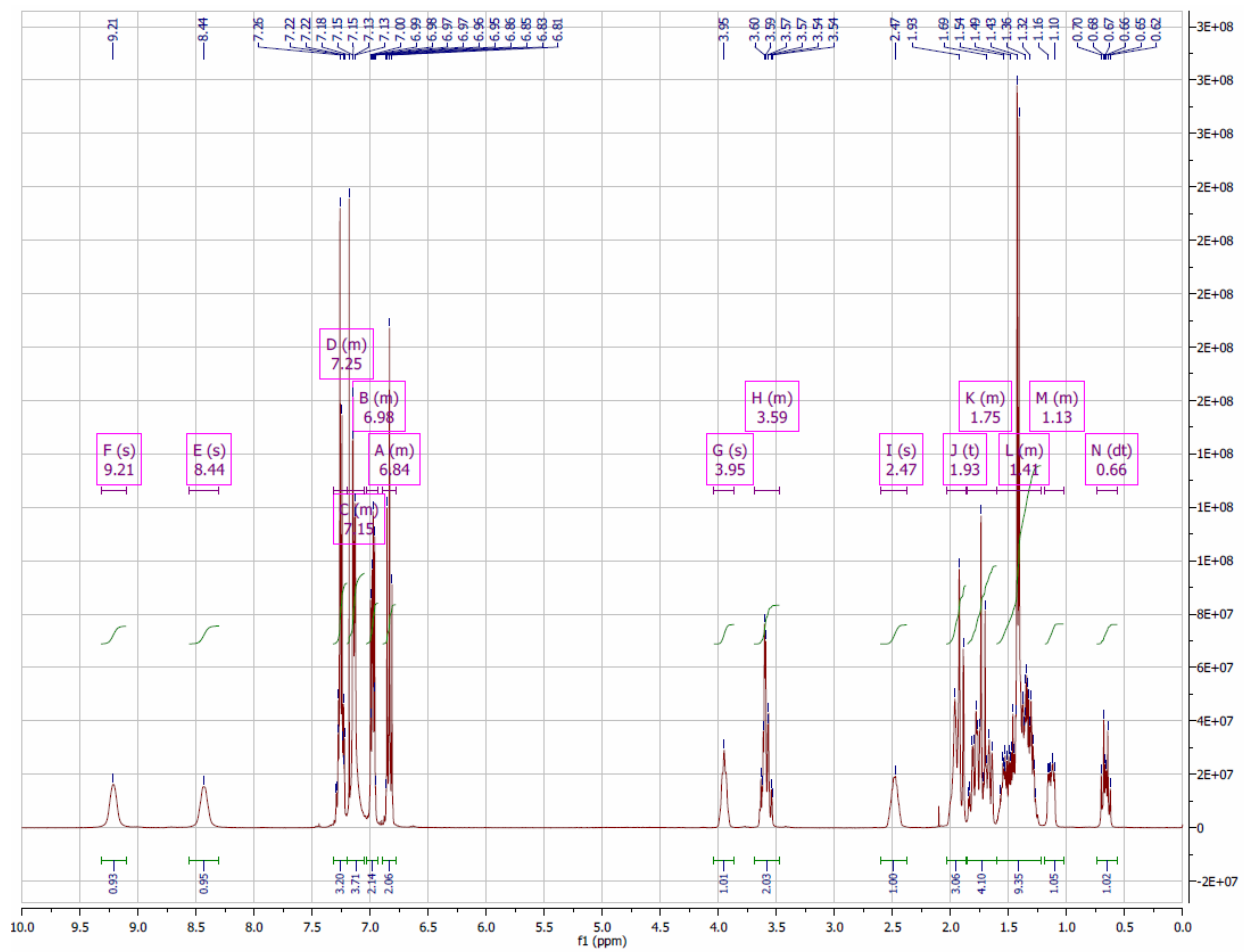


Figure S10.  $^1\text{H}$  NMR of {2-[(9R)-9-(4-Fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(2-phenylpropan-2-yl)amine ((**R**)-**10**)

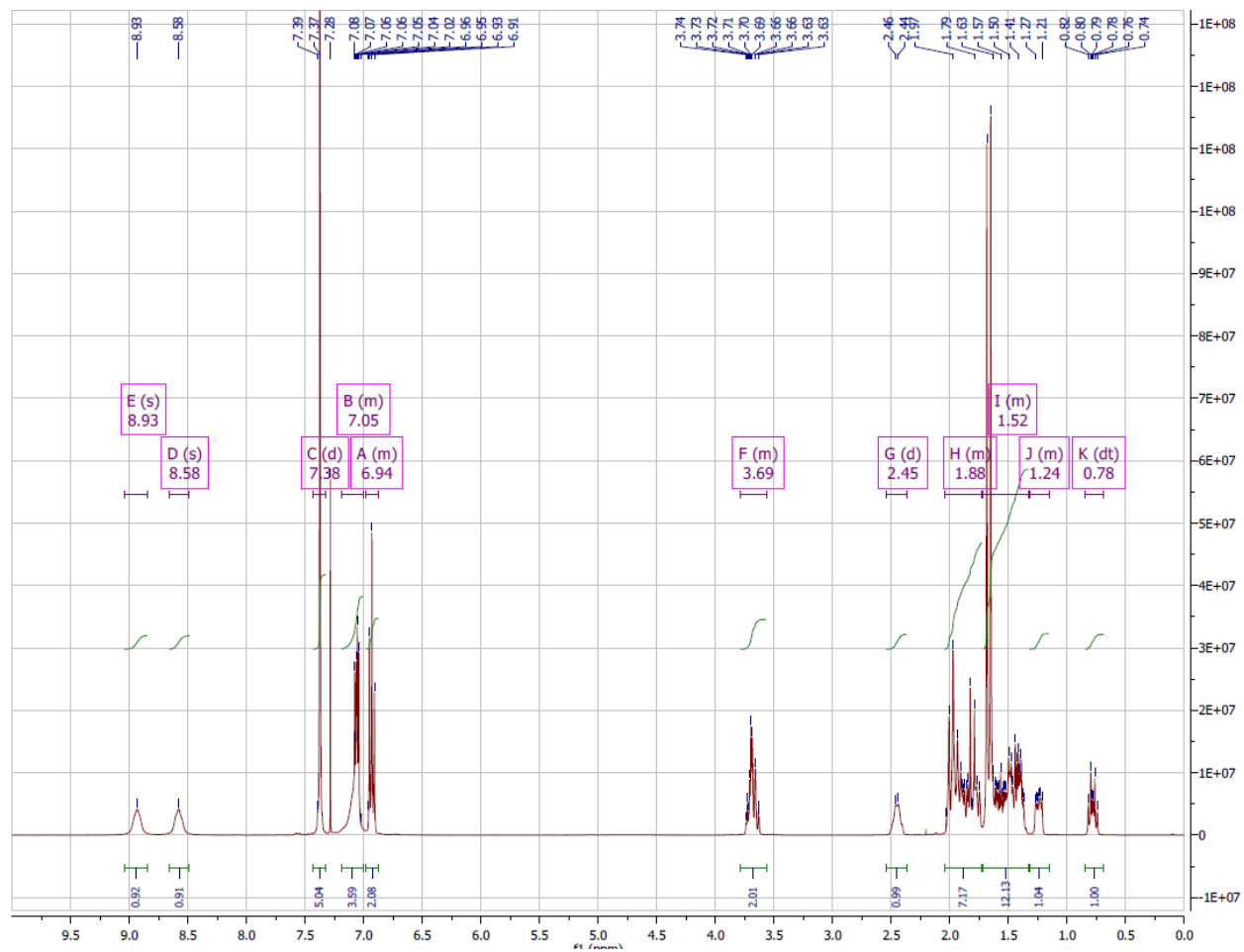


Figure S11.  $^1\text{H}$  NMR of Benzyl({2-[9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine (11)

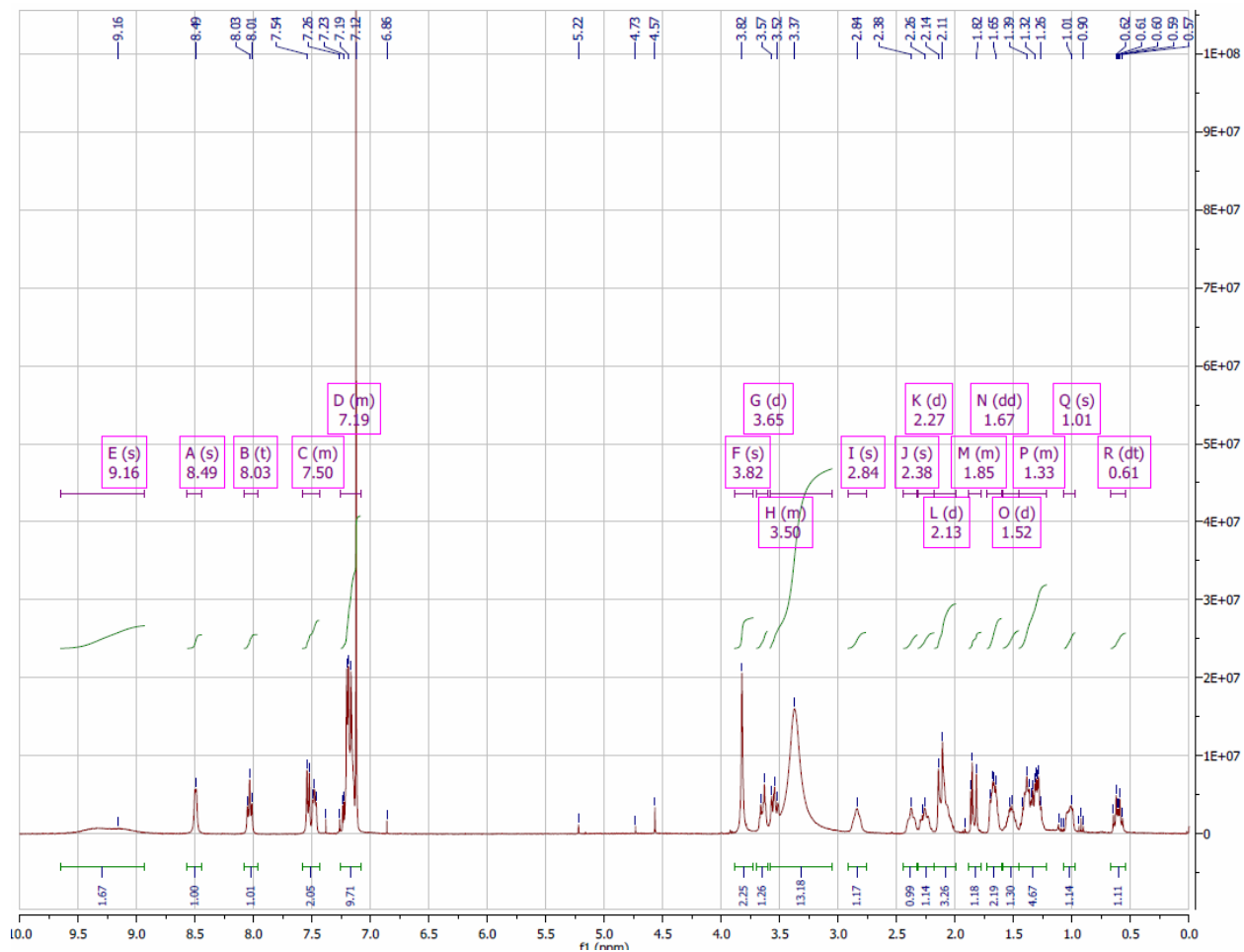


Figure S12.  $^1\text{H}$  NMR of Benzyl({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((**R**)-**11**)

