Supporting Information

Piperidine and valproic acid hybrid compound (F2S4-p-VPA) outperforms methotrexate as anti-proliferative and cells migration inhibition

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This article contains the following complimentary material:

Table 1S. ADMET physicochemical properties for F2S4-p-VPA, F3S4-m-VPA, VPA, and MTX calculated in ADMESTAR

Table 2S. ADMET physicochemical properties for F2S4-p-VPA, F3S4-m-VPA, VPA, and MTX calculated in Data Warrior

S1 Fig. ^{1}H NMR spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).

S2 Fig. ^{13}C NMR spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).

S3 Fig. FT-IR spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).

S4 Fig. Mass spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).

S5 Fig. ^{1}H NMR spectrum of N-(4-methoxy-3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F3S4-m-VPA).

S6 Fig. ^{13}C NMR spectrum of N-(4-methoxy-3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F3S4-m-VPA).

S7 Fig. FT-IR spectrum of N-(4-methoxy-3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F3S4-m-VPA).

S8 Fig. Mass spectrum of N-(4-methoxy-3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F3S4-m-VPA).

S9 Fig. Cell migration without LPS and with LPS (A), and LN-18 cells without F2S4-p-VPA and with the compound.

Table 1S. ADMET physicochemical properties for F2S4-p-VPA, F3S4-m-VPA, VPA, and MTX calculated in ADMESTAR

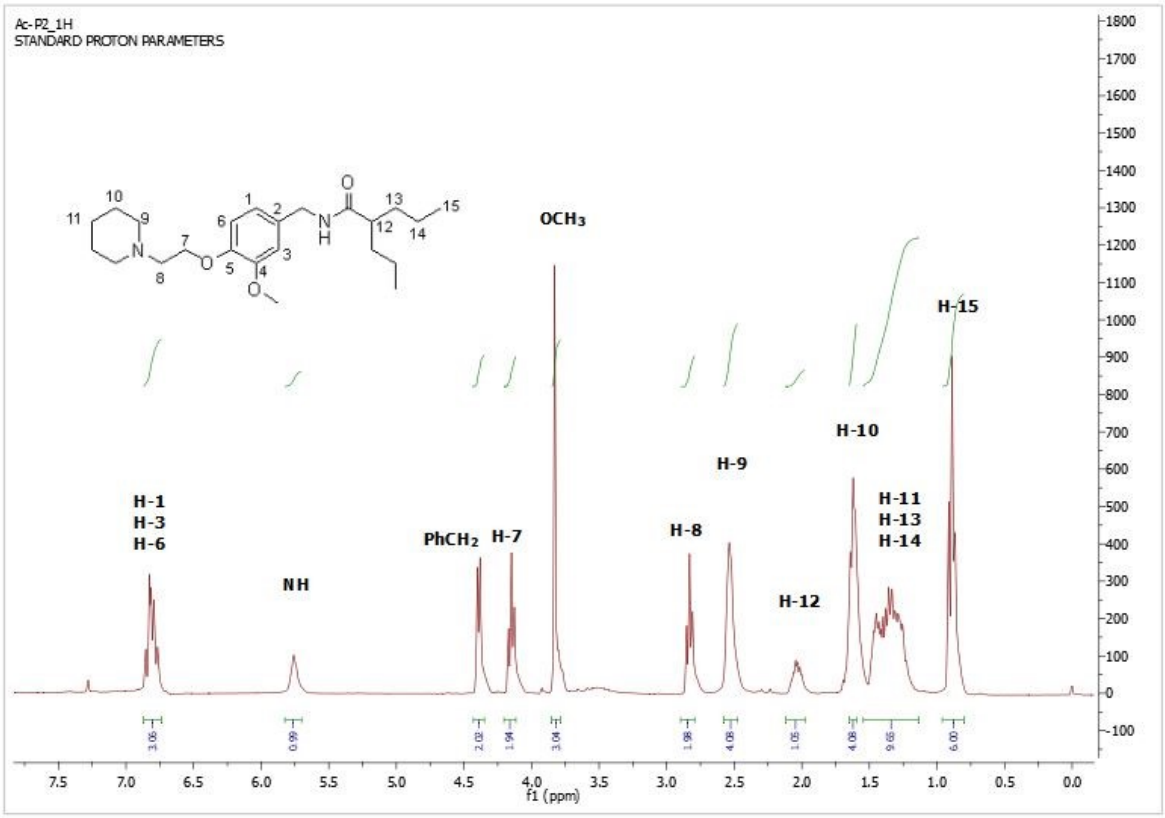
	F2S4p-VPA	F3S4m-VPA	VPA	MTX
Ames mutagenesis	-	-	-	-
Acute Oral Toxicity (c)	III	III	III	II
Androgen receptor binding	-	-	-	-
Aromatase binding	-	+	-	+
Avian toxicity	-	-	-	-
Blood Brain Barrier	+	+	+	-
BRCP inhibitior	-	-	-	-
Biodegradation	+	-	+	-
BSEP inhibitior	+	+	-	-
Caco-2	+	+	+	-
Carcinogenicity (binary)	-	-	-	-
Carcinogenicity (trinary)	Non-required	Non-required	Non-required	Non-required
Crustacea aquatic toxicity	-	-	-	-
CYP1A2 inhibition	-	-	-	-
CYP2C19 inhibition	-	-	-	-
CYP2C9 inhibition	-	-	-	-
CYP2C9 substrate	-	-	+	-
CYP2D6 inhibition	-	-	-	-
CYP2D6 substrate	+	+	-	-
CYP3A4 inhibition	-	-	-	-
CYP3A4 substrate	+	+	-	+
CYP inhibitory promiscuity	-	-	-	-
Eye corrosion	-	-	+	-
Eye irritation	-	-	+	-
Estrogen receptor binding	-	-	-	-
Fish aquatic toxicity	-	-	+	-
Glucocorticoid receptor binding	+	-	-	-
Honey bee toxicity	-	-	-	-
Hepatotoxicity	-	-	+	+
Human Ether-a-go-go-Related Gene inhibition	+	+	-	-

