

Doubly Prenylated Tryptamines: Cytotoxicity, Antimicrobial Activity and Cyclization to the Marine Natural Product Flustramine A

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1. Toxicity against the mouse fibroblast cell line L929 and antimicrobial activities

Compound	Toxicity assay		Antimicrobial assays										
	L-929		Gram(-)ve Bacteria		Gram(+)ve Bacteria		Yeast		Fungi				
	IC50 (µg/ml)	MTT Assay	IZ [mm]	IC50 [µg/ml]	IZ [mm]	IC50 [µg/ml]	IZ [mm]	IC50 [µg/ml]	IZ [mm]	IC50 [µg/ml]	IZ [mm]	Bo c	Py d
1 (Li-0067)	8	23	-	-	-	-	-	-	-	-	-	-	-
2 (Li-0068)	15	>>40	-	-	-	-	-	-	-	-	-	-	-
8 (Li-0071)	14	39	-	-	10 (nc)	>37	-	-	-	-	-	-	-
10 (Li-0094)	12	30	-	-	-	-	-	-	-	-	-	-	-
11 (Li-0097)	20	36	-	-	-	-	-	-	-	-	-	-	-
12 (Li-0098)	18	30	-	-	-	-	-	-	-	-	-	-	-
13 (Li-0022)	10	38	-	-	-	-	-	-	-	-	-	-	-
14 (Li-0102)	18	>40	-	-	-	-	-	-	-	-	-	-	-
15 (Li-0100)	14	30	8	8	-	-	-	-	-	-	-	-	-
16 (Li-0023)	16	>40	-	-	-	-	-	-	-	-	-	-	-
17 (Li-0104)	17	32	-	-	-	-	-	-	-	-	-	-	-
18 (Li-0075)	9	32	-	-	-	-	-	-	-	-	-	-	-
19 (Li-0101)	2,2	3,2	8	9	20	7	15	12	>37	12	24	-	-
20 (Li-0076)	2,4	4	-	-	13	2,3	13	3	13	13	7	-	-
22 (Li-0090)	12	40	-	-	-	-	-	-	-	-	-	-	-
23 (Li-0070)	16	39	-	-	-	-	-	-	-	-	-	-	-
24 (Li-0073)	15	>40	-	-	-	-	-	-	-	-	-	-	-
25 (Li-0074)	12	32	-	-	-	-	11 (nc)	23	-	-	-	-	-
26 (Li-0103)	20	32	-	-	-	-	-	-	-	-	-	-	-
27 (Li-0072)	15	>40	-	-	-	-	-	-	-	-	-	-	-
28 (Li-0069)	15	33	-	-	-	-	-	-	-	-	-	-	-

Mc l: *Micrococcus luteus*

My p: *Mycobacterium phlei*; * the IC50 of the slow growing My p were measured after 9 days of incubation

Hn a: *Hansenula anomala*

Sc c: *Saccharomyces cerevisiae*

Bo c: *Botrytis cinerea*

Py d: *Pythium debaryanum*

- : inhibition zone (IZ) < 7 mm (Disc size 6 mm)

nc: Not clear

2. Cytotoxicity tests (human tumor cell lines)

Tumor cell lines

The characteristics and origin of the 42 cell lines used in the present study are shown in Table 1. Authenticity of cell lines was proven at the DSMZ by STR (short tandem repeat) analysis, a PCR based DNA-fingerprinting methodology [3, 4].

Cell lines comprised 15 different tumor histotypes, each represented by one to six cell lines. They were established from cancer of the bladder (three), colon (five), head and neck (one), liver (one), lung (six), breast (three), pancreas (three), prostate (four), ovary (two), kidney (three), stomach (two) and the uterine body (one), as well as from malignant melanoma (three), sarcoma (two), and pleuramesothelioma (three). The 24 cell lines BXF 1218L, BXF 1352L, CXF 269L, GXF 251L, LIXF 575L, LXFL 1121L, LXFA 289L, LXFA 526L, LXFL 529L, LXFA 629L, MAXF 401NL, MEXF 1341L, MEXF 276L, MEXF 462NL, OVXF 899L, PAXF 1657L, PAXF 546L, PXF 1118L, PXF 1752L, PXF 698L, RXF 1781L, RXF 393NL, RXF 486L, UXF 1138L were established at Oncotest from patient-derived tumor xenografts (for reference, see Roth *et al.* 1999 [5]). The origin of the donor xenografts was described by Fiebig *et al.* 1992 and 1999 [6,7]. The other 18 cell lines were either kindly provided by the NCI (Bethesda; MD), or were purchased from ATCC (Rockville, MD), DSMZ (Braunschweig, Germany) or JCRB (Osaka, Japan).