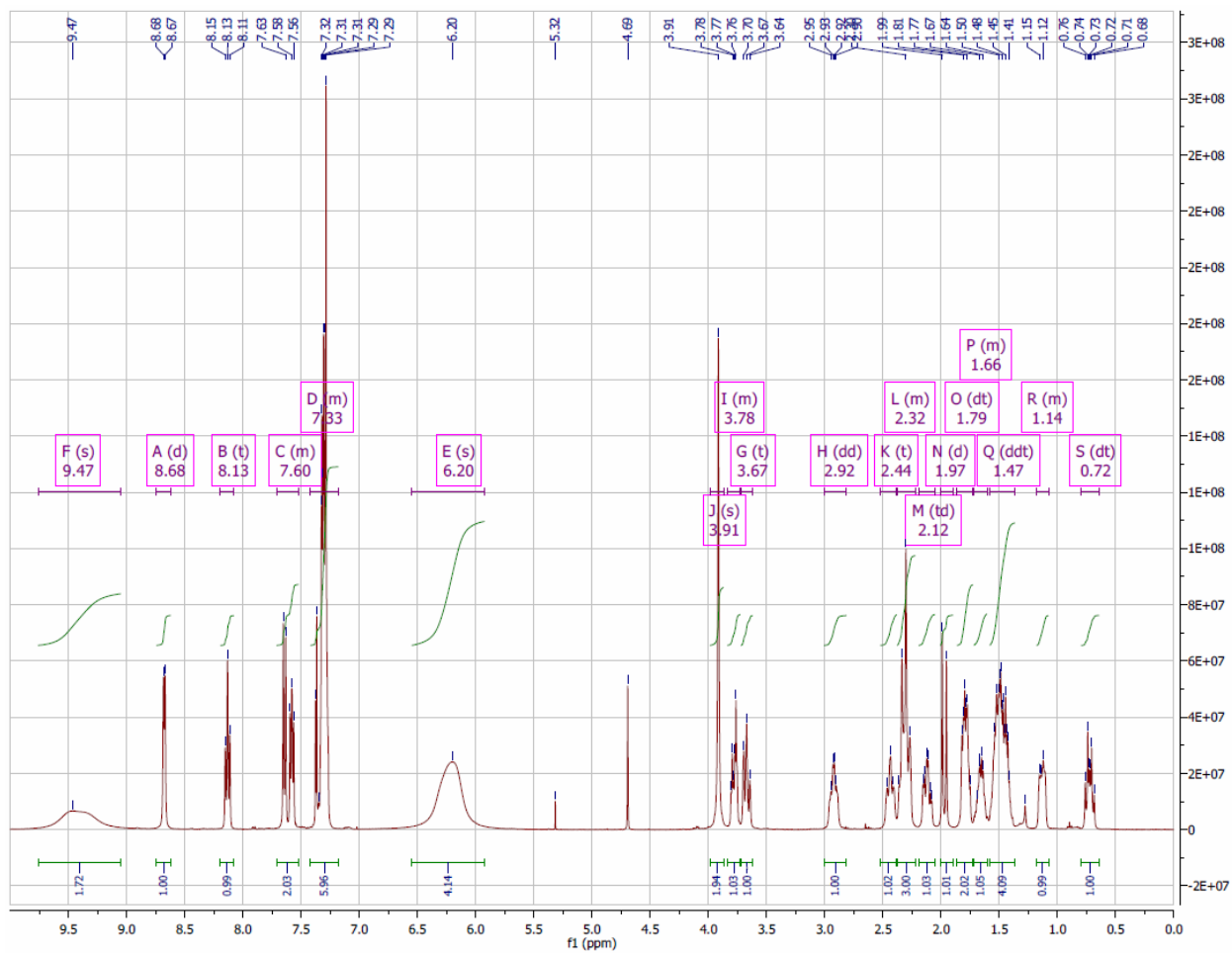


Figure S13.  $^1\text{H}$  NMR of Benzyl({2-[(9*S*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-]ethyl})amine ((*S*)-11)

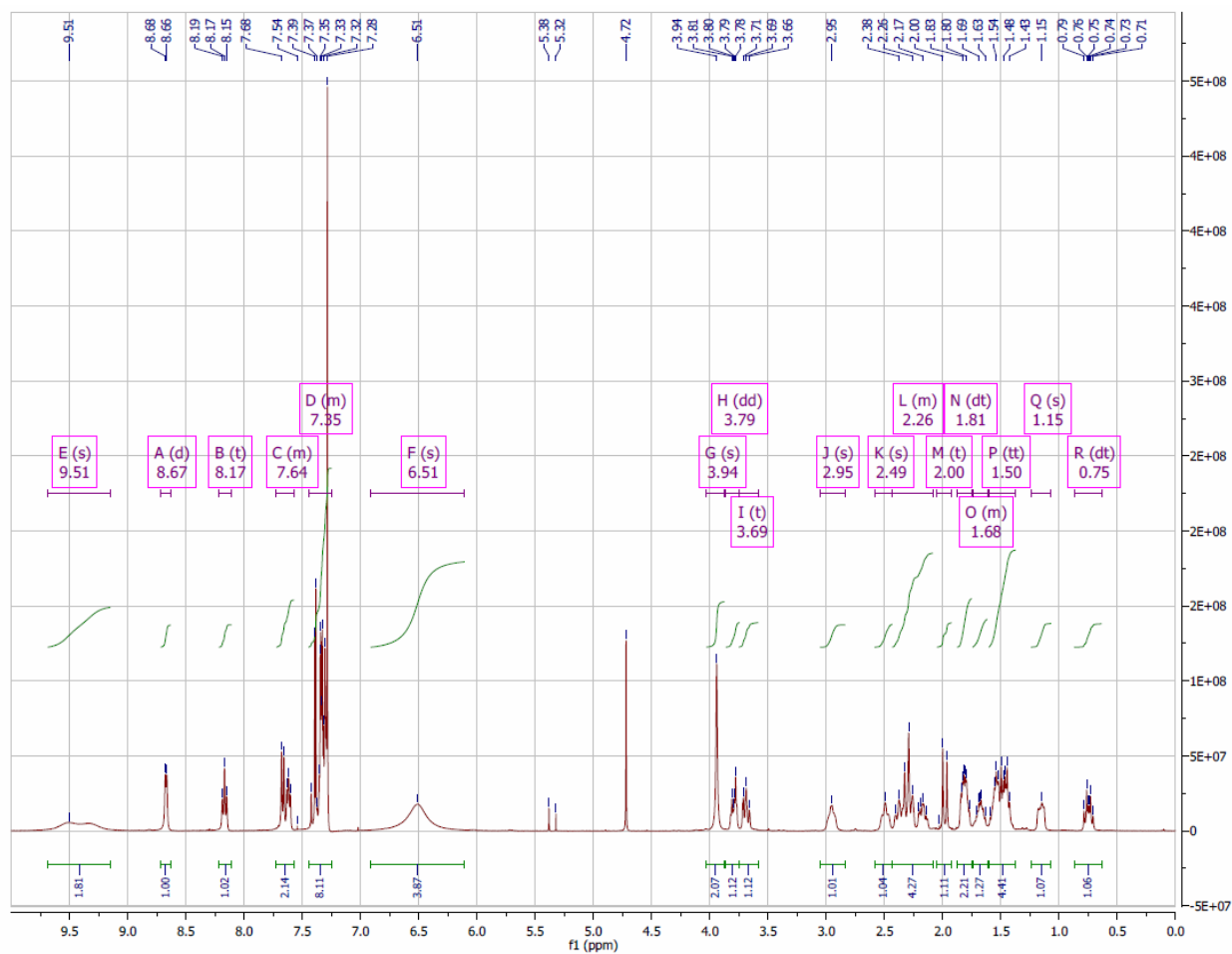




Figure S14.  $^1\text{H}$  NMR of [(2-Chlorophenyl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**12**)