Human Intestinal Absorption	+	+	+	+
Human oral bioavailability	-	-	+	-
MATE1 inhibitior	-	-	-	-
Mitochondrial toxicity	+	+	+	+
Micronuclear	-	-	-	+
Nephrotoxicity	-	-	-	+
Acute Oral Toxicity	1.978913	2.009778	1.584623	2.482646942
OATP1B1 inhibitior	+	+	+	+
OATP1B3 inhibitior	+	+	+	+
OATP2B1 inhibitior	-	-	+	-
OCT1 inhibitior	-	-	-	-
OCT2 inhibitior	-	-	-	-
P-glycoprotein inhibitior	-	-	-	-
P-glycoprotein substrate	+	+	-	+
PPAR gamma	-	-	-	+
Plasma protein binding	0.692681	0.723911	0.960923	0.637697041
Reproductive toxicity	+	+	+	+
Respiratory toxicity	+	+	+	+
Skin corrosion	-	-	-	-
Skin irritation	-	-	-	-
skin sensitisation	-	-	+	-
Subcellular localzation	Mitochondria	Mitochondria	Mitochondria	Mitochondria
Tetrahymena pyriformis	1.002317	0.950426	0.123869642	0.475140363
Thyroid receptor binding	+	+	-	+
UGT catelyzed	-	-	-	-
Water solubility	-2.1863	-2.1863	-1.92252	-3.065080097

