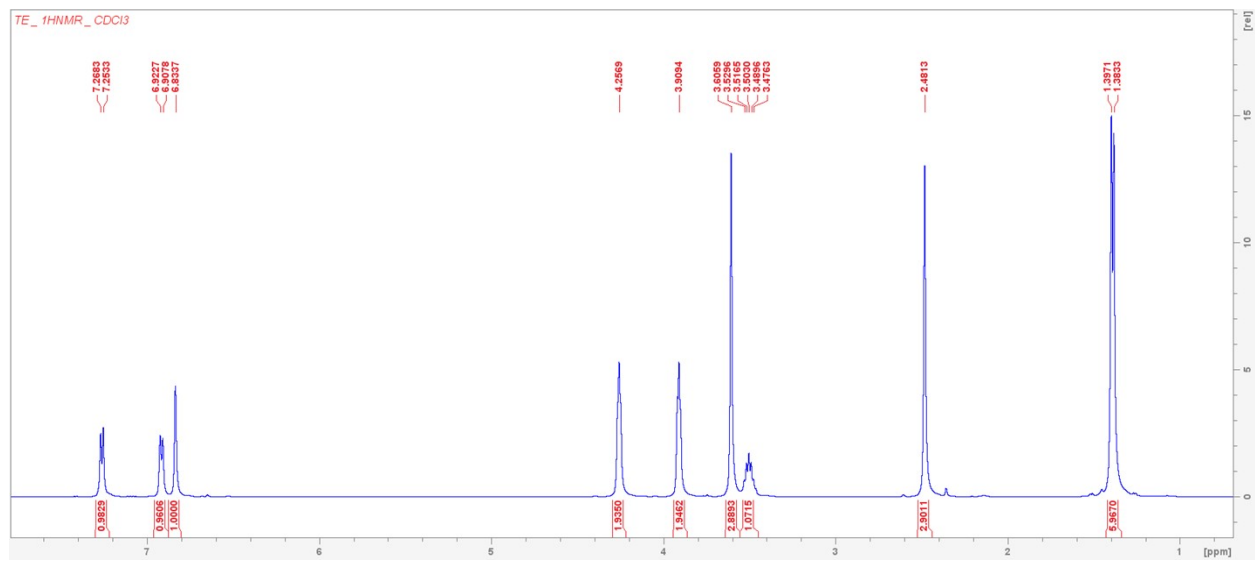


## Thymol and Carvacrol Derivatives as Anticancer Agents; Synthesis, In-Vitro Activity, and Computational Analysis of Biological Targets

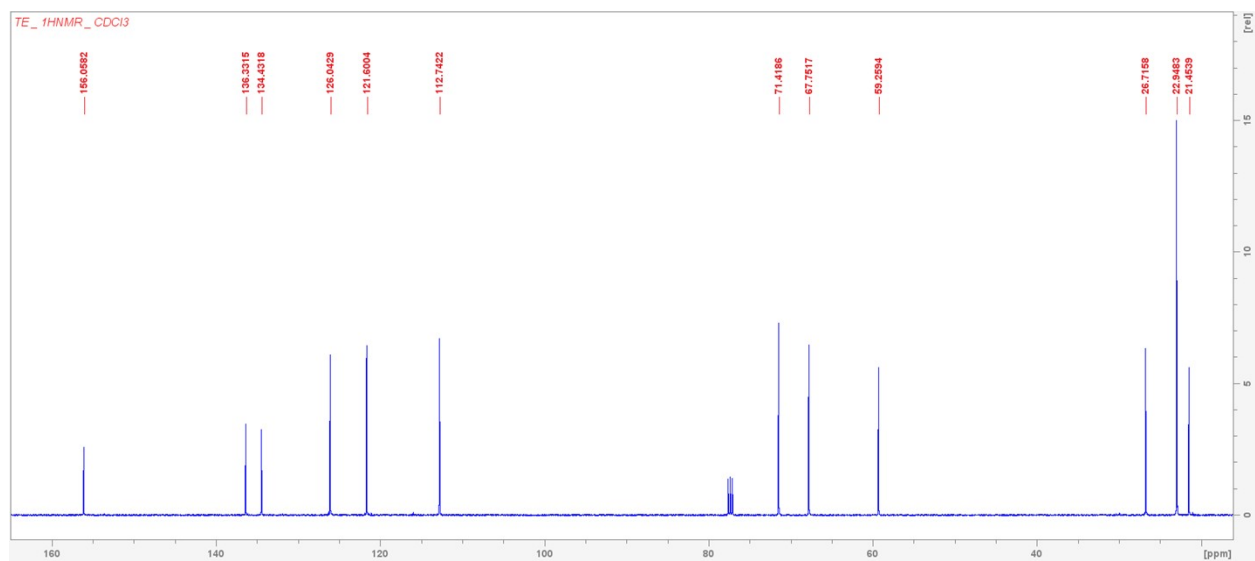
### Supplementary data

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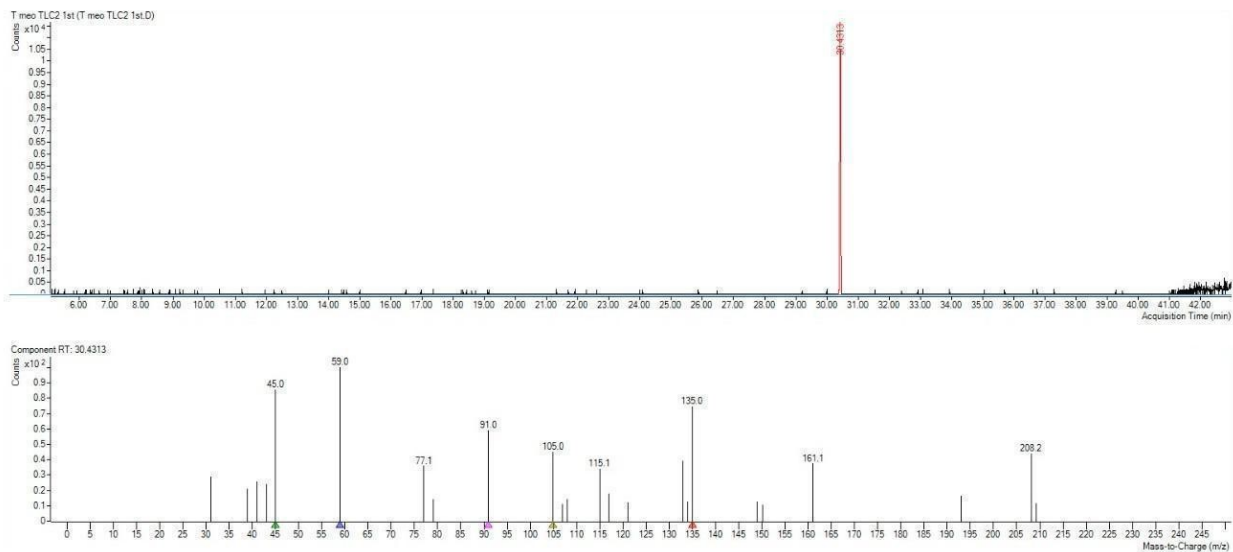
<b>Figure S1.</b>	<sup>1</sup> H-NMR spectrum of 1-isopropyl-2-(2-methoxy-ethoxy)-4-methyl-benzene (TE)
<b>Figure S2.</b>	<sup>13</sup> C-NMR spectrum of 1-isopropyl-2-(2-methoxy-ethoxy)-4-methyl-benzene (TE)
<b>Figure S3.</b>	GCMS analysis of 1-isopropyl-2-(2-methoxy-ethoxy)-4-methyl-benzene (TE)
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<b>Figure S26.</b>	HPLC analysis of 4-nitro-benzoic acid 5-isopropyl-2-methyl-phenyl ester (CN)
<b>Figure S27.</b>	In vitro anticancer activity at 10 μM.
<b>Table S1.</b>	Gene targets of the test compounds.



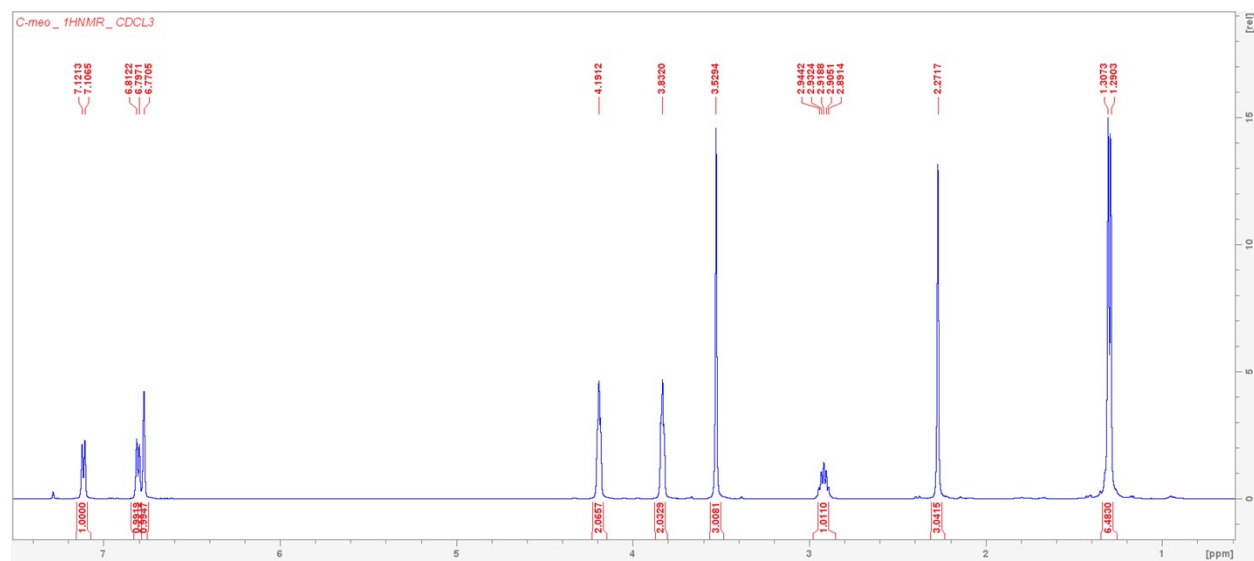
**Figure S1.**  $^1\text{H-NMR}$  spectrum of 2-isopropyl-1-(2-methoxy-ethoxy)-5-methyl-benzene (TE) in  $\text{CDCl}_3$ .