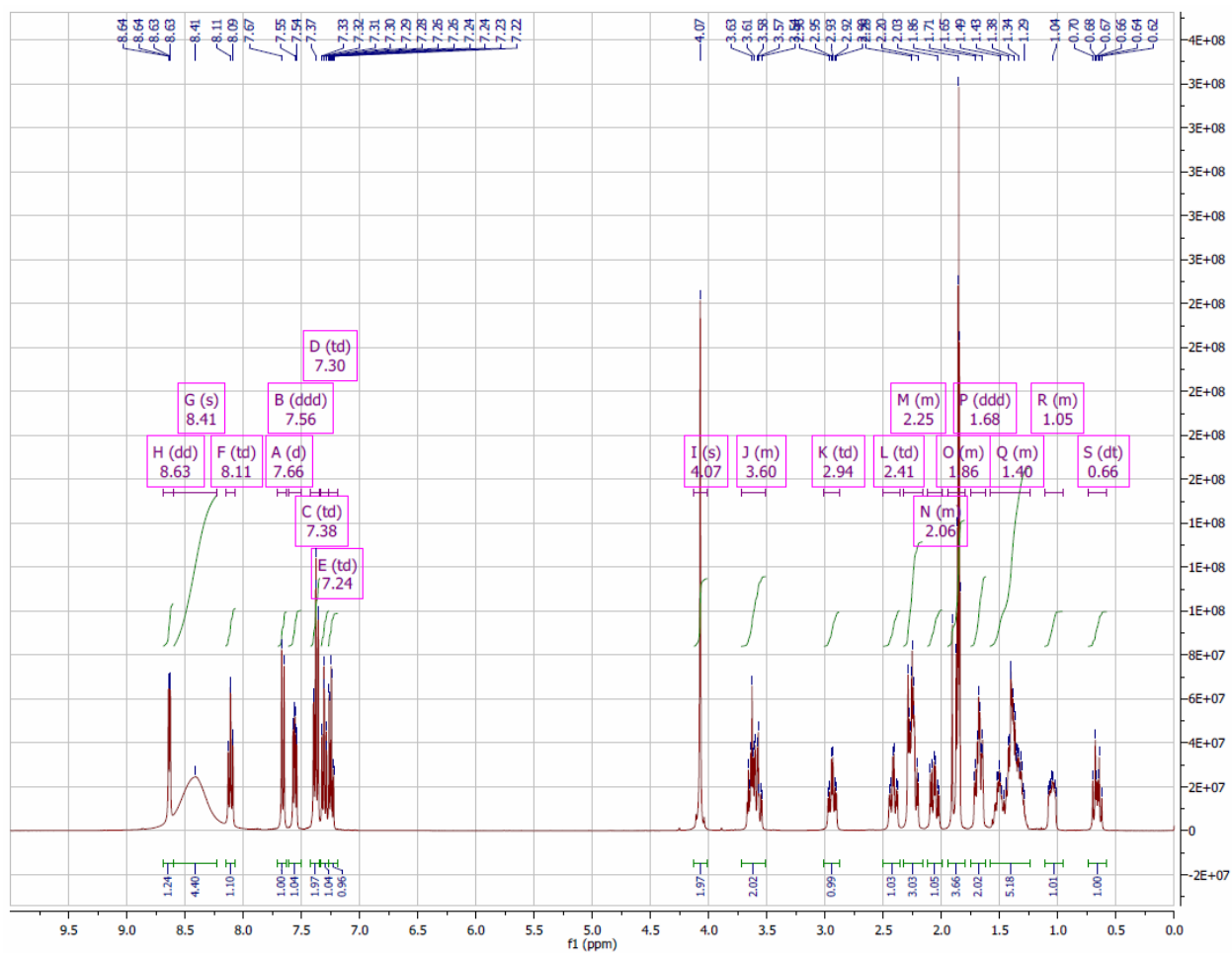


Figure S15.  $^1\text{H}$  NMR of [(3-Chlorophenyl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine (**(*R*)-13**)

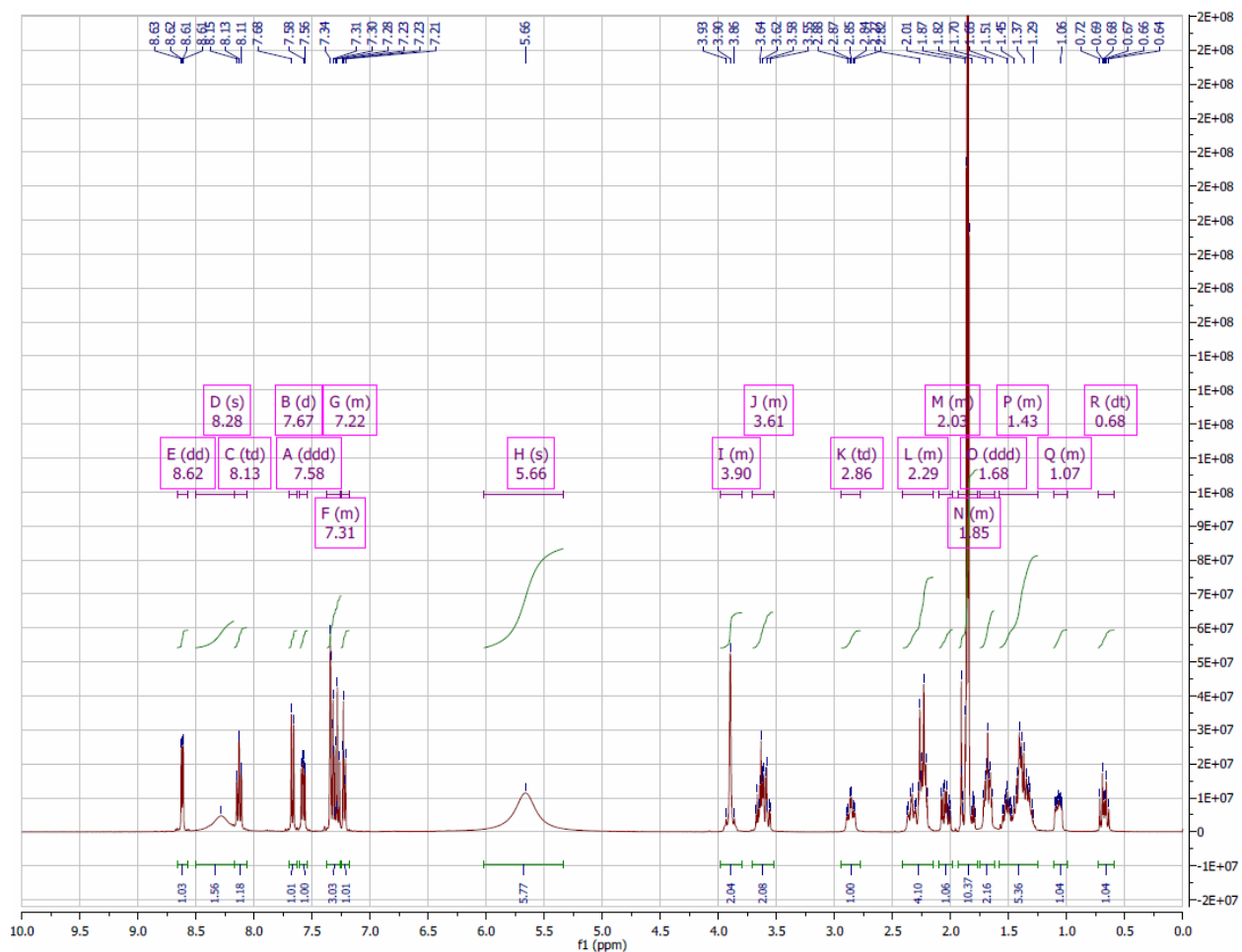


Figure S16.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(Pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyridin-2-ylmethyl)amine ((*R*)-**14**)

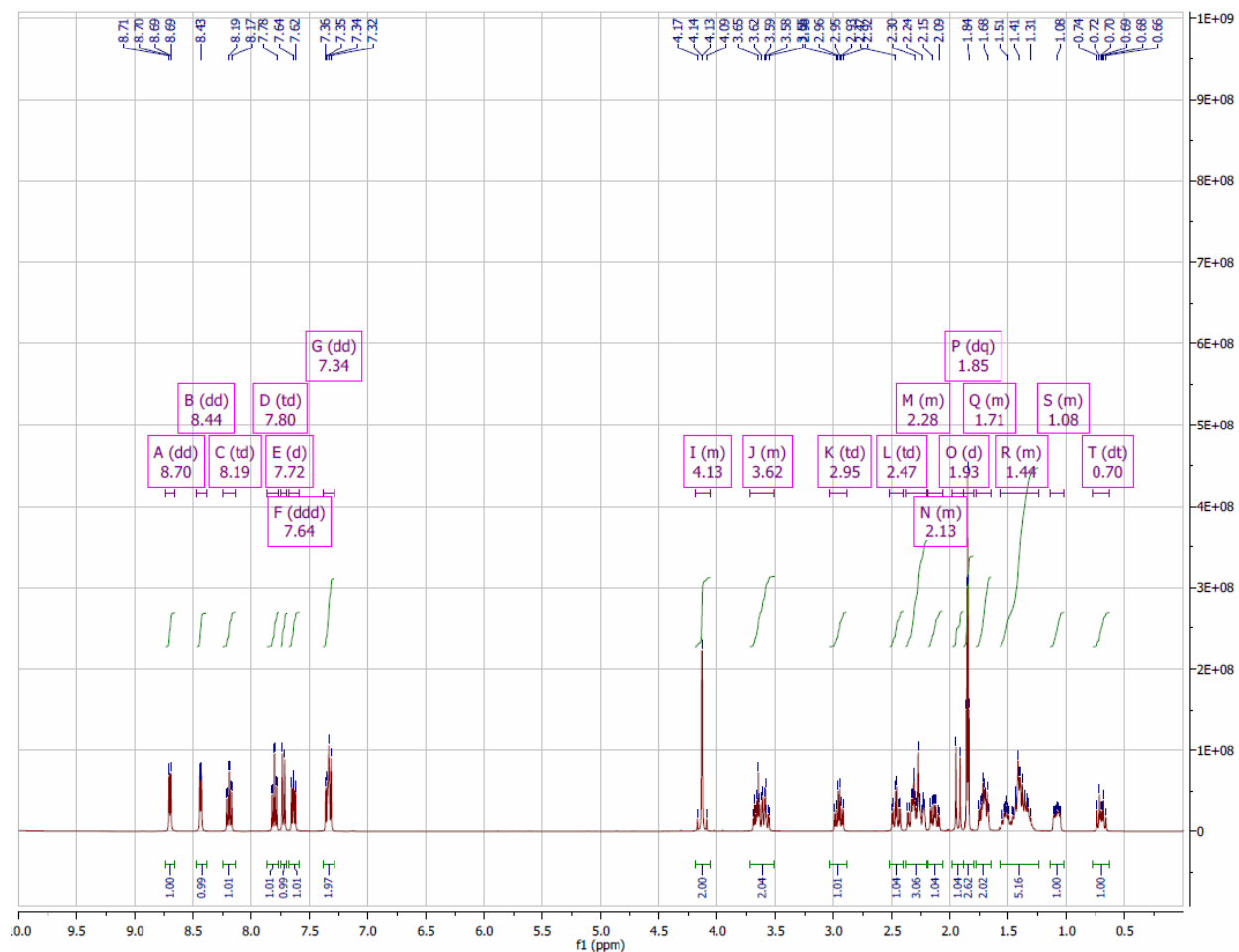


Figure S17.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(Pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyridin-3-ylmethyl)amine ((**R**)-**15**)