Cell lines were routinely passaged once or twice weekly and maintained in culture for up to 20 passages. All cells were grown at 37°C in a humidified atmosphere with 5% CO₂ in RPMI1640 medium supplemented with 10% (v/v) fetal calf serum and 0.1 mg/mL gentamicin (medium and all components from PAA, Cölbe, Germany).

Growth inhibition is expressed as Test/Control x 100 (%T/C) values. Based on the T/C values, absolute IC₅₀ values were calculated by four parameter non-linear curve fit (Oncotest Warehouse Software). The overall potency of a compound was determined by the geometric mean ('geomean') IC₅₀ value of all individual IC₅₀ values.

If an IC₅₀ value could not be determined within the examined dose range (because a compound was either too active or lacked activity), the lowest or highest concentration studied was used for calculation of the geometric mean value.

In the heatmap presentation of IC₅₀ values, the distribution of IC₅₀ values obtained for a test compound in the individual cell lines is given in relation to the geometric mean IC₅₀ value, obtained for all cell lines tested. The individual IC₅₀ values are highlighted in colors ranging from dark green ($\leq 1/32$ -fold geometric mean IC₅₀, equal to very potent compound activity or tumor sensitivity) to dark red (≥ 32 -fold geometric mean IC₅₀, equal to lack of compound

activity or tumor resistance). The heatmap presentation therefore represents an anti-proliferative “fingerprint” profile of a test compound. Furthermore, antitumor activity is displayed as a mean graph presentation of the absolute IC₅₀ values.

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42 solid tumor cell line panel as used in the present study

#	cell line			histopathology	origin
	histotype	name	name		
1	Bladder	BXF	1218L	urothel ca, pd	Xenograft
2	Bladder	BXF	1352L	urothel ca, pd	Xenograft
3	Bladder	BXF	T24	urothel ca	ATCC
4	Colon	CXF	269L	rectum carcinoma, pd	Xenograft
5	Colon	CXF	DIFI	rectum carcinoma ²⁾ , wd	
6	Colon	CXF	HCT116	colon ca, pd	NCI
7	Colon	CXF	HT29	colon adeno ca, pd	NCI
8	Colon	CXF	RKO	epithelial colon ca, pd	ATCC
9	Gastric	GXF	251L	adeno ca, pd	Xenograft
10	Gastric	GXA	MKN45	adeno ca, pd	JCRB
11	Head&Neck	HNXF	CAL27	squamous cell ca, tongue	ATCC
12	Liver	LIXF	575L	hepatoma, wd	Xenograft
13	Lung	LXFA	289L	adeno ca, pd	Xenograft
14	Lung	LXFA	526L	adeno ca, pd	Xenograft
15	Lung	LXFA	629L	adeno ca, pd	Xenograft
16	Lung	LXFL	1121L	large cell, pd	Xenograft
17	Lung	LXFL	529L	large cell, pd	Xenograft
18	Lung	LXFL	H460	large cell, pd	NCI
19	Mammary	MAXF	401NL	adeno ca, wd	Xenograft
20	Mammary	MAXF	MCF7	mamma ca, pd	NCI
21	Mammary	MAXF	MDAMB231	mamma ca, pd	ATCC
22	Melanoma	MEXF	1341L	amelanotic melanoma	Xenograft
23	Melanoma	MEXF	276L	amelanotic melanoma	Xenograft
24	Melanoma	MEXF	462NL	amelanotic melanoma	Xenograft
25	Ovarian	OVXF	899L	papill serous adeno, wd	Xenograft
26	Ovarian	OVXF	OVCAR3	adeno ca	NCI
27	Pancreas	PAXF	1657L	adeno ca, md	Xenograft
28	Pancreas	PAXF	546L	adenosquamous, wd	Xenograft
29	Pancreas	PAXF	PANC1	epitheloid ca	ATCC
30	Prostate	PRXF	22RV1	prostate ca, pd	ATCC
31	Prostate	PRXF	DU145	prostate ca, pd	NCI
32	Prostate	PRXF	LNCAP	prostate ca, pd	DSMZ
33	Prostate	PRXF	PC3M	prostate ca, pd	NCI
34	Pleuramesoth.	PXF	1118L	pleuramesothelioma, pd	Xenograft
35	Pleuramesoth.	PXF	1752L	pleuramesothelioma	Xenograft
36	Pleuramesoth.	PXF	698L	pleuramesothelioma	Xenograft
37	Renal	RXF	1781L	hypernephroma, pd	Xenograft
38	Renal	RXF	393NL	hypernephroma, pd	Xenograft
39	Renal	RXF	486L	hypernephroma, pd	Xenograft
40	Sarcoma	SXF	SAOS2	osteosarcoma	DSMZ
41	Sarcoma	SXF	TE671	Rhabdomyosarcoma	ATCC
42	Uterus	UXF	1138L	endometrium carcino sarcoma, pd	Xenograft

