Supplemental Data

Insights from selective non-phosphinic inhibitors of MMP-12 tailored to a S_1' loop canonical conformation.

Laurent Devel[¶], Sandra Garcia[¶], Fabrice Beau[¶], Dimitris Georgiadis[‡], Bertrand Czarny[¶], Evelyne Lajeunesse[¶], Laura Vera[¶], Enrico A. Stura[¶], Vincent Dive[¶*]

From the [¶] CEA, Commissariat à l'Energie Atomique, Service d'Ingénierie Moléculaire de Protéines (SIMOPRO), CE-Saclay, 91191 Gif /Yvette, Cedex, France and [‡] Laboratory of Organic Chemistry, Department of Organic Chemistry, University of Athens, Panepistimiopolis, Zografou, 15771 Athens, Greece

Address correspondence to : Dr V. Dive, CEA, Commissariat à l'Energie Atomique, Service d'Ingénierie Moléculaire de Protéines (SIMOPRO), 152, CE-Saclay, 91191 Gif /Yvette, Cedex, France, Tel : 33 1 69083585, Fax : 33 1 69089071, vincent.dive@cea.fr

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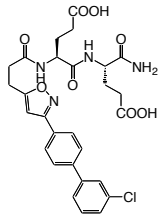
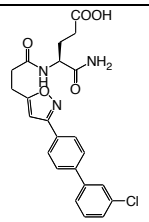
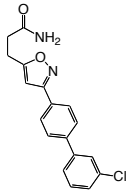
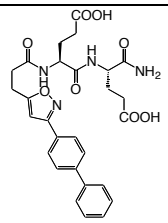
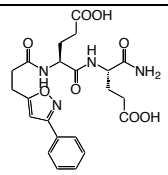
1) Supplemental Data

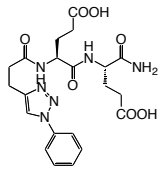
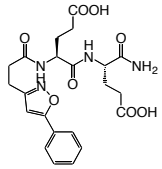
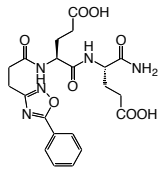
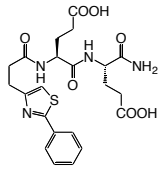
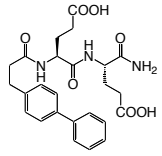
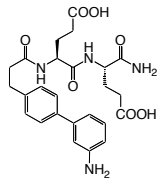
Table S1: Crystallization conditions and data collection statistics

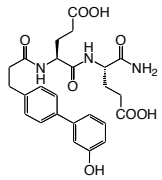
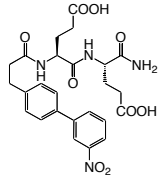
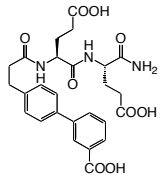
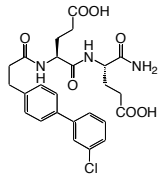
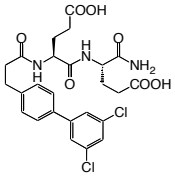
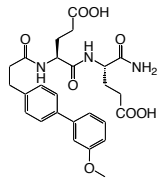
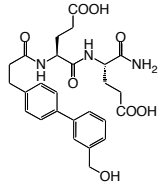
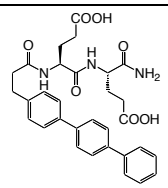
Data set	Compound (**5**)	Compound (**9**)	Compound (**14**)	Compound (**36**)
PDB code	3LIL	3LIR	3LJG	3LIK
Crystallisation conditions	21% w/w PEG 10,000 200 M imidazole malate pH 8.5 at 20°C	21% w/w PEG 10,000 100 mM NaCl 200 mM imidazole malate pH 8.5 at 20°C	22% w/w PEG 3,350 100 mM glycine pH 8.0 at 20°C	25% w/w PEG 10,000 100 mM NaCl 200 mM imidazole malate pH 8.5 at 20°C
Synchrotron	ESRF	ESRF	Soleil	ESRF
Beamline	ID14-2	ID23-1	Proxima-1	ID14-2
Space group and cell parameters (Å)	$P2_12_12$ 68.8 62.7 37.6	$P2_12_12$ 69.1 62.8 37.6	$P2_12_12$ 69.0 63.2 37.6	$P2_12_12$ 68.4 62.9 36.6
Resolution (Å)	1.8 (1.9)	1.9 (2.0)	1.31 (1.35)	1.8 (1.9)
Unique reflections	15718	13419	39828	13458
R_{sym}[b] (%)	9	12.8	10.7	8
$\langle I/\sigma(I) \rangle$	14.6	12.8	13.6	15.2
Completeness (%)	99.99	99.5	100	89.1
R_{work}[c] (%)	15.36 (16.59)	16.05 (18.14)	17.38 (29.70)	15.74 (18.48)
R_{free}[d] (%)	18.96 (19.57)	20.69 (23.93)	19.40 (27.22)	20.93 (25.8)
RMSD				
Bond length (Å)	0.008	0.008	0.006	0.007
Bond angle (°)	1.166	1.167	1.250	1.044
Ramachandran plot				
Most favoured region	159	161	160	159
Additional region	3	1	2	3

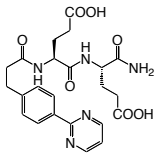
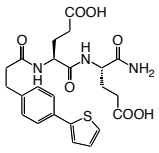
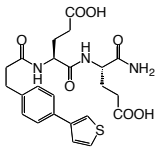
[a]Values in parantheses are for the highest resolution shell.
[b]$R_{sym} = \sum_{hkl}\sum_i|I_i - \langle I \rangle|\sum_{hkl}\sum_i I_i$
[c]$R_{work} = \sum_{hkl}||F_{obs}| - k|F_{calc}||/\sum_{hkl}|F_{obs}|$,
[d]R_{free} was calculated using 5% of data excluded from refinement.

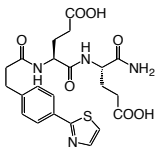
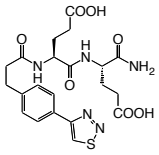
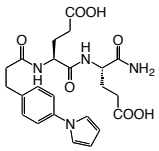
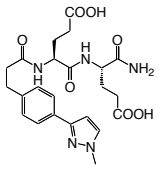
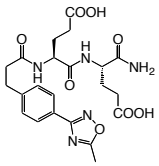
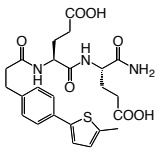
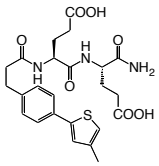
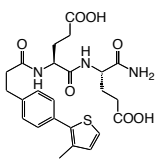
Table S2: Structure, name and analytical data of compounds **5** to **36**