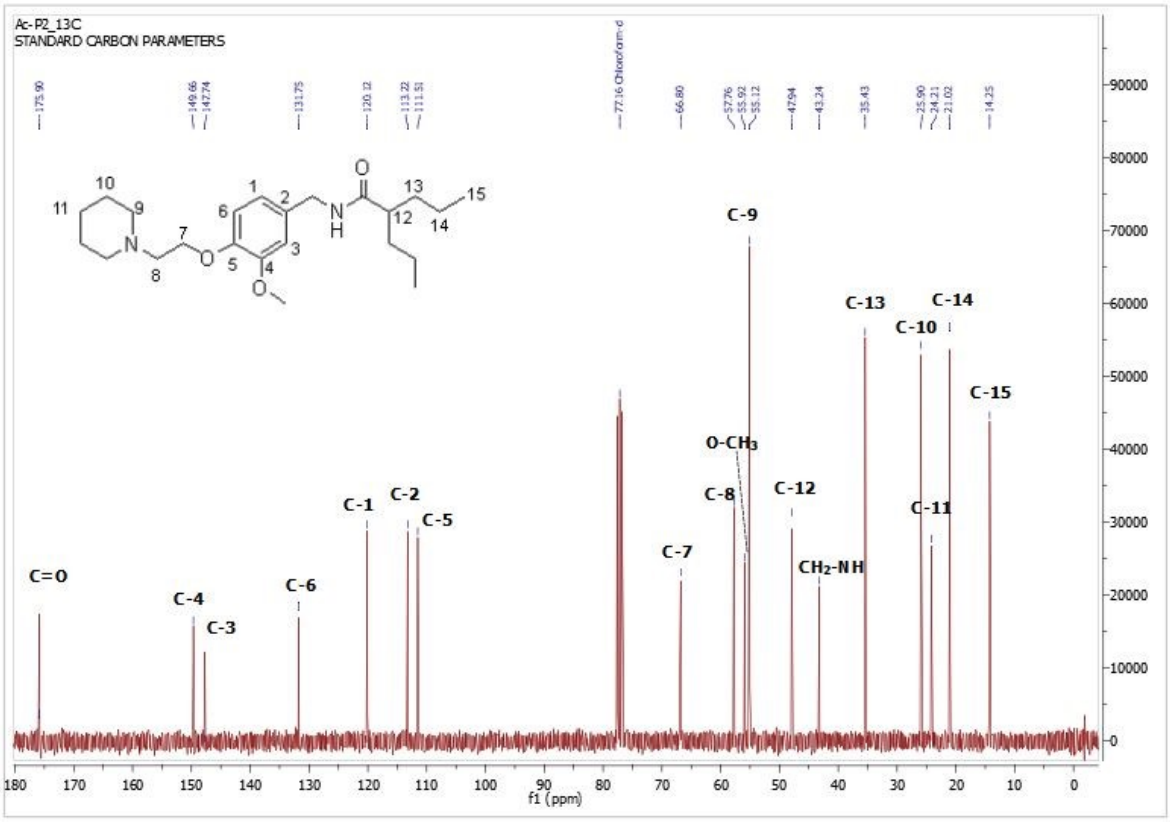
Table 2S. ADMET physicochemical properties for F2S4-p-VPA, F3S4-m-VPA, VPA, and MTX calculated in Data Warrior

Molecule Name	VPA	MTX	F2S4P-VPA	F3S4M-VPA
Total Molweight	144.213	454.446	390.566	376.539
Molweight	144.213	454.446	390.566	376.539
Monoisotopic Mass	144.11503	454.171317	390.288243	376.272593
cLogP	2.1912	-1.2285	4.2558	3.9138
cLogS	-1.969	-3.767	-3.699	-3.429
H-Acceptors	2	13	5	5
H-Donors	1	5	1	1
Total Surface Area	129.66	333.45	333.67	319.91
Relative PSA	0.2016	0.46409	0.144	0.1502
Polar Surface Area	37.3	210.54	50.8	50.8
Druglikeness	-2.6221	-7.5894	2.9034	3.6092

