

1/17

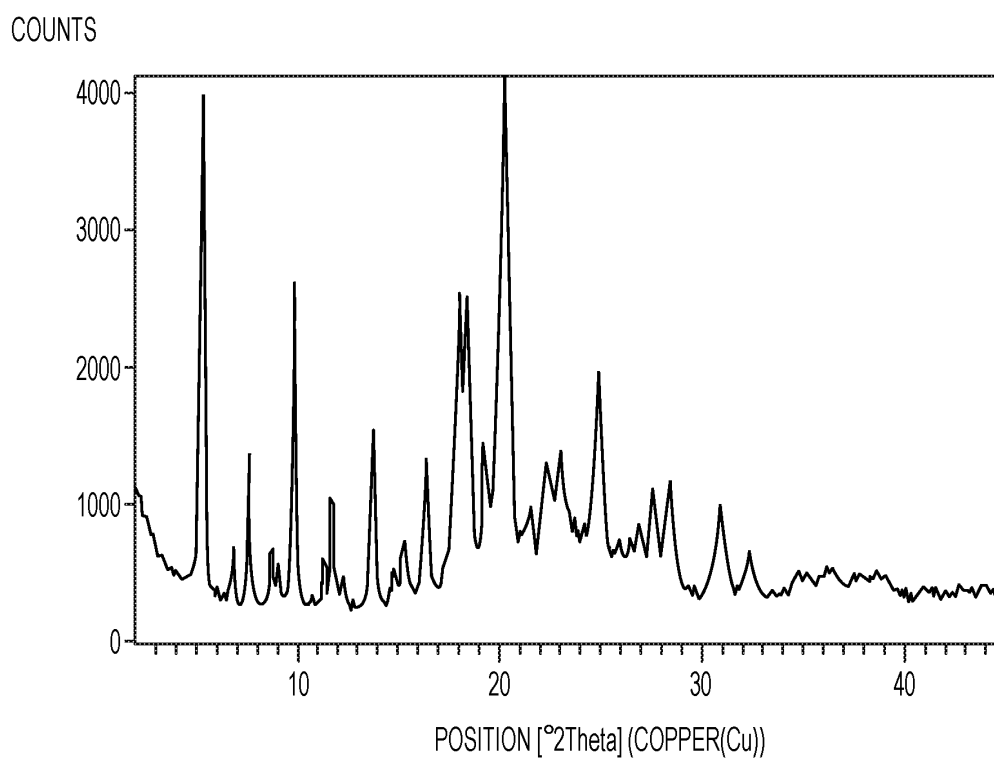


Figure 1

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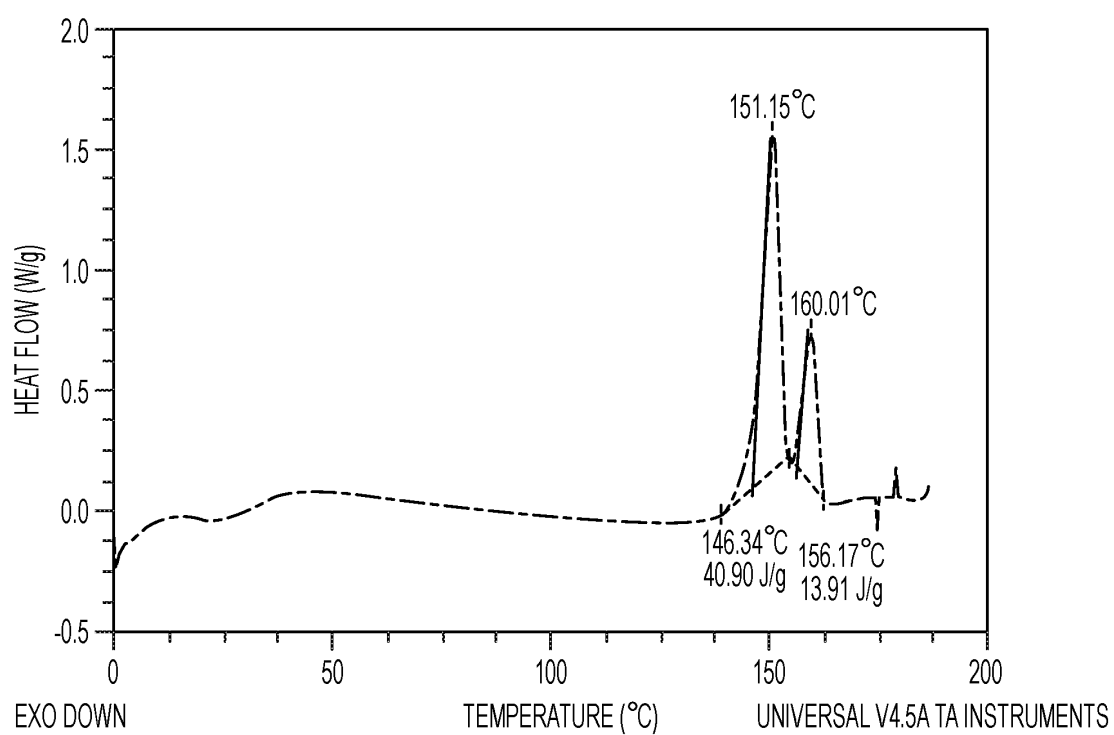