	Structure	Name	Analytical data
5		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3-(3'-chlorobiphenyl-4-yl)isoxazol-5-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express : t_R=5,40min e_{272}=31915 M^{-1}. cm^{-1} ^{1}H NMR (DMSO d_6): δ 1.75 (m, 2H), 1.89 (m, 2H), 2,23 (m, 4H), 2,62 (m, 2H), 3.03 (m, 2H), 4,21 (m, 2H), 6.86 (s, 1H), 7.11 (s, 1H), 7.32 (s, 1H), 7.51 (m, 2H), 7.72 (d, 1H, *J*=7.25Hz), 7.84 (m, 3H), 7.94 (d, 2H, *J*=8.25Hz), 8.00 (d, 1H, *J*=7.75Hz), 8.28 (d, 1H, *J*=7.25Hz), HRMS *m/z* for $C_{28}H_{30}ClN_4O_8$ $(M+H^+)^+$, calcd 585.1752, found 585.1733.
6		(*S*)-5-amino-4-(3-(3-(3'-chlorobiphenyl-4-yl)isoxazol-5-yl)propanamido)-5-oxopentanoic acid	Ascentis Express: t_R=5.69min e_{272}=18230 M^{-1}. cm^{-1} HRMS *m/z* for $C_{23}H_{23}ClN_3O_5$ $(M+H^+)^+$, calcd 456.1326, found 456.1330.
7		3-(3-(3'-chloro-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)propanamide	Ascentis Express: t_R=6.18min MS *m/z* for $C_{23}H_{23}ClN_3O_5$ $(M+H^+)^+$=327.1, $(M+Na^+)^+$=349.1.
8		(*S*)-5-amino-4-((*S*)-2-(3-(3-(biphenyl-4-yl)isoxazol-5-yl)propanamido)-4-carboxybutanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,82min e_{273}=35600 M^{-1}. cm^{-1} HRMS *m/z* for $C_{28}H_{31}N_4O_8$ $(M+H^+)^+$, calcd 551.2142, found 551.2135.
9		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3-phenylisoxazol-5-yl)propanamido)butanamido)-5-oxopentanoic	Ascentis Express: t_R=2,89min e_{241}=11950 M^{-1}. cm^{-1} HRMS *m/z* for $C_{22}H_{27}N_4O_{88}$ $(M+H^+)^+$,

		acid	calcd 475.1828, found 475.1823.
10		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=2,23min e_{248}=4827 M^{-1}. cm^{-1} HRMS *m/z* for $C_{21}H_{27}N_6O_7$ $(M+H^+)^+$, calcd 475.1941, found 475.1953.
11		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(5-phenylisoxazol-3-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=3,27min e_{263}=23750 M^{-1}. cm^{-1} HRMS *m/z* for $C_{22}H_{27}N_4O_8$ $(M+H^+)^+$, calcd 475.1829, found 475.1843.
12		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=3,32min e_{253}=17391 M^{-1}. cm^{-1} HRMS *m/z* for $C_{21}H_{26}N_5O_8$ $(M+H^+)^+$, calcd 476.1782, found 476.1794.
13		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(2-phenylthiazol-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=3,23min e_{294}=13992 M^{-1}. cm^{-1} HRMS *m/z* for $C_{22}H_{27}N_4O_7S$ $(M+H^+)^+$, calcd 491.1601, found 491.1613.
14		(*S*)-5-amino-4-((*S*)-2-(3-(biphenyl-4-yl)propanamido)-4-carboxybutanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,26min e_{253}=22540 M^{-1}. cm^{-1} ^{1}H NMR (DMSO d_6): δ 1.71 (m, 2H), 1.87 (m, 2H), 2,22 (m, 4H), 2,51 (m, 2H), 2.85 (m, 2H), 4,21 (m, 2H), 7.12 (s, 1H), 7.33 (m, 4H), 7.45 (t, 2H, *J*=7.25Hz) 7.56 (d, 2H, *J*=7.25Hz), 7.63 (d, 2H, *J*=7.25Hz), 7.96 (d, 1H, *J*=7.75Hz), 8.13 (d, 1H, *J*=7.5Hz). HRMS *m/z* for $C_{25}H_{30}N_3O_7$ $(M+H^+)^+$, calcd 484.2084, found 484.2084.
15		(*S*)-5-amino-4-((*S*)-2-(3-(3'-aminobiphenyl-4-yl)propanamido)-4-carboxybutanamido)-5-oxopentanoic acid	Ascentis Express: t_R=1,93min e_{260}=9580 M^{-1}. cm^{-1} HRMS *m/z* for $C_{25}H_{30}N_4NaO_7$ $(M+Na^+)^+$, calcd 521.2012, found 521.2019

16		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3'-hydroxybiphenyl-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=3,24min e_{254}=13970 M^{-1}. cm^{-1} HRMS *m/z* for $C_{25}H_{30}N_3O_8$ $(M+H^+)^+$, calcd 500.2033, found 500.2031
17		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3'-nitrobiphenyl-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,20min e_{254}=20158 M^{-1}. cm^{-1} HRMS *m/z* for $C_{25}H_{29}N_4O_9$ $(M+H^+)^+$, calcd 529.1935, found 529.1954
18		4'-(3-((*S*)-1-((*S*)-1-amino-4-carboxy-1-oxobutan-2-ylamino)-4-carboxy-1-oxobutan-2-ylamino)-3-oxopropyl)biphenyl-3-carboxylic acid	Ascentis Express: t_R=3,29min e_{257}=6082 M^{-1}. cm^{-1} HRMS *m/z* for $C_{26}H_{30}N_3O_9$ $(M+H^+)^+$, calcd 528.1982, found 528.1991
19		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3'-chlorobiphenyl-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,84min e_{260}=18195 M^{-1}. cm^{-1} HRMS *m/z* for $C_{25}H_{29}ClN_3O_7$ $(M+Na^+)^+$, calcd 540.1513, found 540.1482
20		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3',5'-dichlorobiphenyl-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=5,48min e_{260}=21808 M^{-1}. cm^{-1} HRMS *m/z* for $C_{25}H_{28}Cl_2N_3O_7$ $(M+H^+)^+$, calcd 552.1304, found 552.1320
21		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3'-methoxybiphenyl-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,37min e_{254}=12000 M^{-1}. cm^{-1} HRMS *m/z* for $C_{26}H_{32}N_3O_8$ $(M+H^+)^+$, calcd 514.2189, found 514.2177
22		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(3'-(hydroxymethyl)biphenyl-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=3,21min e_{254}=21560 M^{-1}. cm^{-1} HRMS *m/z* for $C_{26}H_{32}N_3O_8$ $(M+H^+)^+$, calcd 514.2189, found 514.2164
23		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4'-phenylbiphenyl-4-yl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=5,70min e_{280}=44827 M^{-1}. cm^{-1} ^{1}H NMR (DMSO d_6): δ 1.74 (m, 2H),

