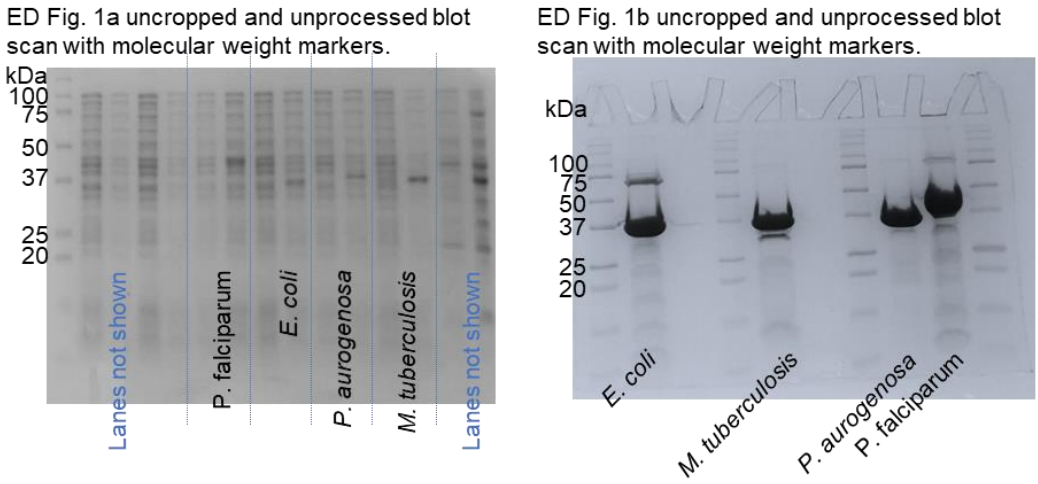
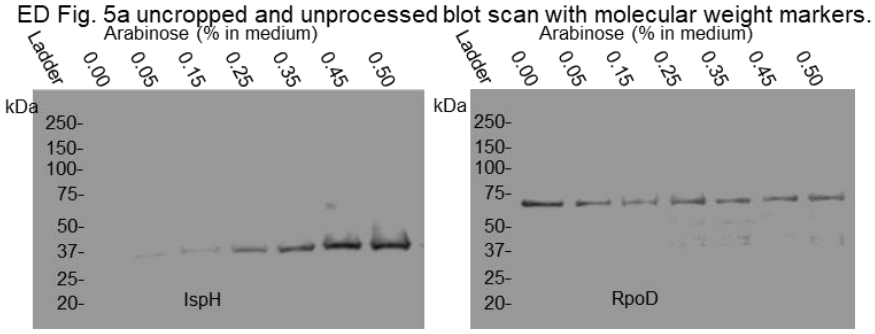
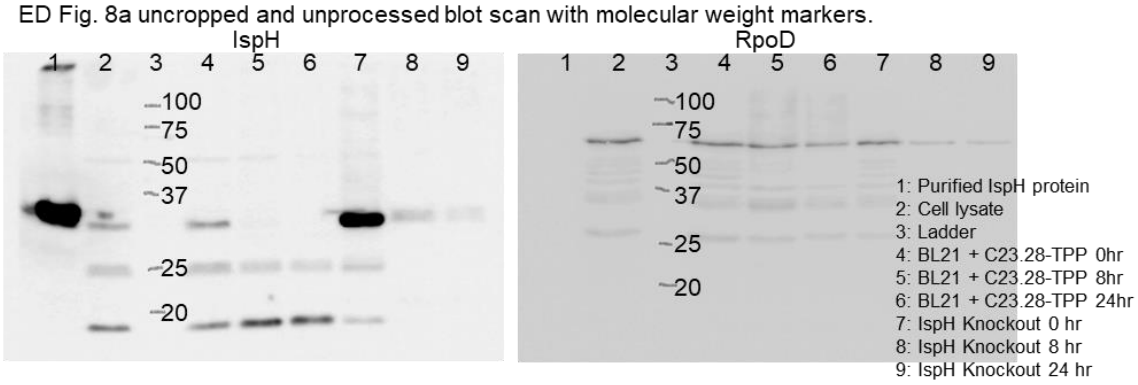
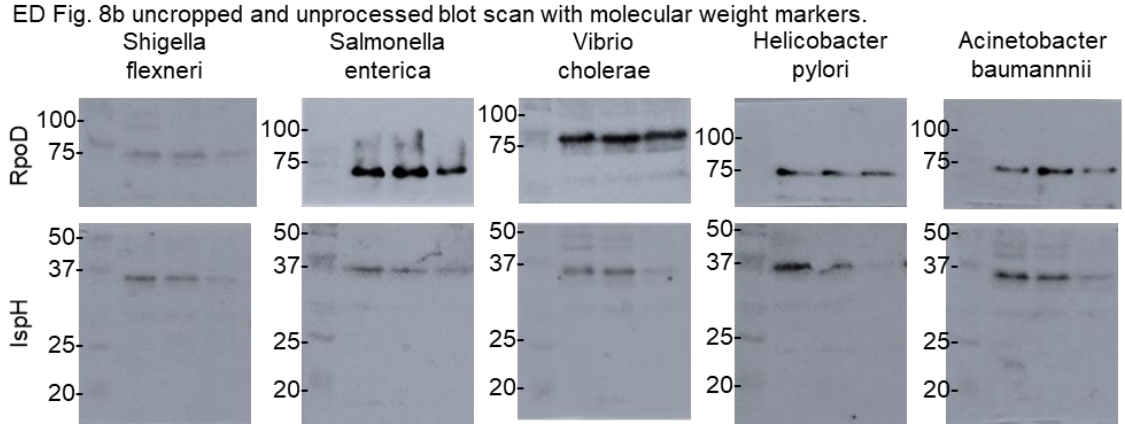


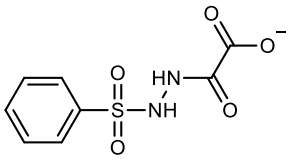






Supplementary Figure 1: Uncropped gel and blot images with molecular weight markers.

a Top 24 IspH inhibitors from molecular docking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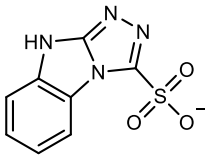
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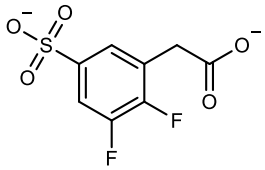
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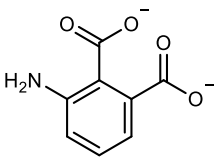
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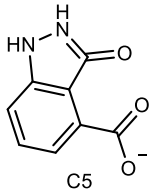
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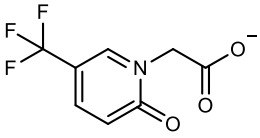
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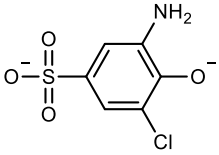
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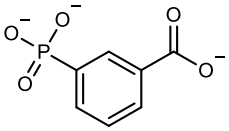
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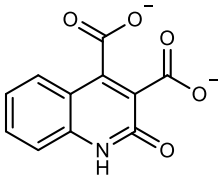
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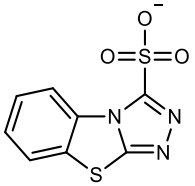
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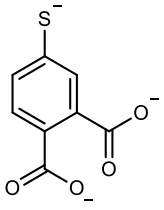
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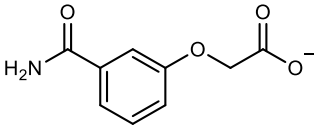
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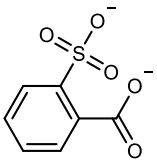
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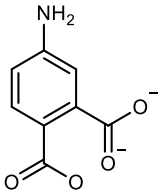
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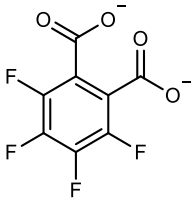
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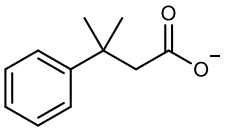
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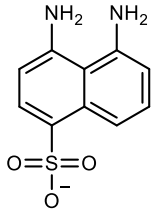
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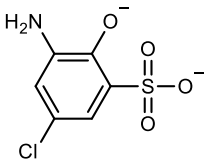
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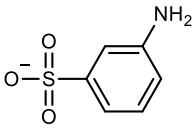
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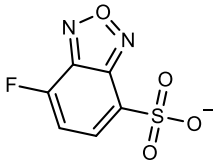
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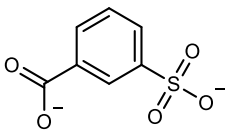
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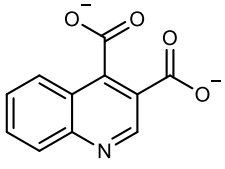
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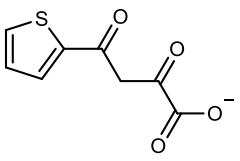
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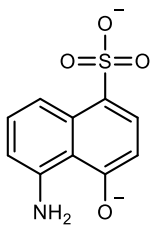
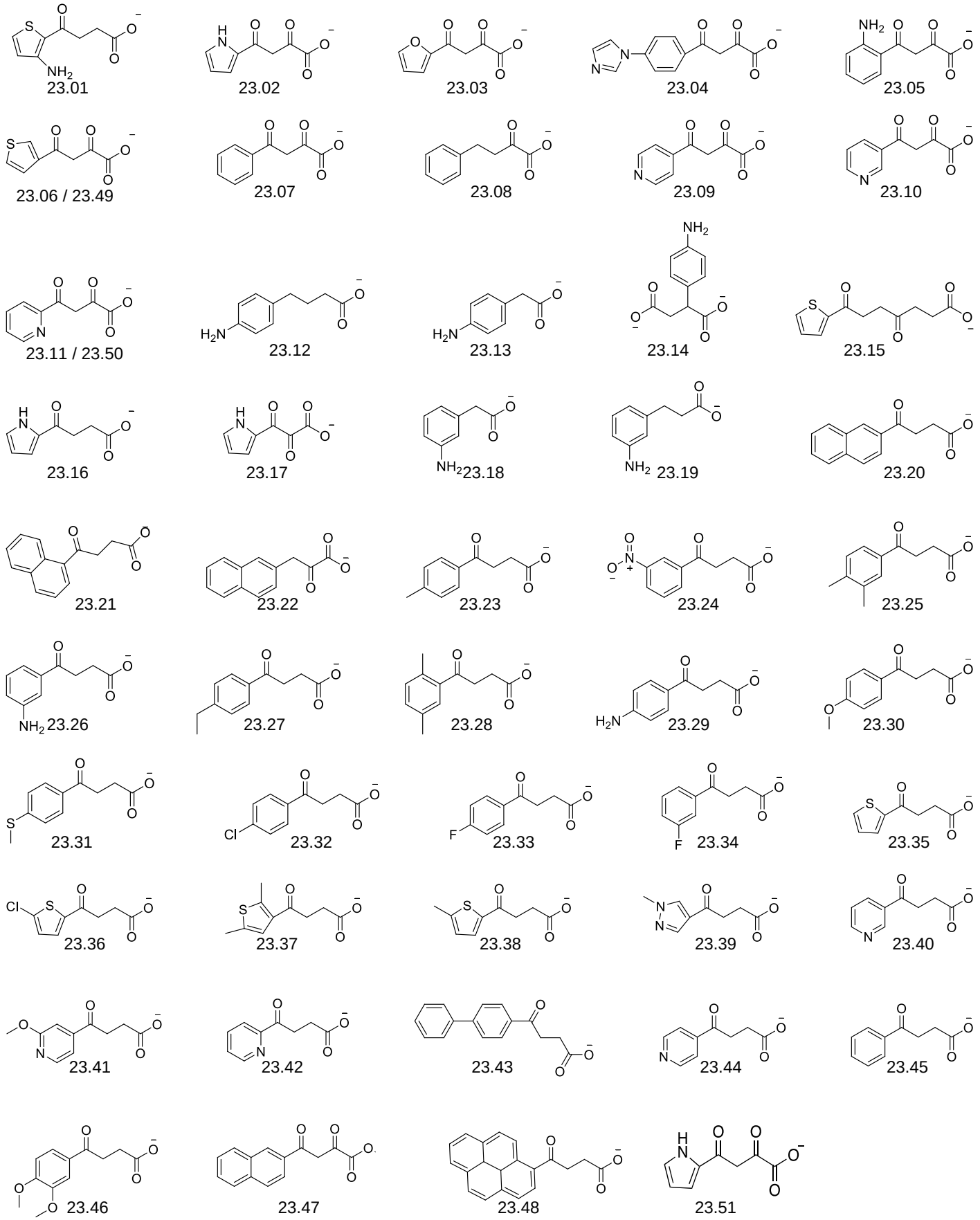
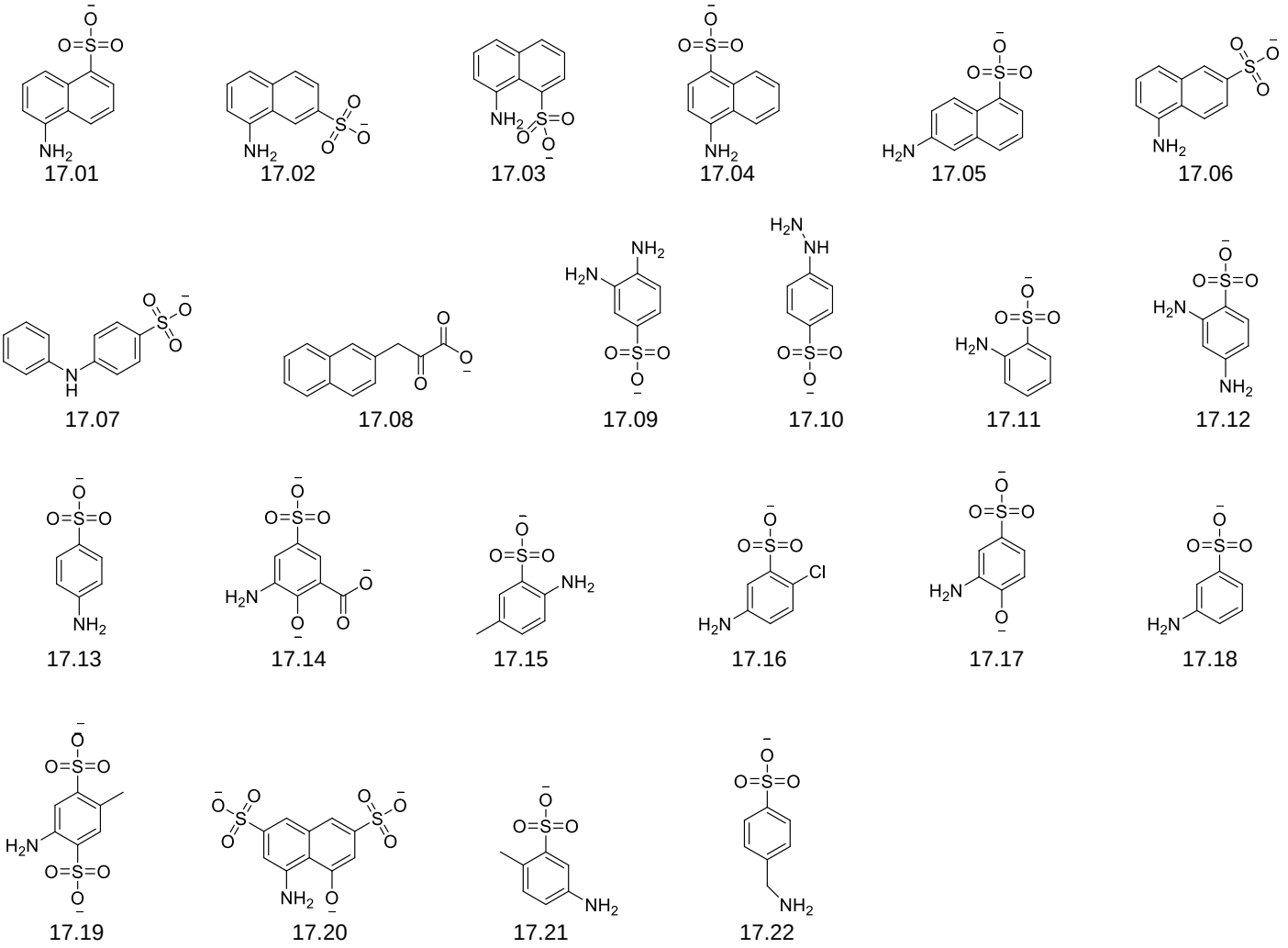