Figure 2

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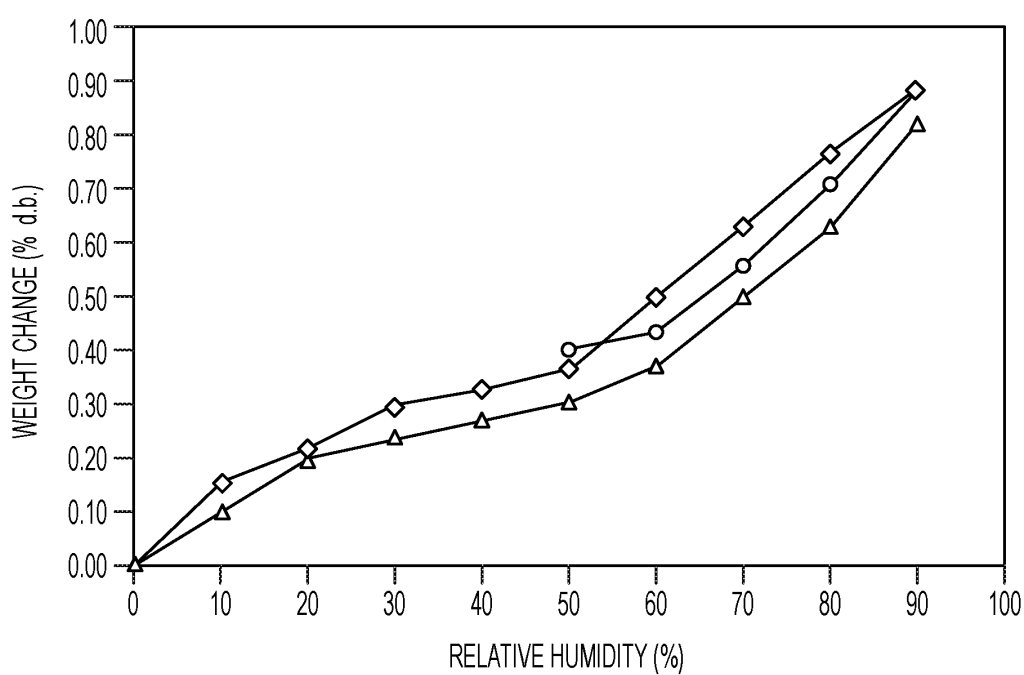


Figure 3

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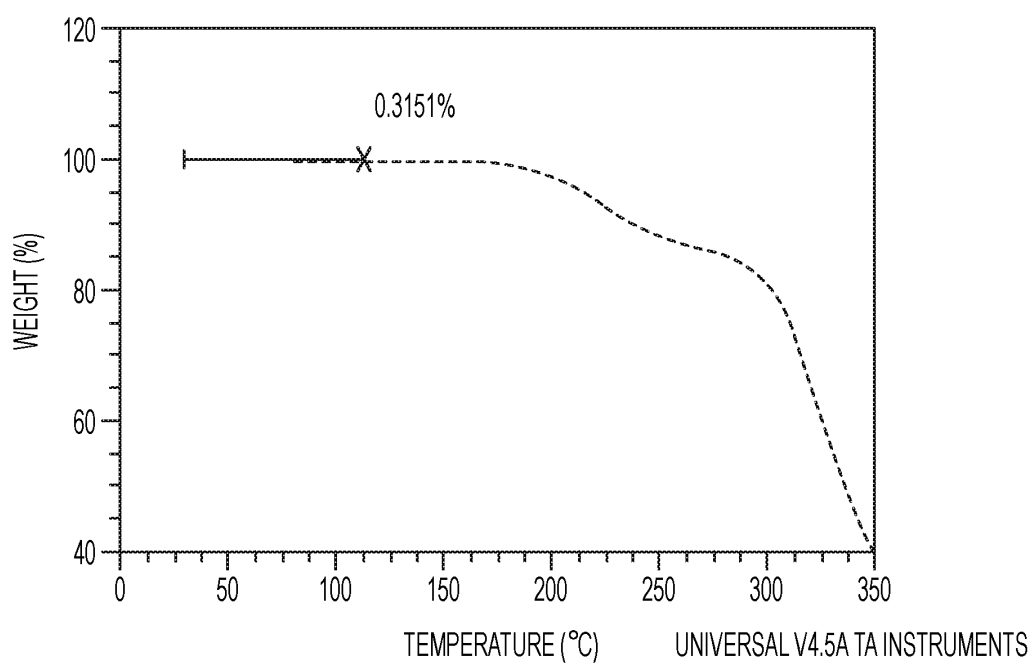