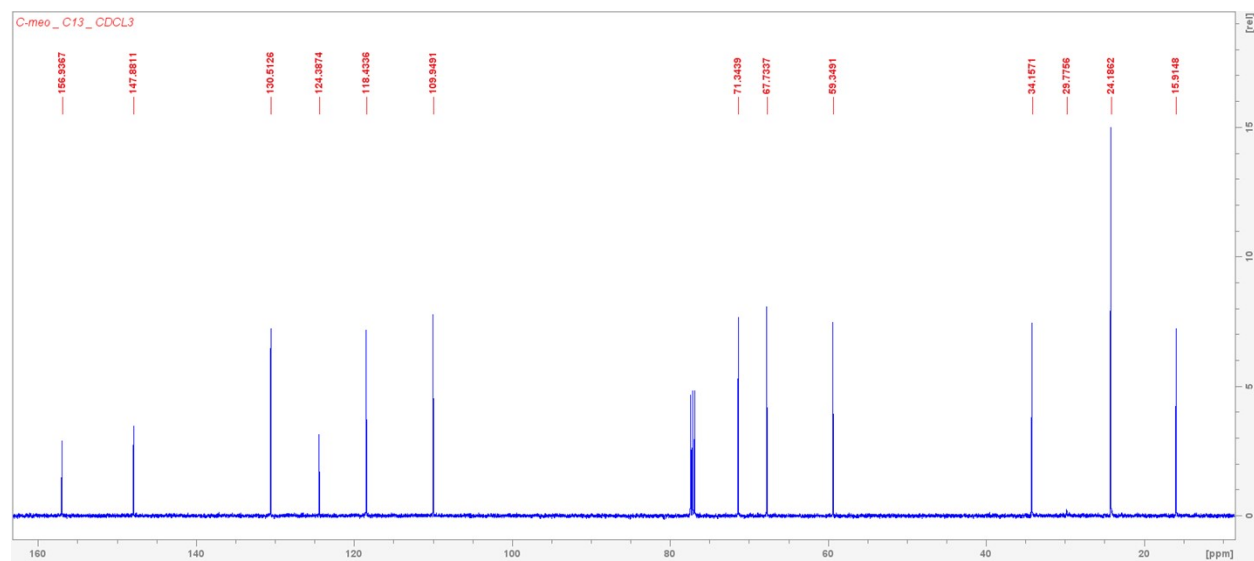
**Figure S2.**  $^{13}\text{C}$ -NMR spectrum of 2-isopropyl-1-(2-methoxy-ethoxy)-5-methyl-benzene (TE) in  $\text{CDCl}_3$ .



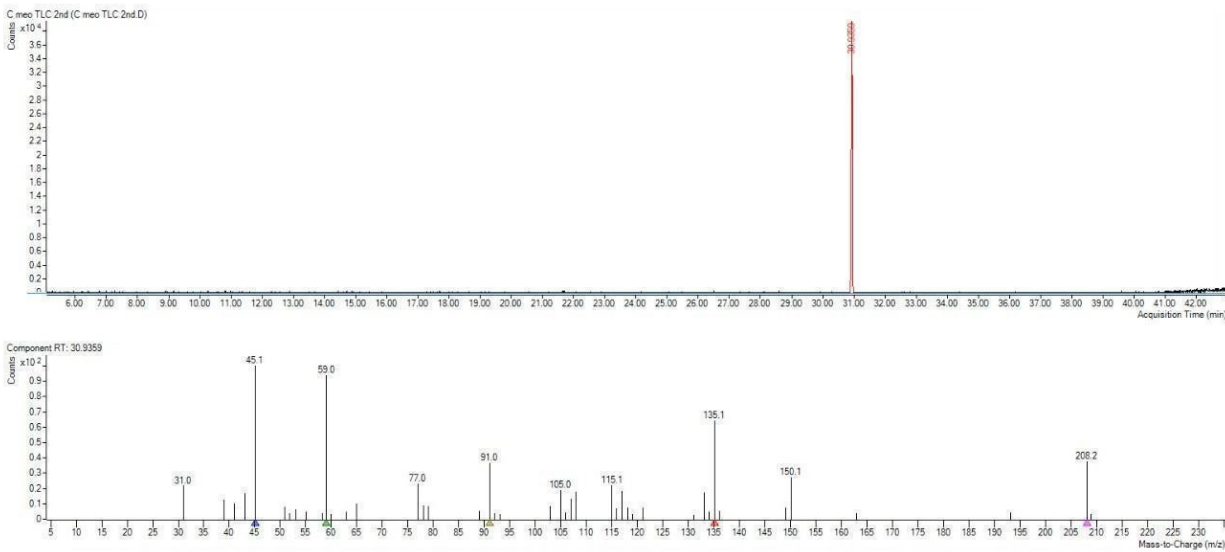
**Figure S3.** GCMS analysis of 2-isopropyl-1-(2-methoxy-ethoxy)-5-methyl-benzene (TE).



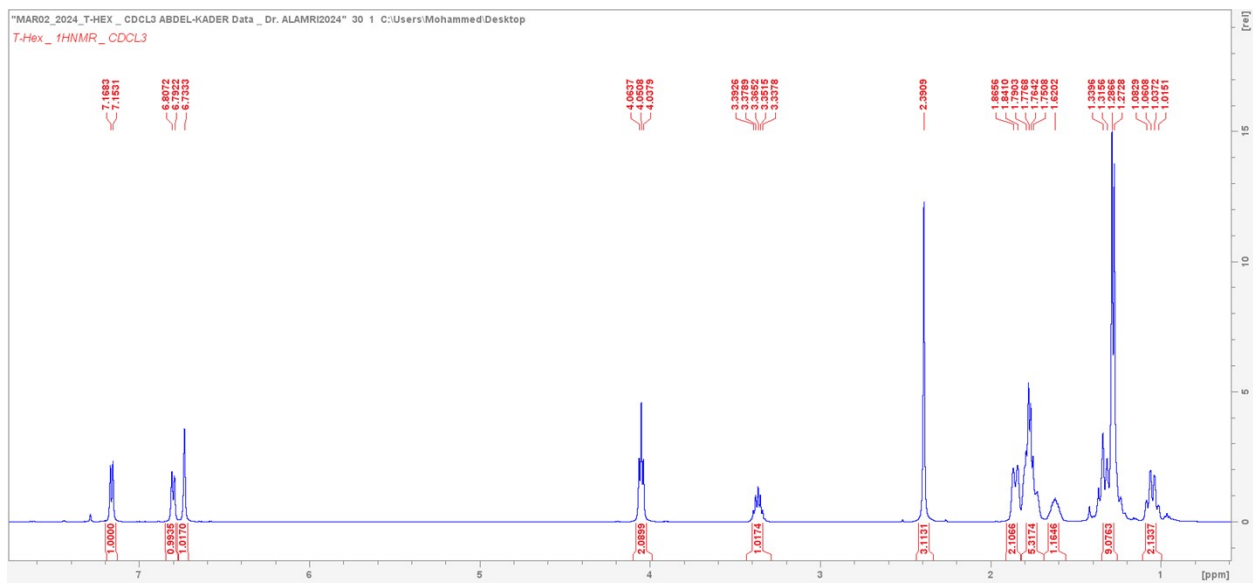
**Figure S4.** <sup>1</sup>H-NMR spectrum of 3-isopropyl-1-(2-methoxy-ethoxy)-6-methyl-benzene (CE) in CDCl<sub>3</sub>.



**Figure S5.** <sup>13</sup>C-NMR spectrum of 3-isopropyl-1-(2-methoxy-ethoxy)-6-methyl-benzene (CE) in CDCl<sub>3</sub>.