ATCC : American Type Culture Collection, Rockville, MD, USA; NCI: National Cancer Institute, Bethesda, MD, USA, DSMZ : German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany

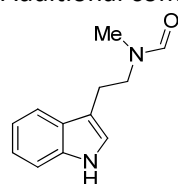
²⁾ established from a familial adenomatous polyposis patient with extracolonic features of the Gardner syndrome

BXF Bladder, CXF Colorectal, GXF Gastric, HNXF head&neck, LIXF Liver, LXF Lung A adeno, L large cell, MAXF Breast, MEXF Melanoma, OVXF Ovarian, PAXF Pancreatic, PXF Pleuramesothelioma, RXF Renal, UXF Uterus Body
 ca = carcinoma, pap = papillary, pd = poorly differentiated, wd = well differentiated, md = moderately differentiated

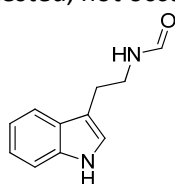
Table. Conversion of compound numbers (manuscript) to Lixxx numbers (used in heat maps below)

compound	Li-xxx
1	Li-0067
2	Li-0068
8	Li-0071
10	Li-0094
11	Li-0097
12	Li-0098
13	Li-0022
14	Li-0102
15	Li-0100
16	Li-0023
17	Li-0104
18	Li-0075
19	Li-0101
20	Li-0076
22	Li-0090
23	Li-0070
24	Li-0073
25	Li-0074
26	Li-0103
27	Li-0072
28	Li-0069

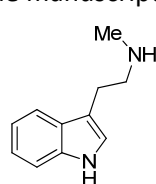
Additional compounds tested, not occurring in the manuscript:



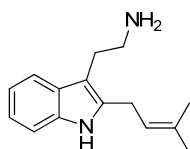
Li-0021



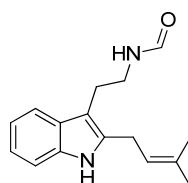
Li-0077



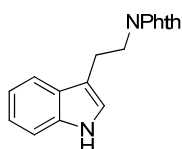
Li-0078



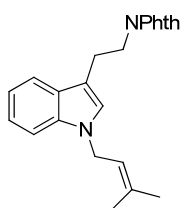
Li-0091



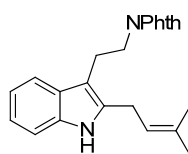
Li-0092



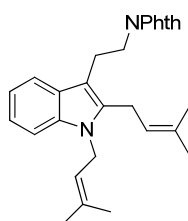
Li-0093



Li-0095



Li-0096



Li-0099

Relative IC₅₀ values [μM] of compounds from Prof Lindel in Oncotest's 42 cell line panel (exp. no. LA447-LA460)