Figure 4

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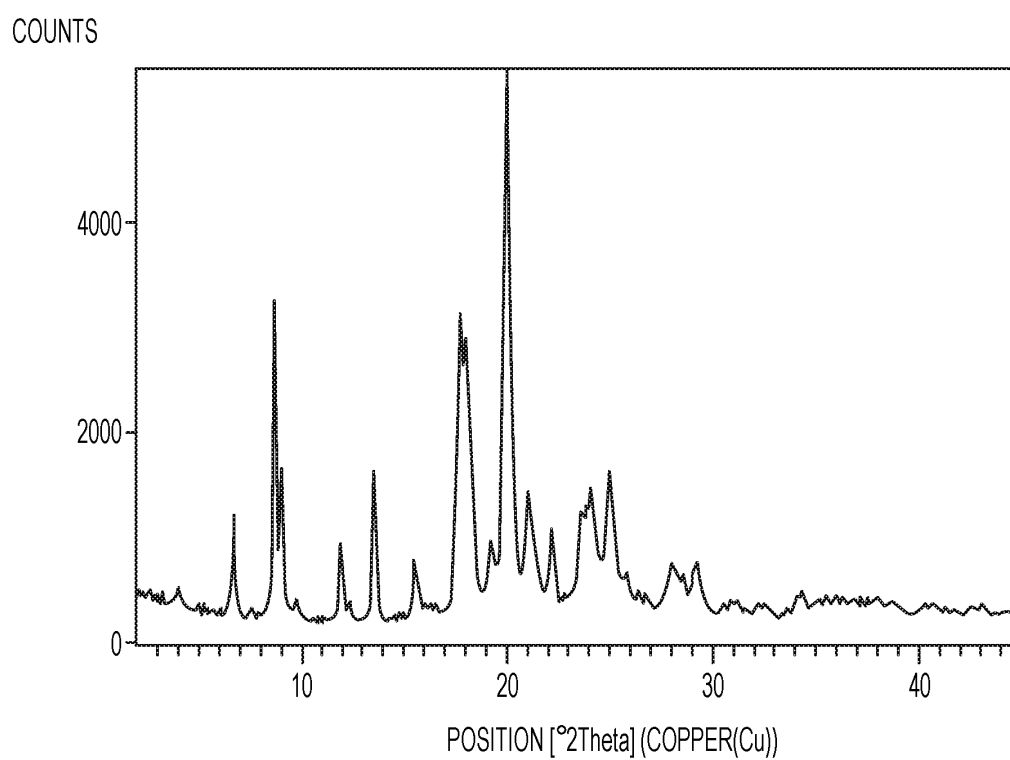


Figure 5

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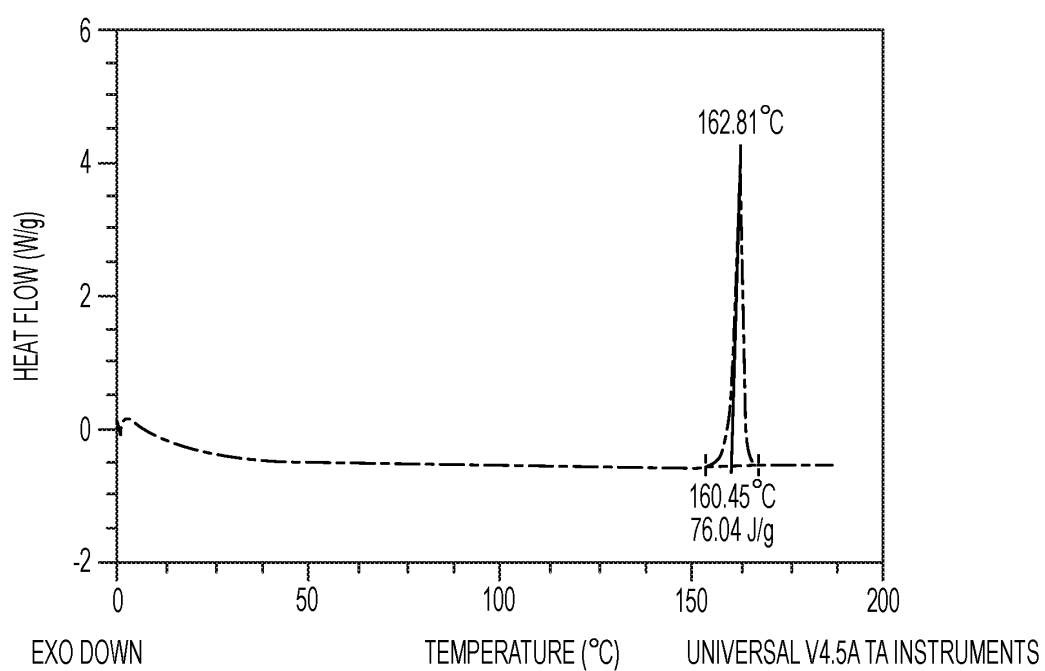