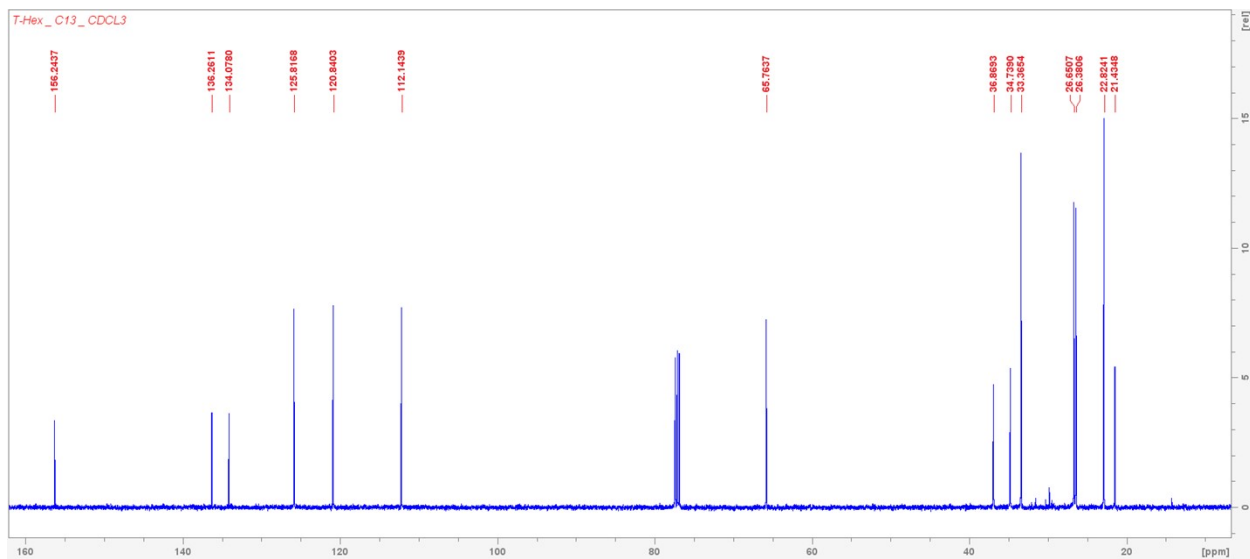


**Figure S6.** GCMS analysis of 3-isopropyl-1-(2-methoxy-ethoxy)-6-methyl-benzene (CE).

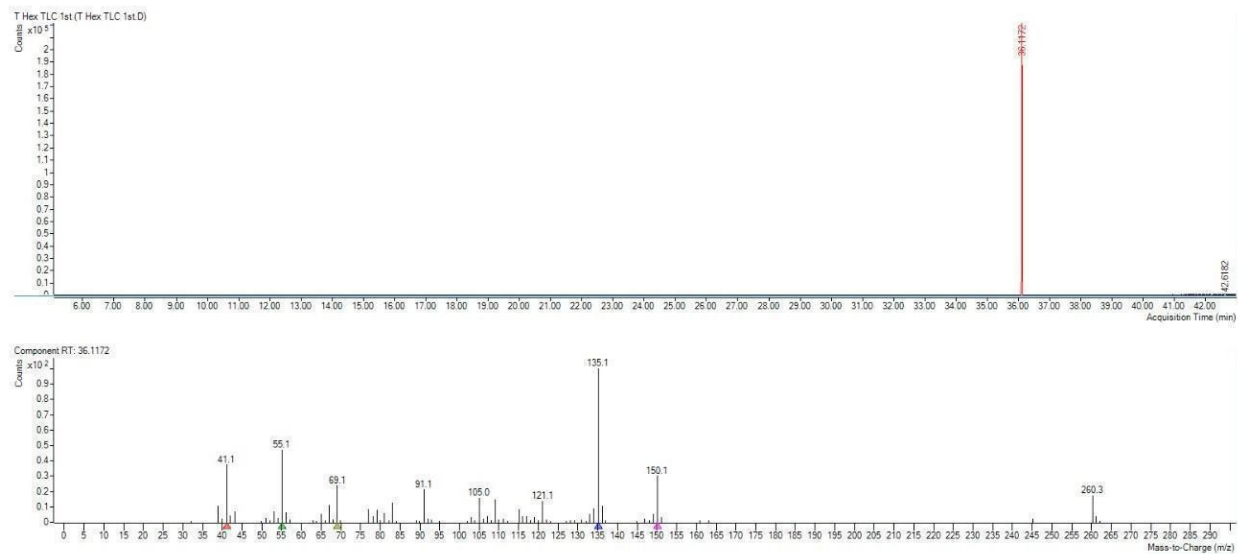


**Figure S7.** <sup>1</sup>H-NMR spectrum of 1-(2-cyclohexyl-ethoxy)-2-isopropyl-5-methyl-benzene (TH) in CDCl<sub>3</sub>.

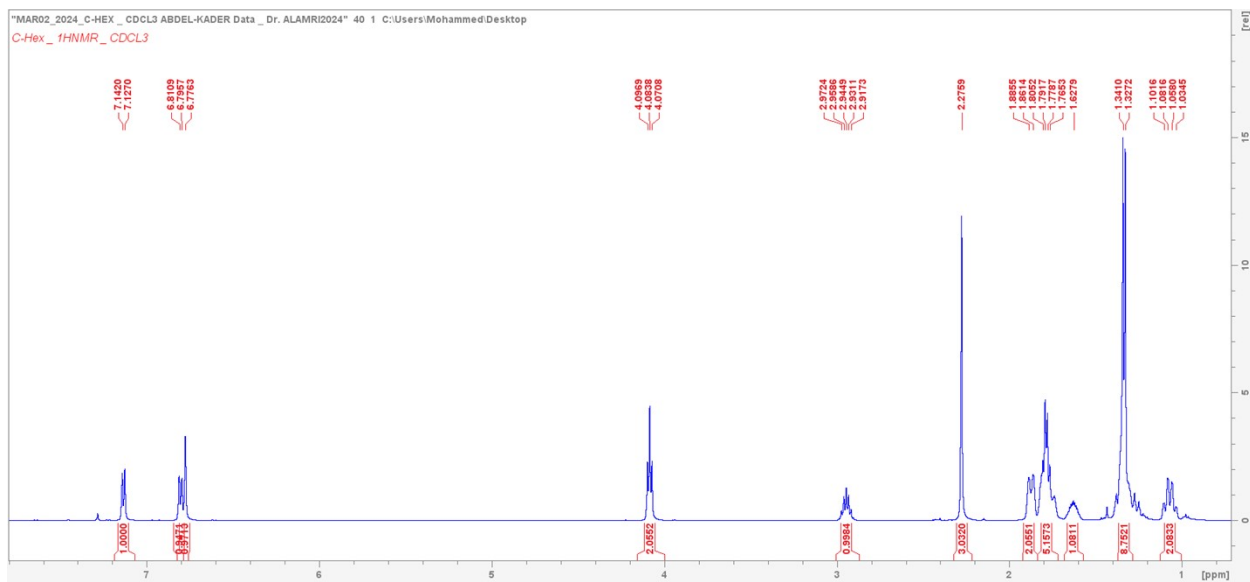




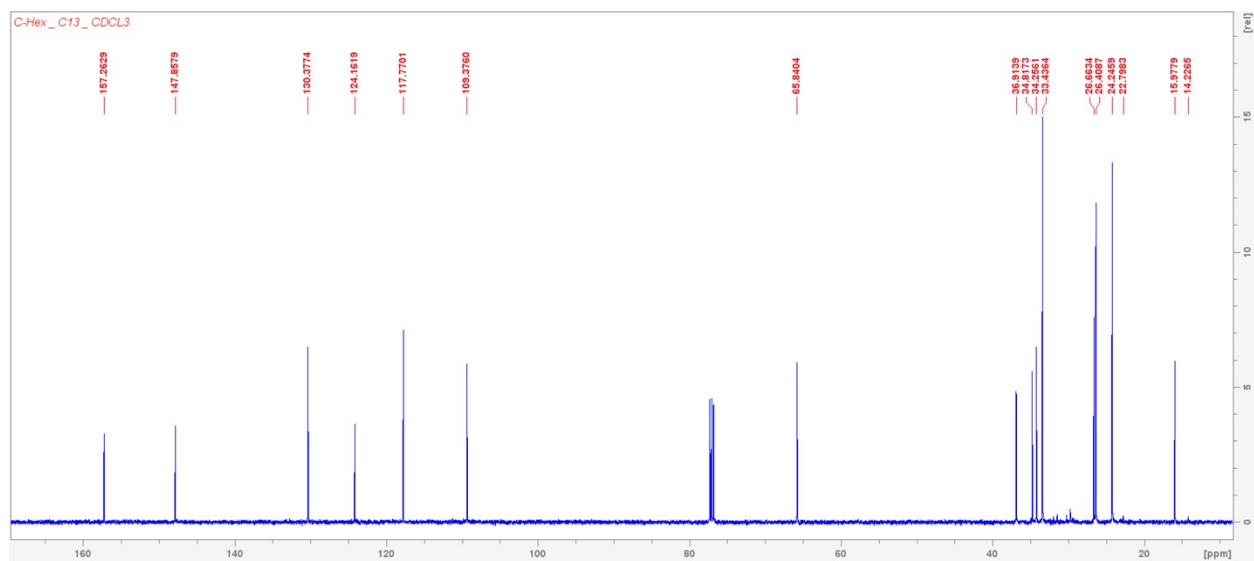
**Figure S8.** <sup>13</sup>C-NMR spectrum of 1-(2-cyclohexyl-ethoxy)-2-isopropyl-5-methyl-benzene (TH) in CDCl<sub>3</sub>.



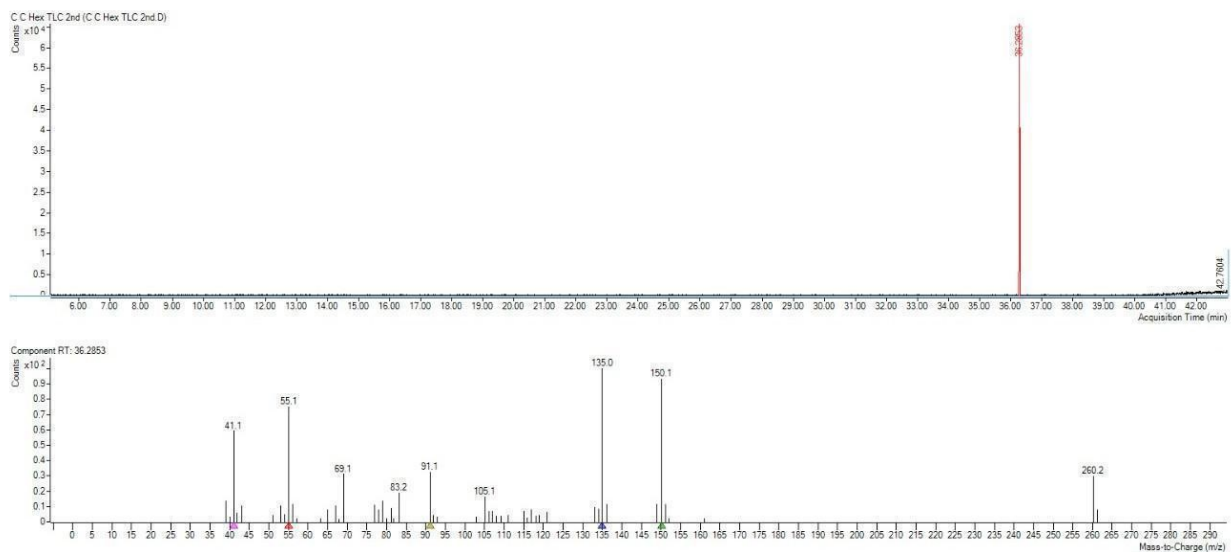
**Figure S9.** GCMS analysis of 1-(2-cyclohexyl-ethoxy)-2-isopropyl-5-methyl-benzene (TH).