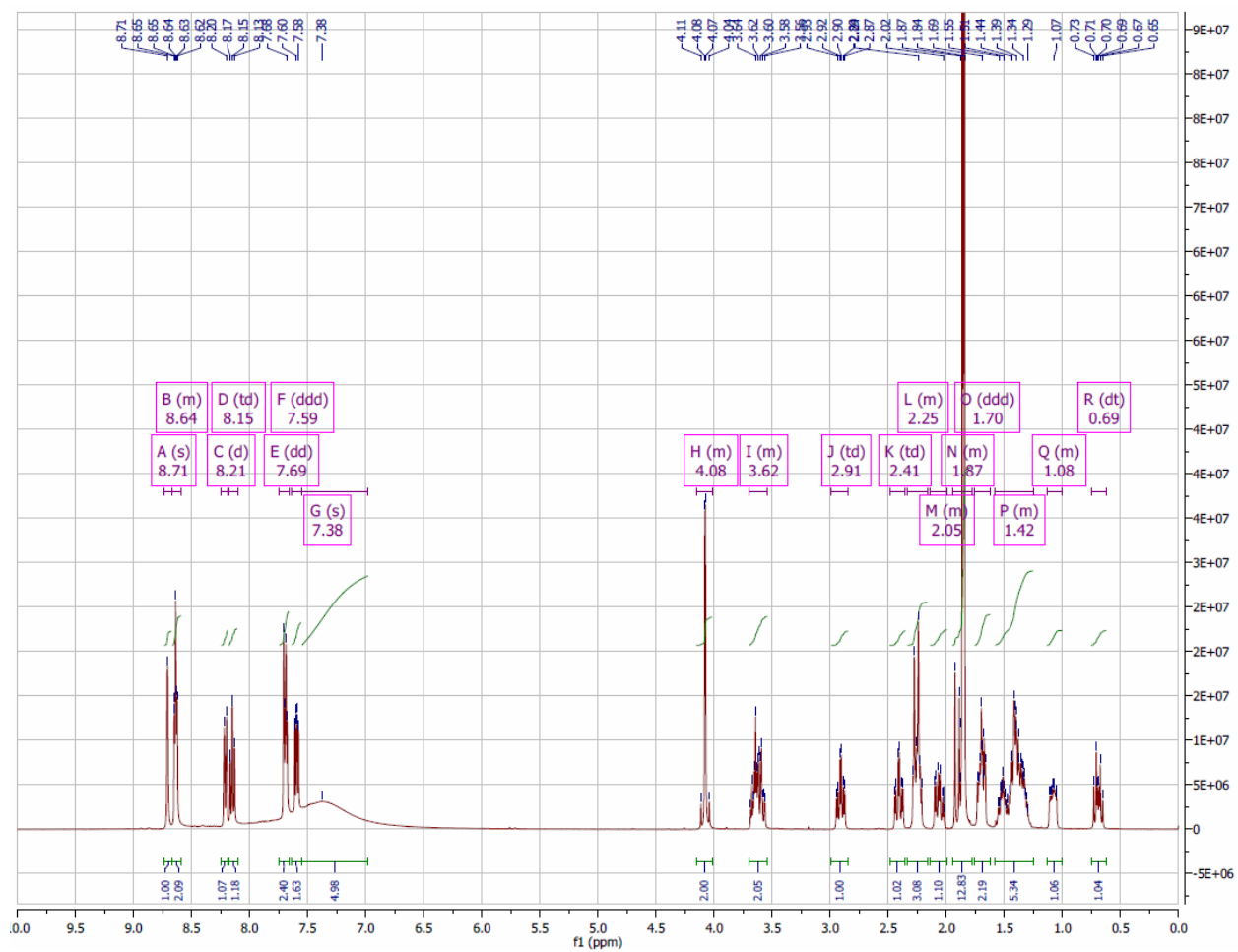


Figure S18.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(Pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyridin-4-ylmethyl)amine ((*R*)-**16**)

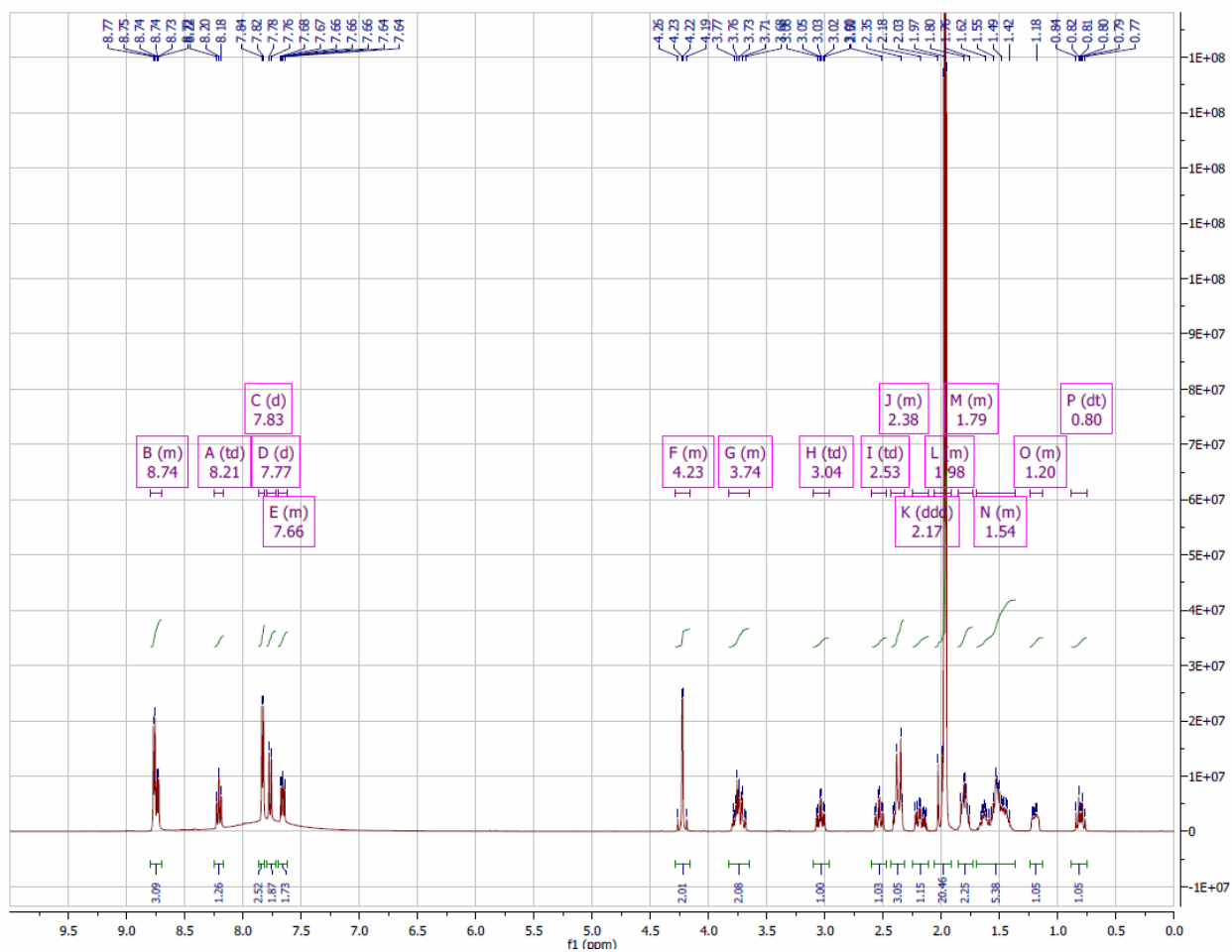


Figure S19.  $^1\text{H}$  NMR of (Pyrazin-2-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((**R**)-**17**)

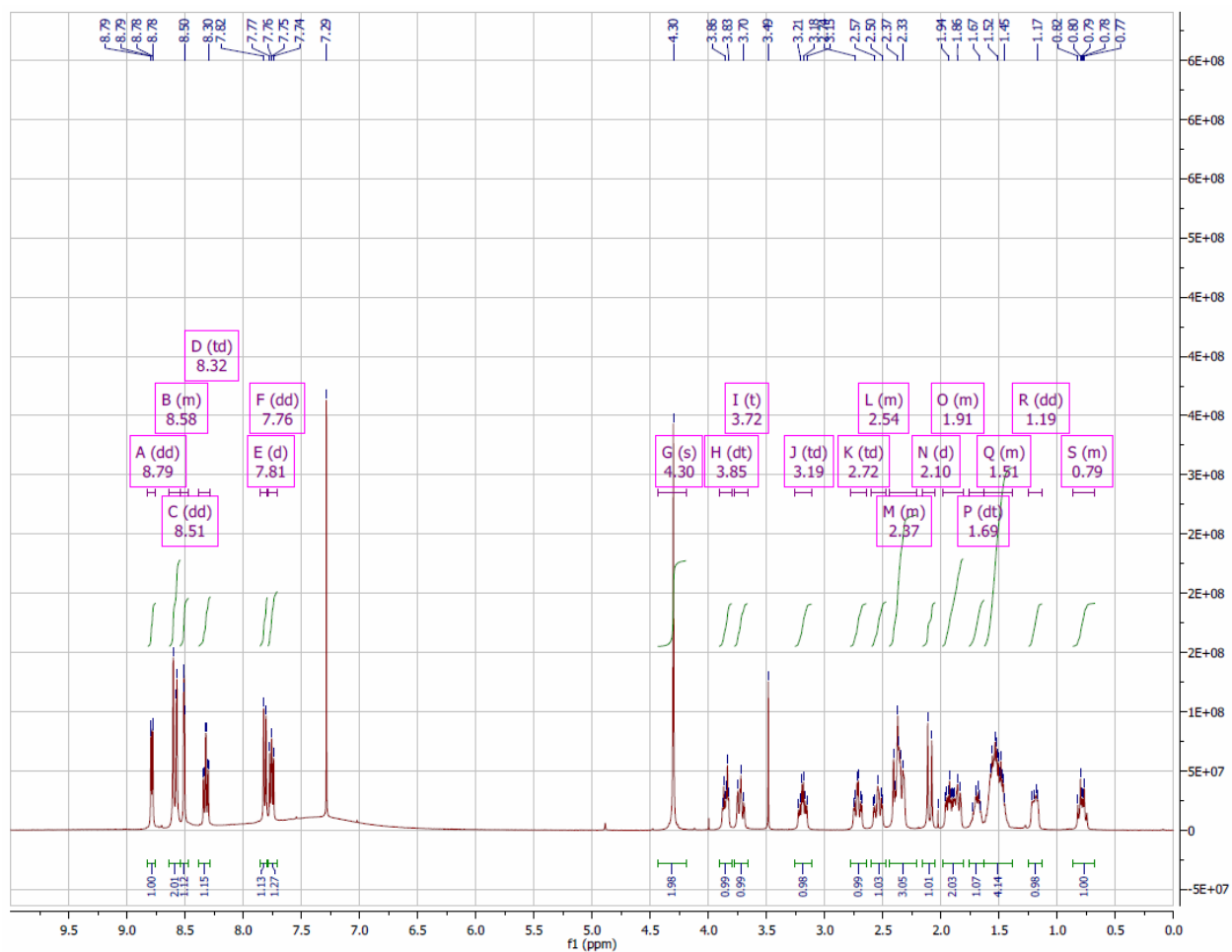


Figure S20.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(Pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyrimidin-4-ylmethyl)amine ((*R*)-**18**)