Figure 6

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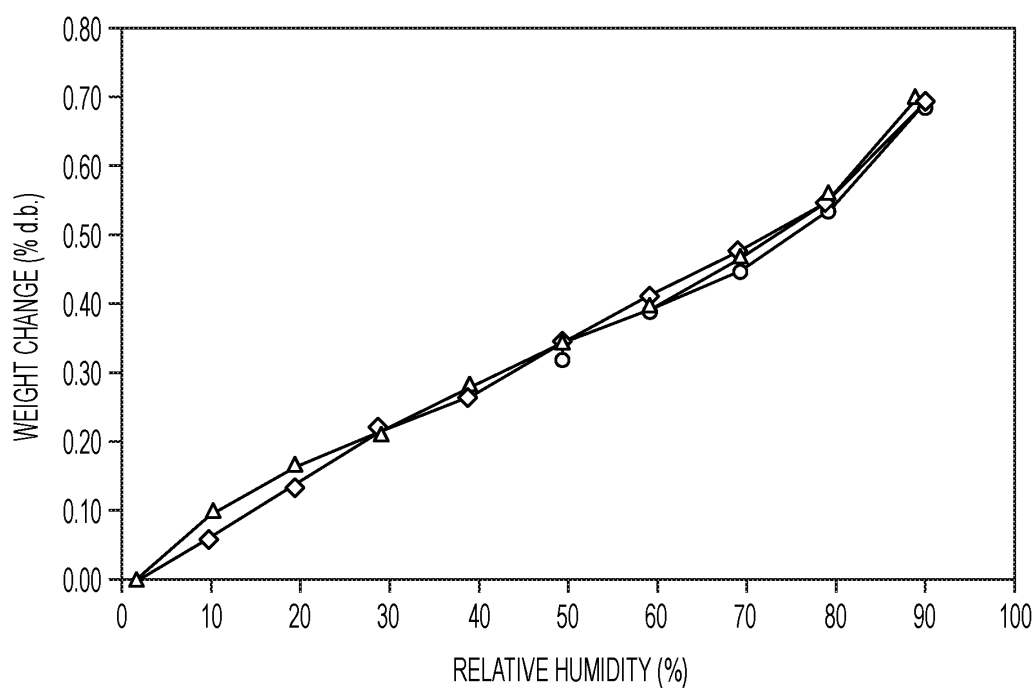


Figure 7

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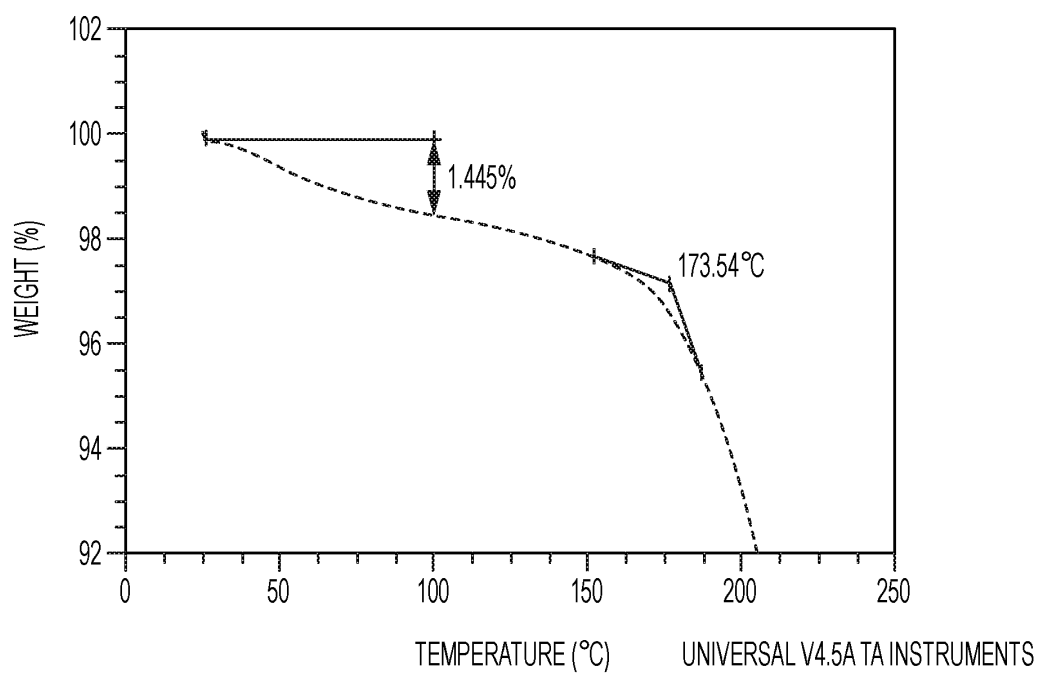