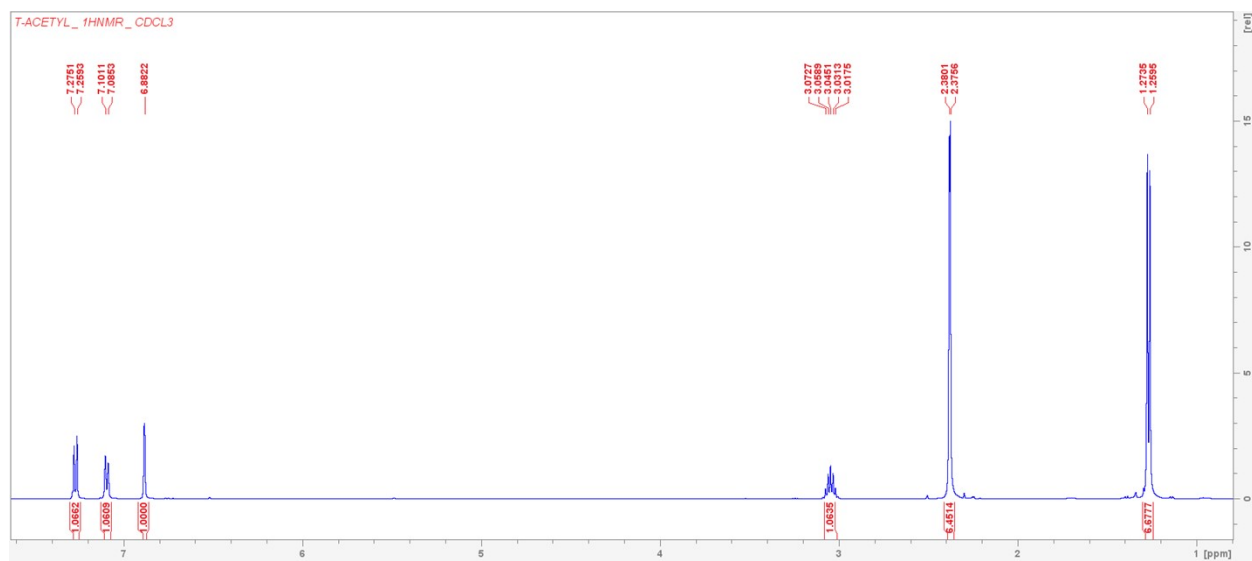
**Figure S10.**  $^1\text{H-NMR}$  spectrum of 1-(2-cyclohexyl-ethoxy)-3-isopropyl-6-methyl-benzene (CH) in  $\text{CDCl}_3$ .



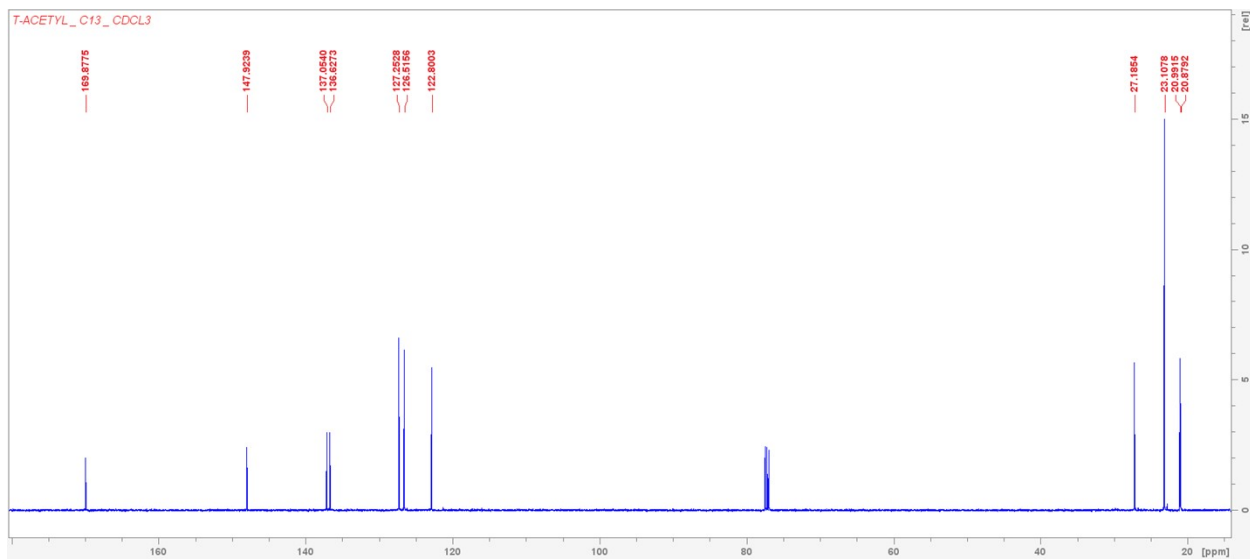
**Figure S11.** <sup>13</sup>C-NMR spectrum of 1-(2-cyclohexyl-ethoxy)-3-isopropyl-6-methyl-benzene (CH) in CDCl<sub>3</sub>.



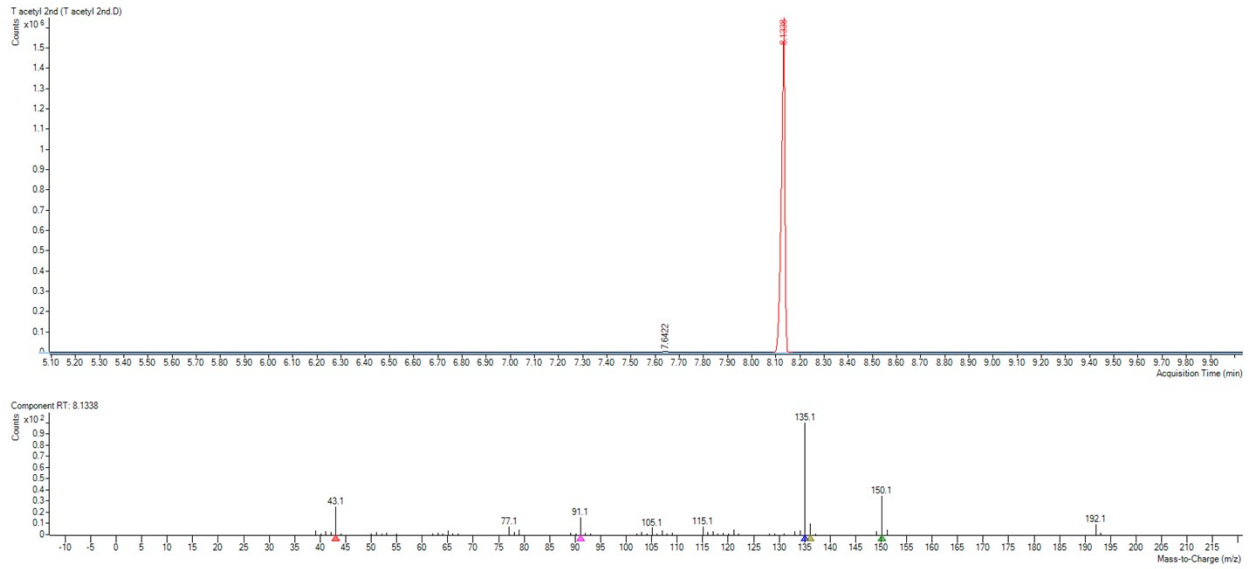
**Figure S12.** GCMS analysis of 1-(2-cyclohexyl-ethoxy)-3-isopropyl-6-methyl-benzene (CH).



**Figure S13.** <sup>1</sup>H-NMR spectrum of acetic acid 2-isopropyl-5-methyl-phenyl ester (TA) in CDCl<sub>3</sub>.

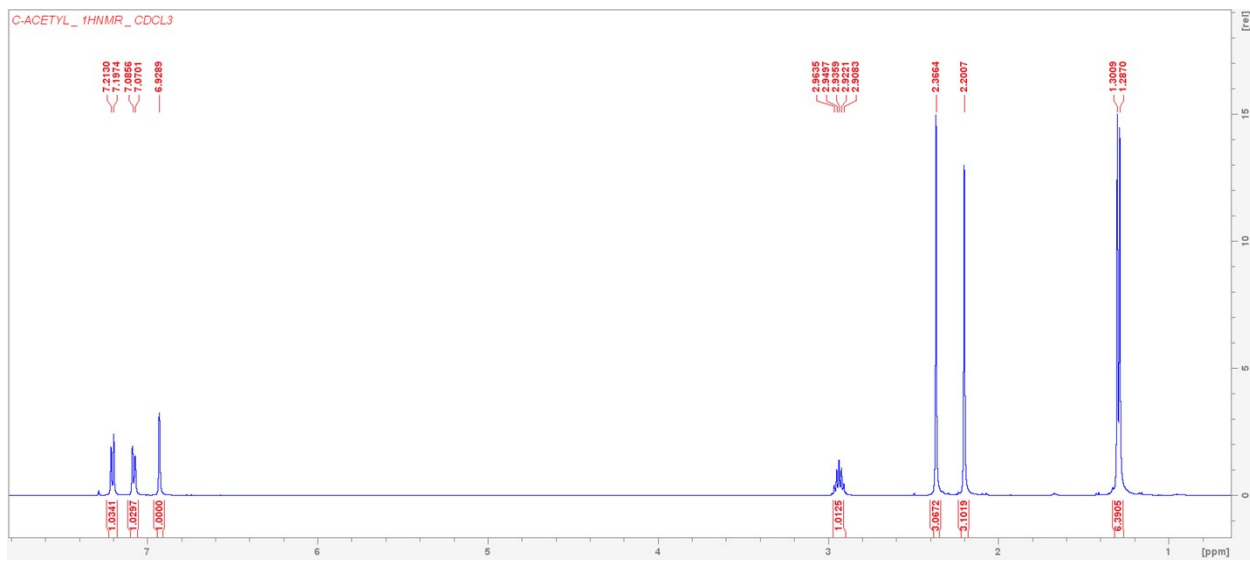


**Figure S14.**  $^{13}\text{C}$ -NMR spectrum of acetic acid 2-isopropyl-5-methyl-phenyl ester (TA) in  $\text{CDCl}_3$ .