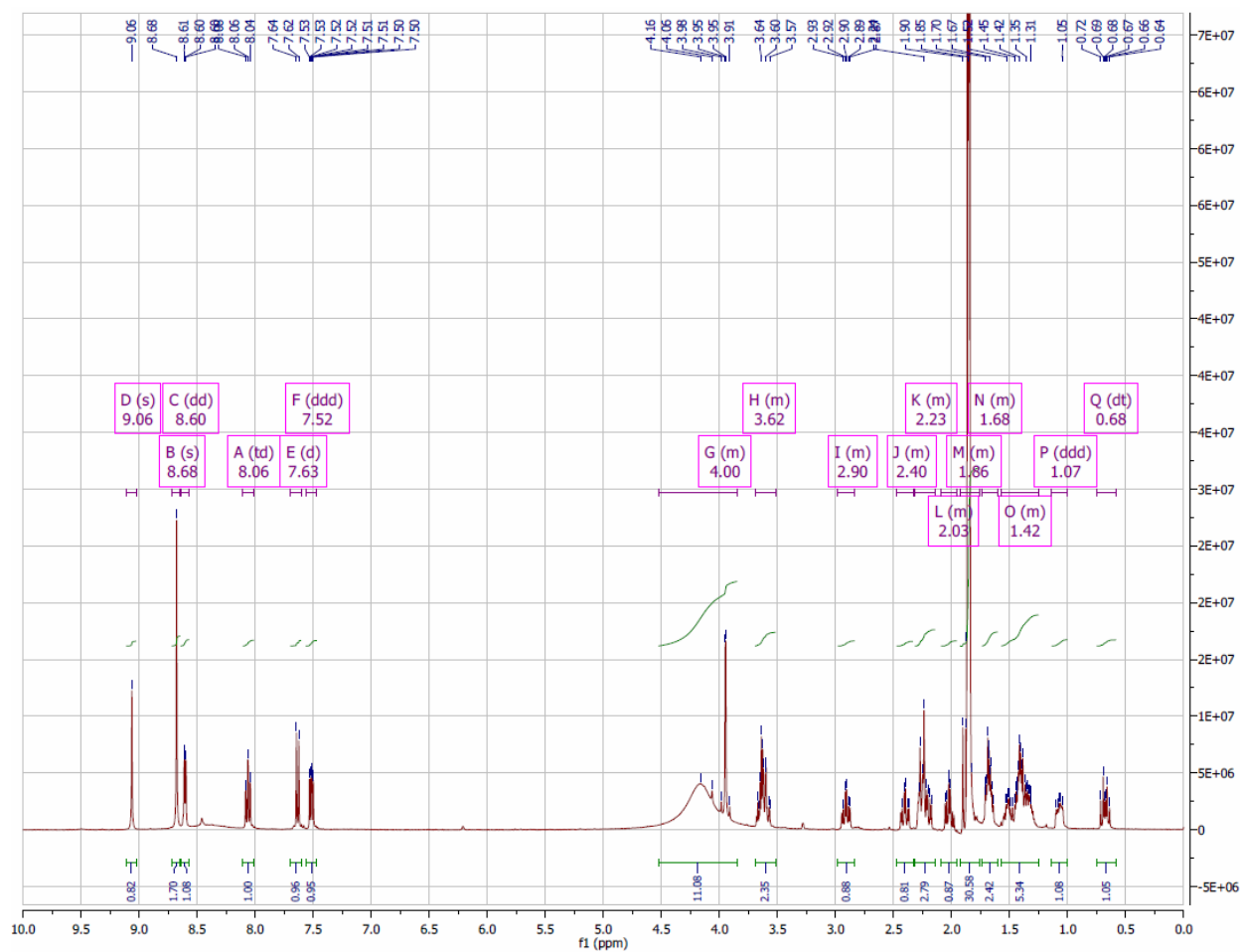


Figure S21.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(Pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine ((*R*)-**19**)

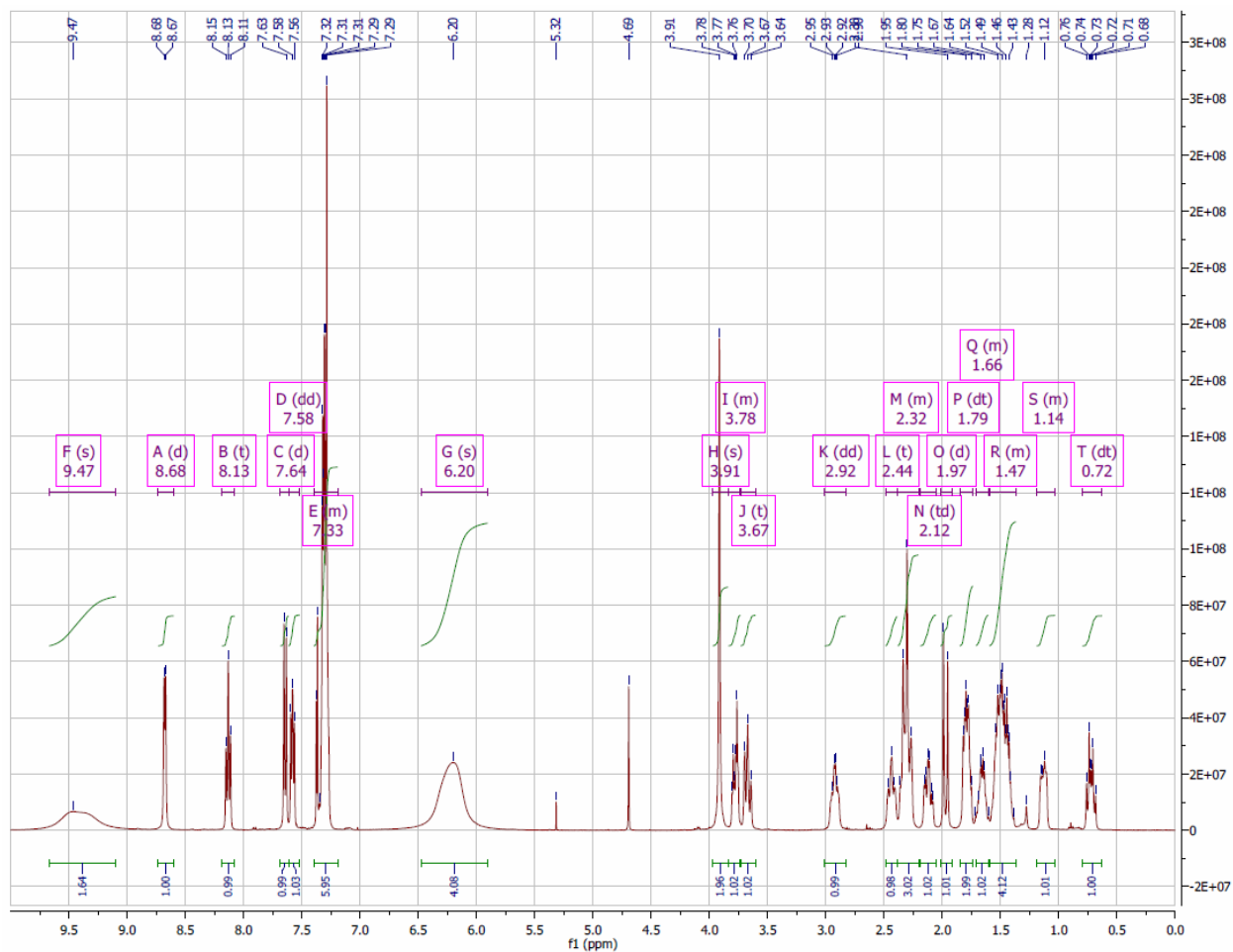




Figure S22.  $^1\text{H}$  NMR of {2-[(9*R*)-9-(Pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-3-ylmethyl)amine ((*R*)-**20**)

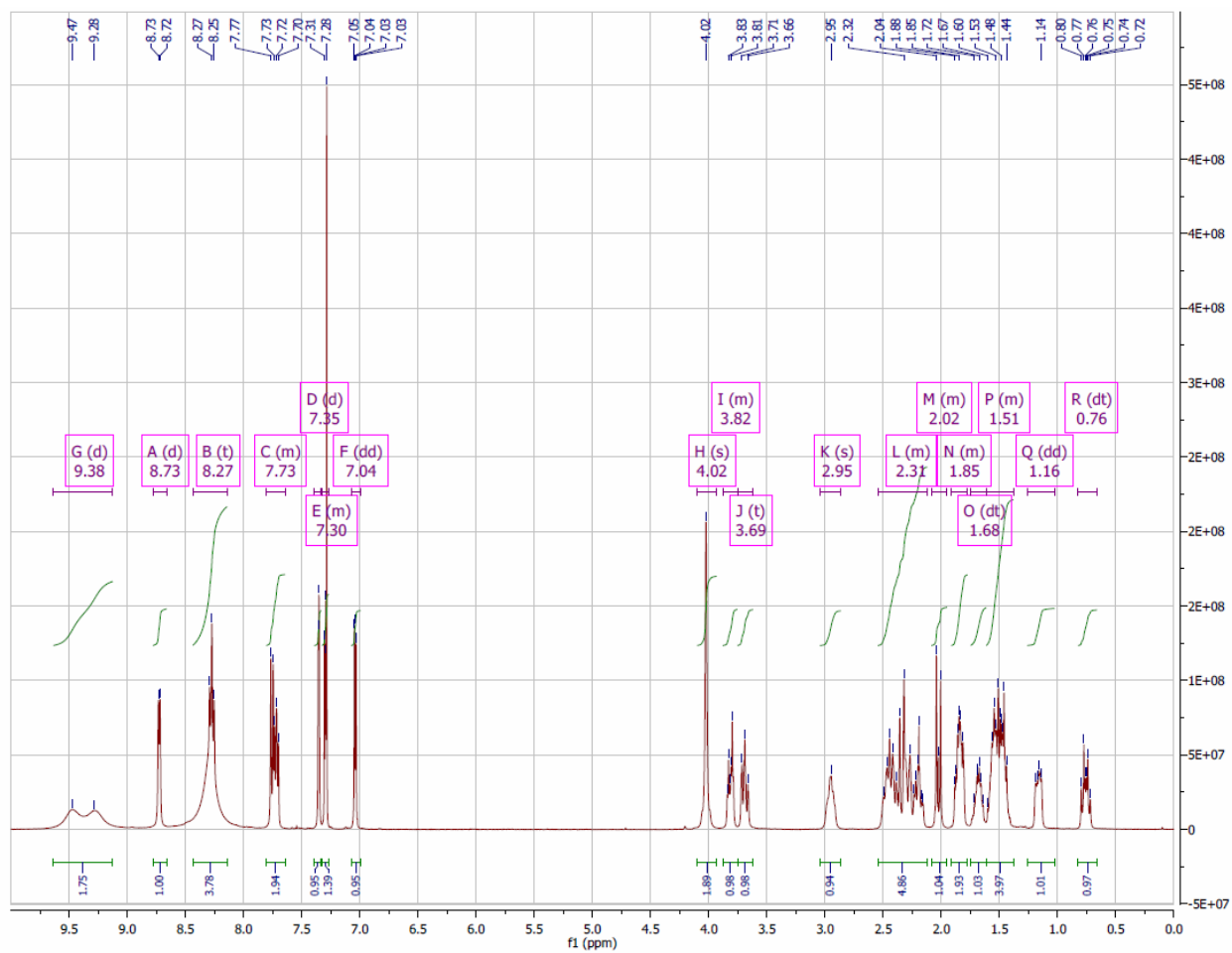


Figure S23. <sup>1</sup>H NMR of (Naphthalen-2-ylmethyl)({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**21**)