			1.90 (m, 2H), 2,21 (m, 4H), 2,51 (m, 2H), 2.83 (m, 2H), 4,19 (m, 2H), 7.11 (s, 1H), 7.31 (m, 3H), 7.38 (d, 1H, *J*=7.25Hz), 7.48 (t, 2H, *J*=7.25Hz), 7.64 (d, 2H, *J*=8Hz), 7.72 (m, 6H), 7.95 (d, 1H, *J*=7.75Hz), 8.14 (d, 1H, *J*=7.5Hz). HRMS *m/z* for $C_{31}H_{33}N_3NaO_7$ $(M+Na^+)^+$, calcd 582.2216, found 582.2210
24		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(pyrimidin-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=2,40min e_{266}=20275 M^{-1}. cm^{-1} HRMS *m/z* for $C_{23}H_{28}N_5O_7$ $(M+H^+)^+$, calcd 486.1989, found 486.1982.
25		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(thiophen-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,10min e_{285}=22000 M^{-1}. cm^{-1} ^{1}H NMR (DMSO d_6): δ 1.75 (m, 2H), 1.91 (m, 2H), 2,22 (m, 4H), 2,51 (m, 2H), 2.82 (m, 2H), 4,20 (m, 2H), 7.11 (m, 2H), 7.25 (d, 2H, *J*=8Hz), 7.32 (s, 1H), 7.46 (d, 1H, *J*=3.5Hz), 7.51 (d, 1H, *J*=5.25Hz), 7.56 (d, 2H, *J*=8Hz), 7.95 (d, 1H, *J*=8Hz), 8.14 (d, 1H, *J*=7.5Hz). HRMS *m/z* for $C_{23}H_{27}N_3NaO_7S$ $(M+Na^+)^+$, calcd 512.1467, found 512.1458
26		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(thiophen-3-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=3,97min e_{262}=14495 M^{-1}. cm^{-1} HRMS *m/z* for $C_{23}H_{28}N_3O_7S$ $(M+H^+)^+$, calcd 490.1648, found 490.1636.

27		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(thiazol-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=2,69min e_{288}=27972 M^{-1}. cm^{-1} HRMS *m/z* for $C_{22}H_{27}N_4O_7S$ $(M+H^+)^+$, calcd 491.1601, found 491.1585.
28		(*S*)-4-(3-(4-(1,2,3-thiadiazol-4-yl)phenyl)propanamido)-5-((*S*)-1-amino-4-carboxy-1-oxobutan-2-ylamino)-5-oxopentanoic acid	Ascentis Express: t_R=3,27min e_{245}=10729 M^{-1}. cm^{-1} HRMS *m/z* for $C_{21}H_{26}N_5O_7S$ $(M+H^+)^+$, calcd 492.1553, found 492.1551.
29		(*S*)-4-(3-(4-(1*H*-pyrrol-1-yl)phenyl)propanamido)-5-((*S*)-1-amino-4-carboxy-1-oxobutan-2-ylamino)-5-oxopentanoic acid	Ascentis Express: t_R=3,69min e_{253}=14677 M^{-1}. cm^{-1} HRMS *m/z* for $C_{23}H_{28}N_4NaO_7$ $(M+Na^+)^+$, calcd 495.1856, found 495.1860.
30		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(1-methyl-1*H*-pyrazol-3-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=2,60min e_{257}=24934 M^{-1}. cm^{-1} HRMS *m/z* for $C_{23}H_{30}N_5O_7$ $(M+H^+)^+$, calcd 488.2145, found 488.2143.
31		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=2,77min e_{246}=15544 M^{-1}. cm^{-1} HRMS *m/z* for $C_{22}H_{28}N_5O_8$ $(M+H^+)^+$, calcd 490.1938, found 490.1922.
32		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(5-methylthiophen-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,61min e_{292}= 21893 M^{-1}. cm^{-1} HRMS *m/z* for $C_{24}H_{29}N_3NaO_7S$ $(M+Na^+)^+$, calcd 526.1624, found 526.1620
33		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(4-methylthiophen-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,58min e_{290}=16369 M^{-1}. cm^{-1} HRMS *m/z* for $C_{24}H_{30}N_3O_7S$ $(M+H^+)^+$, calcd 504.1804 found 504.1782
34		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(3-methylthiophen-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=4,53min e_{271}= 1472 M^{-1}. cm^{-1} HRMS *m/z* for $C_{24}H_{29}N_3NaO_7S$ $(M+Na^+)^+$, calcd 526.1624, found

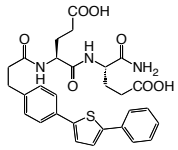
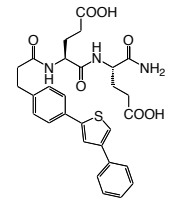
			526.1627
35		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(5-phenylthiophen-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=5,72min e_{338}= 30000 M^{-1}. cm^{-1} ^{1}H NMR (DMSO d_6): δ 1.76 (m, 2H), 1.91 (m, 2H), 2,22 (m, 4H), 2,51 (m, 2H), 2.82 (m, 2H), 4,21 (m, 2H), 7.11 (s, 1H), 7.30 (m, 4H), 7.44 (t, 2H, *J*=7.25Hz), 7.49 (d, 1H, *J*=4Hz), 7.54 (d, 1H, *J*=3.75Hz), 7.60 (d, 2H, *J*=8Hz), 7.70 (d, 2H, *J*=7.5Hz), 7.96 (d, 1H, *J*=7.75Hz), 8.16 (d, 1H, *J*=7.25Hz). HRMS *m/z* for $C_{29}H_{31}N_3NaO_7S$ $(M+Na^+)^+$, calcd 588.1780, found 588.1776
36		(*S*)-5-amino-4-((*S*)-4-carboxy-2-(3-(4-(4-phenylthiophen-2-yl)phenyl)propanamido)butanamido)-5-oxopentanoic acid	Ascentis Express: t_R=5,61min e_{259}=34583 M^{-1}. cm^{-1} ^{1}H NMR (DMSO d_6): δ 1.76 (m, 2H), 1.91 (m, 2H), 2,22 (m, 4H), 2,51 (m, 2H), 2.84 (m, 2H), 4,21 (m, 2H), 7.11 (s, 1H), 7.30 (m, 4H), 7.44 (t, 2H, *J*=7Hz), 7.65 (d, 2H, *J*=8.25Hz), 7.79 (d, 2H, *J*=7.25Hz), 7.85 (s, 1H), 7.96 (m, 2H), 8.16 (d, 1H, *J*=7.5Hz). HRMS *m/z* for $C_{29}H_{32}N_3O_7S$ $(M+H^+)^+$, calcd 566.1961, found 566.1953

Table S3: Ki values (nM) of compounds **4** to **36** towards a set of MMPs.

	Ki (nM)									
	MMP-1h	MMP-2h	MMP-3h	MMP-7h	MMP-8h	MMP-9h	MMP-10h	MMP-12h	MMP-13h	MMP-14h
4	1000	72	58	1000	77	850	8,3	0,2	13	80
5	17900	76	62	1200	181	565	48	8,3	40	2060
6	ND	90	118	ND	119	120	122	11.8	46	1130
7	ND	225	1700	ND	49	768	2500	190	85	2500
8	ND	83	78	ND	383	1720	114	3.4	60	1990
9	17300	756	11200	16300	112	3510	1770	119	2000	3100
10	ND	5000	2000	ND	1000	1500	3300	2200	2000	2000
11	ND	1400	1000	ND	332	1000	1600	130	580	2500
12	ND	1000	5000	ND	1000	1500	7000	3300	1000	8000
13	ND	2000	1000	ND	2300	1000	1000	4000	864	1000
14	>100000	445	6700	24700	226	1090	1110	18,6	689	5900
15	ND	2140	2100	ND	2140	1440	2390	190	2380	3350
16	ND	11400	29900	ND	1660	4340	3070	176	28700	28700
17	ND	2600	24100	ND	1250	1365	3390	73	463	8020