C24

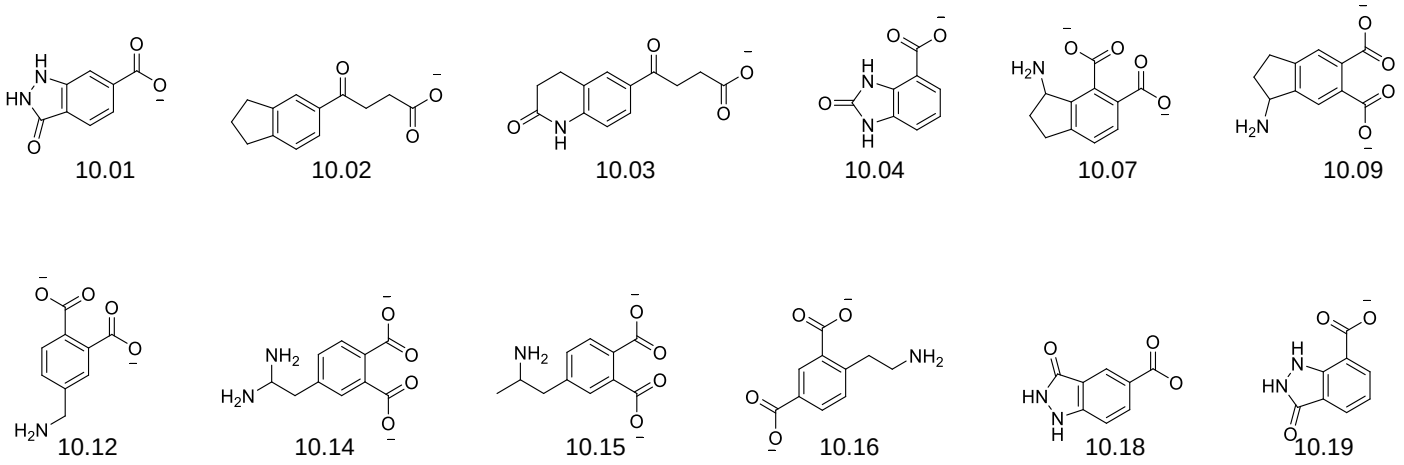
b C23 analogs



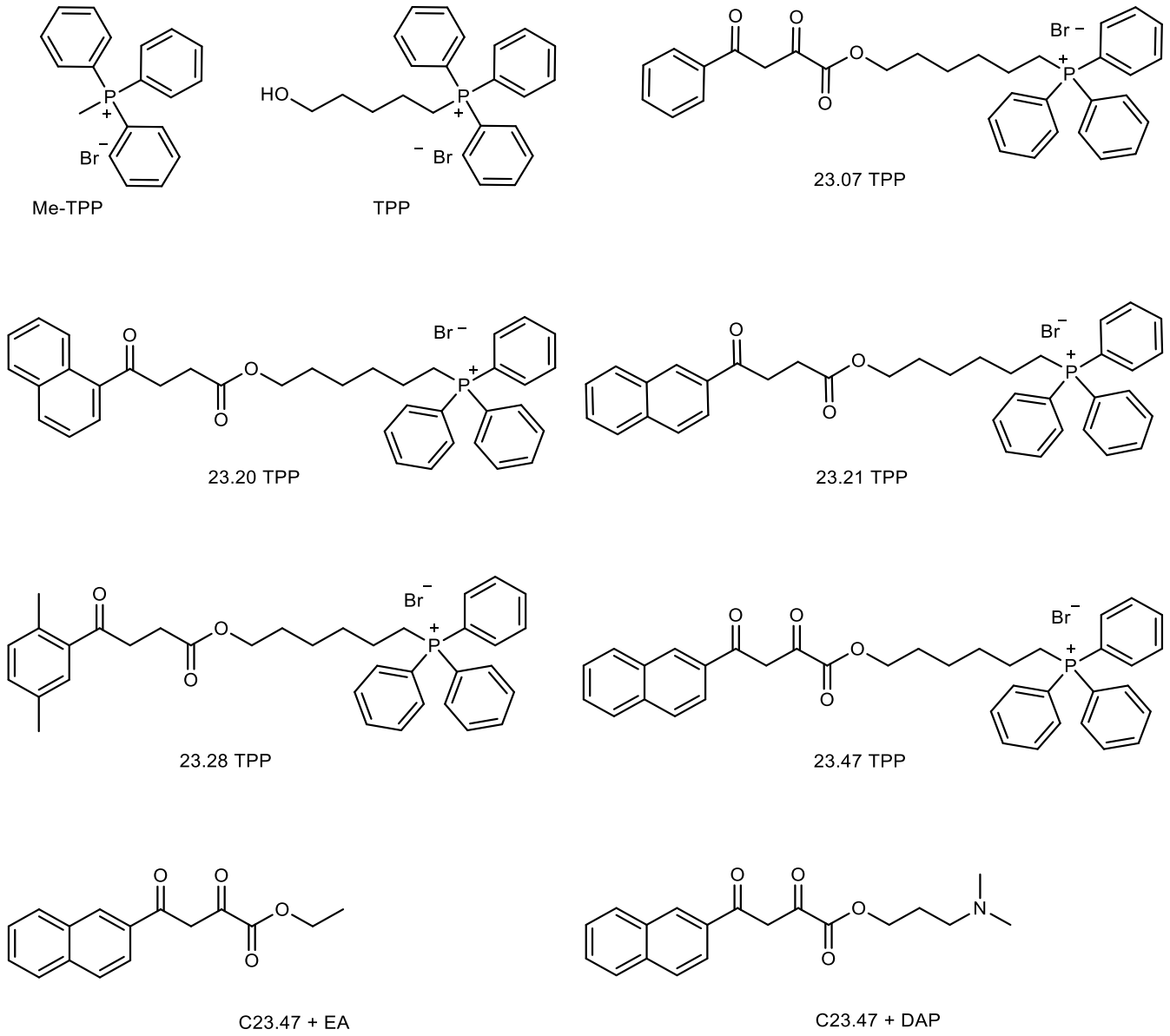
c C17 analogs



d C10 analogs



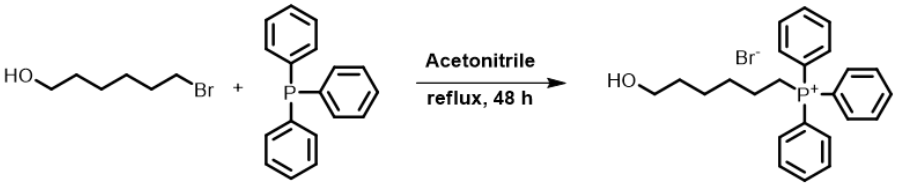
e TPP carrier and prodrugs

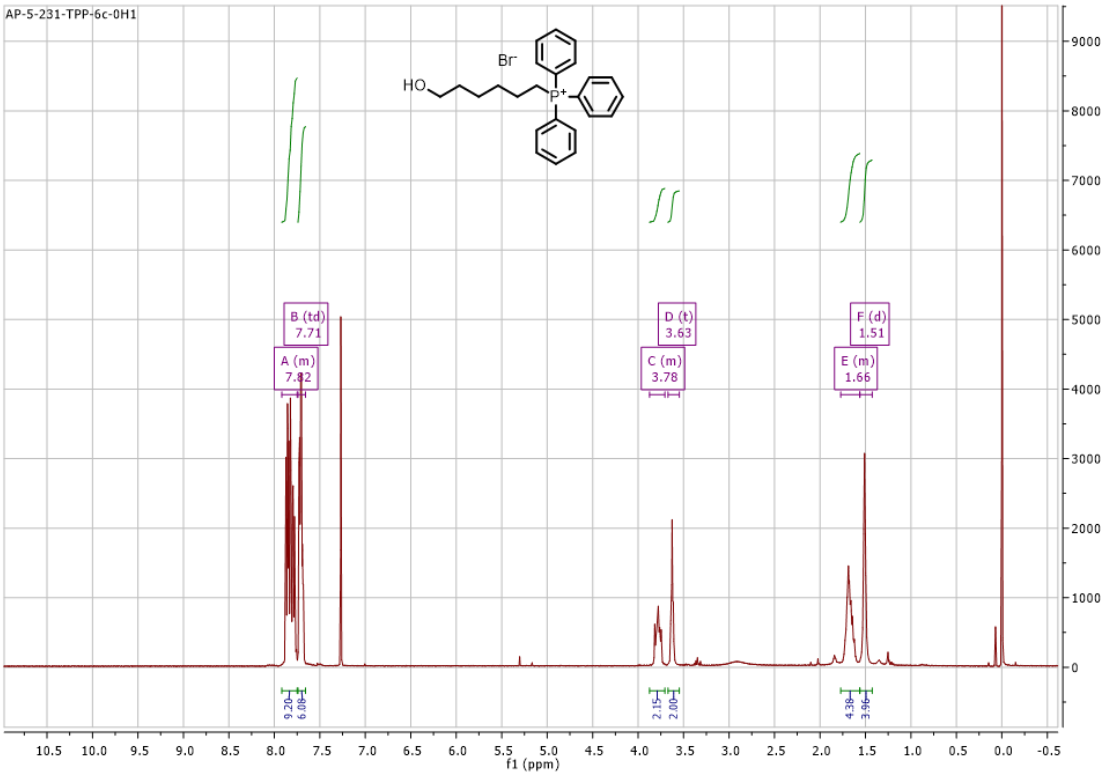


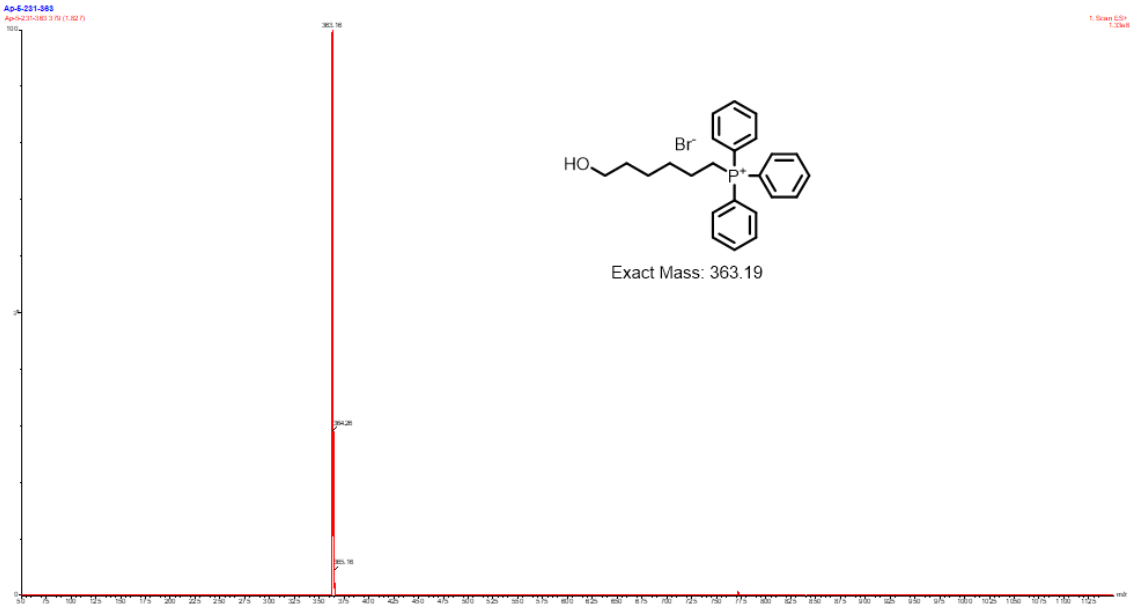
Supplementary Figure 2: Chemical structures of analogs, carriers and prodrugs. a, Chemical structures of C1-24, the top 24 candidate IspH inhibitors from molecular docking (Extended Data Fig. 3a). Chemical structures of analogs of **b,** C23, **c,** C17 