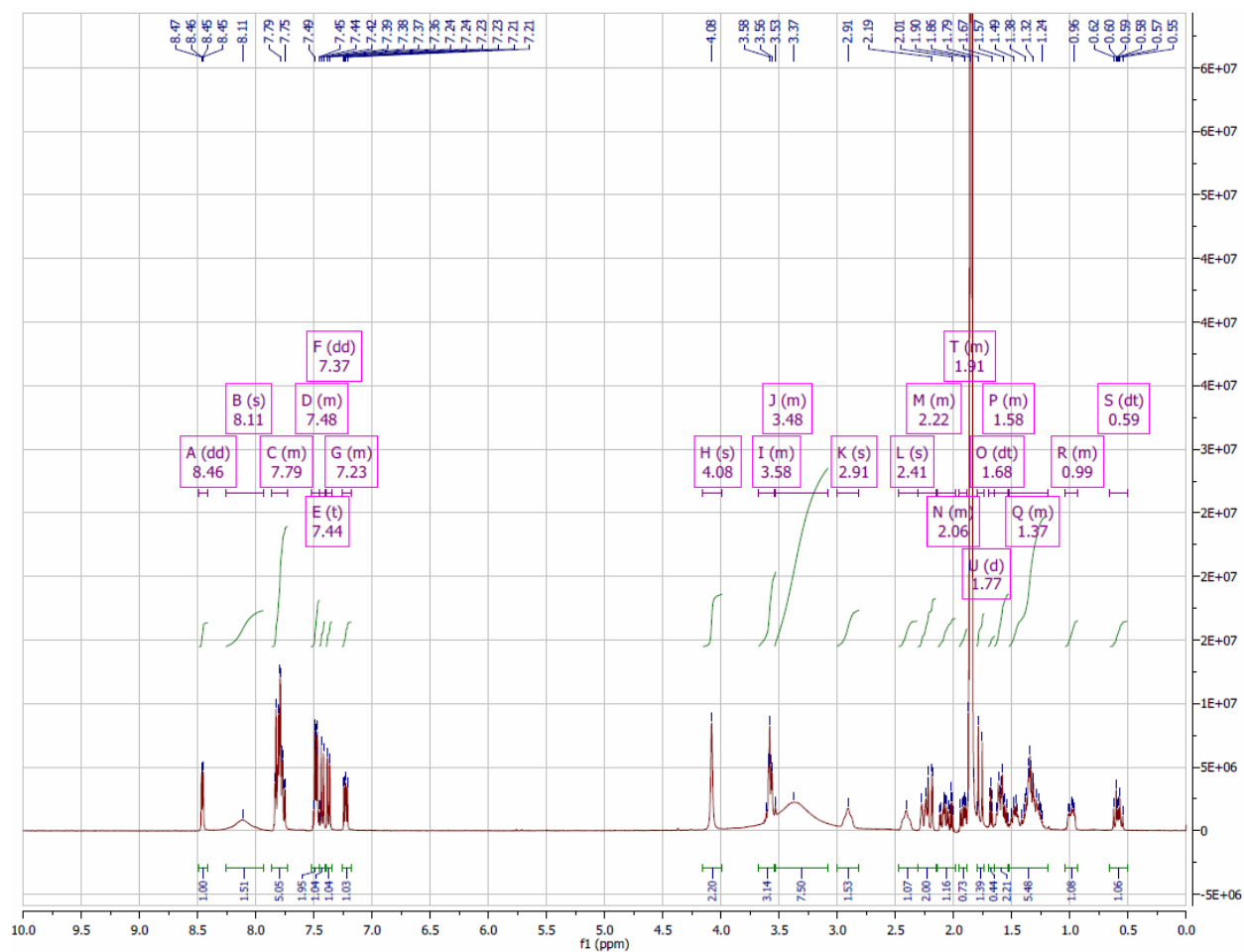


Figure S24.  $^1\text{H}$  NMR of (Cyclopentylmethyl)(2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl)amine ((*R*)-**22**)

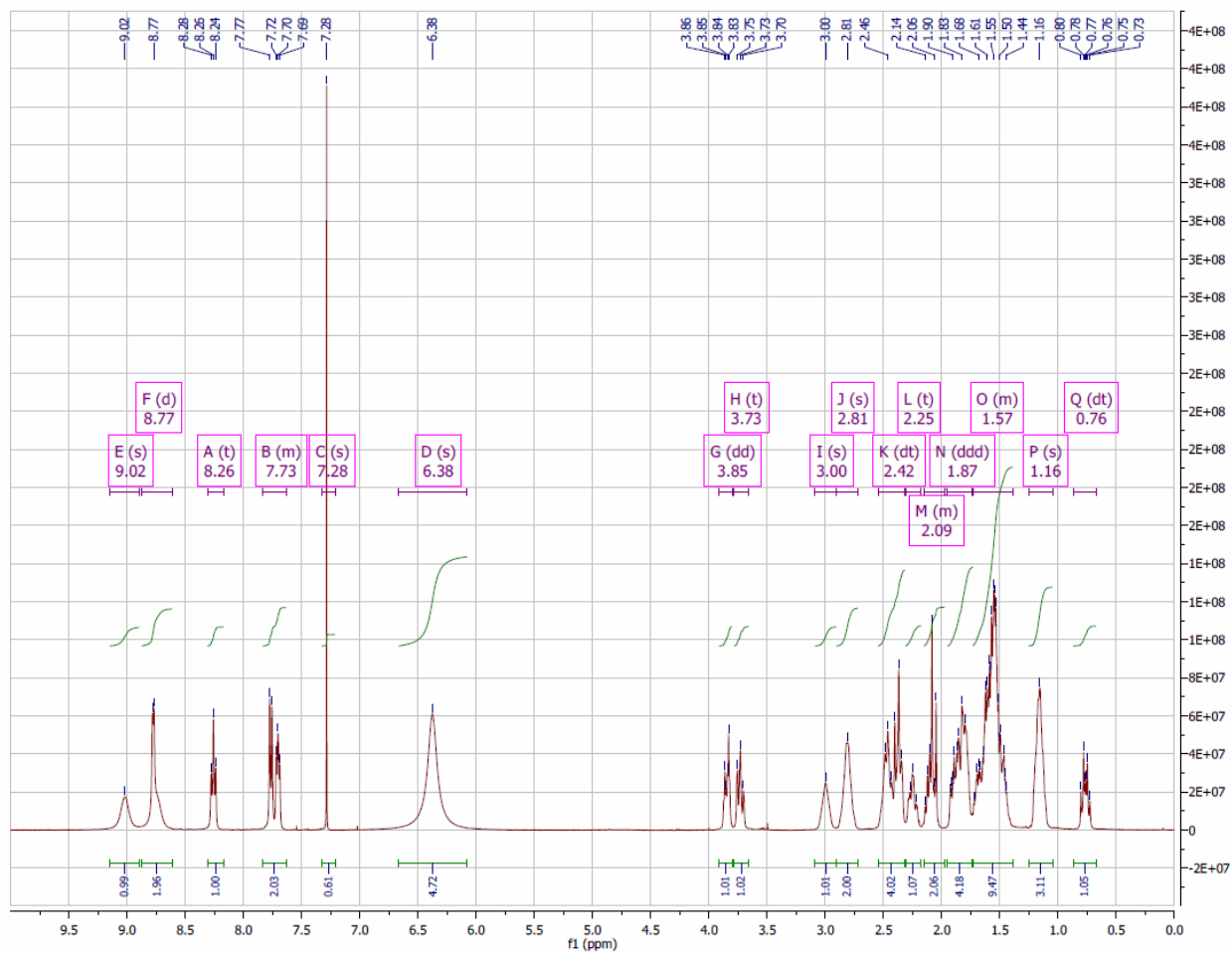


Figure S25.  $^1\text{H}$  NMR of [(3-Methylthiophen-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**23**)