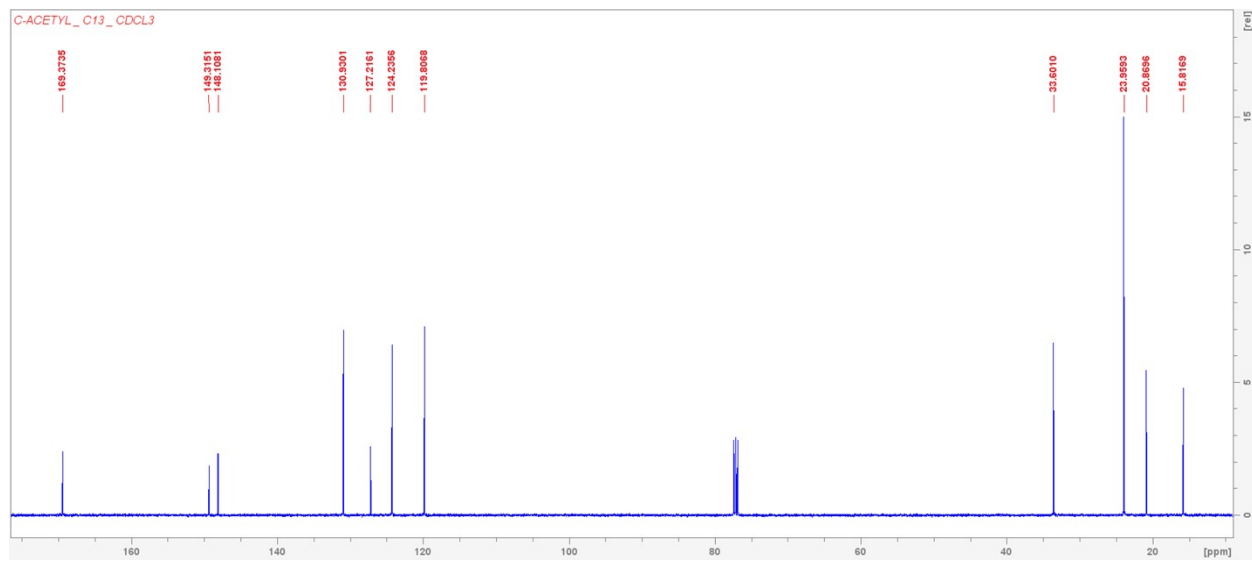


**Figure S15.** GCMS analysis of acetic acid 2-isopropyl-5-methyl-phenyl ester (TA).

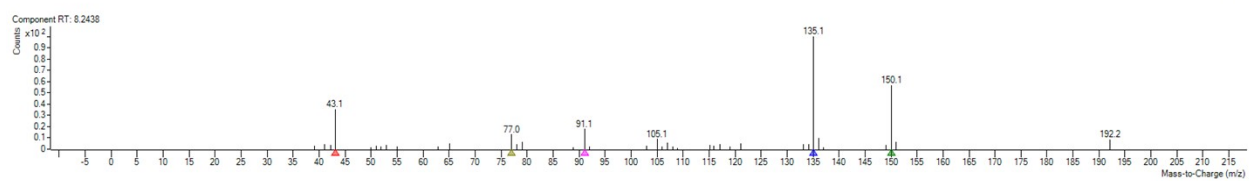
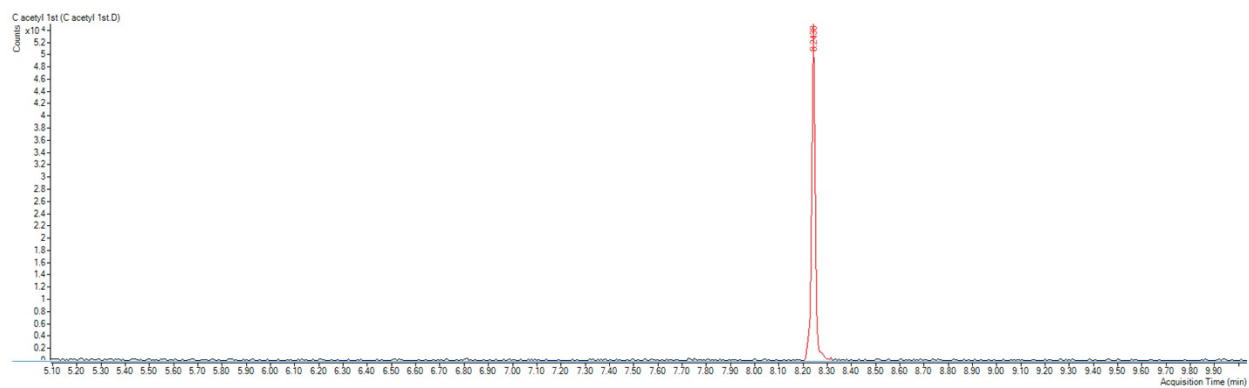




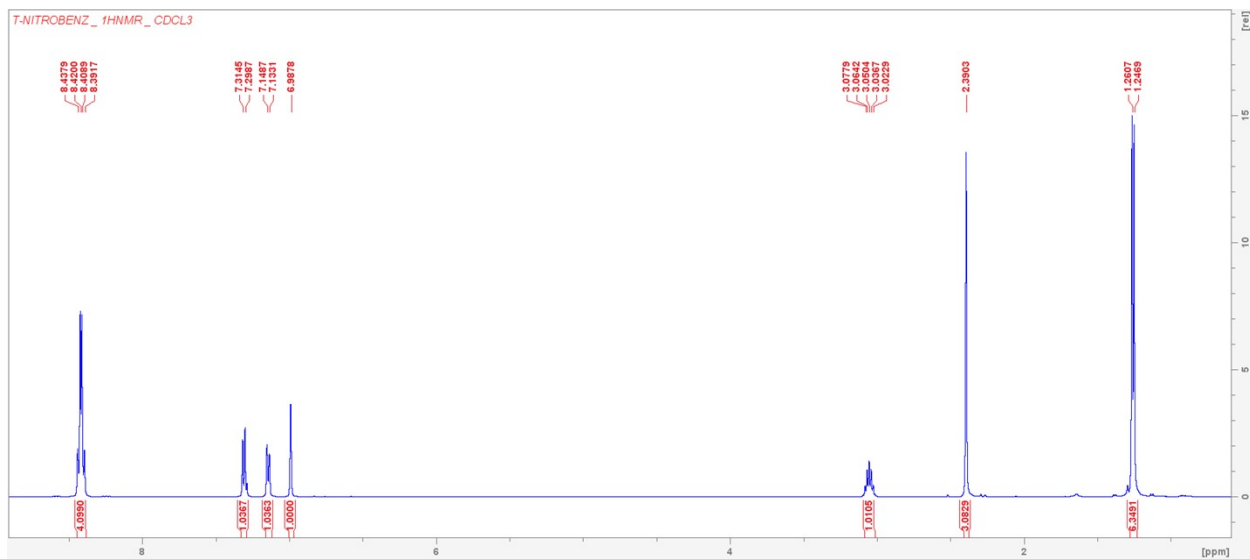
**Figure S16.** <sup>1</sup>H-NMR spectrum of acetic acid 3-isopropyl-6-methyl-phenyl ester (CA) in CDCl<sub>3</sub>.



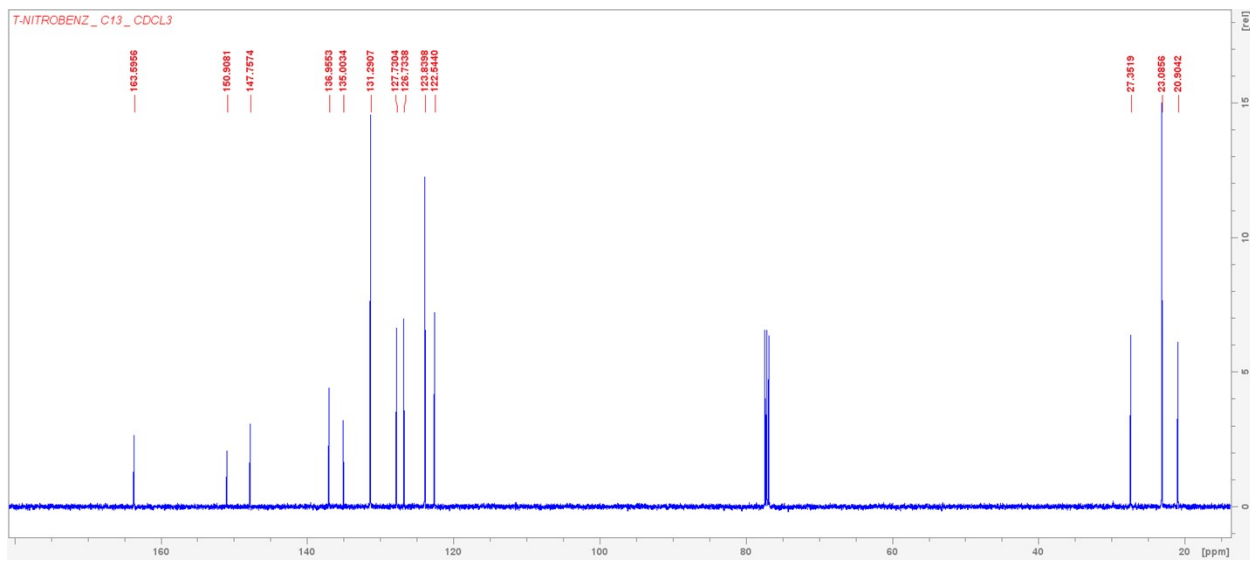
**Figure S17.**  $^{13}\text{C}$ -NMR spectrum of acetic acid 3-isopropyl-6-methyl-phenyl ester (CA) in  $\text{CDCl}_3$ .