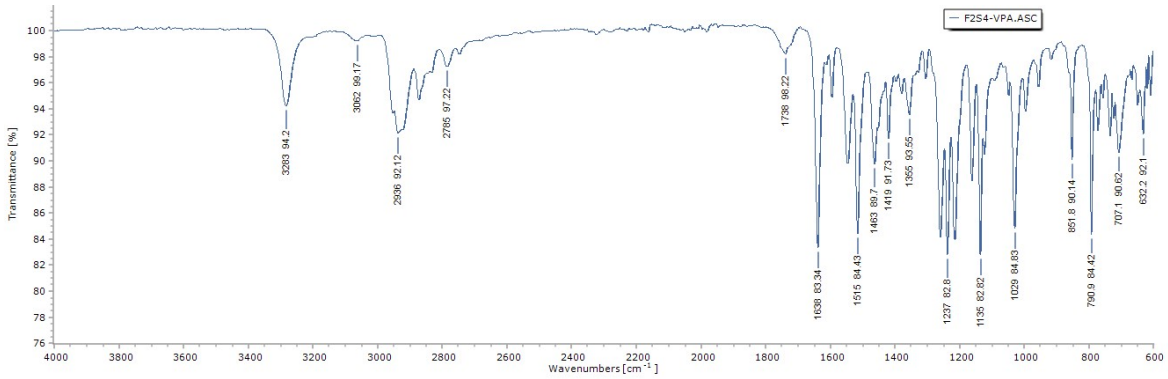
Mutagenic	none	none	none	none
Tumorigenic	none	high	none	none
Reproductive Effective	high	none	none	low
Irritant	none	none	none	none
Nasty Functions				
Shape Index	0.7	0.60606	0.64286	0.59259
Molecular Flexibility	0.76811	0.52001	0.55102	0.54429
Molecular Complexity	0.54931	0.82714	0.69536	0.69646



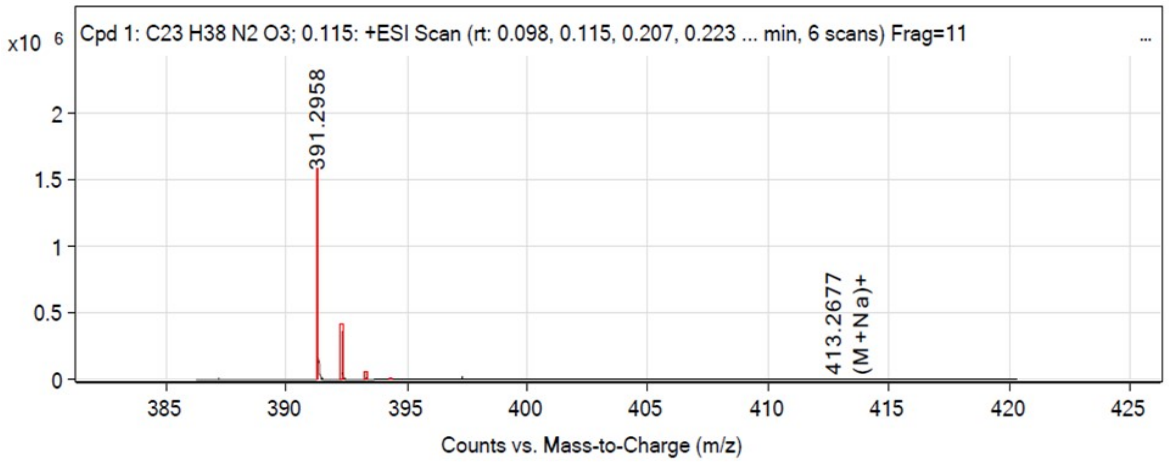
S1 Fig. ^{1}H NMR spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).