Figure 8

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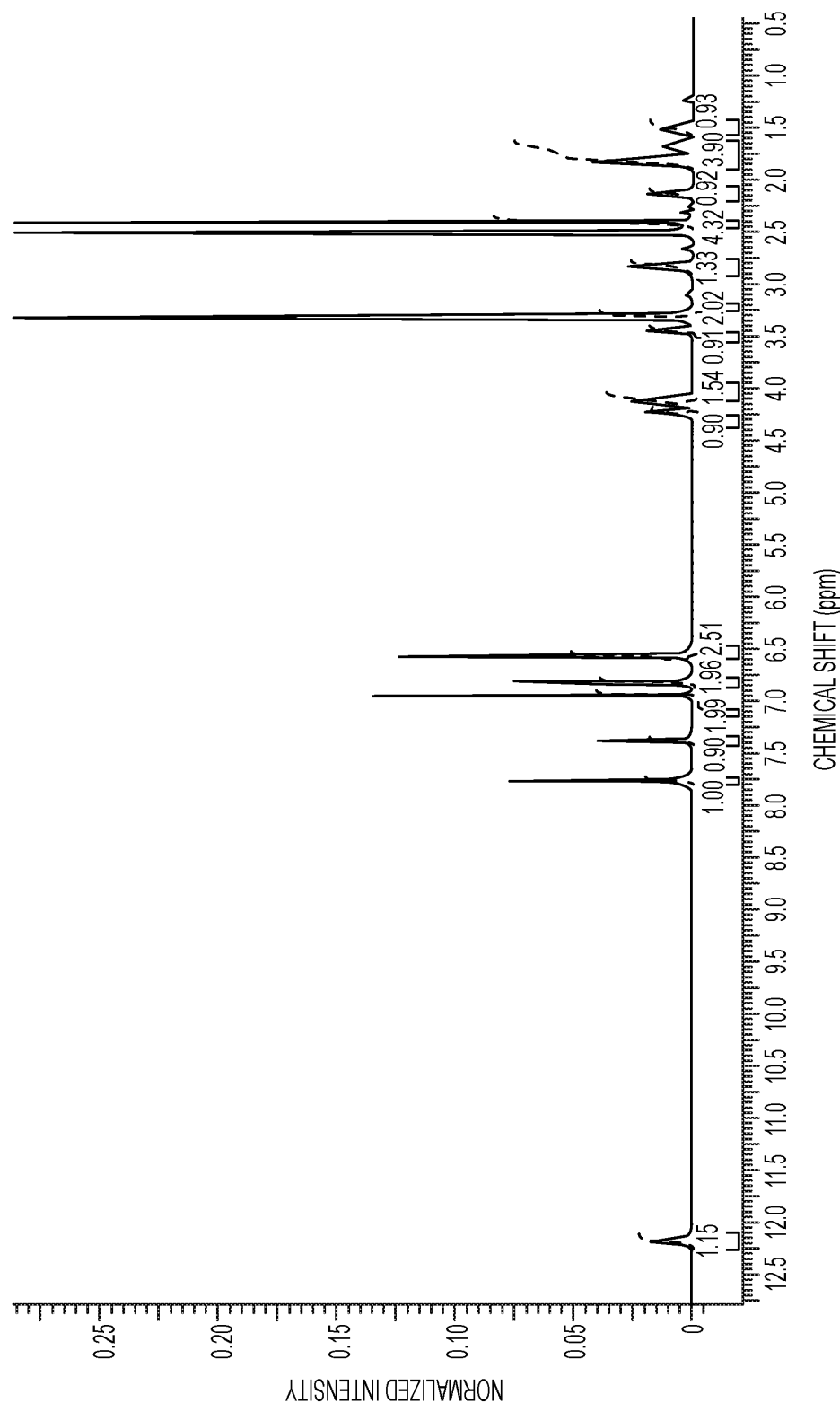


Figure 9

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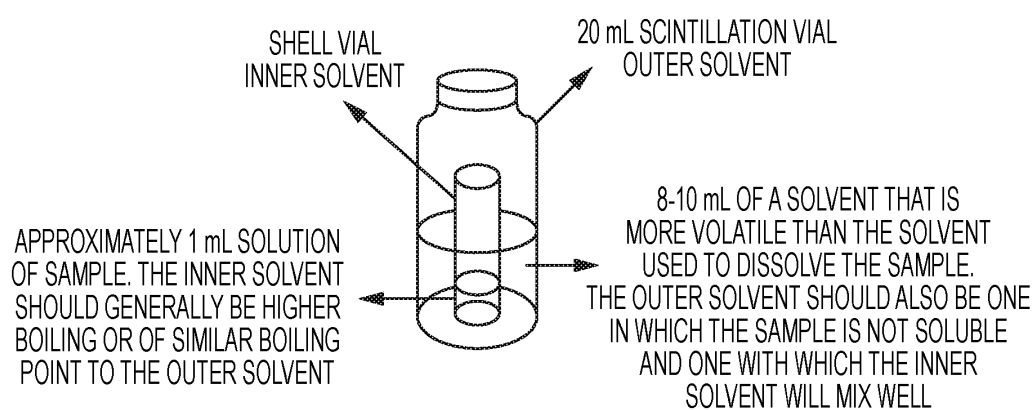
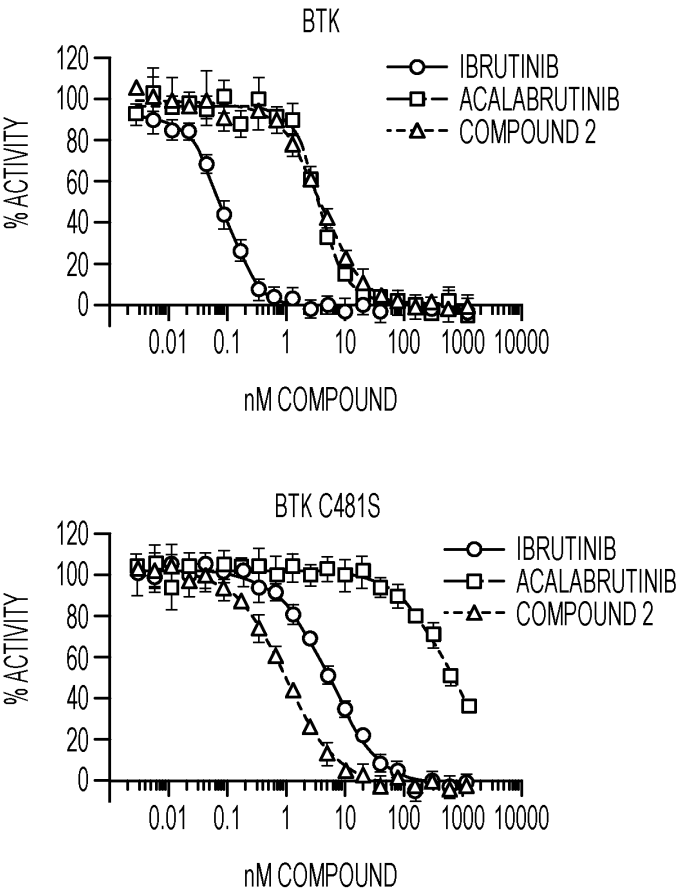