#	Cell line		LI067			LI068			LI074			LI075			LI076		
	type	name	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot
1	BXF	1218L	39,9	95	0	48,0	92	0	n.e.			21,3	92	2	3,70	97	6
2	BXF	1352L	33,6	100	0	47,8	109	0	47,3	98	0	33,0	99	0	9,51	99	7
3	BXF	T24	58,7	113	9	83,0	100	21	82,3	100	1	22,3	97	4	9,64	99	5
4	CXF	269L	21,0	95	2	38,7	93	0	n.e.			22,0	101	2	3,89	95	4
5	CXF	DIFI	12,6	103	3	40,5	98	1	30,2	105	8	16,4	98	0	3,78	105	8
6	CXF	HCT116	27,5	96	1	46,2	99	0	39,6	100	0	15,8	94	2	3,92	101	2
7	CXF	HT29	16,4	99	2	46,6	98	0	10,6	100	2	14,9	97	2	3,55	100	2
8	CXF	RKO	13,8	104	1	42,1	99	0	18,5	98	1	15,5	98	1	3,98	93	1
9	GXF	251L	31,4	76	4	39,1	99	0	29,9	93	0	19,6	99	3	3,23	97	5
10	GXF	MKN45	48,4	95	0	36,3	100	19	40,5	102	11	31,6	99	5	4,83	98	5
11	HNXF	CAL27	41,8	115	0	42,3	105	6	49,1	122	0	25,5	109	2	3,76	104	4
12	LIXF	575L	n.e.			23,2	95	1	n.e.			12,8	113	3	n.e.		
13	LXF	H460	36,0	96	2	49,9	97	0	35,4	96	1	29,1	94	0	12,9	97	2
14	LXFA	289L	18,1	105	2	38,4	98	0	n.e.			23,0	105	0	10,7	101	4
15	LXFA	526L	35,7	106	5	39,7	112	9	38,8	100	0	29,7	108	0	3,74	103	5
16	LXFA	629L	13,4	88	3	37,0	100	0	13,7	99	3	15,2	103	3	1,88	97	4
17	LXFL	1121L	30,5	97	0	40,2	95	0	n.e.			18,4	95	2	12,1	97	2
18	LXFL	529L	27,0	103	0	32,2	107	0	31,7	96	0	19,7	107	1	3,75	99	5
19	MAXF	401NL	12,1	91	3	29,5	95	0	22,9	104	4	12,8	96	3	2,41	104	9
20	MAXF	MCF7	21,5	98	0	38,5	98	0	20,8	101	0	15,8	95	2	14,5	100	2
21	MAXF	MDA231	36,7	102	0	56,2	101	0	41,7	102	0	32,0	95	0	12,8	96	3
22	MEXF	1341L	13,7	107	4	36,6	98	5	n.e.			17,2	102	4	3,88	100	3
23	MEXF	276L	41,2	100	0	51,3	102	0	46,3	101	0	22,9	104	4	8,99	105	8
24	MEXF	462NL	56,7	96	0	62,7	97	0	48,8	98	0	25,5	103	0	8,09	95	4
25	OVXF	899L	28,3	99	3	47,2	102	0	39,6	102	0	15,9	101	7	10,3	104	10
26	OVXF	OVCAR3	47,9	100	0	77,0	104	0	77,0	99	0	28,5	100	0	10,8	93	14
27	PAXF	1657L	57,8	100	0	88,9	100	13	51,4	93	0	48,9	102	0	6,88	103	10
28	PAXF	546L	30,2	99	0	37,3	101	26	40,7	104	0	32,4	102	0	11,3	104	10
29	PAXF	PANC1	40,9	103	0	59,6	109	0	49,8	102	0	21,4	103	0	3,79	98	6
30	PRXF	22RV1	46,3	98	0	51,0	102	0	51,8	100	0	17,2	100	3	3,66	93	7
31	PRXF	DU145	39,9	98	0	47,3	97	0	42,5	100	0	24,5	101	6	3,88	100	5
32	PRXF	LNCAP	31,5	100	0	13,6	98	0	21,7	99	0	4,14	98	3	5,82	100	8
33	PRXF	PC3M	29,7	99	1	41,2	98	0	43,1	100	0	18,2	99	3	4,01	101	4
34	PXF	1118L	28,3	100	0	51,6	98	0	45,9	101	0	48,1	103	0	3,91	107	20
35	PXF	1752L	44,0	97	0	39,7	98	9	39,1	100	0	29,2	98	4	3,81	97	6
36	PXF	698L	42,6	105	0	50,6	102	0	37,9	104	0	46,0	106	0	3,84	107	8
37	RXF	1781L	30,9	102	0	46,5	100	0	37,1	99	0	15,5	97	0	3,40	98	6
38	RXF	393NL	44,6	106	0	37,9	99	14	45,4	101	0	21,7	101	0	3,71	101	10
39	RXF	486L	23,9	99	0	50,1	97	0	31,5	100	0	21,2	111	0	3,72	97	4
40	SXF	SAOS2	47,3	93	0	63,5	98	0	48,0	98	0	23,5	98	8	4,00	96	14
41	SXF	TE671	51,3	95	0	38,0	100	23	51,9	100	0	22,6	98	2	4,02	102	5
42	UXF	1138L	16,6	101	3	27,7	102	0	24,5	99	0	15,7	105	2	3,38	99	4
geomean IC₅₀			30,5			43,4			36,7			21,2			5,14		

