Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

Supplementary information
Natural product inspired antibacterial tetramic acid libraries with dual enzyme inhibition

Yong-Chul Jeong, Muhammad Anwar, and Mark G. Moloney*

Chemistry Research Laboratory, University of Oxford, Mansfield Rd, University of Oxford, OX1 3TA, U.K.

Tel: +44 1865 275656; e-mail: mark.moloney@chem.ox.ac.uk

Zsolt Bikadi, and Eszter Hazai

Virtua Drug, 4C Csalogany Budapest, H-1015 Hungary

Contents

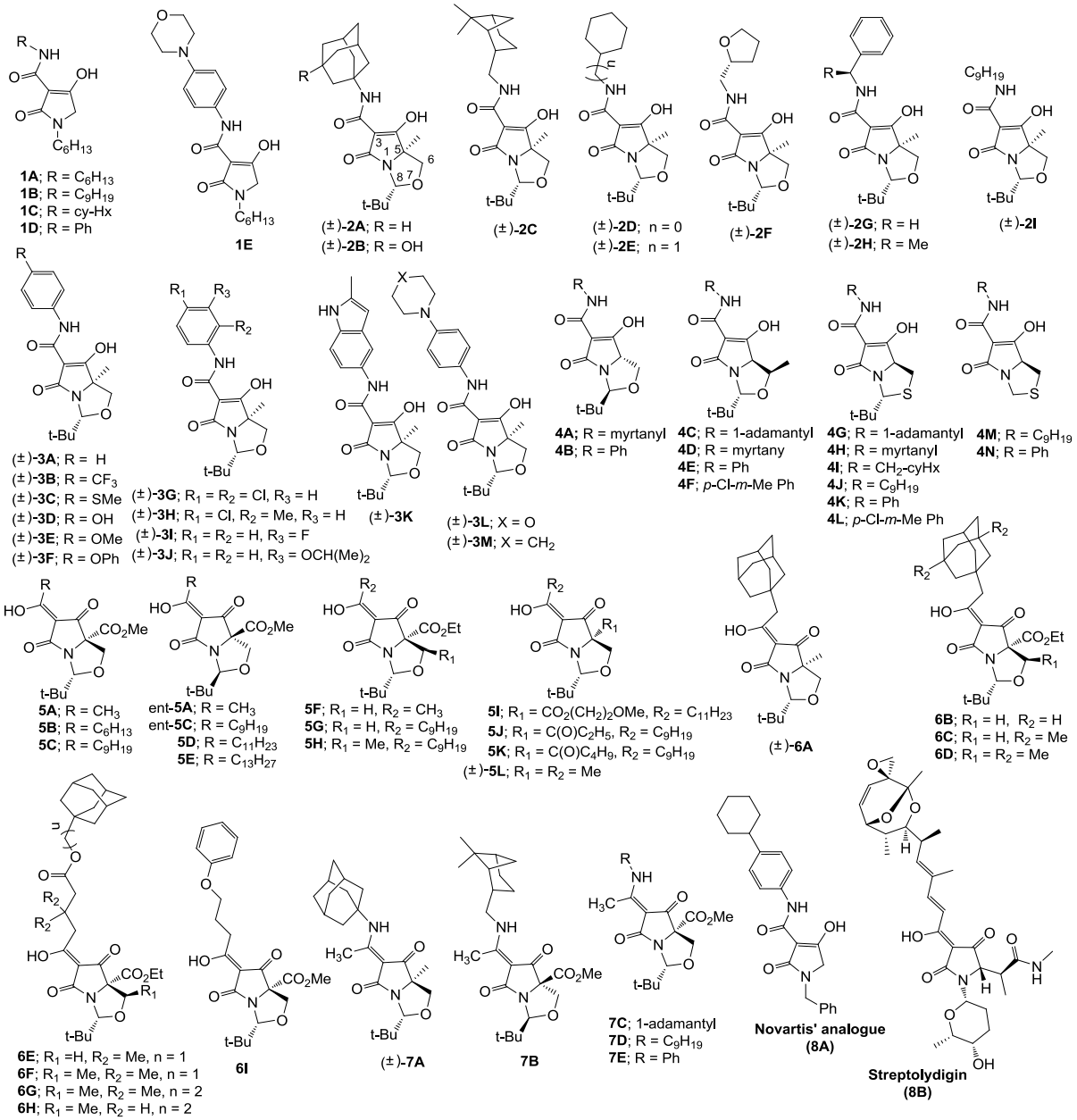


Figure S1. A diverse TA library (69 analogues) used for enzyme inhibition studies and whole cell antibacterial

This journal is © The Royal Society of Chemistry 2013

activity. Analogues **8A**, reported by Novartis and natural streptolydigin **8B** were used for comparison.