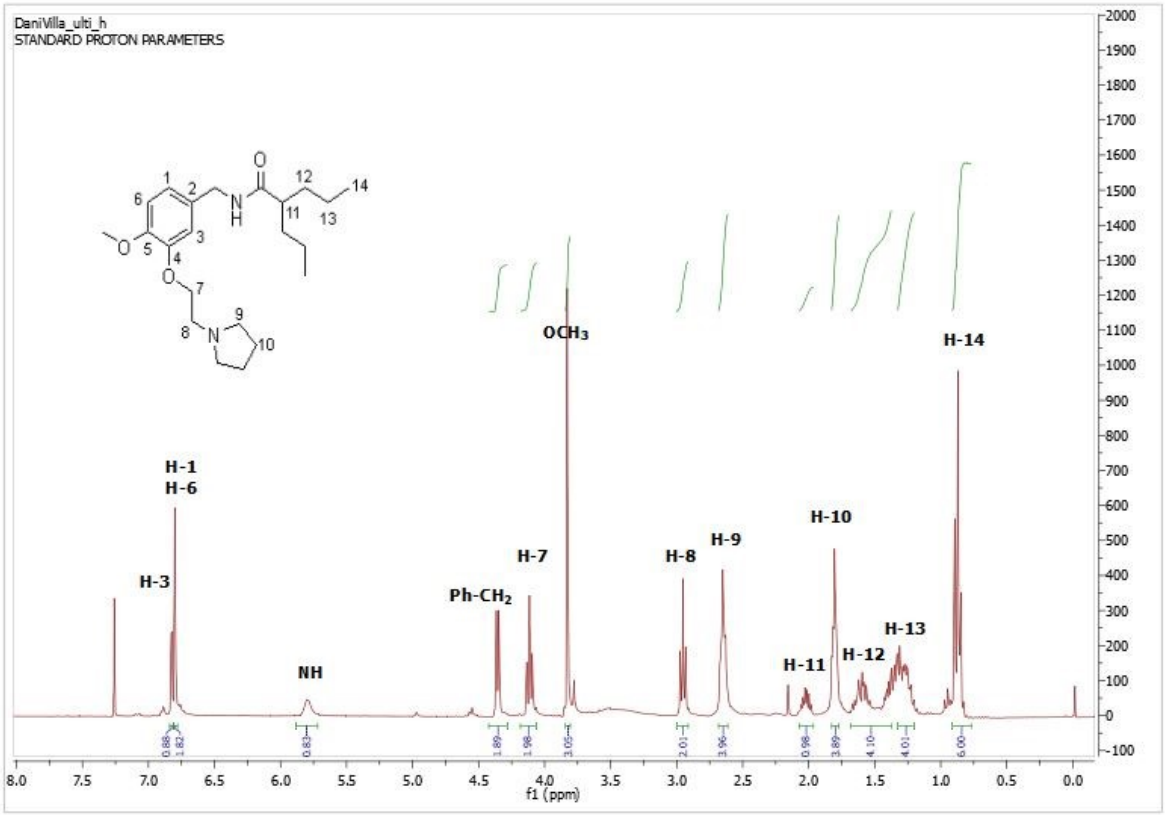
S2 Fig. ^{13}C NMR spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).



S3 Fig. FT-IR spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).



S4 Fig. Mass spectrum of N-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F2S4-p-VPA).