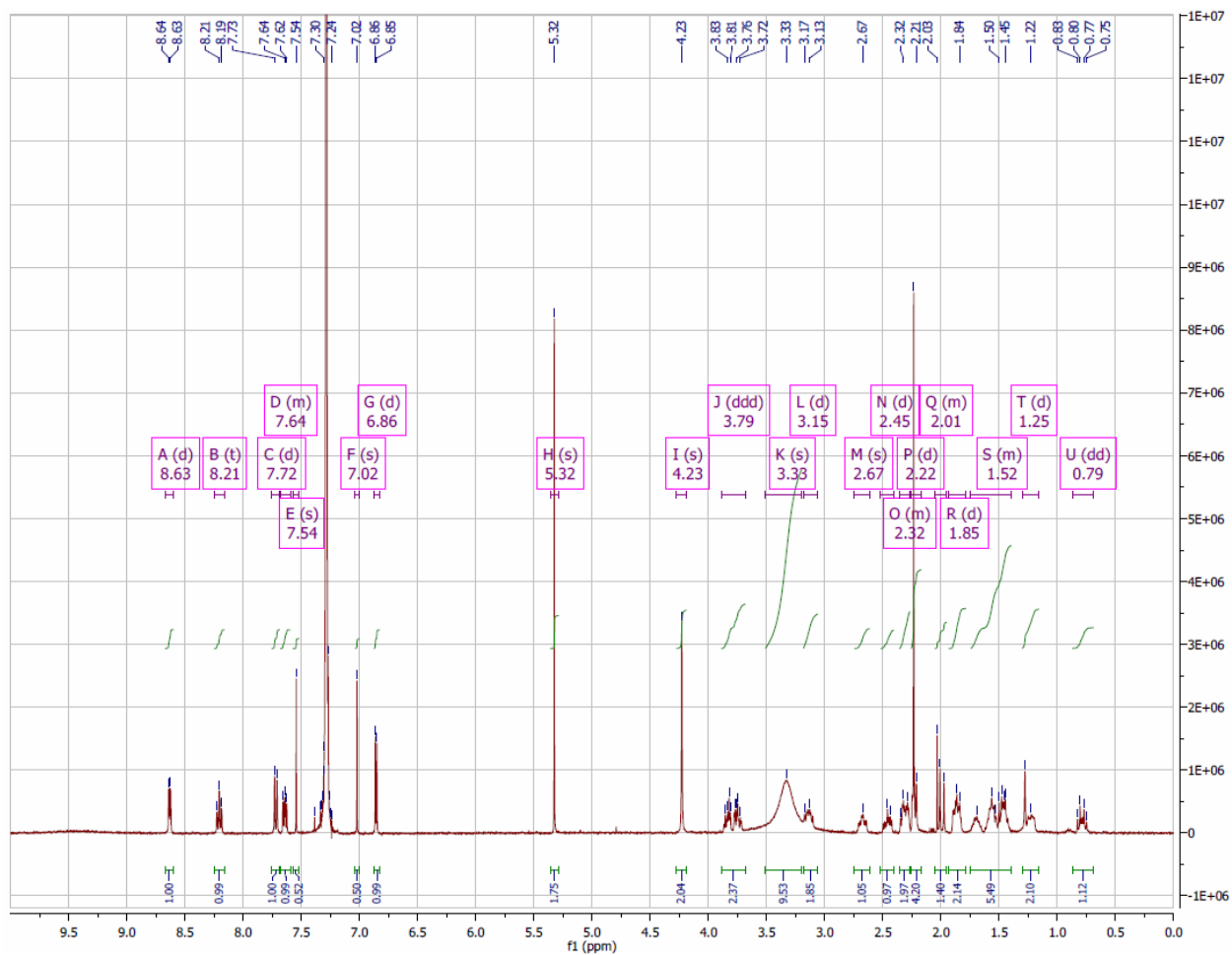


Figure S26.  $^1\text{H}$  NMR of [(4-Methylthiophen-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**24**)



Figure S27.  $^1\text{H}$  NMR of [(5-Methylthiophen-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**25**)

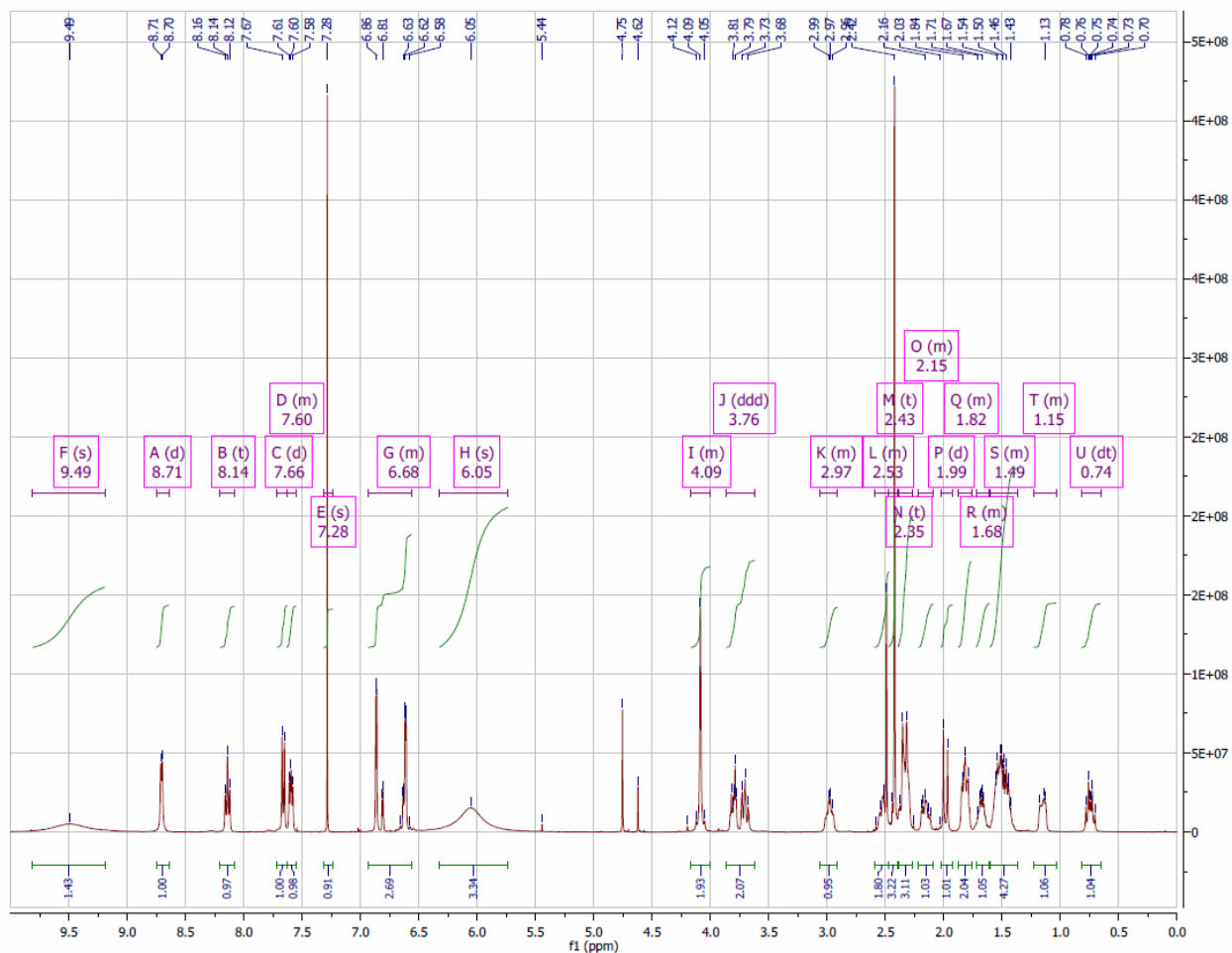


Figure S28.  $^1\text{H}$  NMR of [(5-Methylfuran-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**26**)

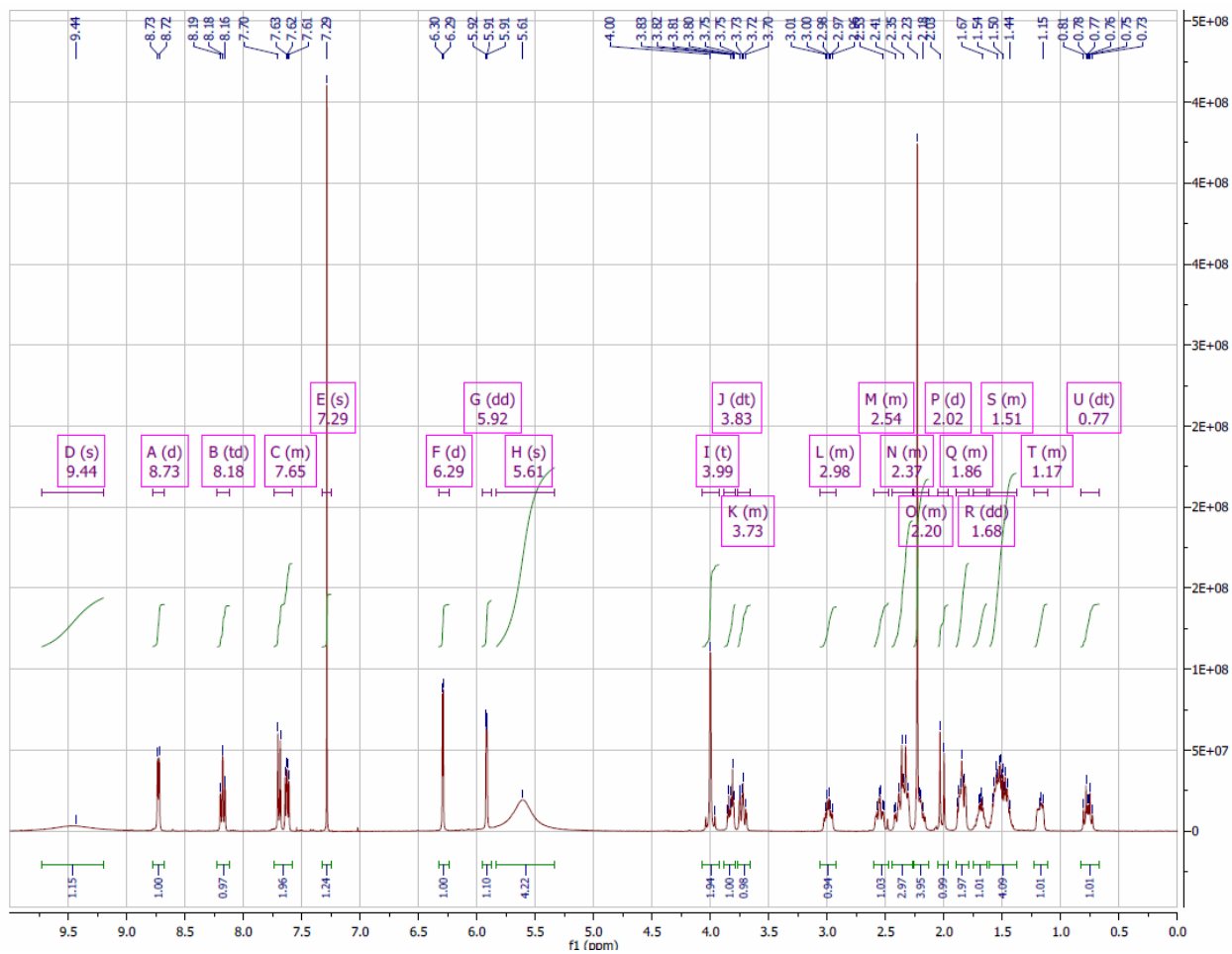


Figure S29.  $^1\text{H}$  NMR of [(3,5-Dimethylthiophen-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**27**)