Figure 10

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EFFECTS OF Cys481Ser ON THE ACTIVITY OF BTK INHIBITORS^a



IC ₅₀ (nM), [ATP] = 50 μM	WT BTK	Cys481Ser BTK	FOLD CHANGE
COMPOUND 2	4.6	1.1	0.2
IBRUTINIB	0.1	6.6	66
ACALABRUTINIB	4.2	707	168

^aDIRECT MEASUREMENT OF KINASE ACTIVITY OF HUMAN RECOMBINANT WT BTK OR Cys481Ser MUTANT BTK WAS PERFORMED IN A FRET KINASE ASSAY

Figure 11

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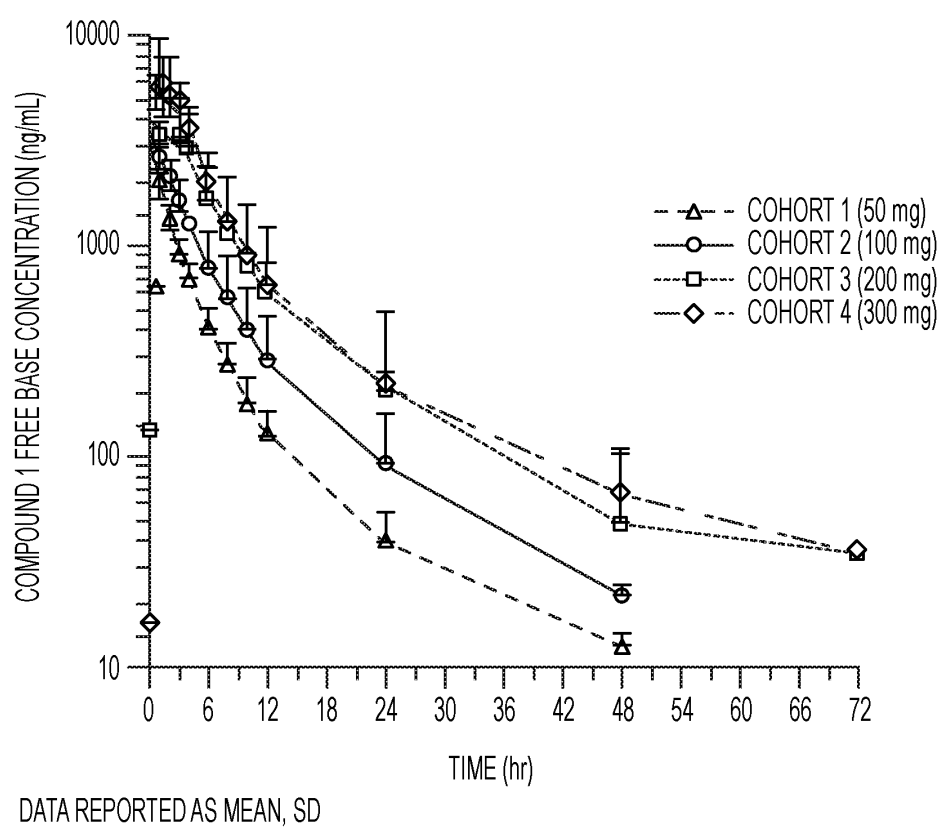
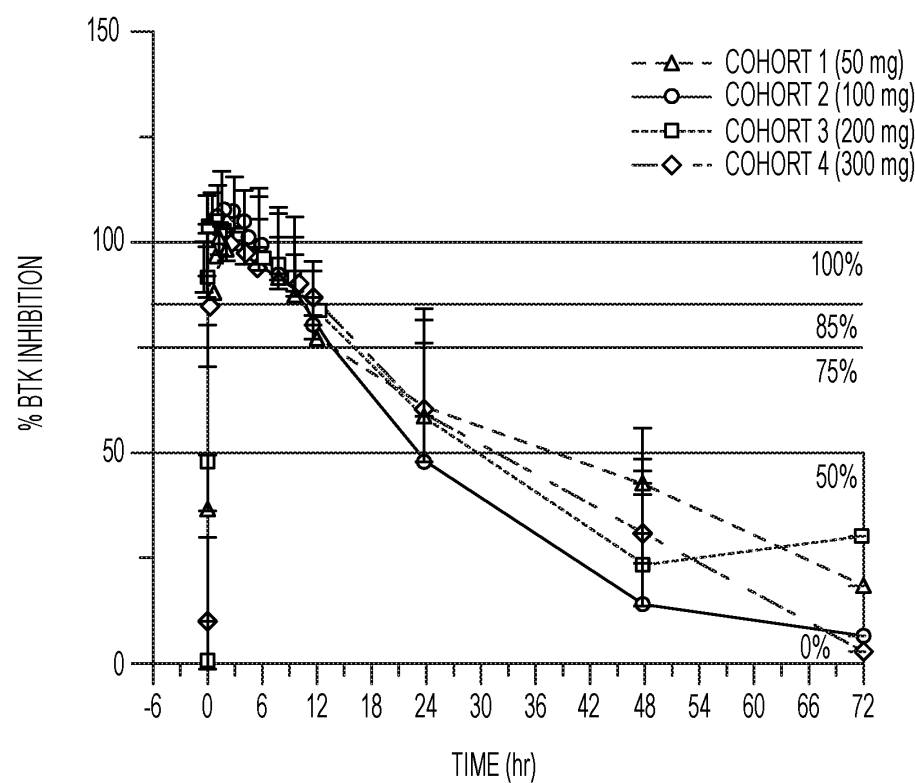