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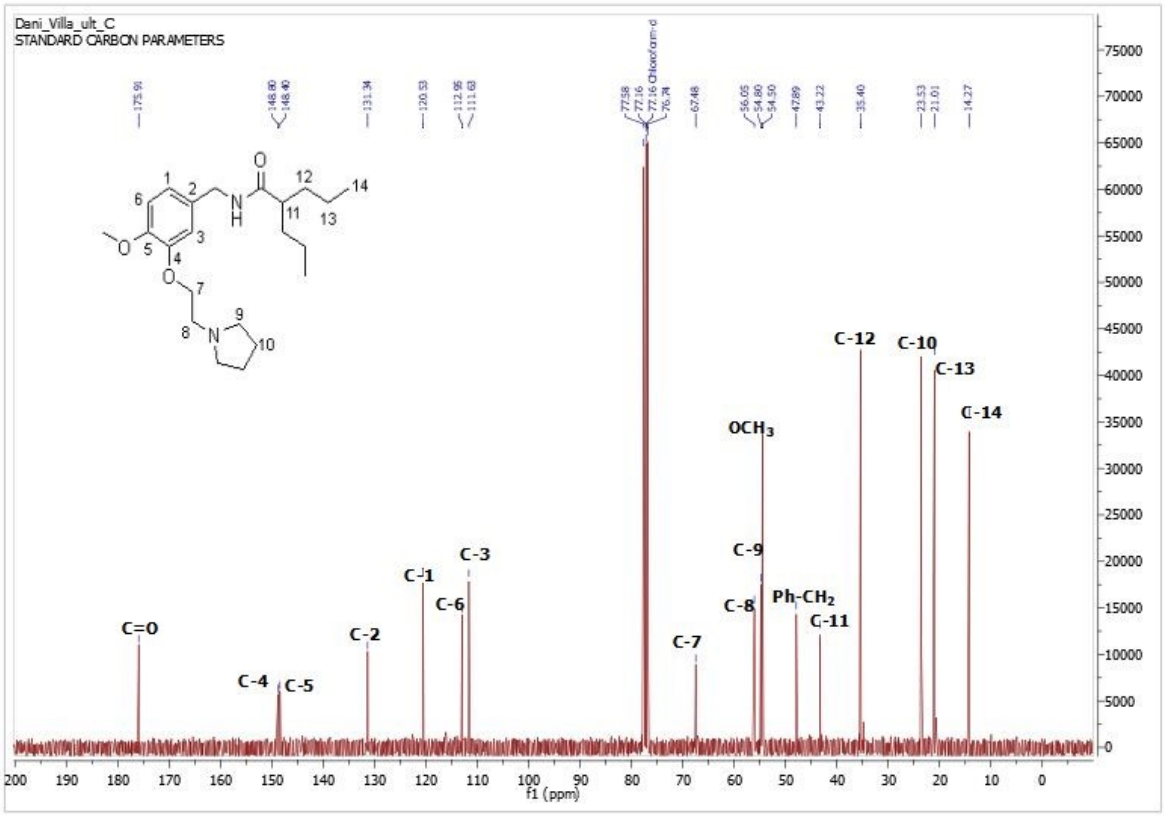
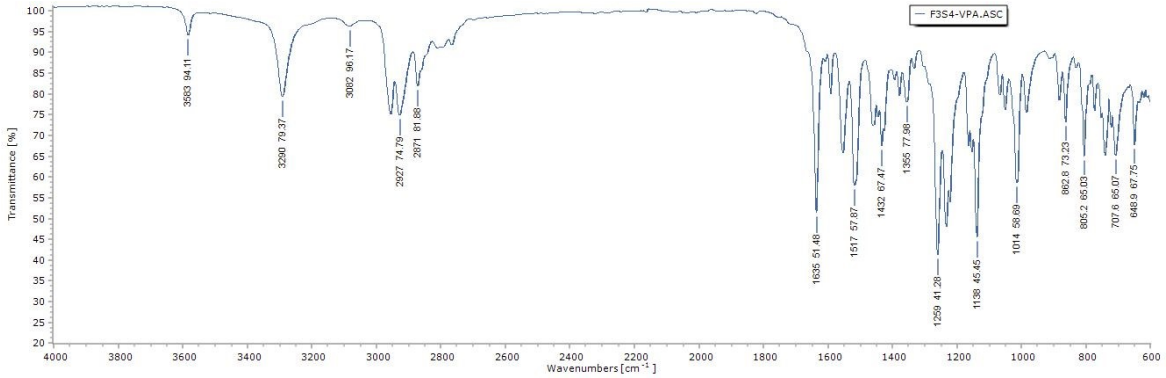
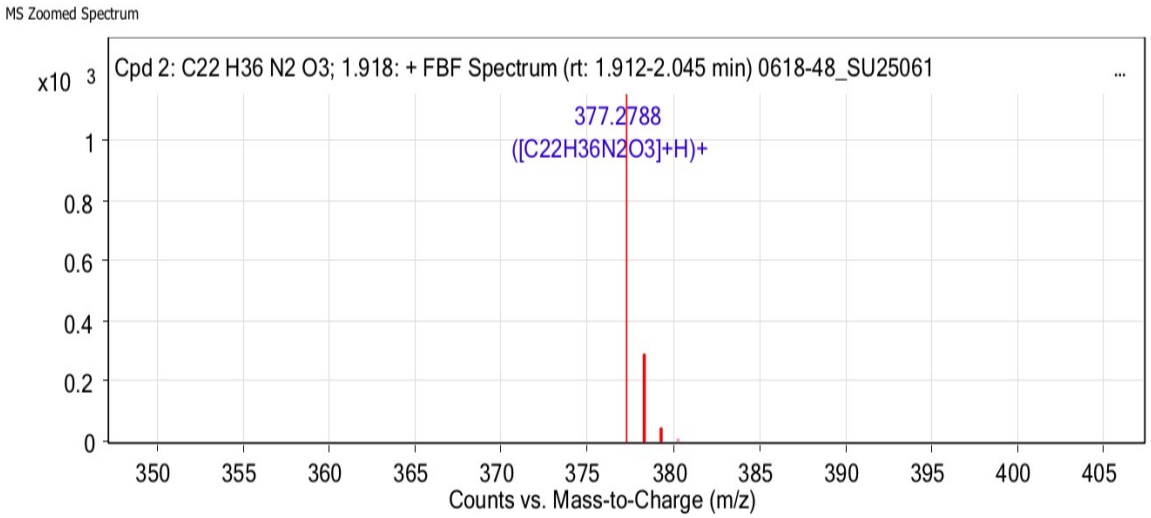