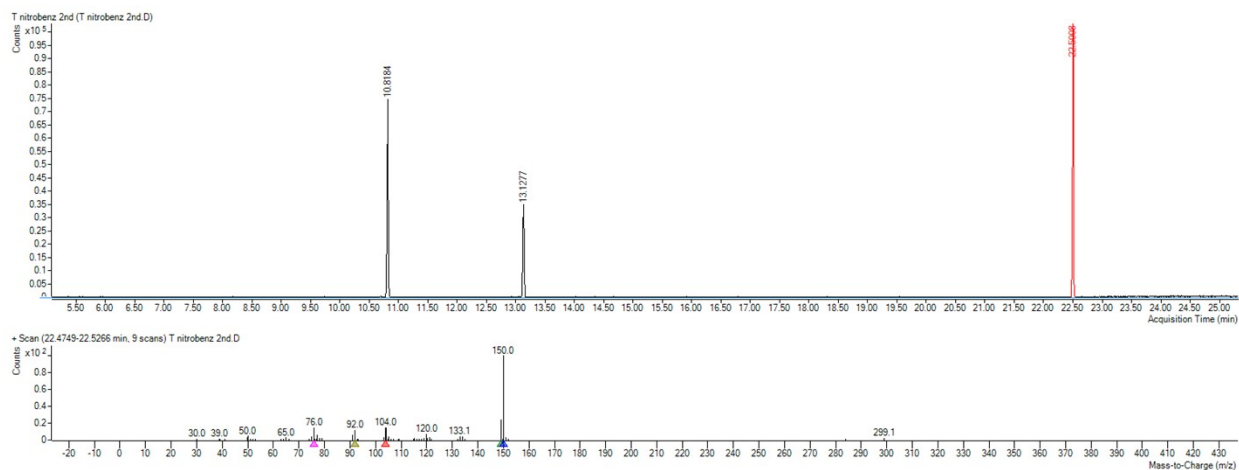
**Figure S18.** GCMS analysis of acetic acid 3-isopropyl-6-methyl-phenyl ester (CA).



**Figure S19.**  $^1\text{H-NMR}$  spectrum of 4-nitro-benzoic acid 2-isopropyl-5-methyl-phenyl ester (TN) in  $\text{CDCl}_3$ .



**Figure S20.** <sup>13</sup>C-NMR spectrum of 4-nitro-benzoic acid 2-isopropyl-5-methyl-phenyl ester (TN) in CDCl<sub>3</sub>.



**Figure S21.** GCMS analysis of 4-nitro-benzoic acid 2-isopropyl-5-methyl-phenyl ester (TN). Fragmentation occurred possibly due to high temperature.

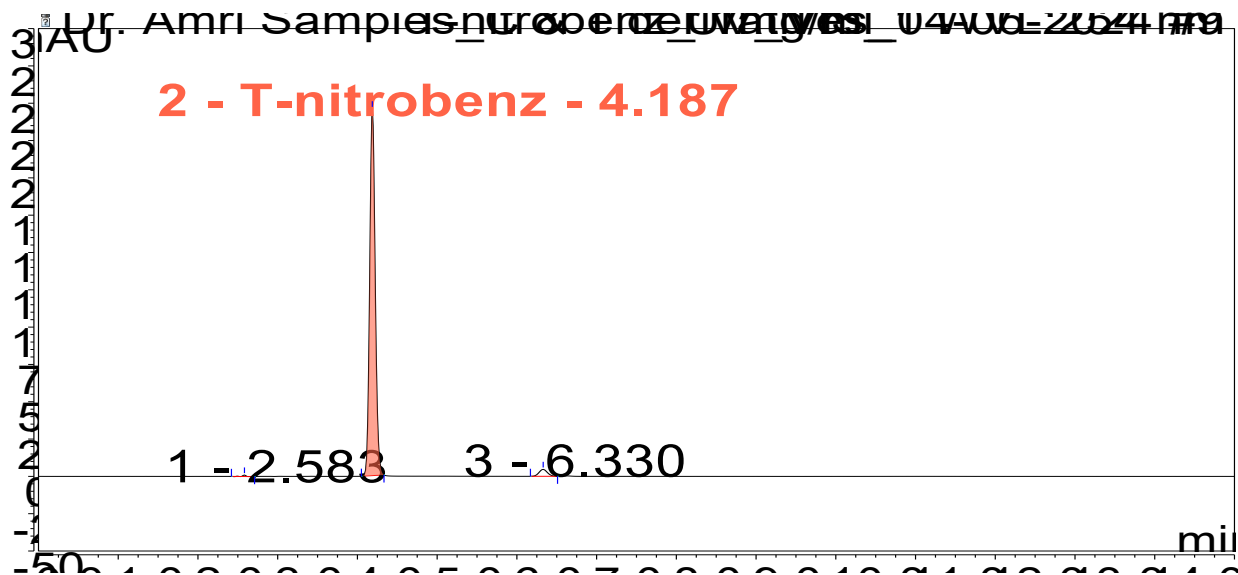
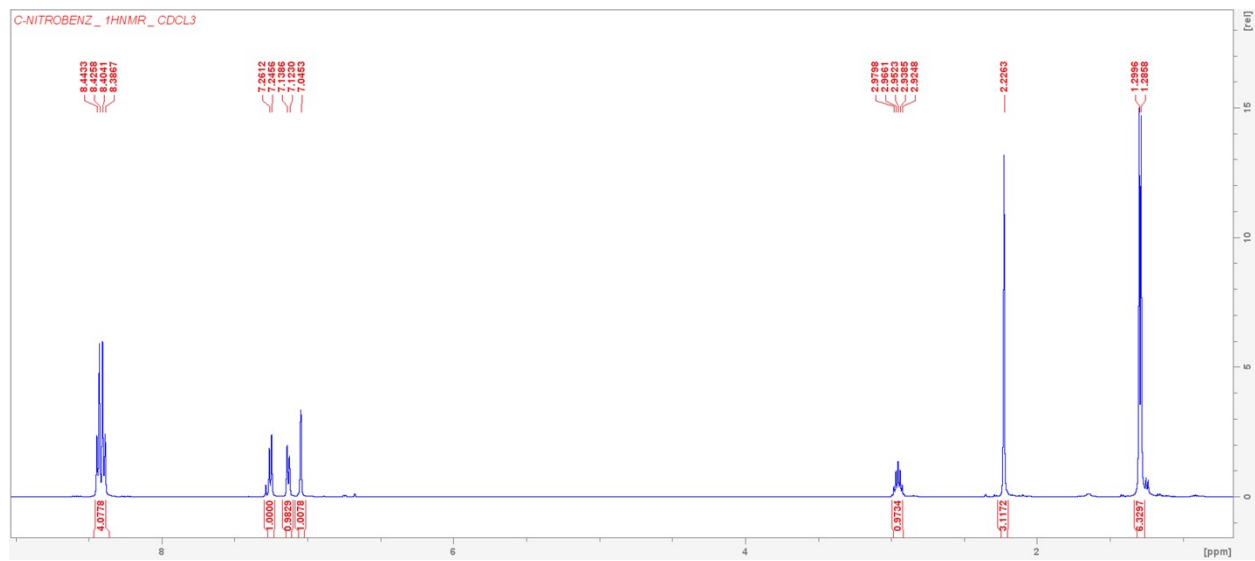
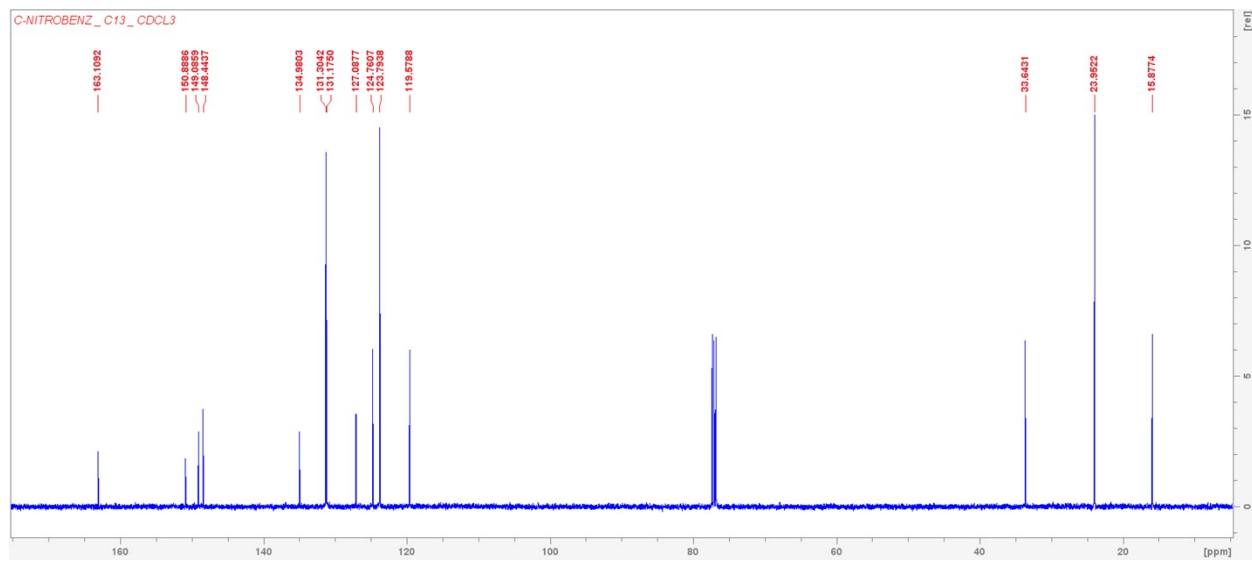


Figure S22. HPLC analysis of 4-nitro-benzoic acid 2-isopropyl-5-methyl-phenyl ester (TN).