18	ND	6380	13100	ND	4450	4150	11700	91	6930	26000
19	ND	2820	55000	ND	1890	1880	6920	57	1850	2370
20	ND	1200	1810	ND	4820	1665	2850	56	1630	2340
21	ND	8930	25300	ND	1640	8070	4170	35	5460	15800
22	ND	7465	13300	ND	809	9100	7650	52	4730	12500
23	7800	53	74	502	132	1740	76	1.63	20	1980
24	ND	7860	1670	ND	1470	1460	4920	6540	12500	1010
25	>100000	142	2210	4000	40	1540	373	8.6	321	1710
26	ND	492	3070	ND	60	1790	661	11.9	895	2630
27	ND	657	5000	ND	1000	1070	1850	369	240	2820
28	ND	442	281	ND	231	199	679	158	212	438
29	ND	1370	2040	ND	373	1050	1840	59	1220	4850
30	ND	1175	14200	ND	2190	1900	10200	797	518	1000
31	ND	3400	6040	ND	839	2060	8320	155	1090	2650
32	ND	97	2210	ND	10.3	242	353	1.84	564	1700
33	ND	868	3260	ND	233	2760	1415	22	1300	9930
34	ND	3380	12600	ND	766	9130	2190	84	1780	6310

35	ND	279	108	ND	381	874	156	2.58	200	2280
36	11800	1060	3880	2000	410	9890	872	1.92	684	3010

Ki (nM) were determined in 50 mM Tris/HCl Buffer, pH 6.8, 10 mM $CaCl_2$ at 25°

2) Supplemental experimental procedures

All Commercially available reagents and solvents were used as received without further purification. Synphase Lanterns® (Polyamide, D-series lantern, Rink amide Fmoc protected, 8µmol/lantern) were purchased from Mimotopes (Australia). Fmoc-amino acids-OH were purchased from Novabiochem. 6-Chloro-1-Hydroxybenzotriazole (ClHOBt) was purchased from Molekula. Diisopropylcarbodiimide (DIC), Trifluoroacetic acid (TFA) and triisopropylsilane (TIS) were from Aldrich. Anhydrous N,N-dimethyl formamide (DMF) was from Fluka. Microwave experiments were performed with a Discover apparatus (CEM mWave) in 10mL sealed reactions tubes or using open vessel mode with SPS kit. TLC plates were Merck TLC aluminum sheets coated with silica gel $60F_{254}$. Compounds were purified by Flash chromatography (Silica gel Si 60, 40-43mm).

^{1}H NMR spectra were recorded on 250 MHz Bruker instrument. Chemical shifts are reported in ppm with the solvent as internal standard ($CDCl_3$: 7.26ppm, MeOH d_4=3.31ppm, DMSO d_6 =2.50ppm). Data are reported as followed: chemical shift, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, br= broad, m= multiplet), integration and coupling constants (Hz). ^{13}C NMR spectra were recorded on 125MHz NMR instruments with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as internal standard ($CDCl_3$: 77.16ppm, MeOH d_4=49.00ppm, DMSO d_6 =39.52ppm). DO measurements were performed with a Beckman DU640B spectrophotometer.

Electron spray mass spectrometry (ESMS) was performed with an ESI-QTRAP (Applied Biosystems-MDS Sciex, mass spectrometry platform at UPMC, Paris, France). HRMS spectra were registered using a 4800 MALDI-TOF mass spectrometer (Applied Biosystems, Foster City, USA) in positive reflectron mode in the m/z range of 100-700. Each spectrum was the result of 1000 to 2000 shots (20 different positions into each spot and 50 shots per sub-spectrum) and internal calibration was applied by using 4-HCCA matrix m/z.

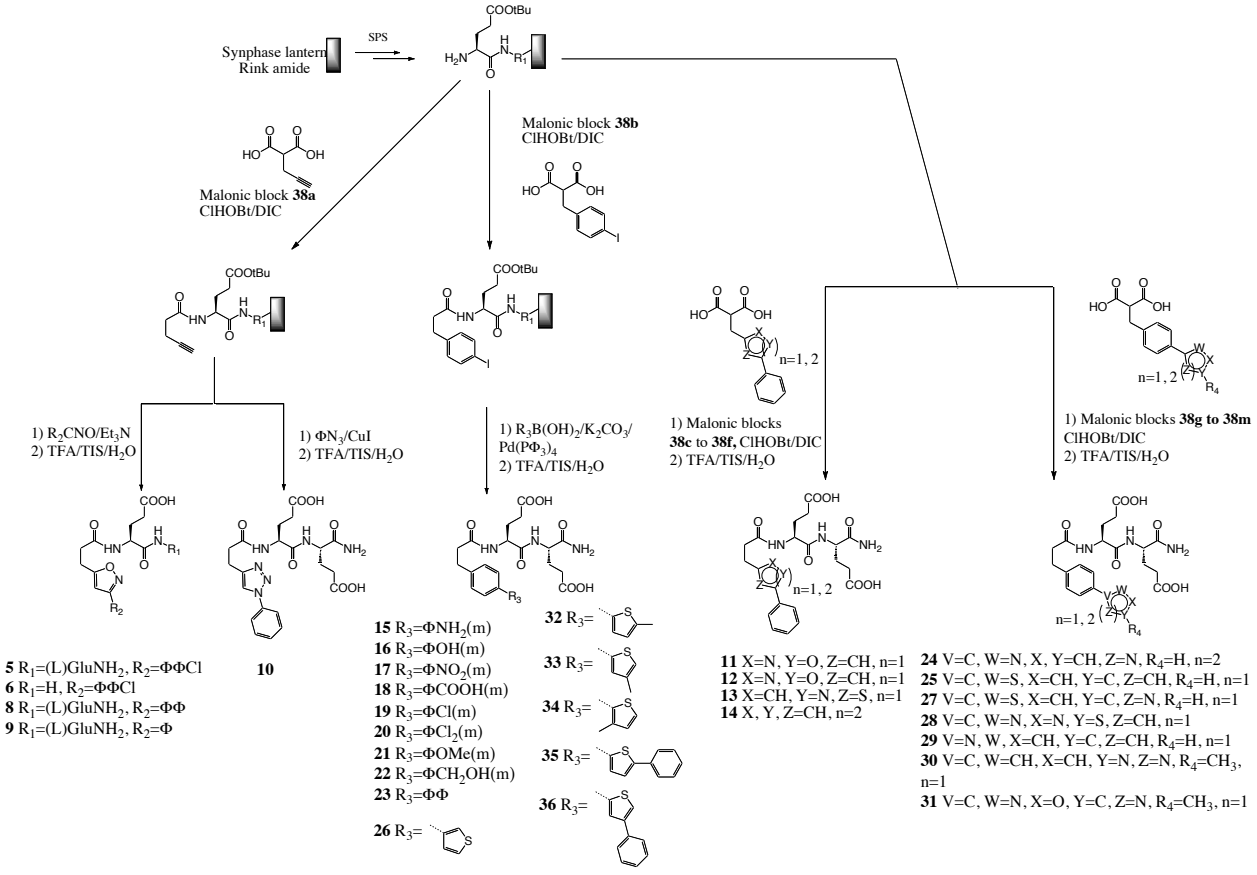
Analytical and preparative RP-HPLC separations were respectively performed on a Thermo separation product and Gilson apparatus using analytical Supelco Ascentis® Express (100x4,6mm, 2,7mm, Gradient: 0 to 10 min/0 to 100% (B), flow rate=1,8mL.min^{-1}) and AIT C18 Kromasil (250x20 mm, 10mm, 100Å,

Gradient: 0 to 40 min/0 to 100% (B), flow rate=3mL.min^{-1}). UV detection was performed at 230 nm. A solvent system consisting of (A) 0,1% TFA in 90% water-10% acetonitrile and (B) 0,09% TFA in 90% acetonitrile-10% water was used. Retention times (t_R) from analytical RP-HPLC are reported in minutes.