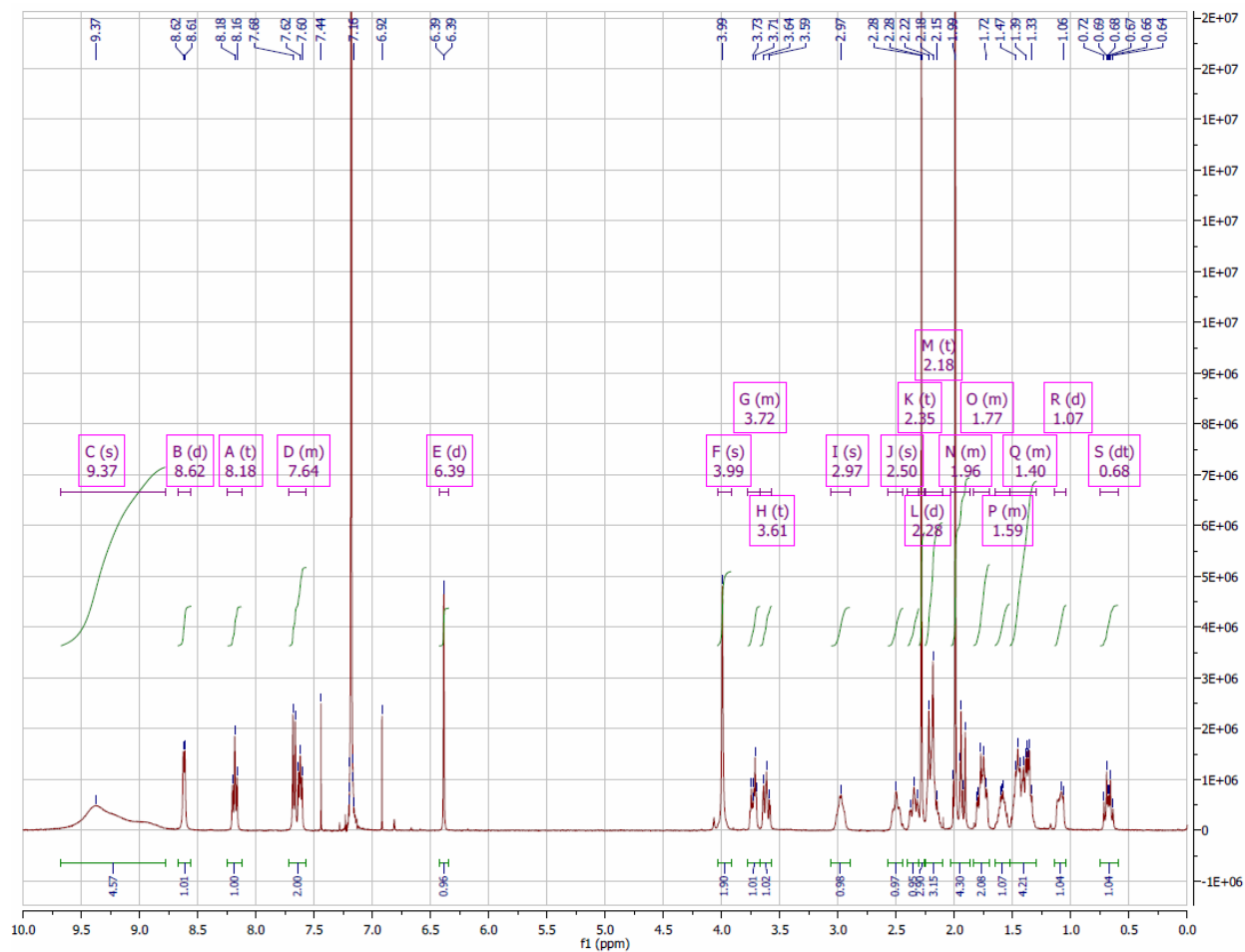




Figure S30.  $^1\text{H}$  NMR of [(4,5-Dimethylthiophen-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**28**)

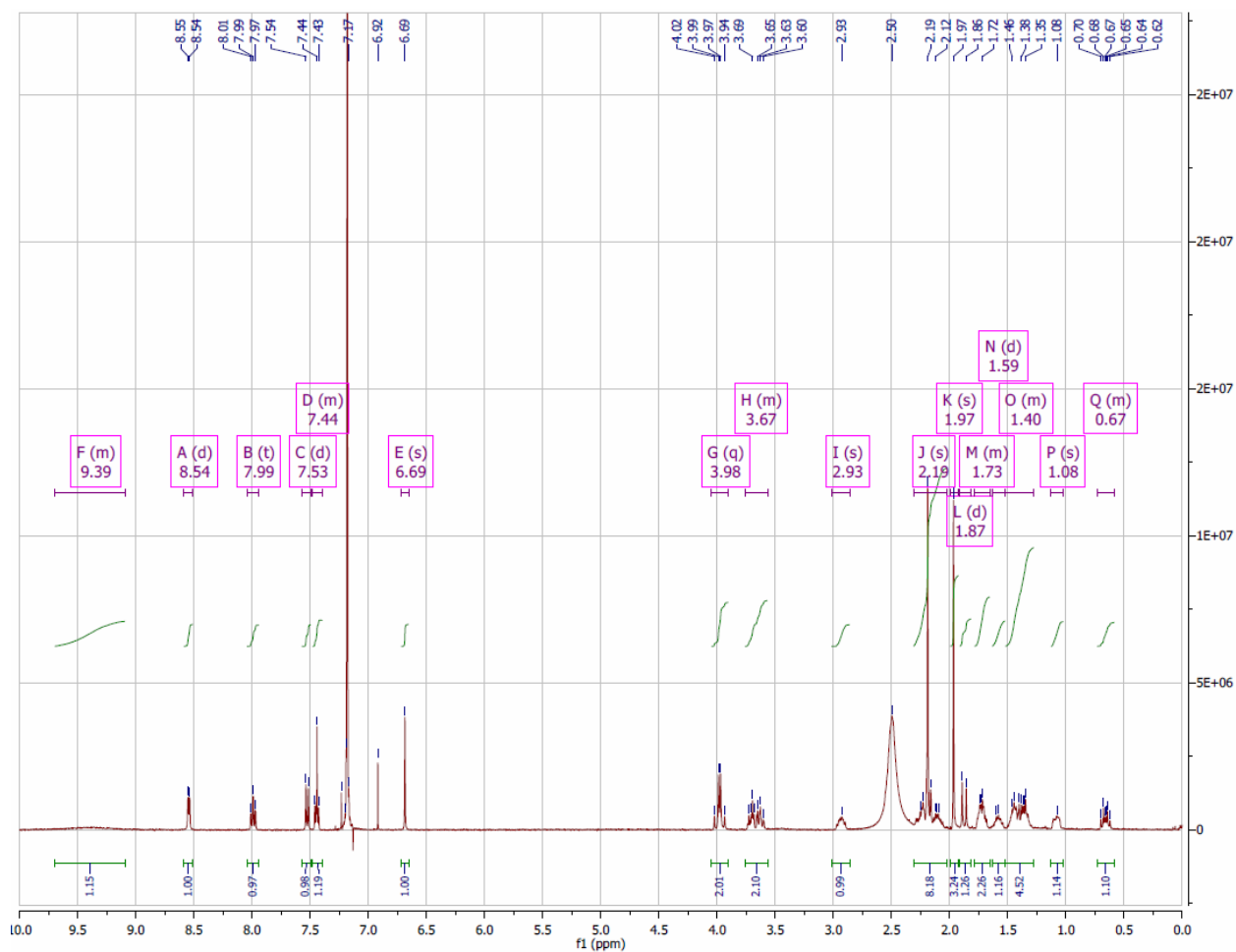


Figure S31.  $^1\text{H}$  NMR of [(4,5-Dimethylfuran-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**29**)

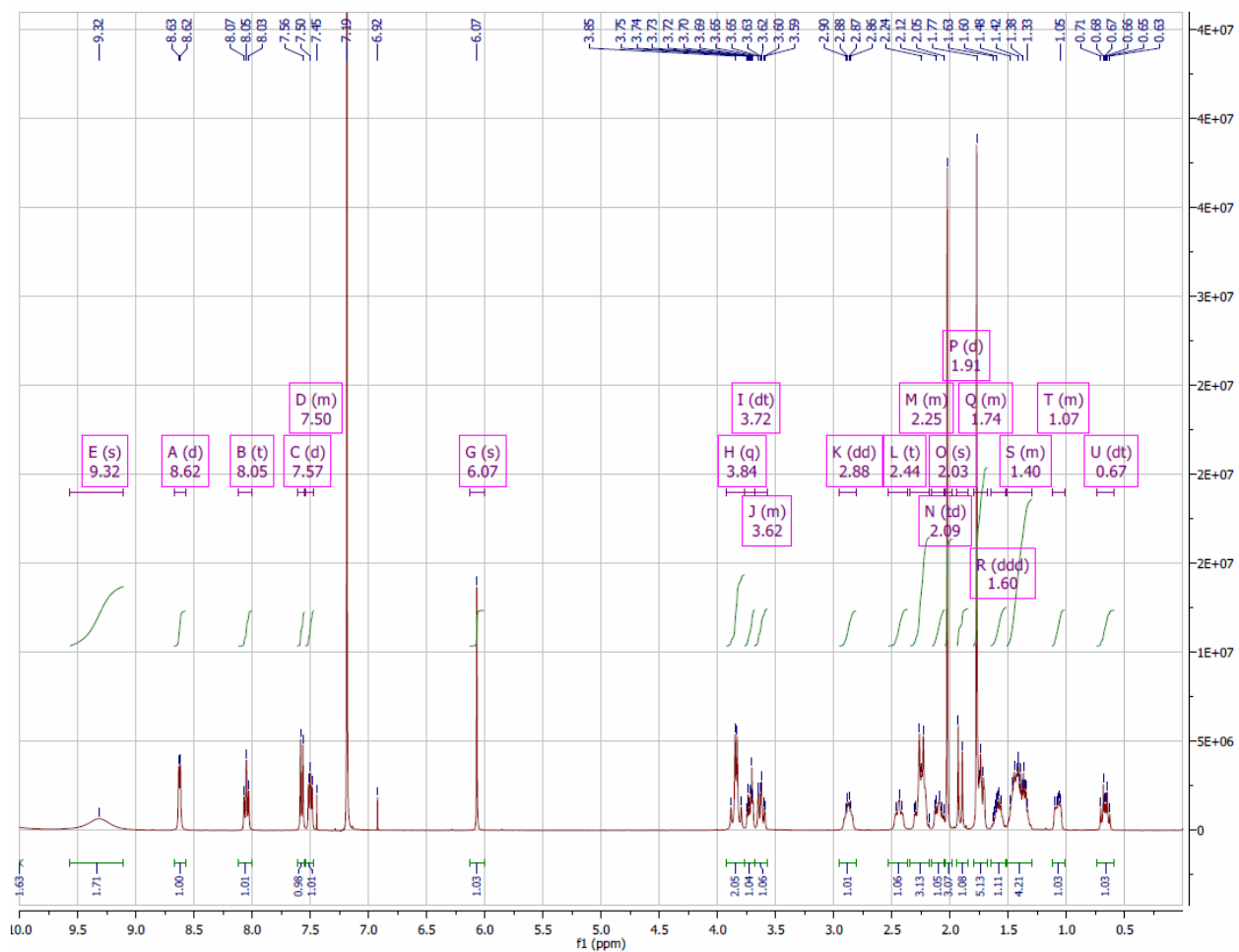


Figure S32.  $^1\text{H}$  NMR of [(3-Methoxythiophen-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine ((*R*)-**30**)