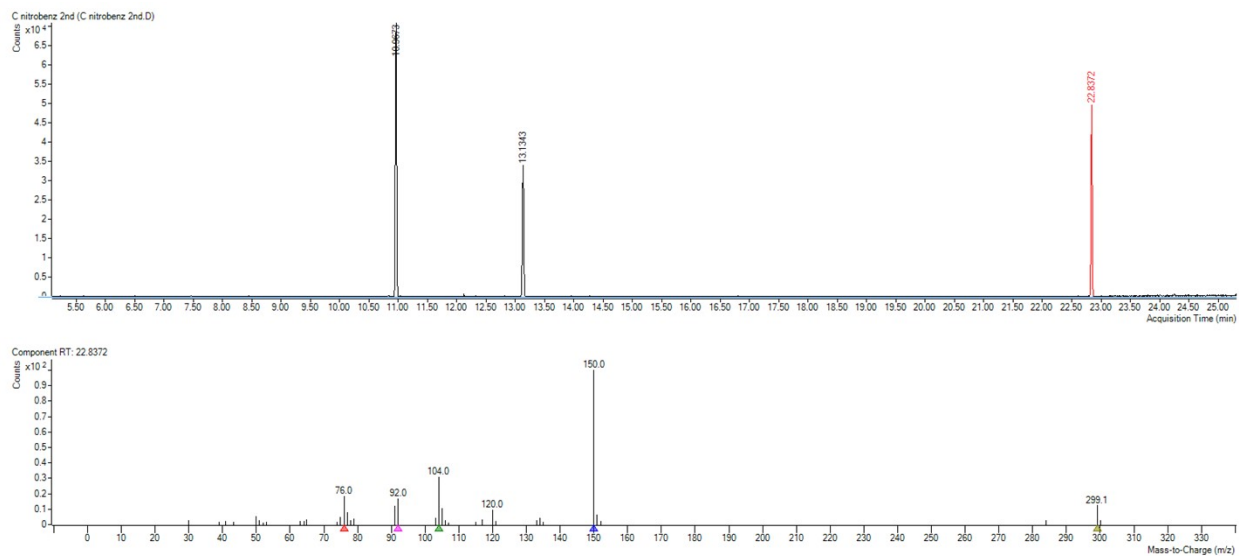


**Figure S23.** <sup>1</sup>H-NMR spectrum of 4-nitro-benzoic acid 3-isopropyl-6-methyl-phenyl ester (CN) in CDCl<sub>3</sub>.





**Figure S24.**  $^{13}\text{C}$ -NMR spectrum of 4-nitro-benzoic acid 3-isopropyl-6-methyl-phenyl ester (CN) in  $\text{CDCl}_3$ .



**Figure S25.** GCMS analysis of 4-nitro-benzoic acid 3-isopropyl-6-methyl-phenyl ester (CN). Fragmentation occurred possibly due to high temperature.

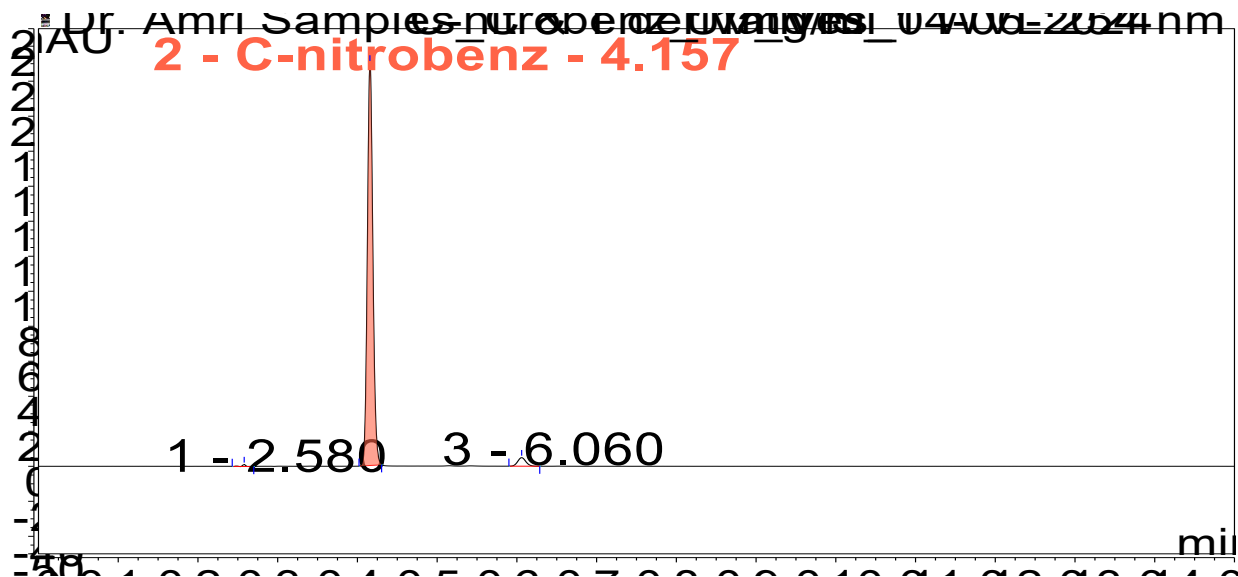
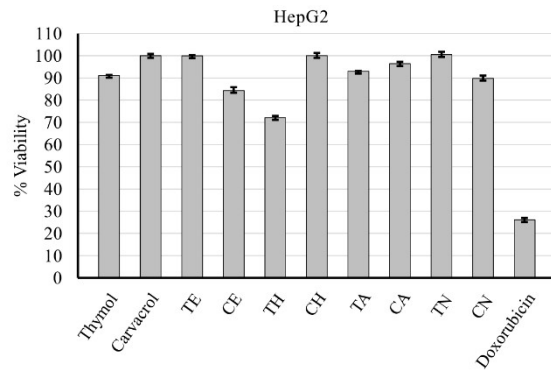
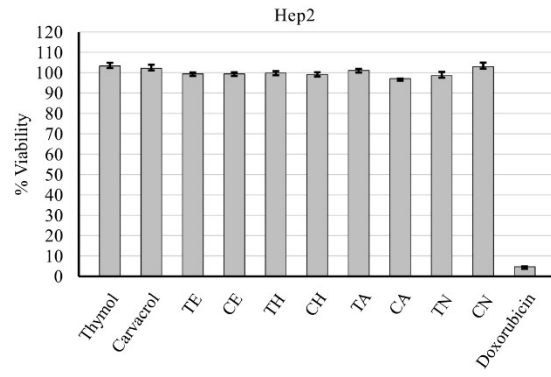
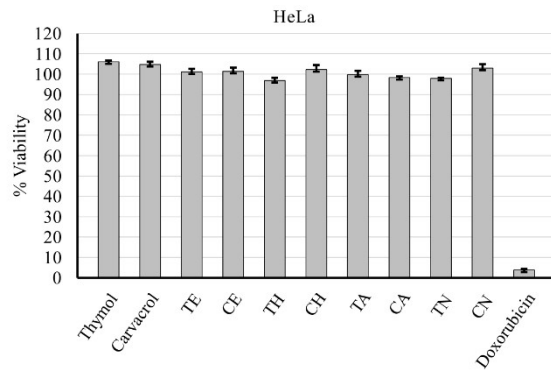
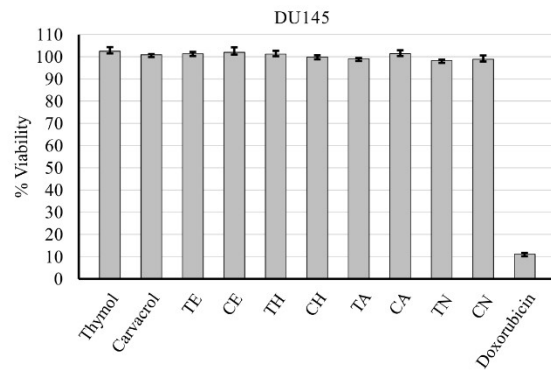
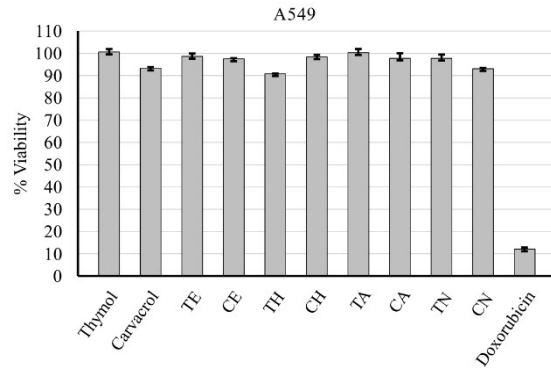
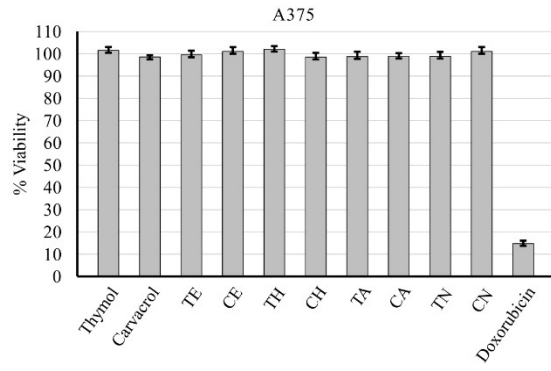
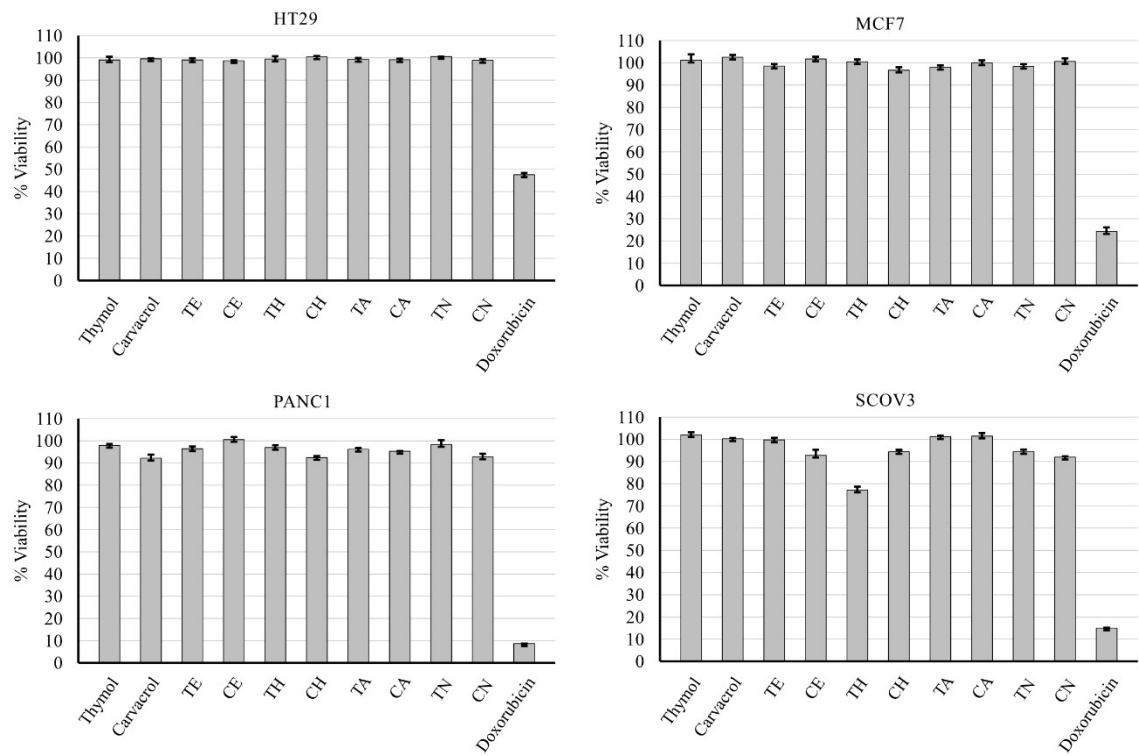