Amino acids compositions were made under standard conditions: samples were vaccum dried and sealed in glass tubes using the PicoTag system (Waters Associates, Milford, MA) and hydrolyzed under vapor phase of 6N HCl with a cristal of phenol through 17h at 110°C. The hydrolyzed sample was dissolved in 100 µl of MilliQ water and 90 µl of the HCl hydrolysate (containing a minimum of 200pmol of each AA) were analyzed and quantified *via* ninhydrin derivatization on an aminoTac JLC-500/V amino acids analyzer (JEOL, Japan). A calibration with an amino acids standard H solution was performed at the beginning of each analysis series.

*Pseudo peptide synthesis (**5** to **36**)*

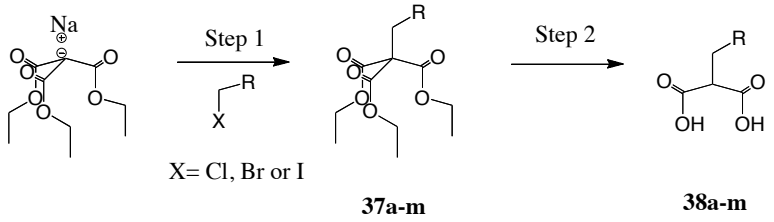
Pseudo peptides **5** to **36** were synthesized on solid support according to the general pathway described in scheme 1S.



Scheme 1S: General pathway of synthesis for compounds **5** to **36**

Malonic building blocks synthesis.

Malonic building blocks **38a** to **38m** were synthesized in 2 steps according to scheme 2.

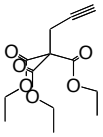


Scheme 2S: 2 steps malonic building blocks synthesis.

Step 1, general procedure: In a 10ml microwave reactor triethyl methane carboxylate sodium derivative (3,9mmol, 1eq) halogeno alkyl derivative (4,3 mmol, 1,1eq) and anhydrous DMF (5mL) were mixed and stirred at 100°C under microwave irradiation (300W) for 5min. The reaction completion was monitored by TLC (CHX/EtOAc : 9/1). The reaction mixture was then evaporated under reduced pressure and crude solution was suspended in EtOAc/H_2O (1/1:10mL/10mL). Aqueous layer was extracted with EtOAc (2x10mL) combined organic layers were washed with brine (20mL) and dried over anhydrous $MgSO_4$. The solvent was then concentrated under vacuum and crude compound was purified by Flash chromatography (CHX/EtOAc) to afford triester **37**.

Step 2, general procedure : Triester **37** (3,93mmol) was dissolved in EtOH (10mL) and potassium hydroxide (23,58mmol, 6eq) was added. The solution mixture was stirred at room temperature for 1h and then evaporated. Crude solid was suspended in 1M HCl_{aq} solution/EtOAc (1/1: 10mL/10mL). Aqueous layer was saturated with NaCl and extracted with EtOAc (2x10mL). Combined organic layers were washed with brine (20mL) and dried over anhydrous $MgSO_4$. After evaporation, crude solid was triturated in DCM (1mL) and filtrated to afford malonic acid derivative **38**.

Triethyl but-3-yne-1,1,1-tricarboxylate **37a**

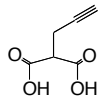


37a

Prepared from propargyl bromide (Fluka 81831, 80% in toluene) according to the alkylation protocol to provide the title compound as a pale yellow oil (88% yield).^{1}H NMR ($CDCl_3$): δ 1.29 (t, 9H, *J*=7Hz), 2.05

(t, 1H, *J*=2,75Hz), 3.01 (d, 2H, *J*=2,75Hz), 4,29 (q, 6H, *J*=7Hz). ^{13}C NMR ($CDCl_3$): δ 14.00, 23.41, 62.70, 64.68, 70.88, 78.87, 165.90.

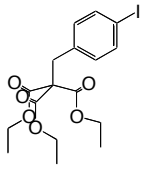
2-(prop-2-ynyl)malonic acid **38a**



38a

Prepared from triester **37a** according to the saponification protocol to provide the title compound as a white solid (86 % yield).^{1}H NMR (MeOH d_4): δ 2.33 (t, 1H, *J*=2.75Hz), 2.69 (dt, 2H, *J*=2.75Hz, *J*=5.25Hz), 3.51 (t, 1H, *J*=5.25Hz). ^{13}C NMR (MeOH d_4): δ 19,13, 71,27, 81,34, 171.51.

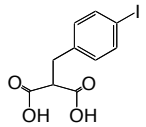
Triethyl 2-(4-iodophenyl)ethane-1,1,1-tricarboxylate **37b**



37b

Prepared from 4-Iodobenzyl bromide (Aldrich 515604) according to the alkylation protocol to provide the title compound as a pale yellow oil (94% yield). ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 9H, *J*=6,75Hz), 3.44 (s, 2H), 4,19 (q, 6H, *J*=6,75Hz), 7.05 (d, 2H, *J*=8Hz), 7.56 (d, 2H, *J*=8Hz).

2-(4-iodobenzyl)malonic acid **38b**

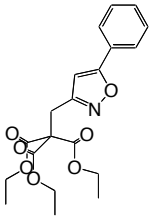


38b

Prepared from triester **37b** according to the saponification protocol to provide the title compound as a white solid (78% yield). ^{1}H NMR (MeOH d_4): δ 3.10 (d, 2H, *J*=7,75Hz), 3.61 (t, 1H, *J*=7,75Hz). 7.04 (d,

2H, *J*=8Hz), 7.61 (d, 2H, *J*=8Hz), ^{13}C NMR (MeOH d_4): δ 35.20, 54.72, 92.45, 132.11, 138.60, 139.58, 172.33. HRMS *m/z* for $C_{10}H_9INaO_4$ $(M+Na^+)^+$, calcd 342.9443, found 342.9430.

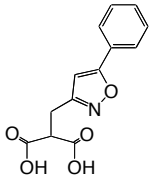
Triethyl 2-(5-phenylisoxazol-3-yl)ethane-1,1,1-tricarboxylate **37c**



37c

Prepared from 3-chloromethyl-5-phenyl isoxazole (Maybridge CC30524) according to the alkylation protocol to provide the title compound as a pale yellow oil (73% yield). ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 9H, *J*=7,25Hz), 3.59 (s, 2H), 4.28 (q, 6H, *J*=7.25Hz), 6.53 (s, 1H), 7.44 (m, 3H), 7.74 (m, 2H).