n.e., not evaluated

*top and bottom (bot) are the plateaus given in T/C (%) reflecting the maximum response (top) or the maximal level of inhibition (bot)

IC₅₀ values shown in red (white in case of red backgr) are estimated based on visual inspection of the concentration effect curves (IC₅₀ values could not be calculated by non-linear regression)

If T/C<50% for all test concentrations was detected, the lowest concentration was given and used for calculation of the mean IC₅₀ values

If no clear activity was detected (T/C>70% at all test concentrations), the highest test concentration was given and used for calculation of the mean IC₅₀ values



Relative IC₅₀ values [μM] of compounds supplied by Prof. Lindel in a panel of 11 human tumor cell lines (exp. no. LA392-LA395)

Cell line		LI0021			LI0022			LI0023			LI0067			LI0068			LI0069			LI0070			LI0071		
type	name	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot
GXF	251L	100			80			100			31,7	91	3	39,6	93	9	32,6	94	2	38,1	92	35	80		
LXFA	629L	100			100			100			12,9	95	2	41,2	92	3	12,9	92	2	52,3	94	35	100		
MEXF	462NL	100			100			100			41,5	98	3	40,5	95	6	75,5	94	1	47,6	95	20	41,7	97	11
RXF	486L	100			100			100			22,8	97	0	49,8	99	0	38,4	95	0	100			100		
UXF	1138L	100			80			100			19,7	101	2	28,2	100	0	37,2	100	2	41,8	99	10	43,7	103	0
LXFL	529L	100			58,6	101	0	12,1	97	56	12,8	92	3	21,0	100	0	18,7	100	1	49,0	99	0	46,9	100	0
OVXF	899L	100			100			100			16,0	102	3	45,0	101	0	29,2	103	0	68,8	106	0	100		
PAXF	1657L	100			100			100			29,4	99	4	58,7	102	0	44,8	101	0	91,9	98	0	87,9	101	0
PXF	1752L	100			100			100			18,3	102	5	36,0	102	12	15,7	105	6	38,0	101	33	59,7	109	0
CXF	HT29	100			100			100			12,3	107	2	34,0	111	0	8,76	118	2	49,8	111	0	42,4	108	0
PRXF	22RV1	100			50,6	105	26	100			21,1	103	0	30,8	98	0	16,7	103	1	44,6	98	0	27,7	101	3
geom. mean IC ₅₀		100,0			86,0			82,6			20,1			37,3			25,1			53,6			60,8		

Cell line		LI0072			LI0073			LI0074			LI0075			LI0076			LI0077			LI0078			TAXOL		
type	name	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot	IC ₅₀	top	bot
GXF	251L	100			80			34,5	98	0	12,9	100	0	4,15	105	5	100			100			0,0021	104	14
LXFA	629L	87,1	103	35	80			13,8	100	2	12,8	102	1	3,12	108	5	100			100			0,0012	97	18
MEXF	462NL	100			68,5	102	0	78,2	96	1	14,6	100	2	12,4	98	5	100			100			0,0019	96	9
RXF	486L	100			100			42,6	101	0	11,8	99	1	3,73	98	3	100			100			0,0869	105	6
UXF	1138L	100			80			47,7	105	0	10,9	110	0	3,71	104	3	100			100			0,0013	102	6
LXFL	529L	59,4	104	0	51,6	99	0	14,5	106	1	9,83	106	1	3,41	105	5	100			100			0,0025	94	11
OVXF	899L	97,3	102	0	100			17,0	104	3	13,2	109	5	3,66	109	6	100			100			0,102	107	0
PAXF	1657L	100			87,6	103	0	41,1	104	0	16,0	108	4	3,55	108	6	100			100			0,0015	105	19
PXF	1752L	87,4	113	0	62,0	114	0	17,1	108	7	16,4	113	8	3,33	111	9	100			100			0,0015	117	13
CXF	HT29	48,1	114	13	42,5	113	10	9,10	112	2	11,7	116	2	2,43	114	2	100			100			0,0010	115	5
PRXF	22RV1	37,3	107	25	57,0	104	0	23,1	98	0	8,49	105	0	2,99	98	4	100			100			0,0010	106	10
geom. mean IC ₅₀		79,4			71,2			25,3			12,4			3,80			100,0			100,0			0,0031		