Figure 12

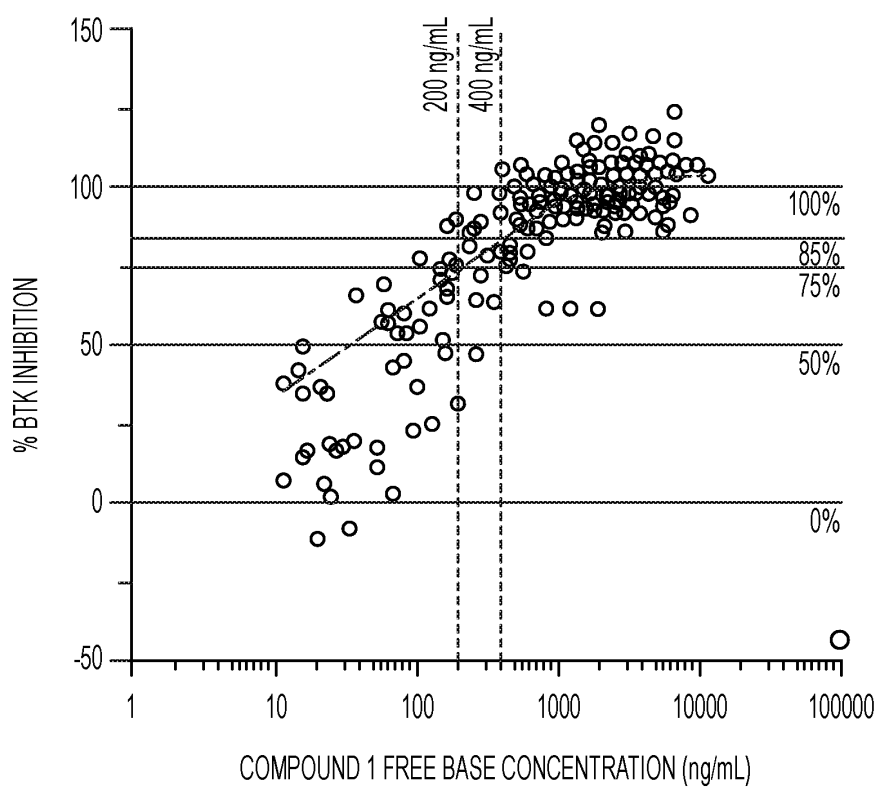
PERCENT BTK INHIBITION VS. TIME^a



%BTK INHIBITION (MEAN, SD) DETERMINED BY ASSESSMENT OF pBTK AS DESCRIBED IN METHODS BTK, BRUTON'S TYROSINE KINASE; pBTK, PHOSPHORYLATED BTK.

Figure 13

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PERCENT BTK INHIBITION VS. COMPOUND 1 PLASMA CONCENTRATION^a

%BTK INHIBITION DETERMINED BY ASSESSMENT OF pBTK AS DESCRIBED
IN METHODS; COMPOUND 1 FREE BASE CONCENTRATION DETERMINED BY LC-MS/MS
BTK, BRUTON'S TYROSINE KINASE; pBTK, PHOSPHORYLATED BTK.