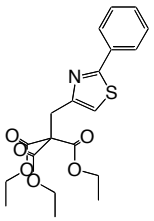
2-((5-phenylisoxazol-3-yl)methyl)malonic acid **38c**



38c

Prepared from triester **37c** according to the saponification protocol to provide the title compound as a white solid (53% yield). ^{1}H NMR (MeOH d_4): δ 3.26 (d, 2H, *J*=7.5Hz), 3.86 (t, 1H, *J*=7.5Hz), 6.71 (s, 1H), 7.49 (m, 3H), 7.81 (m, 2H). ^{13}C NMR (MeOH d_4): δ 26.51, 51.66, 100.83, 126.73, 128.58, 130.19, 131.44, 163.40, 171.28, 171.97. HRMS *m/z* for $C_{13}H_{12}NO_5$ $(M+H^+)^+$, calcd 262.0715, found 262.0714.

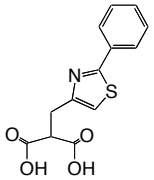
triethyl 2-(2-phenylthiazol-4-yl)ethane-1,1,1-tricarboxylate **37d**



37d

Prepared from 4-(Chloromethyl)-2-phenyl-1,3-thiazole (Maybridge CC18324) according to the alkylation protocol to provide the title compound as a yellow oil (58% yield). ^{1}H NMR ($CDCl_3$): δ 1,25 (t, 9H, *J*=7,25Hz), 3,70 (s, 2H), 4,24 (q, 6H, *J*=7,25Hz), 7,11 (s, 1H), 7,43 (m, 3H), 7,9 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 13.95, 14.03, 34.49, 62.31, 62.54, 65.73, 116.16, 126.51, 128.94, 129.91, 133.75, 152. 20, 164.07, 166.75, 166.63. $[M+H]^+$ = 406.1, $[M+Na]^+$ =428,1.

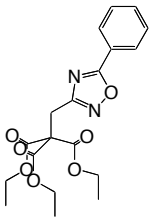
2-((2-phenylthiazol-4-yl)methyl)malonic acid **38d**



38d

Prepared from triester **37d** according to the saponification protocol to provide the title compound as a white solid (35% yield). ^{1}H NMR (MeOH d_4): δ 3.37 (d, 2H, *J*=7.75Hz), 3.93 (t, 1H, *J*=7.75Hz), 7.32 (s, 1H), 7.49 (m, 3H), 7.94 (m, 2H). ^{13}C NMR (MeOH d_4): δ 31.17, 52.76, 116.79, 127.47, 127.62, 130.20, 131.51, 131.66, 134.03, 154.62, 172.25. HRMS *m/z* for $C_{13}H_{12}NO_4S$ $(M+H^+)^+$, calcd 278.0496, found 278.0488.

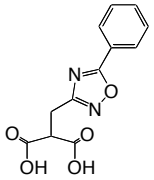
Triethyl 2-(5-phenyl-1,2,4-oxadiazol-3-yl)ethane-1,1,1-tricarboxylate **37e**



37e

Prepared from 3-chloromethyl-5 phenyl 1,2,4 oxadiazole (Maybridge, SEW02030) according to the alkylation protocol to provide the title compound as a yellow oil (55% yield). ^{1}H NMR ($CDCl_3$): δ 1,21 (t, 9H, *J*=7,25Hz), 3,72 (s, 2H), 4,29 (q, 6H, *J*=7,25Hz), 7,5 (m, 3H), 8,02 (d, 2H, *J*=8Hz). ^{13}C NMR ($CDCl_3$): δ 13.94, 14.05, 29.59, 62.56, 62.75, 64.35, 124.33, 128.14, 129.13, 132.74, 164.08, 166.06, 167.77, 175.15. $[M+H]^+$ = 391.3, $[M+Na]^+$ =413,2.

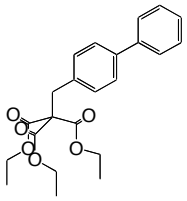
2-((5-phenyl-1,2,4-oxadiazol-3-yl)methyl)malonic acid **38e**



38e

Prepared from triester **37e** according to the saponification protocol to provide the title compound as a white solid (30 % yield). ^{1}H NMR (MeOH d_4): δ 3.35 (d, 2H, *J*=7,5Hz), 3.99 (t, 1H, *J*=7,5Hz). 7.55-7,66 (m, 3H), 8,12 (m, 2H). ^{13}C NMR (MeOH d_4): δ 26.54, 125.21, 128.99, 129.03, 130.41, 134.19, 170.21, 171.62, 177.05. HRMS *m/z* for $C_{12}H_{11}N_2O_5$ $(M+H^+)^+$, calcd 263.0668, found 263.0661.

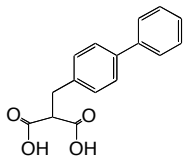
Triethyl 2-(biphenyl-4-yl)ethane-1,1,1-tricarboxylate **37f**



37f

Prepared from 4-(bromomethyl)-4-biphenyl 96% (Acros 368950050) according to the alkylation protocol to provide the title compound as a pale yellow oil (91% yield). ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 9H, *J*=7,25Hz), 3.56 (s, 2H), 4.28 (q, 6H, *J*=7.25Hz), 7.29-7.58 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 13.99, 27.05, 38.46, 62.32, 66.89, 126.80, 127.15, 127.31, 128.86, 131.10, 134.80, 140.00, 141.00, 166.66.

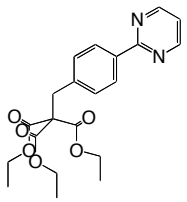
2-(biphenyl-4-ylmethyl)malonic acid **38f**



38f

Prepared from triester **37f** according to the saponification protocol to provide the title compound as a white solid (66% yield). ^{1}H NMR (MeOH d_4): δ 3.20 (d, 2H, *J*=8Hz), 3.67 (t, 1H, *J*=8Hz), 7.30-7.59 (m, 9H). ^{13}C NMR (MeOH d_4): δ 35.50, 55.02, 127.85, 128.02, 128.20, 129.82, 130.38, 138.87, 140.81, 142.16, 172.50. HRMS *m/z* for $C_{16}H_{14}NaO_4$ $(M+Na^+)^+$, calcd 293.0790, found 293.0797.

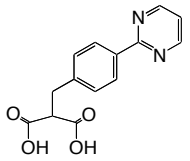
Triethyl 2-(4-(pyrimidin-2-yl)phenyl)ethane-1,1,1-tricarboxylate **37g**



37g

Prepared from 2-[4-(Chloromethyl)phenyl]pyrimidine (Maybridge, CC56224) according to the alkylation protocol to provide the title compound as a pale yellow oil (≥95% yield). ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 9H, *J*=7,25Hz), 3.59 (s, 2H), 4.19 (q, 6H, *J*=7.25Hz), 7.17 (s, 1H, *J*=4.75Hz), 7.40 (d, 2H, *J*=8.25Hz), 8,32 (d, 2H, *J*=8.25Hz), 8.78 (d, 2H, *J*=4.75Hz).

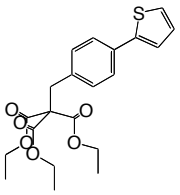
2-(4-(pyrimidin-2-yl)benzyl)malonic acid **38g**



38g

Prepared from triester **37g** according to the saponification protocol to provide the title compound as a white solid (59% yield). ^{1}H NMR (MeOH d_4): δ 3.22 (d, 2H, *J*=7.75Hz), 3.69 (t, 1H, *J*=7.75Hz), 7.33 (m, 3H), 8.28 (d, 2H, *J*=8.25Hz), 8.79 (d, 2H, *J*=4.75Hz). ^{13}C NMR (MeOH d_4): δ 35.60, 54.70, 120.62, 129.30, 130.22, 137.09, 142.97, 158.68, 165,60, 172.40. HRMS *m/z* for $C_{14}H_{13}N_2O_4$ $(M+H^+)^+$, calcd 273.0875, found 273.0881.