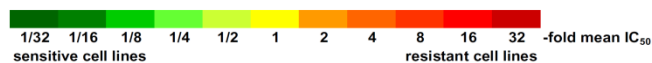
n.e., not evaluated

*top and bottom (bot) are the plateaus given in T/C (%) reflecting the maximum response (top) or the maximal level of inhibition (bot)

IC₅₀ values shown in red (white in case of red backgr) are estimated based on visual inspection of the concentration effect curves (IC₅₀ values could not be calculated by non-linear regression)

If T/C<50% for all test concentrations was detected, the lowest concentration was given and used for calculation of the mean IC₅₀ values

If no clear activity was detected (T/C>70% at all test concentrations), the highest test concentration was given and used for calculation of the mean IC₅₀ values



Cell line	LI-0090 [μM]	LI-0091 [μM]	LI-0092 [μM]	LI-0093 [μM]	LI-0094 [μM]	LI-0095 [μM]	LI-0096 [μM]	LI-0097 [μM]	LI-0098 [μM]	LI-0099 [μM]	LI-0100 [μM]	LI-0101 [μM]	LI-0102 [μM]	LI-0103 [μM]	LI-0104 [μM]
CXF HT-29	37,2	32,0	82,1	100,0	23,3	28,9	15,1	42,7	16,2	65,1	17,1	2,95	64,8	13,9	71,9
GXF 251	n.e.	27,4	44,2	100,0	16,1	24,4	8,3	24,1	16,1	36,1	21,0	3,96	69,4	29,0	55,3
LXFA 629	n.e.	43,8	73,6	100,0	40,2	87,8	22,2	100,0	28,8	100,0	37,9	3,64	96,7	20,0	51,5
LXFL 529	39,1	49,4	81,2	100,0	21,9	34,5	13,7	36,6	15,1	44,1	29,6	4,68	51,7	38,0	37,7
MAXF 401	n.e.	39,4	86,4	100,0	19,9	47,1	17,8	38,0	14,2	100,0	22,6	3,20	48,4	23,9	40,8
MEXF 462	83,4	77,2	100,0	100,0	45,5	100,0	48,5	52,4	15,4	100,0	16,7	5,01	60,2	37,8	50,3
OVXF 899	49,4	75,7	100,0	100,0	30,2	100,0	27,0	31,8	19,5	100,0	22,1	4,26	59,5	20,5	42,0
PAXF 1657	67,8	60,3	100,0	100,0	32,0	100,0	23,7	100,0	33,3	100,0	37,8	4,46	100,0	41,6	70,0
PRXF 22RV1	40,9	44,4	100,0	100,0	16,7	34,8	17,9	32,1	11,2	39,2	15,6	3,59	42,6	30,8	45,7
PXF 1752	54,8	46,7	100,0	100,0	36,4	43,6	28,7	46,4	15,3	62,6	29,5	3,94	66,7	23,9	70,0
RXF 486	61,4	50,1	100,0	100,0	29,8	78,8	32,9	25,2	15,4	41,1	20,2	3,17	41,2	15,1	32,7
UXF 1138	41,7	77,1	100,0	100,0	14,0	49,9	19,8	98,3	10,8	36,0	14,6	2,90	39,8	23,7	33,6
mean IC50	51,0	49,4	87,0	100,0	25,4	53,9	20,9	45,92	16,7	62,8	22,6	3,76	59,1	25,1	48,3



3. ^1H and ^{13}C NMR spectra