and **d,** C10 tested for their inhibitory activity on Ec-IspH (Fig. 2d, and Extended Data Fig 3c-e). **e,** Structures of prodrugs and TPP carrier molecules (Fig 2e and Extended Data Fig. 4c & 5d)

a

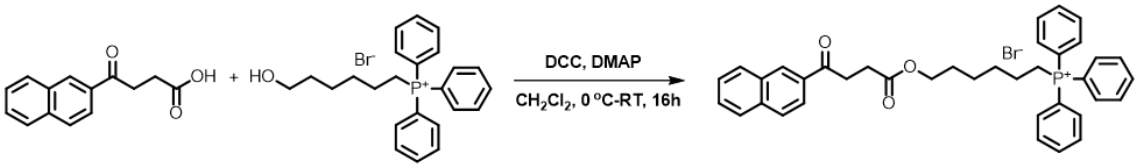
(6-Hydroxyhexyl)triphenylphosphonium bromide synthesis, NMR & Mass:

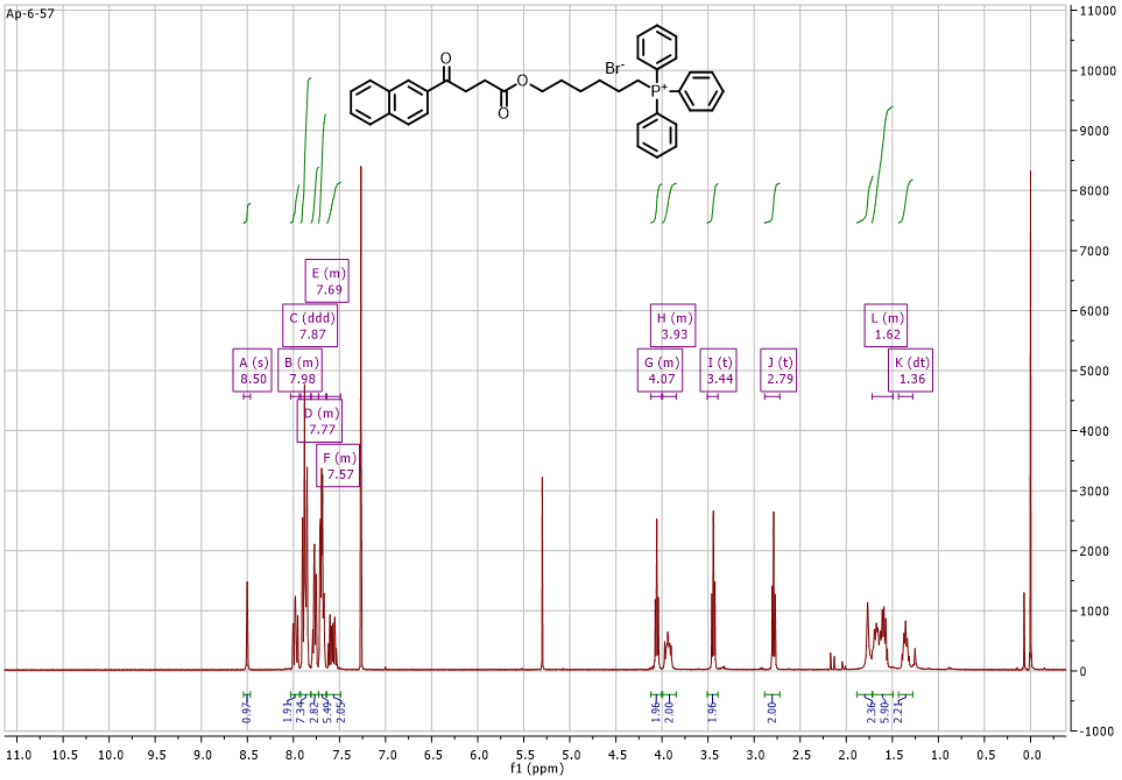


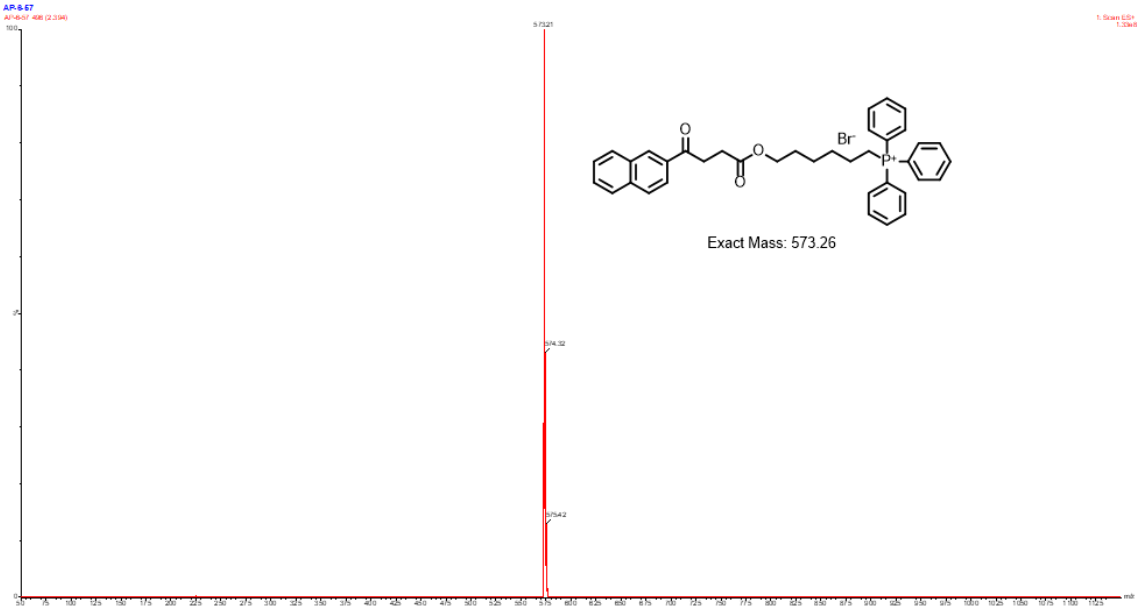




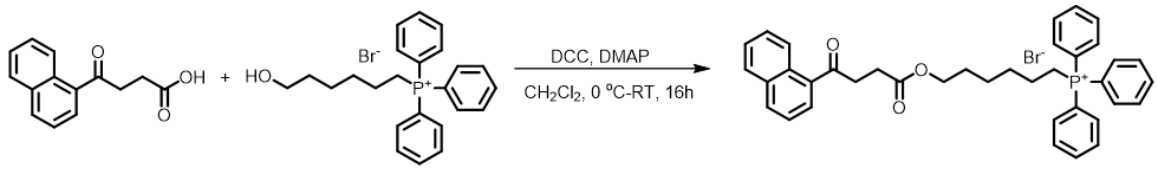
b (6-(4-(Naphthalen-2-yl)-4-oxobutanoyloxy)hexyl)triphenylphosphonium bromide synthesis, NMR & Mass:

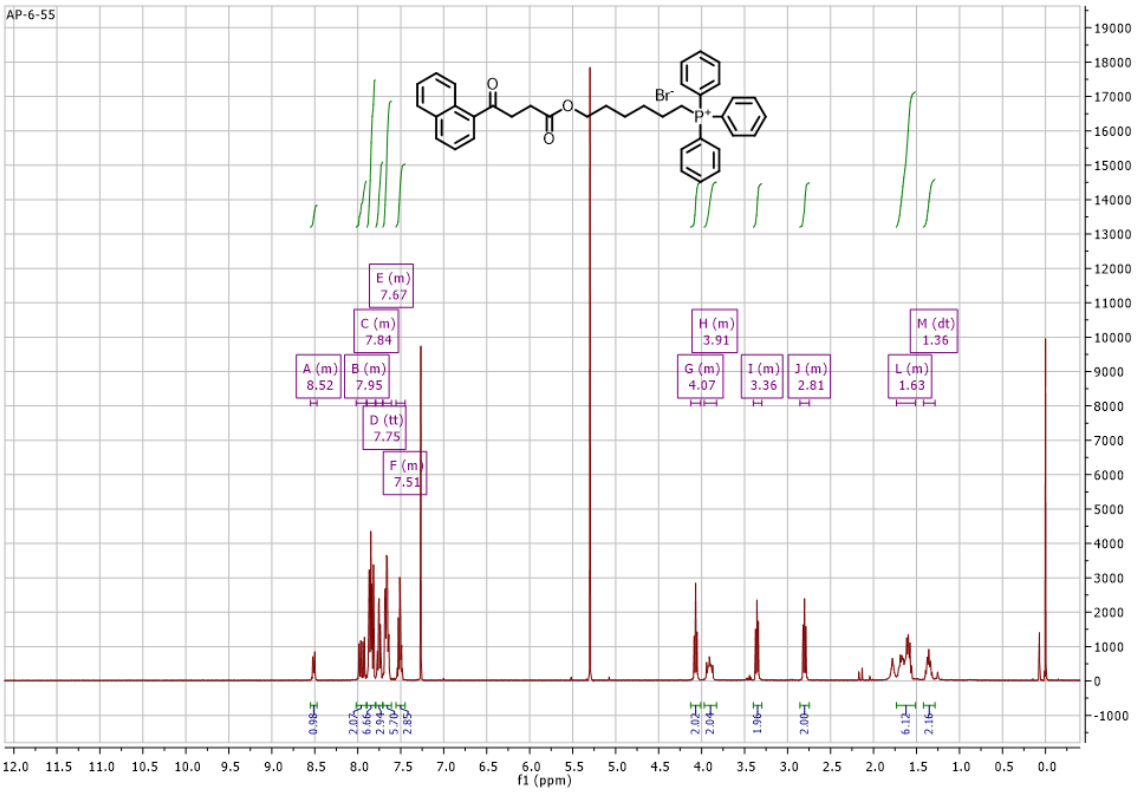


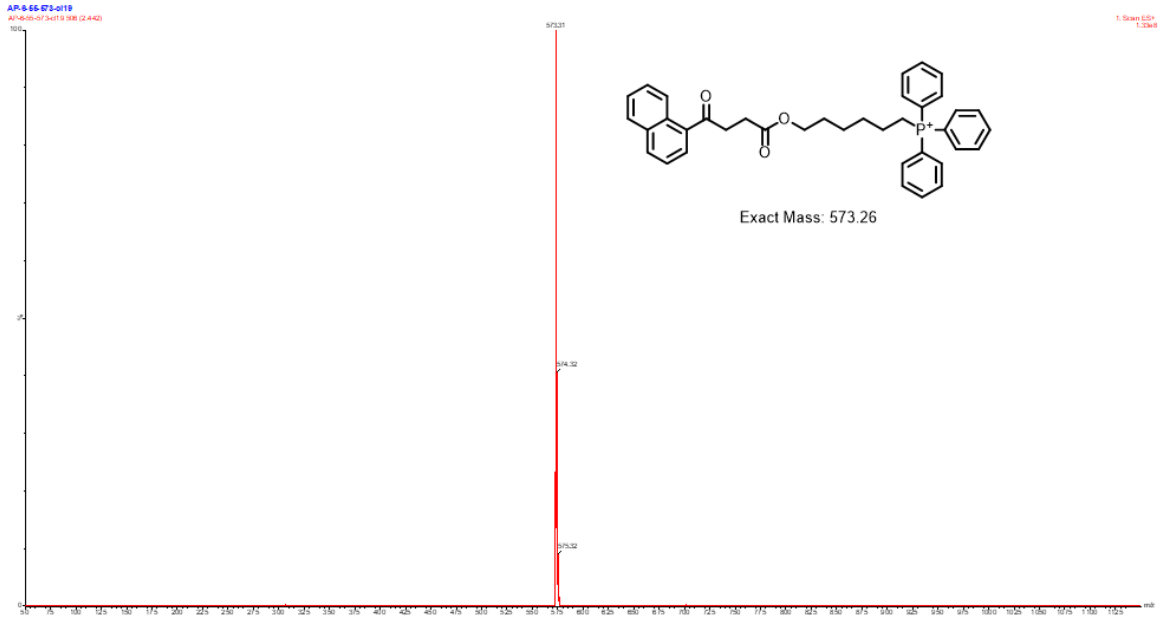




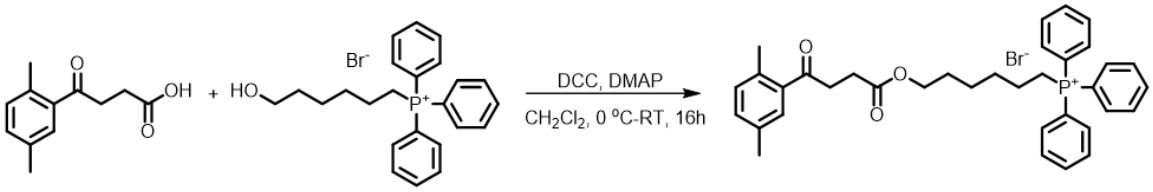
c (6-(4-(Naphthalen-1-yl)-4-oxobutanoyloxy)hexyl)triphenylphosphonium bromide synthesis, NMR & Mass:

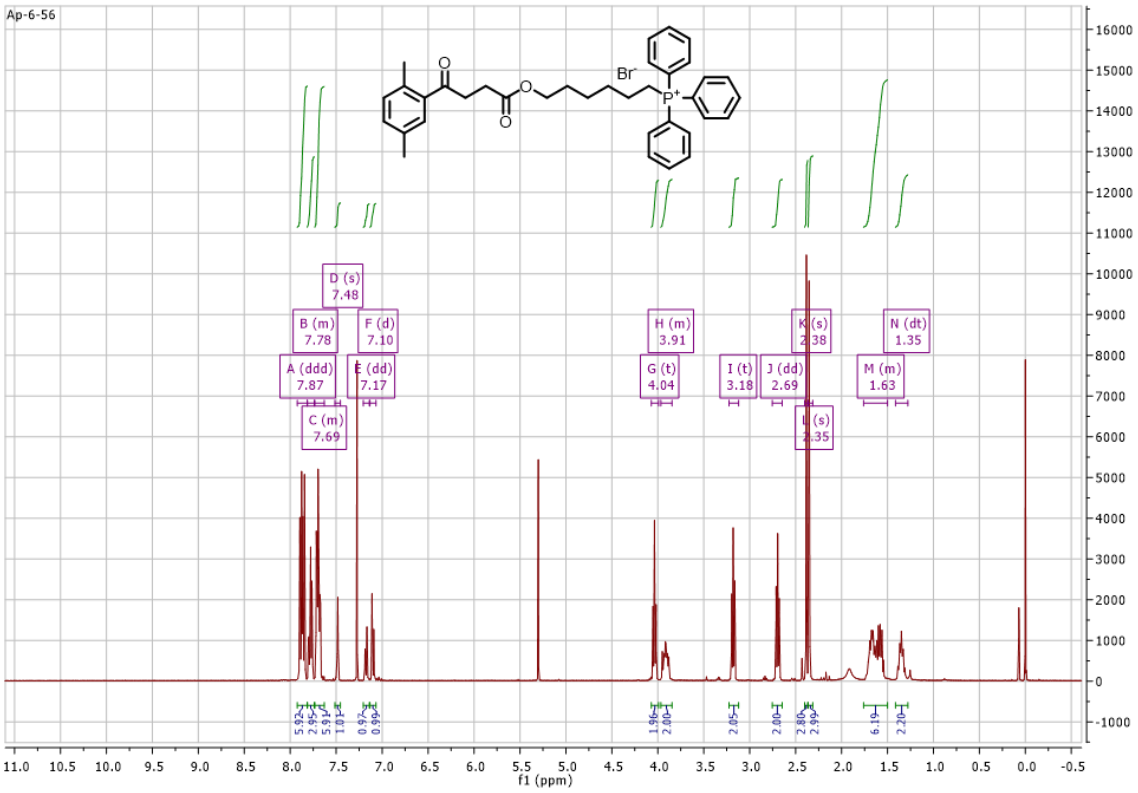


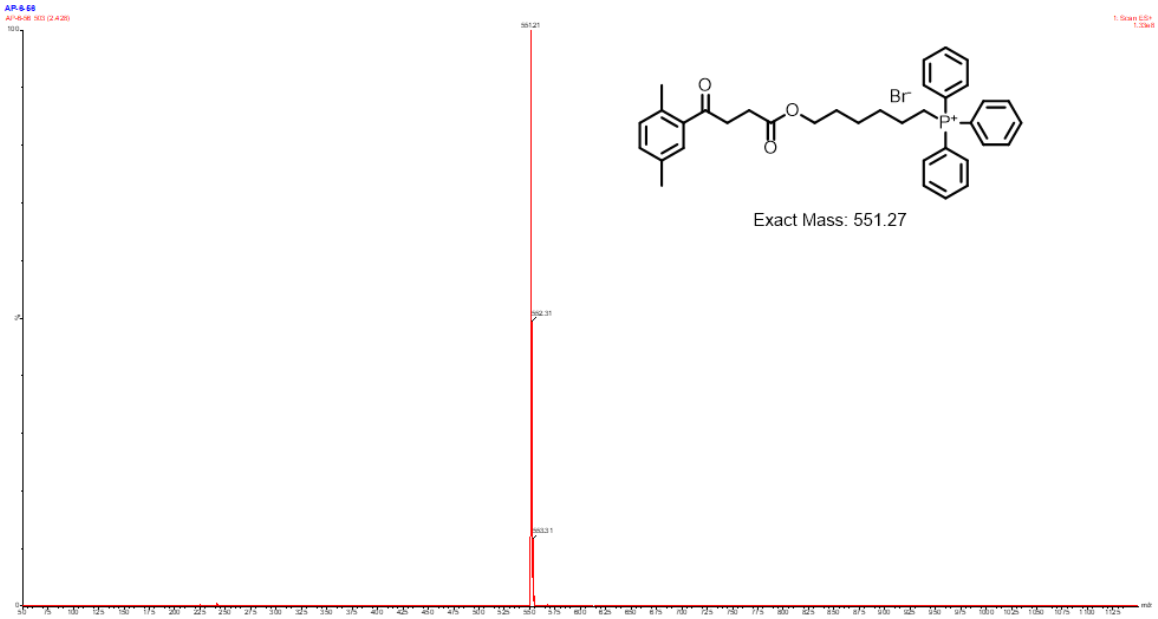




d (6-(4-(2,5-Dimethylphenyl)-4-oxobutanoyloxy)hexyl)triphenylphosphonium bromide synthesis, NMR & Mass:

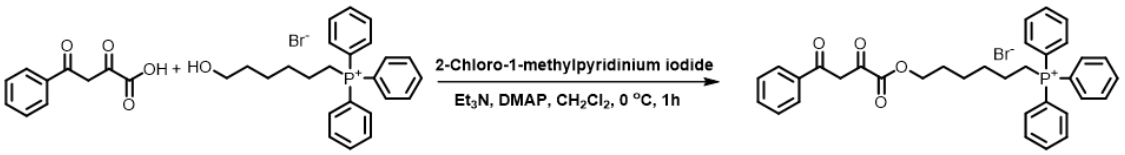


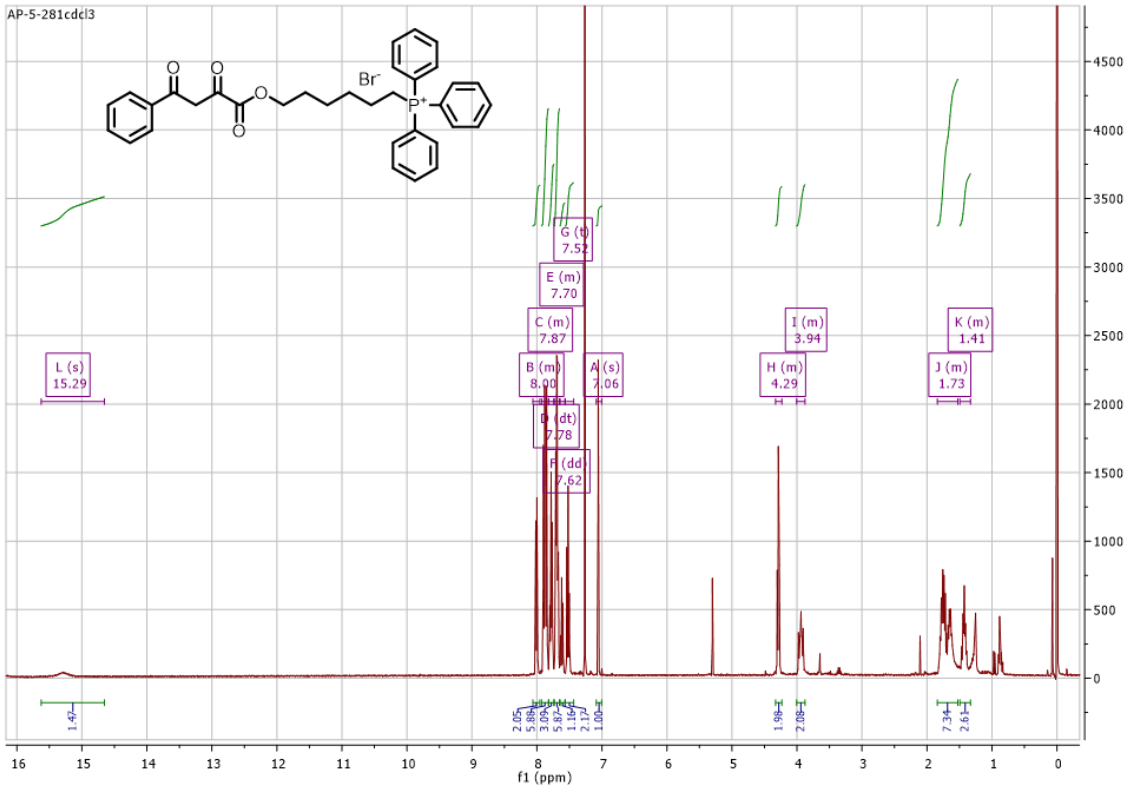


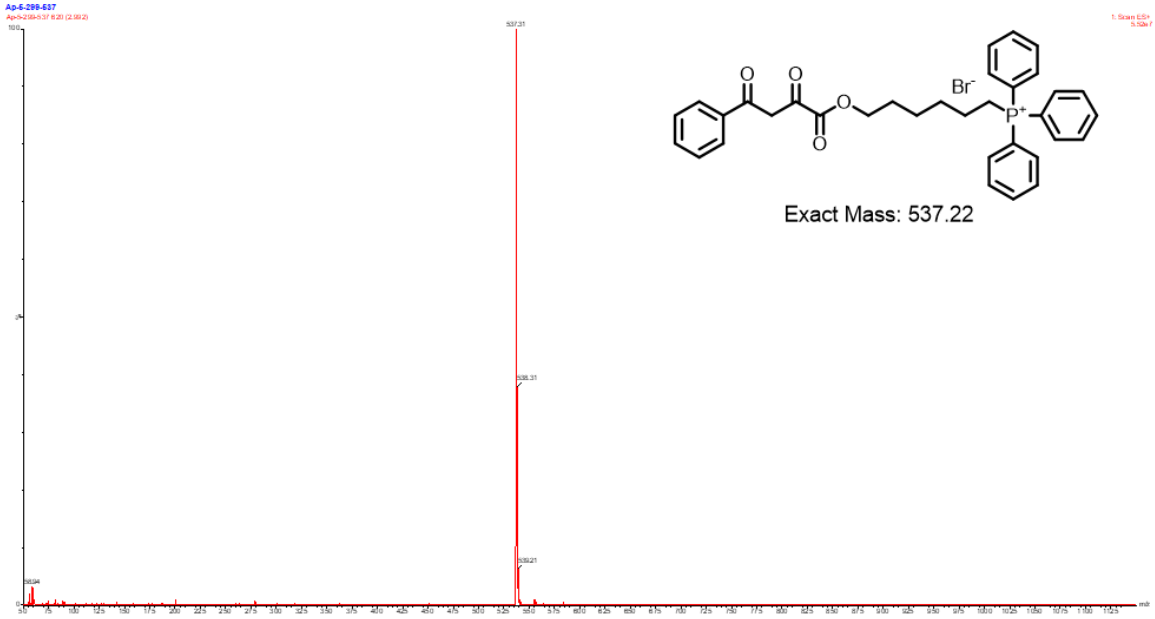


e

(6-(2,4-Dioxo-4-phenylbutanoyloxy)hexyl)triphenylphosphonium bromide synthesis, NMR & Mass:



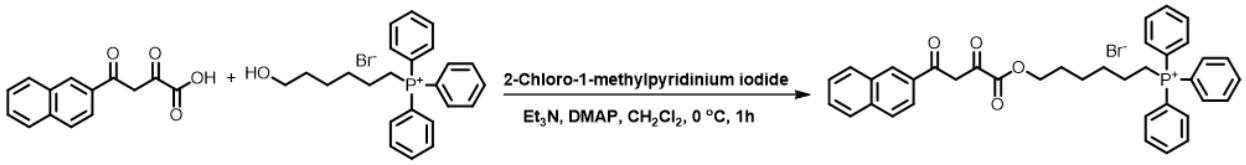


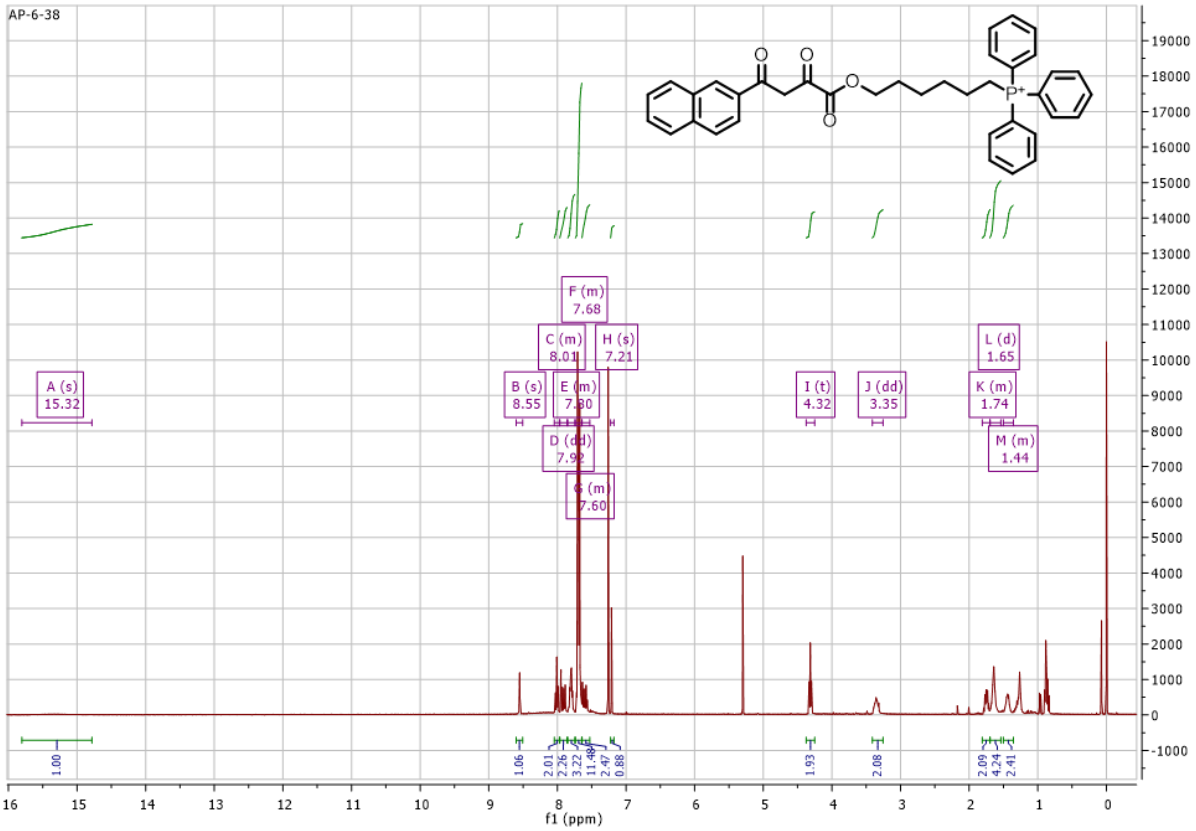


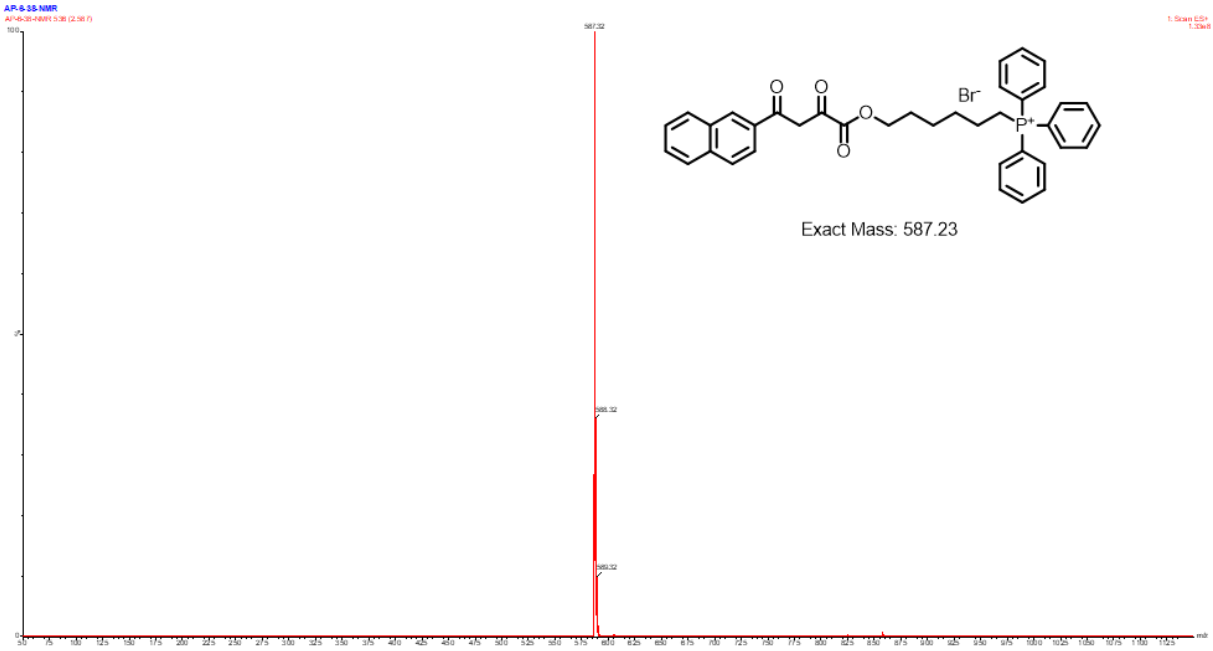
Exact Mass: 537.22

f

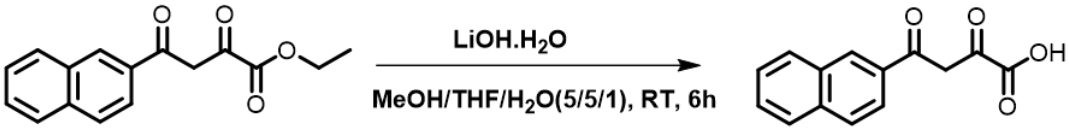
(6-(4-(Naphthalen-2-yl)-2,4-dioxobutanoyloxy)hexyl)triphenylphosphonium bromide synthesis, NMR & Mass:

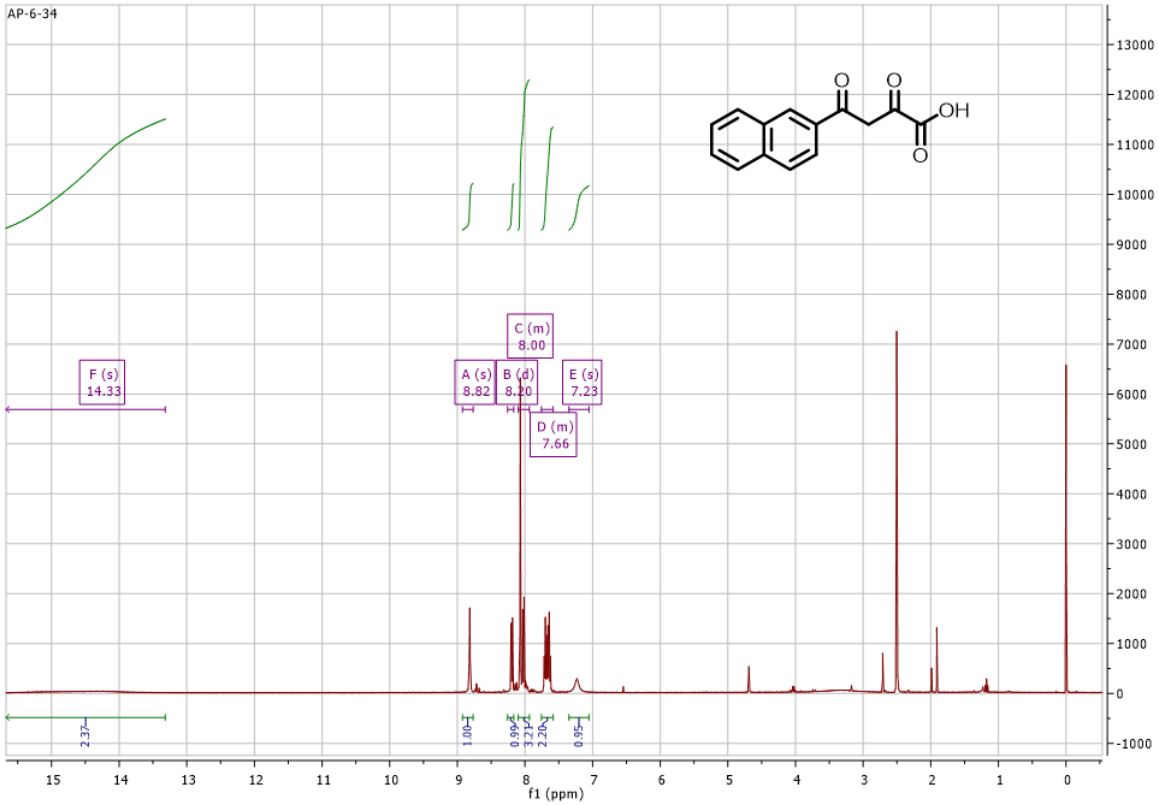


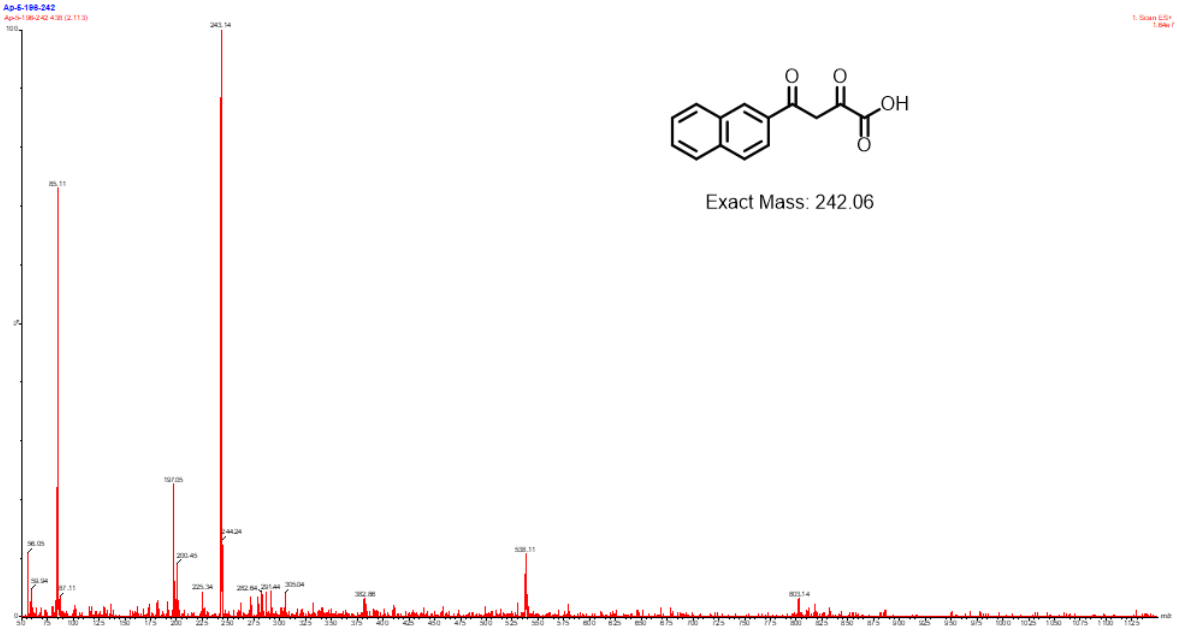




g 4-(Naphthalen-2-yl)-2,4-dioxobutanoic acid synthesis, NMR & Mass:

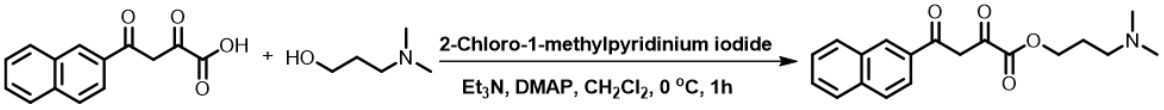


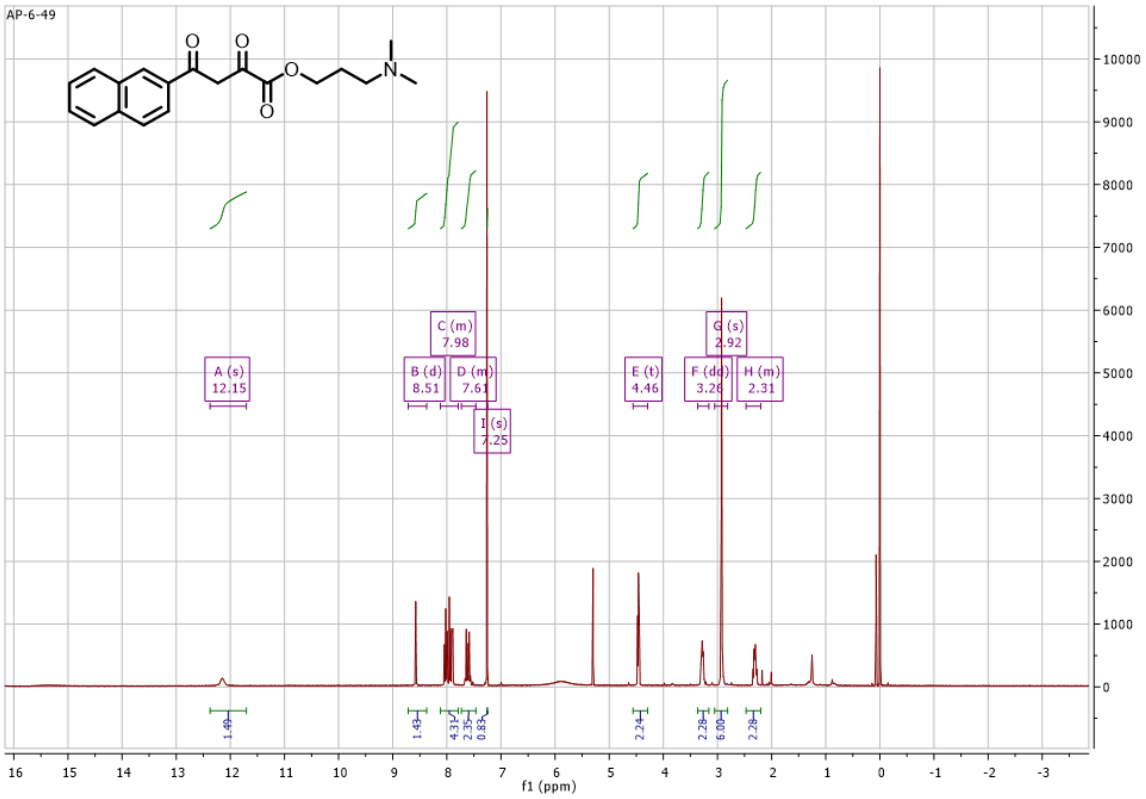


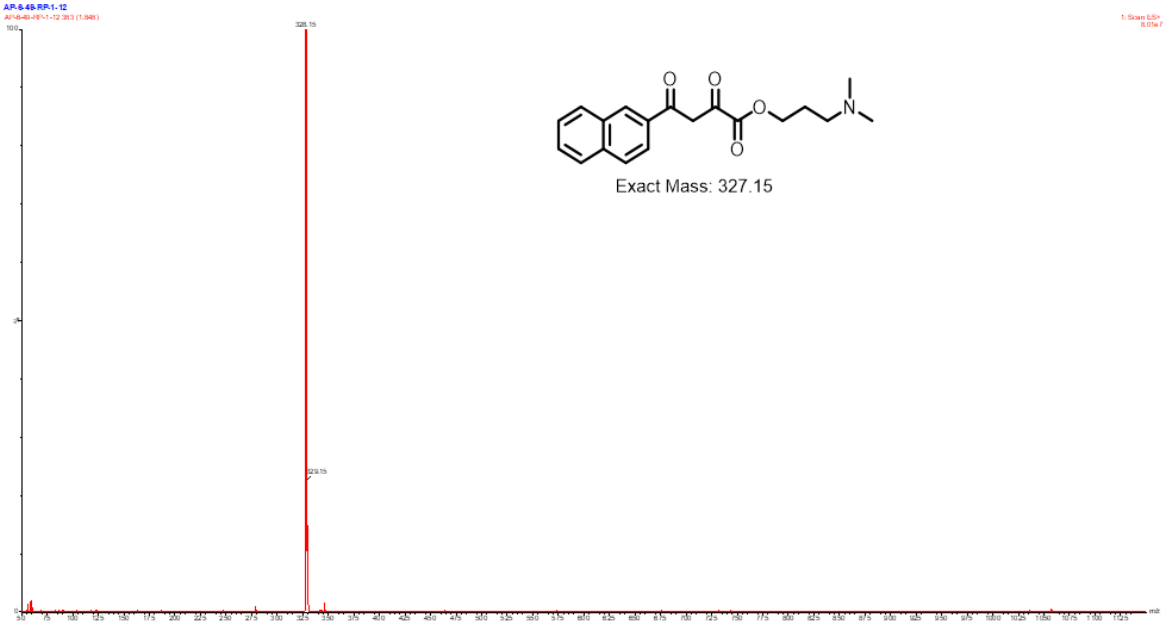


h

3-(Dimethylamino)propyl 4-(naphthalen-2-yl)-2,4-dioxobutanoate synthesis, NMR & Mass:

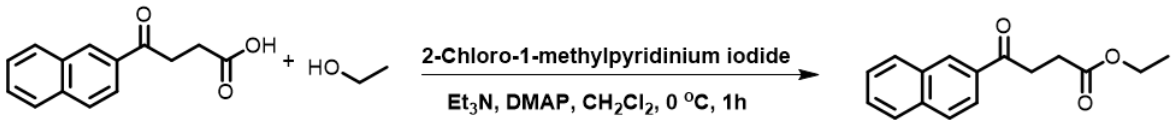


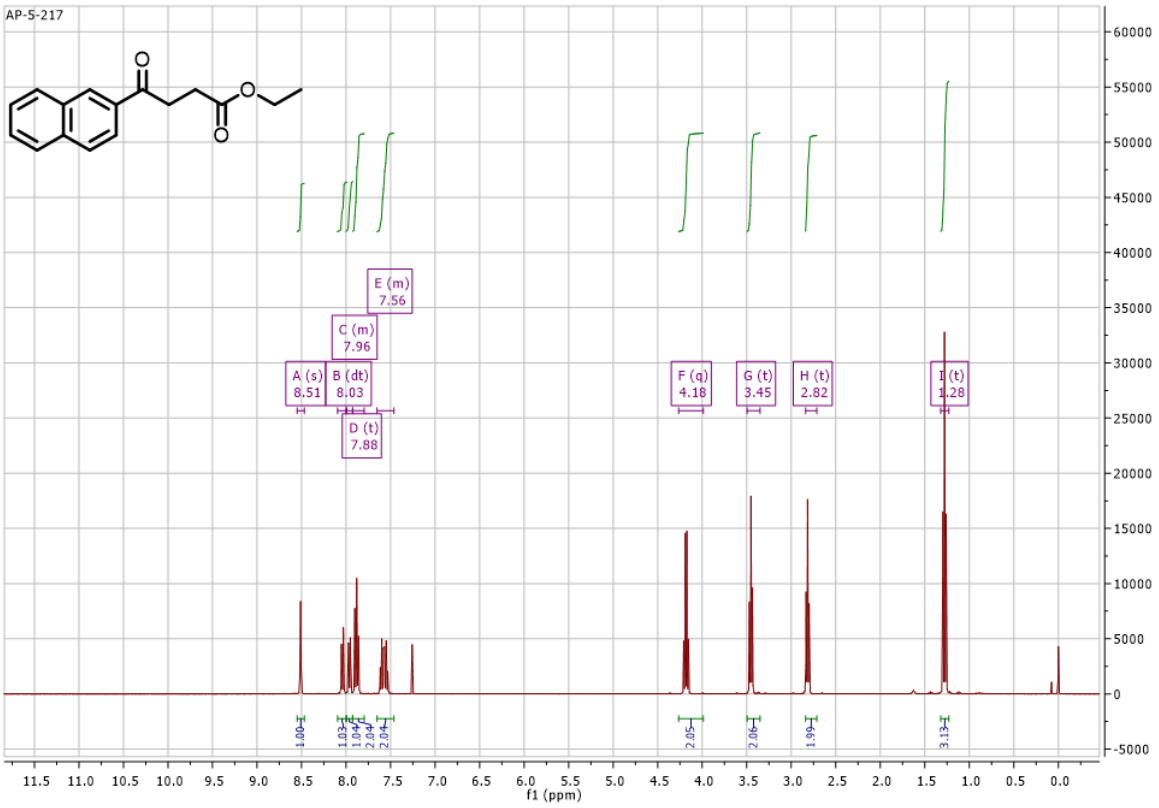


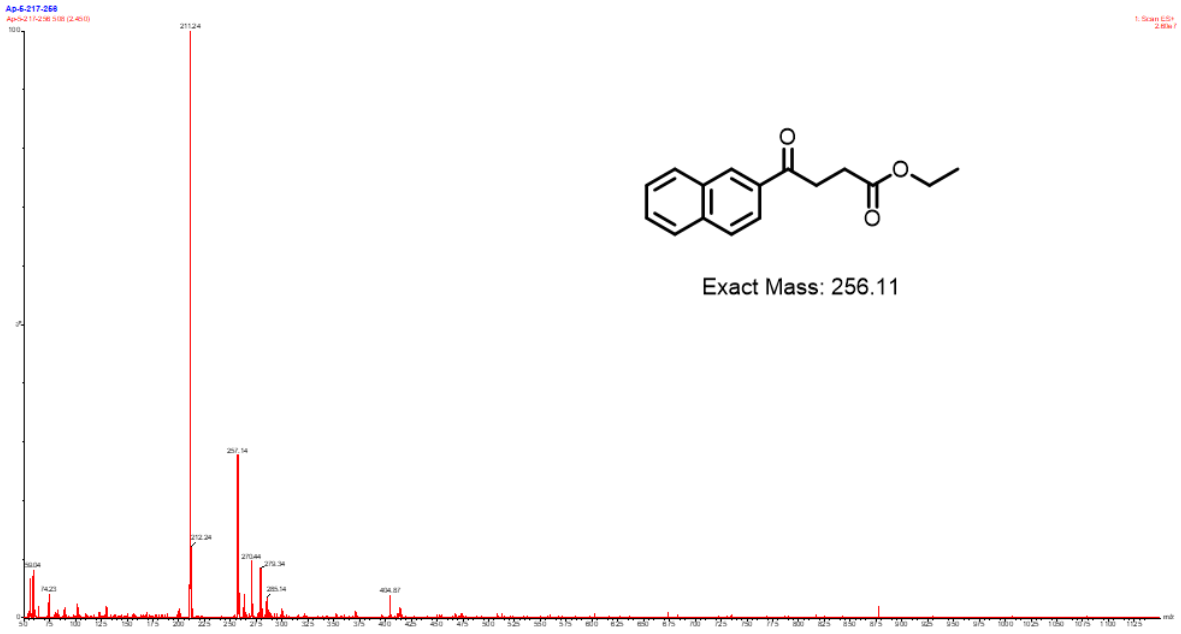


Exact Mass: 327.15

i Ethyl 4-(naphthalen-2-yl)-4-oxobutanoate synthesis, NMR & Mass:



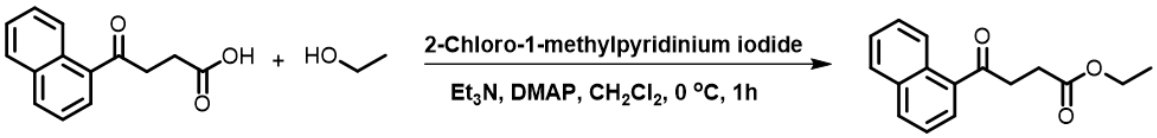


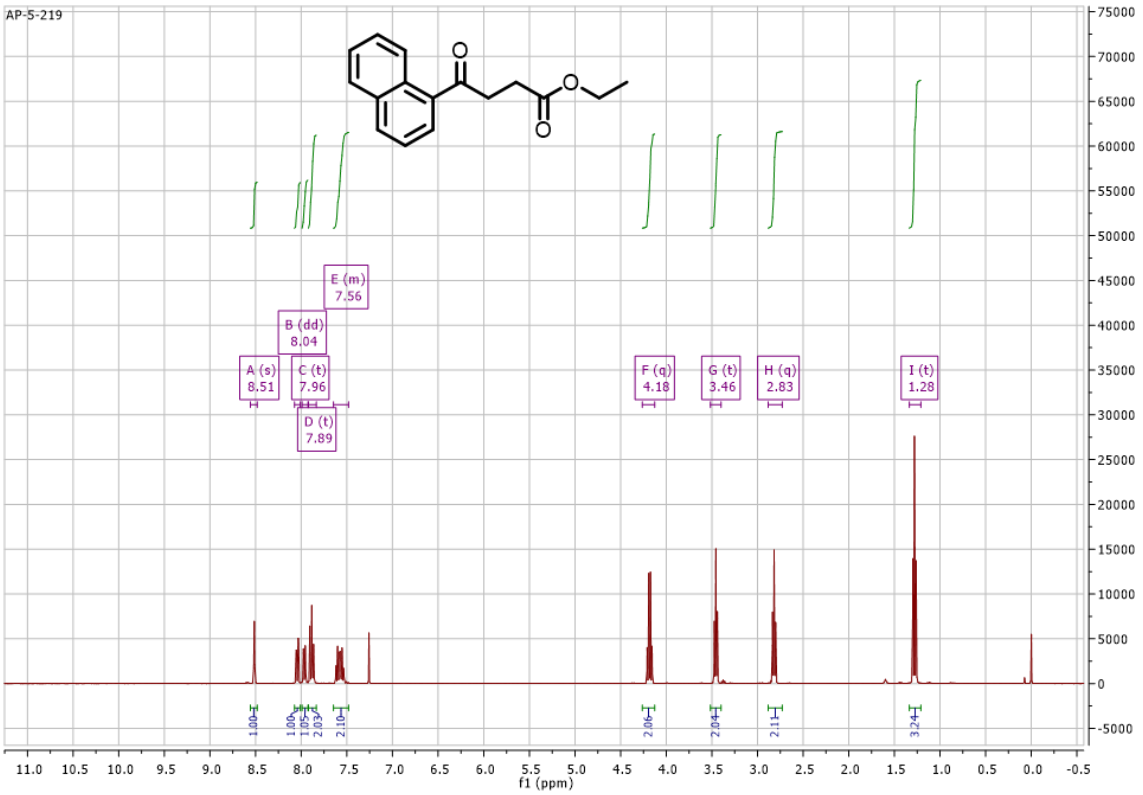


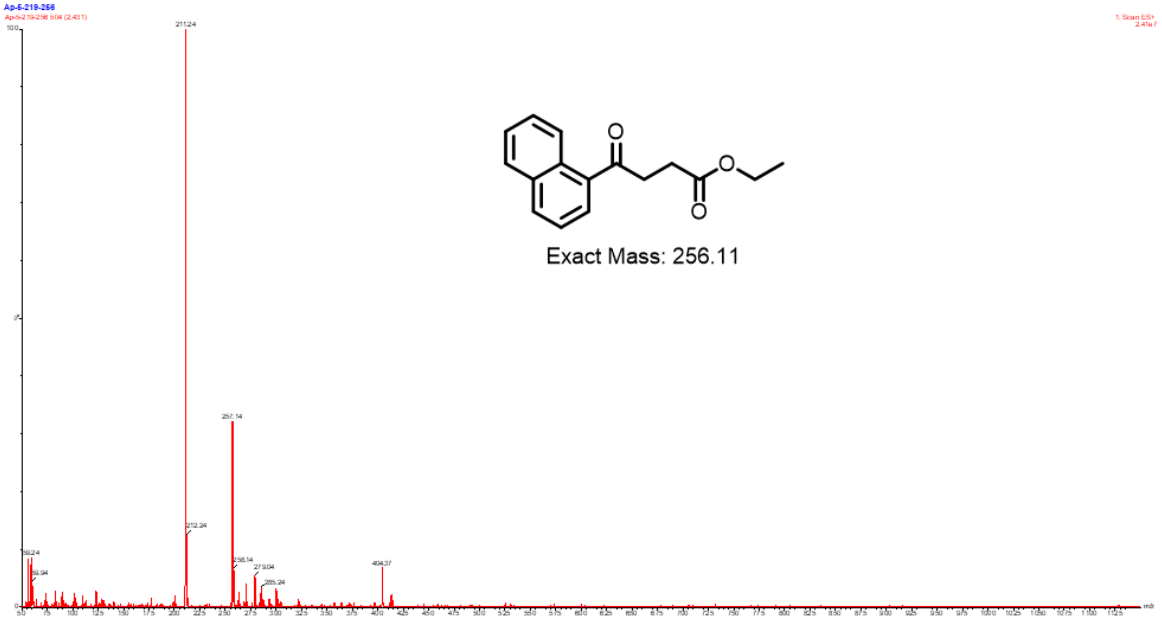
Exact Mass: 256.11

j

Ethyl 4-(naphthalen-1-yl)-4-oxobutanoate synthesis, NMR & Mass:



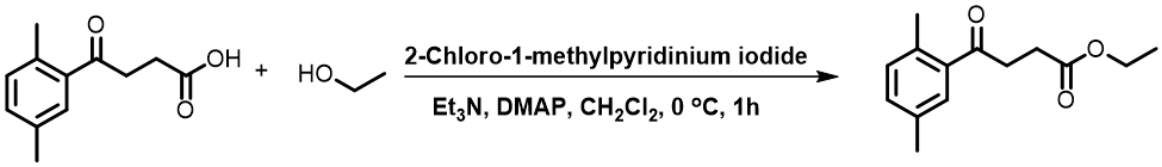


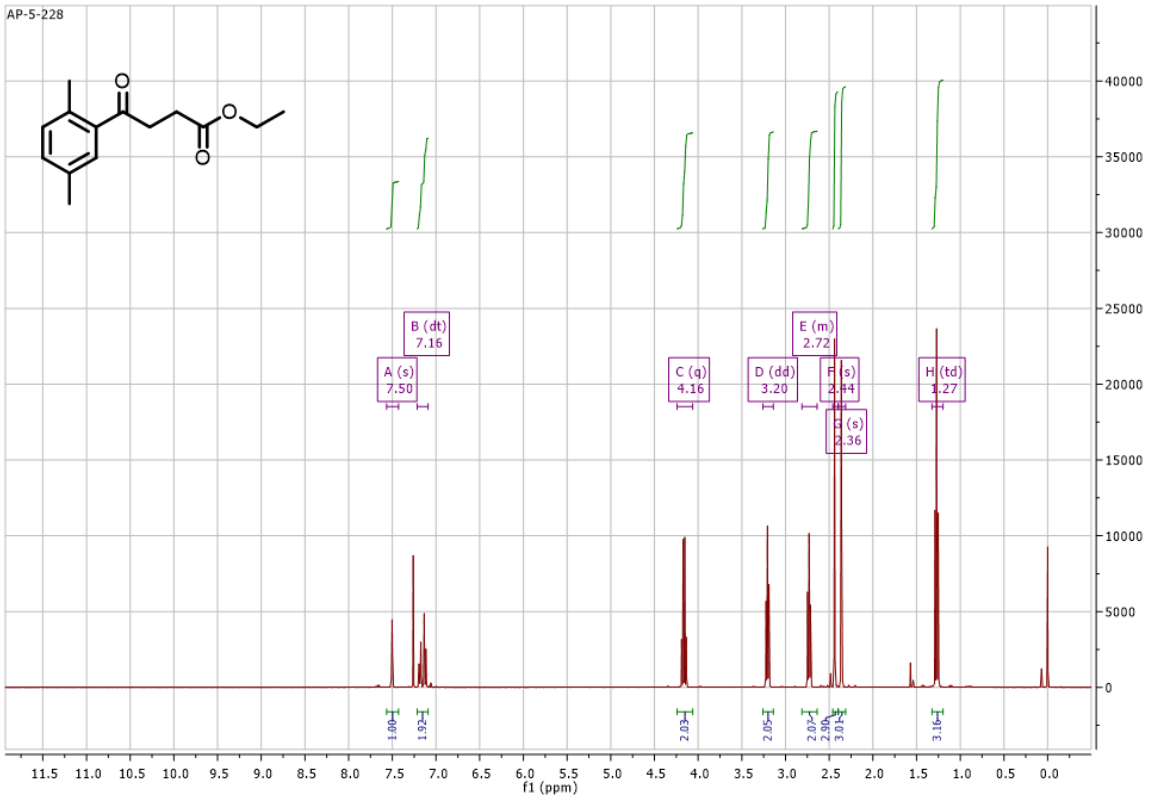


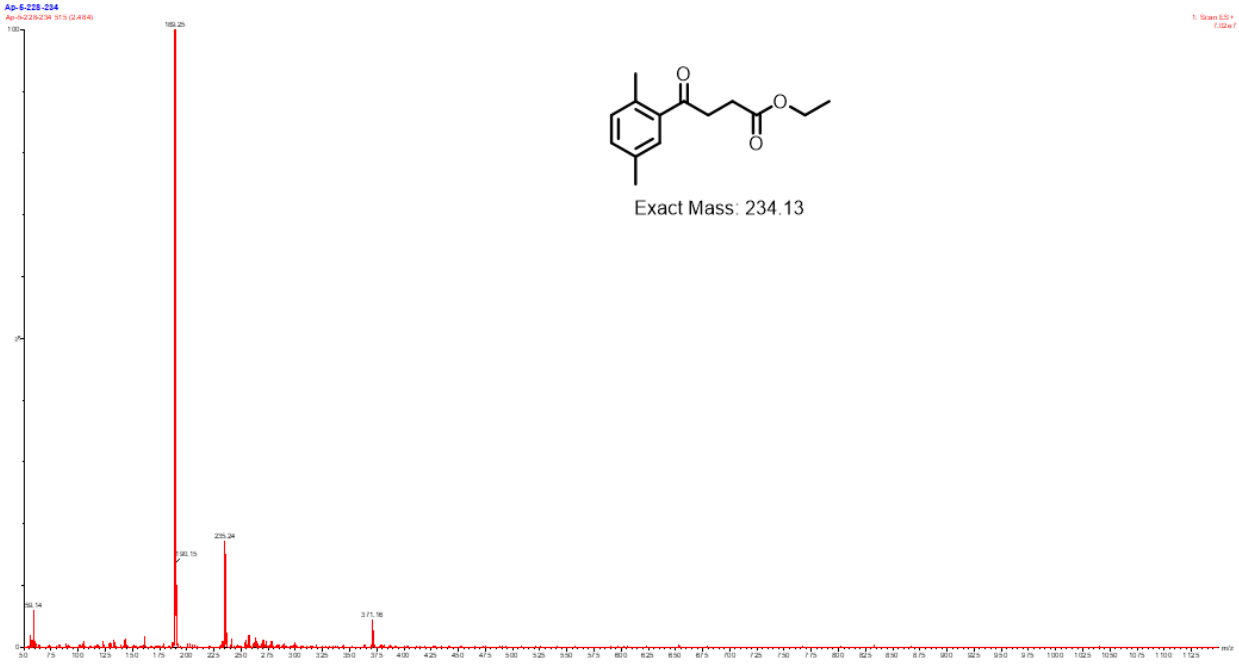
Exact Mass: 256.11

k

Ethyl 4-(2,5-dimethylphenyl)-4-oxobutanoate synthesis, NMR & Mass:



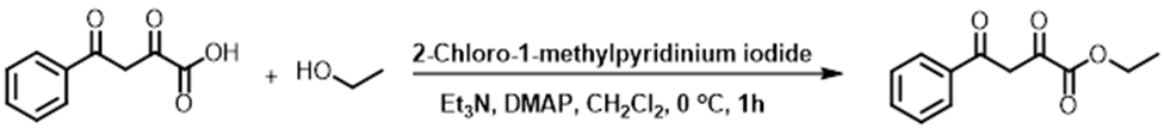


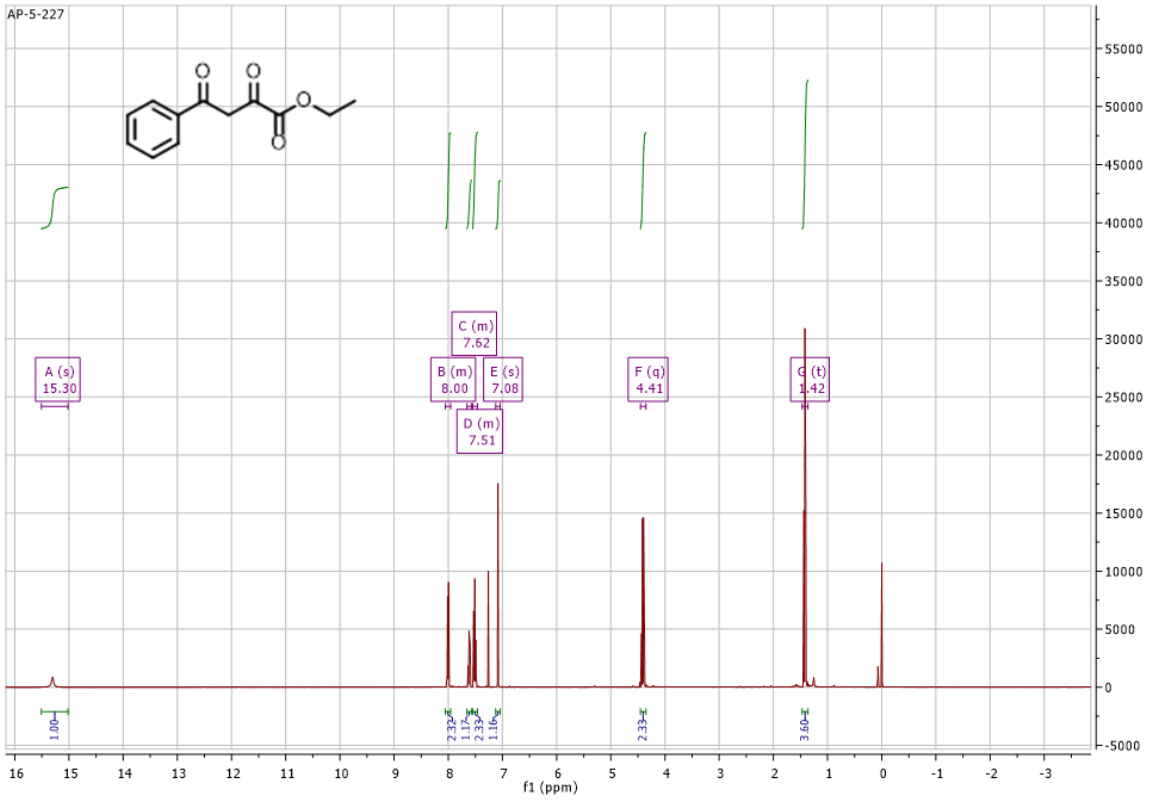


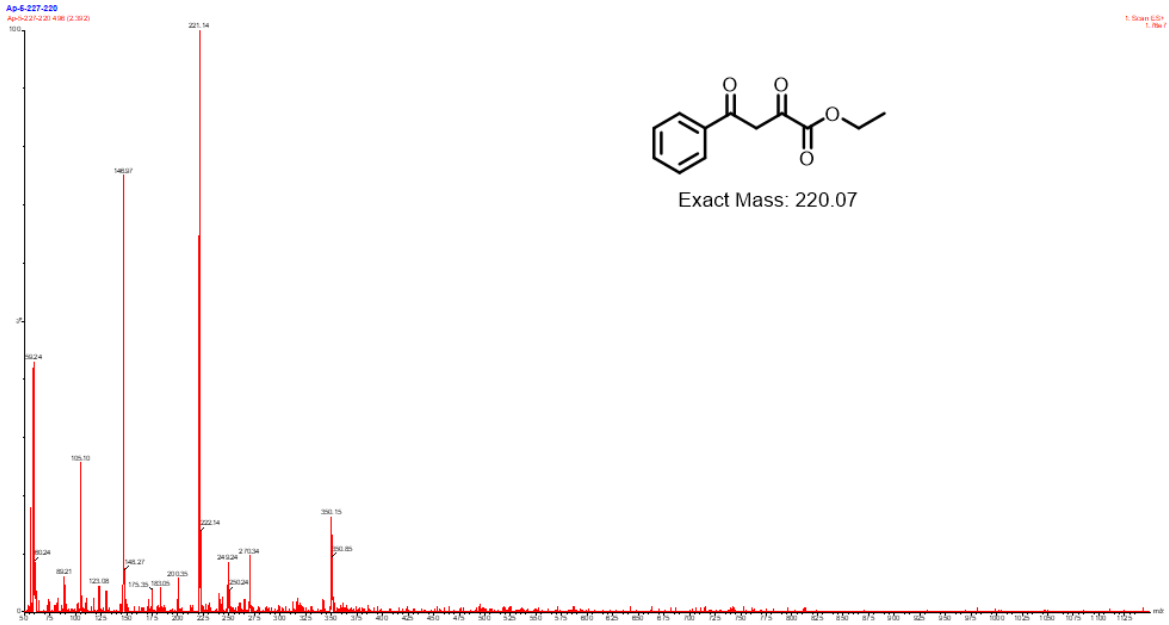
Exact Mass: 234.13

I

Ethyl 2,4-dioxo-4-phenylbutanoate synthesis, NMR & Mass:







Exact Mass: 220.07

Supplementary Figure 3: Chemical synthesis and validation of prodrugs by NMR and MS. Chemical synthesis and NMR / MS validation of **a,** (6-Hydroxyhexyl)triphenylphosphonium bromide (TPP carrier molecule). This TPP carrier molecule was used to synthesize ester prodrugs **b,** (6-(4-(Naphthalen-2-yl)-4-oxobutanoyloxy)hexyl)triphenylphosphonium bromide (C23.20-TPP) **c,** (6-(4-(Naphthalen-1-yl)-4-oxobutanoyloxy)hexyl)triphenylphosphonium bromide (C23.21-TPP) **d,** (6-(4-(2,5-Dimethylphenyl)-4-oxobutanoyloxy)hexyl)triphenylphosphonium bromide (C23.28-TPP) **e,** (6-(2,4-Dioxo-4-phenylbutanoyloxy)hexyl)triphenylphosphonium bromide (C23.07-TPP) **f,** (6-(4-(Naphthalen-2-yl)-2,4-dioxobutanoyloxy)hexyl)triphenylphosphonium bromide (C23.47-TPP). **g,** Synthesis of 4-(Naphthalen-2-yl)-2,4-dioxobutanoic acid (C23.47). **h,** 3-(Dimethylamino)propyl 4-(naphthalen-2-yl)-2,4-dioxobutanoate (C23.47-DAP). **i,** Ethyl 4-(naphthalen-2-yl)-4-oxobutanoate (C23.20-EA). **j,** Ethyl 4-(naphthalen-1-yl)-4-oxobutanoate synthesis (C23.21-EA). **k,** Ethyl 4-(2,5-dimethylphenyl)-4-oxobutanoate (C23.28-EA). **l,** Ethyl 2,4-dioxo-4-phenylbutanoate (C23.07-EA).