Triethyl 2-(4-(thiophen-2-yl)phenyl)ethane-1,1,1-tricarboxylate **37h**

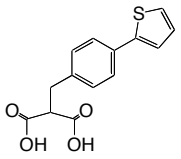


37h

Prepared from 2-[4-(Bromomethyl)phenyl]thiophene (Maybridge, CC12008) according to the alkylation protocol to provide the title compound as a yellow oil (≥95% yield).

^{1}H NMR ($CDCl_3$): δ 1.22 (t, 9H, *J*=7Hz), 3.51 (s, 2H), 4.31 (q, 6H, *J*=7Hz), 7.05 (m, 1H), 7.27 (m, 4H), 7.50 (d, 2H, *J*=8.25Hz).

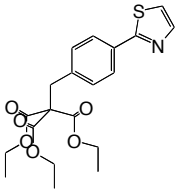
2-(4-(thiophen-2-yl)benzyl)malonic acid **38h**



38h

Prepared from triester **37h** according to the saponification protocol to provide the title compound as a pale green solid (68% yield). ^{1}H NMR (MeOH d_4): δ 3.16 (d, 2H, *J*=7.75Hz), 3.65 (t, 1H, *J*=7.75Hz), 7.06 (m, 1H), 7.26 (d, 2H, *J*=8.25Hz), 7.33 (m, 2H), 7.54 (d, 2H, *J*=8.25Hz). ^{13}C NMR (MeOH d_4): 34.06, 53.47, 122.55, 124.14, 125.34, 127.61, 129.06, 129.09, 132.76, 137.70, 143.80, 170.97. HRMS *m/z* for $C_{14}H_{13}O_4S$ $(M+H^+)^+$, calcd 277.0535, found 277.0538.

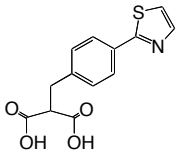
Triethyl 2-(4-(thiazol-2-yl)phenyl)ethane-1,1,1-tricarboxylate **37i**



37i

Prepared from 2-[4-(Chloromethyl)phenyl]-1,3-thiazole (Maybridge, CC40224) according to the alkylation protocol to provide the title compound as a yellow oil (≥95% yield). ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 9H, *J*=7.25Hz), 3.54 (s, 2H), 4.19 (q, 6H, *J*=7.25Hz), 7.33 (m, 4H), 7.83 (m, 2H).

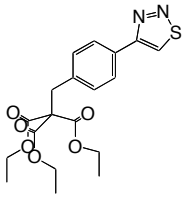
2-(4-(thiazol-2-yl)benzyl)malonic acid **38i**



38i

Prepared from triester **37i** according to the saponification protocol to provide the title compound as a pale blue solid (84% yield). ^{1}H NMR (MeOH d_4): δ 3.19 (d, 2H, *J*=7.5Hz), 3.68 (t, 1H, *J*=7.5Hz), 7.35 (d, 2H, *J*=8.25Hz), 7.54 (d, 1H, *J*=3.25Hz), 7.82 (m, 3H). ^{13}C NMR (MeOH d_4): 34.17, 53.25, 119.20, 126.33, 129.35, 131.46, 141.08, 142.81, 168.66, 170.83. HRMS *m/z* for $C_{13}H_{12}NO_4S$ $(M+H^+)^+$, calcd 278.0487, found 278.0483.

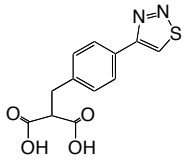
Triethyl 2-(4-(1,2,3-thiadiazol-4-yl)phenyl)ethane-1,1,1-tricarboxylate **37j**



37j

Prepared from 4-[4-(Bromomethyl)phenyl]-1,2,3-thiadiazole (Maybridge, CC16408) according to the alkylation protocol to provide the title compound as a yellow oil (≥95% yield). ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 9H, *J*=7Hz), 3.58 (s, 2H), 4.21 (q, 6H, *J*=7Hz), 7.42 (d, 2H, *J*=8.25Hz), 7.92 (d, 2H, *J*=8.25Hz), 8.61 (s, 1H).

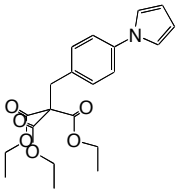
2-(4-(1,2,3-thiadiazol-4-yl)benzyl)malonic acid **38j**



38j

Prepared from triester **37j** according to the saponification protocol to provide the title compound as a pale yellow solid (70% yield). ^{1}H NMR (MeOH d_4): δ 3.23 (d, 2H, *J*=7.75Hz), 3.71 (t, 1H, *J*=7.75Hz), 7.40 (d, 2H, *J*=8.25Hz), 7.99 (d, 2H, *J*=8.25Hz), 9.14 (s, 1H). ^{13}C NMR (MeOH d_4): δ 34.18, 53.39, 126.99, 129.23, 129.33, 131.04, 139.85, 162.43, 170.92. HRMS *m/z* for $C_{12}H_{11}N_2O_4S$ $(M+H^+)^+$, calcd 279.0440, found 279.0434.

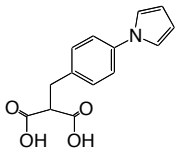
Triethyl 2-(4-(1*H*-pyrrol-1-yl)phenyl)ethane-1,1,1-tricarboxylate **37k**



37k

Prepared from 1-[4-(Bromomethyl)phenyl]-1H-pyrrole (Maybridge, CC25508) according to the alkylation protocol to provide the title compound as a yellow oil (≥95% yield). ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 9H, *J*=7.25Hz), 3.52 (s, 2H), 4.20 (q, 6H, *J*=7.25Hz), 6.31 (m, 2H), 7.04 (m, 2H), 7.29 (m, 4H).

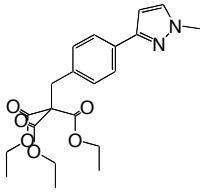
2-(4-(1*H*-pyrrol-1-yl)benzyl)malonic acid **38k**



38k

Prepared from triester **37k** according to the saponification protocol to provide the title compound as a pale yellow solid (84% yield). ^{1}H NMR (MeOH d_4): δ 3.17 (d, 2H, *J*=8Hz), 3.65 (t, 1H, *J*=8Hz), 6.25 (m, 2H), 7.14 (m, 2H), 7.35 (m, 4H). ^{13}C NMR (MeOH d_4): 33.76, 53.56, 109.80, 109.84, 118.51, 119.53, 119.55, 129.70, 129.74, 135.53, 139.32, 170.94. HRMS *m/z* for $C_{14}H_{14}NO_4$ $(M+H^+)^+$, calcd 260.0923, found 260.0908.