Figure 14

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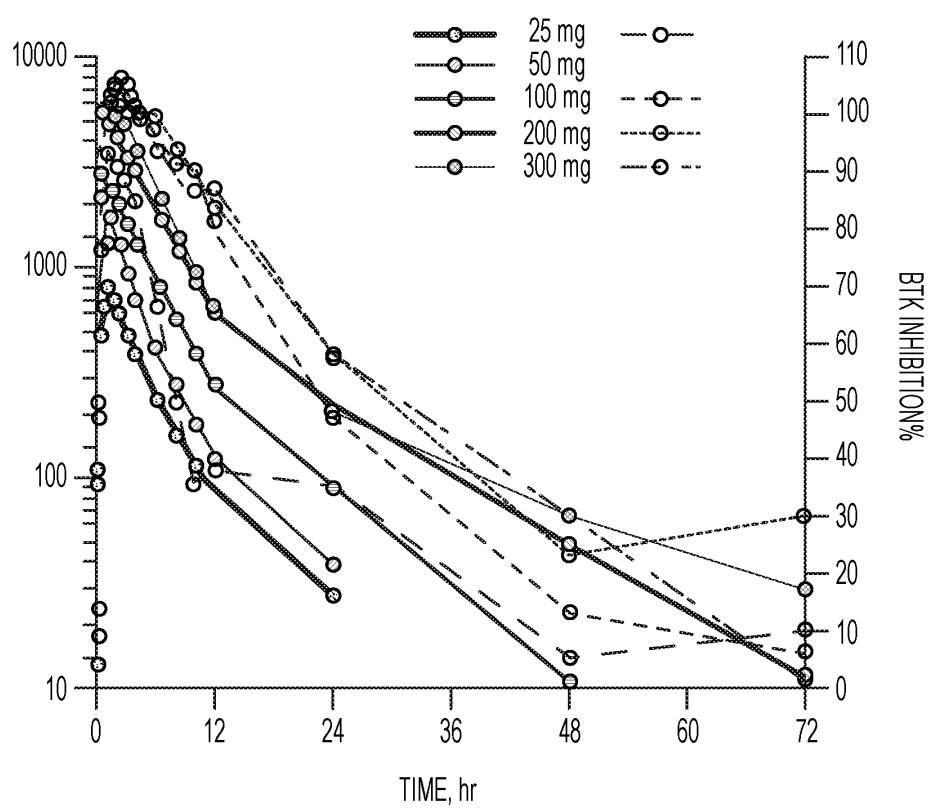


Figure 15

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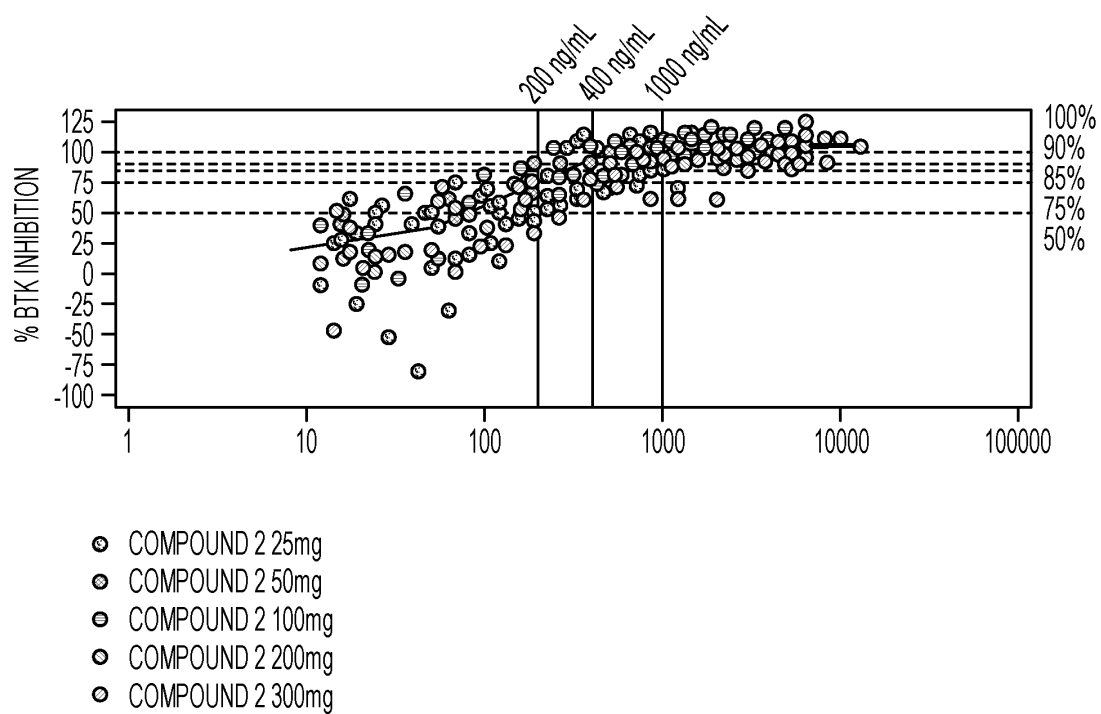


Figure 16

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COMPOUND	WT C481 BTK IC ₅₀ nM	C481S BTK IC ₅₀ nM	FOLD CHANGE ^a
COMPOUND 1	570	800	1.4
IBRUTINIB	16	1700	>100

^aEXPRESSED AS IC₅₀ OF COMPOUND AGAINST C481S-BTK DIVIDED BY IC₅₀ OF COMPOUND AGAINST WT BTK.

Figure 17