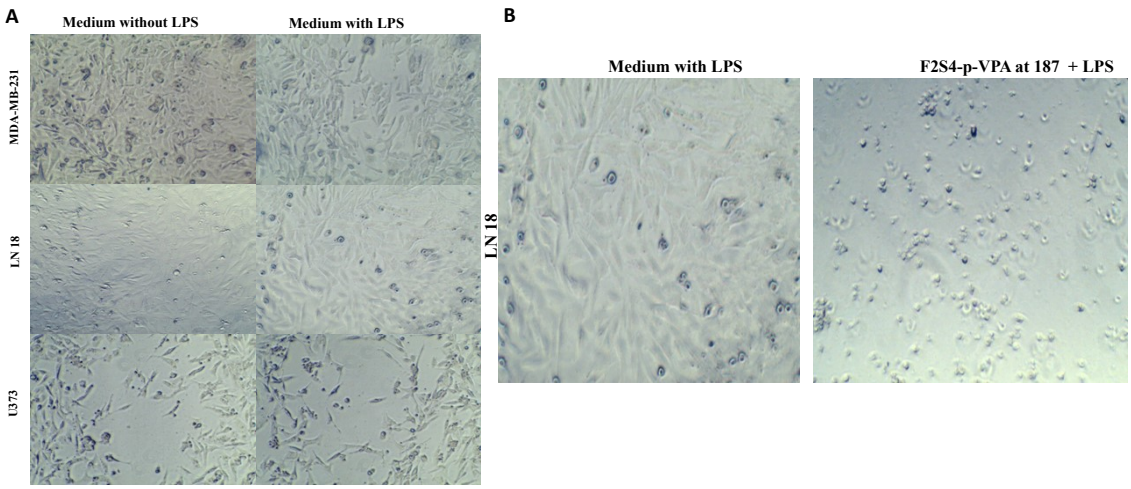
S6 Fig. ^{13}C NMR spectrum of N-(4-methoxy-3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F3S4-m-VPA).



S7 Fig. FT-IR spectrum of N-(4-methoxy-3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F3S4-m-VPA).



S8 Fig. Mass spectrum of N-(4-methoxy-3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)-2-propylpentanamide (F3S4-m-VPA).



S9 Fig. Cell migration without LPS and with LPS (A), and LN-18 cells without F2S4-p-VPA and with the compound.