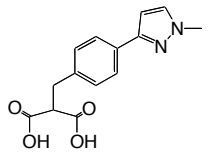
triethyl 2-(4-(1-methyl-1*H*-pyrazol-3-yl)phenyl)ethane-1,1,1-tricarboxylate **37l**



37l

Prepared from 3-[4-(chloromethyl)phenyl]-1-methyl-1h-pyrazole (Maybridge, CC23824) according to the alkylation protocol to provide the title compound as a yellow oil (≥95% yield). ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 9H, *J*=7.25Hz), 3.51 (s, 2H), 3.93 (s, 3H), 4.19 (q, 6H, *J*=7.25Hz), 6.49 (d, 1H, *J*=2.25Hz), 7.28 (d, 2H, *J*=8Hz), 7.65 (d, 2H, *J*=8Hz), 7.99 (s, 1H).

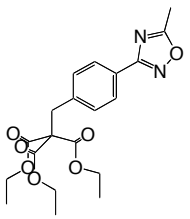
2-(4-(1-methyl-1*H*-pyrazol-3-yl)benzyl)malonic acid **38l**



38l

Prepared from triester **37l** according to the saponification protocol to provide the title compound as a pale yellow solid (94% yield). ^{1}H NMR (MeOH d_4): δ 3.16 (d, 2H, *J*=7.75Hz), 3.64 (t, 1H, *J*=7.75Hz), 3.88 (s, 3H), 6.55 (d, 1H, *J*=2.25Hz), 7.26 (d, 2H, *J*=8Hz), 7.54 (d, 1H, *J*=2.25Hz), 7.65 (d, 2H, *J*=8Hz). ^{13}C NMR (MeOH d_4): δ 34.17, 37.37, 53.53, 102.41, 125.26, 128.77, 128.80, 131.51, 132.07, 137.93, 151.37, 171.02. HRMS *m/z* for $C_{14}H_{15}N_2O_4$ $(M+H^+)^+$, calcd 275.1032, found 275.1020.

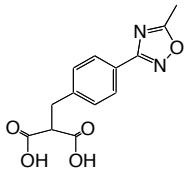
Triethyl 2-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)ethane-1,1,1-tricarboxylate **37m**



37m

Prepared from 3-[4-(Bromomethyl)phenyl]-5-methyl-1,2,4-oxadiazole (Maybridge, CC34808) according to the alkylation protocol to provide the title compound as a yellow oil (≥95% yield). ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 9H, *J*=7Hz), 2.64 (s, 3H), 3.58 (s, 2H), 4.20 (q, 6H, *J*=7Hz), 7.39 (d, 2H, *J*=8.25Hz), 7.93 (d, 2H, *J*=8.25Hz).

2-(4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl)malonic acid **38m**



38m

Prepared from triester **37m** according to the saponification protocol to provide the title compound as a pale yellow solid (89% yield). ^{1}H NMR (MeOH d_4): δ 2,64 (s, 3H), 3.22 (d, 2H, *J*=7.75Hz), 3.69 (t, 1H, *J*=7.75Hz), 7.40 (d, 2H, *J*=8Hz), 7.94 (d, 2H, *J*=8.25Hz). ^{13}C NMR (MeOH d_4): δ 10.62, 34.26, 53.22, 124.92, 126.90, 129.16, 142.07, 167.82, 170.79, 177.28. HRMS *m/z* for $C_{13}H_{13}N_2O_5$ $(M+H^+)^+$, calcd 277.0824, found 277.0831.

Solid phase synthesis general procedure on Rink amide PA Synphase lantern

Standard Fmoc methodology was used to build amino acids sequences. Lanterns were first swelled in DCM for 15min at room temperature. Fmoc deprotection was performed with piperidine 20% in DMF under microwave irradiation (3x3min, 60°C, 25W). Lanterns were then washed with DMF (2x5min) and DCM (2x5min). After a pre-activation mixing protocol (10 equiv of Fmoc-AA-OH, 10 equiv of Cl-HOBt and 10 equiv of DIC in anhydrous DMF, 5min, room temperature), lanterns were then immersed in the coupling solution and coupling reaction was performed under microwave irradiation (10min, 60°C, 25W). This operation was repeated twice. This cycle of Fmoc deprotection/ amino acid coupling step was repeated once for pseudodipeptdides synthesis.

Malonic building block incorporation

Malonic building blocks **38** (5 equiv) were pre-activated in presence of DIC (5eq) and Cl-HOBt (5eq) in anhydrous DMF (pre-activation protocol, 5min, room temperature) and lanterns were then immersed in coupling solution. Reaction was carried out under microwave irradiation (10min, 60°C, 25W). Lanterns were then washed with DMF (2x5min) and DCM (2x5min).

Dipolar cycloaddition on solid support access to pseudopeptides **5** to **10**

Isoxazole pathway (**5-9**): Isoxazole derivatives were obtained according to one-pot method[1] that has been slightly modified. Corresponding oxime (10eq) were dissolved in anhydrous DCM and two drops of pyridine were added. NCS (10 eq) was added at room temperature and after 10 min the resulting mixture was stirred for 1h at 45°C and then cooled down to room temperature. Lanterns were immersed and Et_3N (20eq) was added. The reaction mixture was gently stirred for 12h at room temperature. This operation was repeated three times. Lanterns were then washed with DMF (2x5min) and DCM (2x5min).

1,4 triazole pathway (**10**): Lanterns were immersed in reaction mixture containing phenyl azide (10eq), copper iodide dissolved in THF (0,18M estimated concentration, 2eq) and Et_3N (50eq). Dipolar cycloaddition was carried out under microwave irradiation in a sealed reactor (80°C,10 min, 300W). Lanterns were then washed with THF (1x5min), 0.1M solution of EDTA (1x5min) water (1x5min) DMF (2x5min) and DCM (2x5min).

Suziki coupling step on solid support, access to pseudopeptides **15-23**, **26** and **32-36**.

Lanterns were immersed in a mixture of boronic acid derivative (10eq, 0,2M DMF solution), potassium carbonate (10eq, 0,16M aqueous solution) and Pd $(PPh_3)_4$ (1eq, 0,08M DMF solution). Cross coupling reaction was then carried out under microwave irradiation in a sealed reactor (80°C, 5min, 300W). Lanterns were then washed with DMF (2x5min) and DCM (2x5min).

Cleavage, purification and storage**.**

Each synthesized pseudo peptides were cleaved from lanterns. This cleavage is first performed in TFA/TIS/H_2O (95/2,5/2,5). After gentle stirring at room temperature for 1h, lanterns were then transferred into a fresh TFA/DCM (1/1) solution and stirred for 30 minutes at room temperature. Combined cleavage solutions were then evaporated and crude pseudo peptides were taken in a (A)/(B): 1/1 solution. RP-HPLC separations were performed on AIT C18 Kromasil (250x20 mm, flow rate=3mL.min^{-1}, UV detection at 230 nm) using a gradient as followed: 0 to 40 min: 0 to 100% (B). After lyophilization, each pure pseudo peptide is stored at +4°C in a water/Ethanol: 1/1 solution after neutralization with 1M $NaHCO_3$ aqueous solution. Determination of pseudo peptide concentration is performed by Amino acid composition analysis and UV measurements.

3) Supplemental references

1- Diastereoselective solution and multipin-based combinatorial array synthesis of a novel class of potent phosphinic metalloprotease inhibitors. Makaritis A, Georgiadis D, Dive V, Yiotakis A. Chemistry. 2003 May 9;9(9):2079-94.