Figure S26. HPLC analysis of 4-nitro-benzoic acid 3-isopropyl-6-methyl-phenyl ester (CN).





**Figure S27.** In vitro anticancer activity at 10  $\mu$ M.

Compound genes overlapping with top 25k cancer genes

Thymol	Carvacrol	TE	CE	TH	CH	TA	CA	TN	CN	All	KCNMA1
DRD3	ALB	UTS2R	TNKS2	PTPN1	PTPN1	TNKS2	EGFR	CDC25B	MMP2	JAK2	KCNMA1
ALB	SLC6A2	BRD3	TNKS	CTSK	TNKS	ALDH2	ALDH2	GSTP1	CDC25B	CASP1	NO52
HTR2B	ACHE	CLK2	ALDH2	GRM1	ALDH2	CTSB	CTSB	ACR	GSTP1	CASN1	ELANE
NOS3	HTR2A	MAPK14	HOAC1	EPHX1	CSAR1	UTS2R	UTS2R	ACR	EPHX2	CACNA1C	BRD4
TRPA1	TRPA1	CTSK	BRD3	VCP	EPHX1	KCN33	KCN33	MALT1	MBO2	SELE	CLK3
HDAC8	SLC6A4	CTSK	BRD3	CRHR1	VCP	HSD17B3	ABCC1	MAP3K8	NY5R	CTSH	GSK3B
CA2	CA2	PK3CD	CXCR2	DUSP3	EPHX2	EPHX2	EPHX2	ADAMTSS	SNCA	FGFR1	IDO1
CHRM2	CHRM2	MGILL	MAPK14	CNRI	CNRI	CBFB	EPHX1	CYP22A19	MBO2	PRKDC	CXCR1
PRKCA	PRKCA	BCHE	PDE10A	TTR	TTR	EPHX1	PDE10A	PDE4D	ACR	CHRM2	CDK2
CYP19A1	TYR	PDE10A	CTSK	PSMB5	PSMB5	PDE10A	TRPM8	MAPK1	HMOX1	HMOX1	GABRA5
DRD5	HTR2C	MPO	MGILL	TLR9	ACT1	TRPM8	QPCT	HSD17B3	IRAK4	IRAK4	FLT4
JAK1	JAK1	GABRA6	CYP19A1	ACT1	MC4R	CYP11B2	MAPK8	MAPK8	PGR	IRAK4	CHRNA7
JAK1	CHRM1	CLK1	PDE10A	MC4R	ROBA	GPIR	HMOX1	PDE4B	ALB	RPS6KB1	CDCA25A
AR	CHRM1	PIK3CG	MPO	ROBA	SLCSA1	PIK3CG	KCN22	EPHX2	CASP4	MAPKAPK2	HRH4
PTGS1	JAK2	SYK	GABRA6	CNRI	CNRI	EPHX1	FAAH	EPHX1	BRD3	C5AR1	LIPE
CHRM1	ESRRG	TLR9	CLK1	SLCSA1	ROBB	GSK3A	HTR6	GSK3A	SLC6A2	ROCK2	ILK
JAK2	FLT3	PRKDC	PRKDC	CNRI	AVPR2	HMOX1	PABPC1	IRAK4	MALT1	BGHE	TGFBRI
NOS1	CDK2	PLA2G7	PLA2G7	ROBB	PHLPP1	KCN22	EGLN3	IRAK4	AKR1B10	PDE4A	MAOB
ESRRG	AURKA	CYP11B1	CYP11B1	AVPR2	P2RX4	TSP0	CTSH	MYC	CLK2	CYP17A1	SRC
HTR6	SLC6A3	TSP0	KDR	PHLPP1	CCR5	ADORA1	PLA2G6	MMP1	MAP2	NRIH3	PK3CA
HSD11B1		CLK4	TSP0	ILK	ILK	ADORA1	PLA2G6	MMP1	MAP2	KDR	PPME1
FLT3		CLK4	TSP0	ILK	ILK	ADORA1	PLA2G6	MMP1	MAP2	CXCR2	PPME1
HDAC6		PIK3CB	CLK4	NRI12	METAP1	PIK3CB	CTRBB1	MMP3	MAPK14	ROBA	KCN11
IDO1		KNMA5	KNMA5	RORC	RORC	FAAH	TBXAS1	DUSP3	MAPK14	TRPV1	IGFIR
AURKA		HSD11B1	HSD11B1	SLCSA4	SLCSA4	CYP11B1	KCNMA1	CEP	MAPK14	TRPV1	IGFIR
CA4		SCN9A	GABRA1	ALOX5	KNNA4	EPGN3	GSK3B	ROCK2	MAPK14	TRPV1	IGFIR
SLC6A3		BRD2	GABRA1	KCNNA4	KCNNA4	HSD11B1	HRH4	TRPM8	MAPK14	TRPV1	IGFIR
		BRD2	BRD2	ILK	ILK	CTSH	LIPE	TBXAS1	MAPK14	TRPV1	IGFIR
		P2RX7	P2RX7	PLA2G6	TGFBRI	PLA2G6	PDE4C	DYSK2	MAPK14	TRPV1	IGFIR
		NLRP3	NLRP3	IDH1	KCN11	PDE4C	LRRK2	TRPM8	MAPK14	TRPV1	IGFIR
		CTSS	TBXAS1	TBXAS1	F2	AURKA	LRRK2	DYSK2	MAPK14	TRPV1	IGFIR
		TBXAS1	MAPK14	KCNMA1	KNNA4	KNMA1	PKG1	CLK1	CLK1	CLK1	F2
		RAPGEF4	RAPGEF4	ELANE	ELANE	ELANE	ALOX5	PIK3CG	TRPA1	PDGFRB	METAP1
		CYS15	CYS15	GSK3B	GSK3B	HRH4	ROCK1	JAK1	TRPA1	PDGFRB	METAP1
		HDAC6	HDAC6	HRH4	HRH4	HRH4	ROCK1	JAK1	TRPA1	PDGFRB	METAP1
		CCR5	NOS2	LIPE	LIPE	LIPE	VCAM1	AKT1	TRPA1	PDGFRB	METAP1
		NOS2	BRD4	BRD4	BRD4	BRD4	ROCK1	JAK1	TRPA1	PDGFRB	METAP1
		GSK3B	GSK3B	CXCR1	CXCR1	CXCR1	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		GABRA5	GABRA5	REL	REL	REL	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		PIK3CA	PIK3CA	VCAM1	VCAM1	VCAM1	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		SLC6A3	SLC6A3	VCAM1	VCAM1	VCAM1	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		YS1	YS1	CASP1	CASP1	CASP1	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		DTOR	DTOR	CACNA1C	CACNA1C	CACNA1C	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		DYSK1B	DYSK1B	PDE9A	PDE9A	PDE9A	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		CTSL	CTSL	MPI	MPI	MPI	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1
		FKBP1A	FKBP1A	SCN9A	SCN9A	SCN9A	TRPC3	PRKCZ	TRPA1	PDGFRB	METAP1

Table S1. Gene targets of the test compounds.