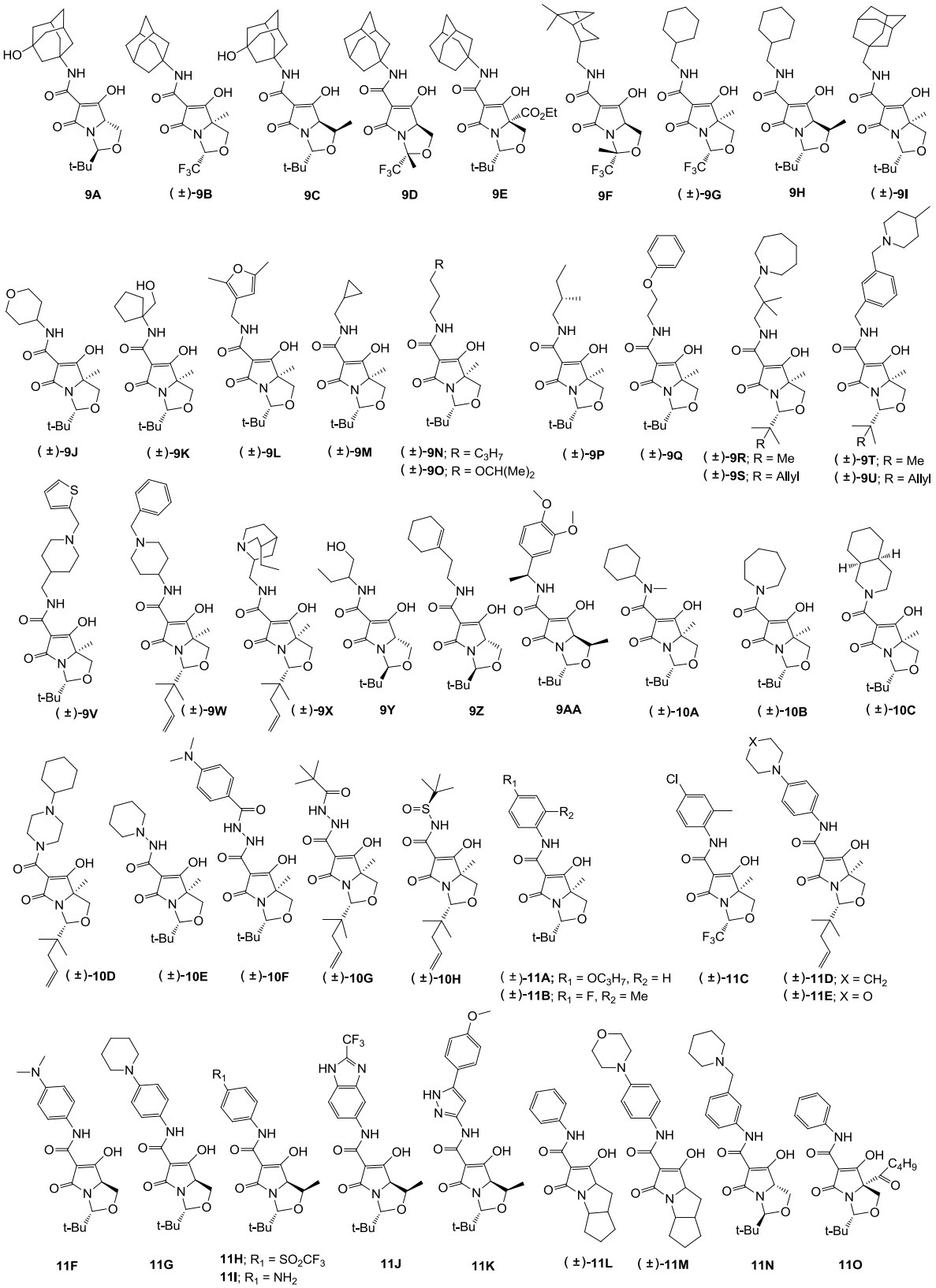


Figure S2. Bicyclic 3-carboxamides (50 analogues) synthesised and used for whole cell antibacterial assay

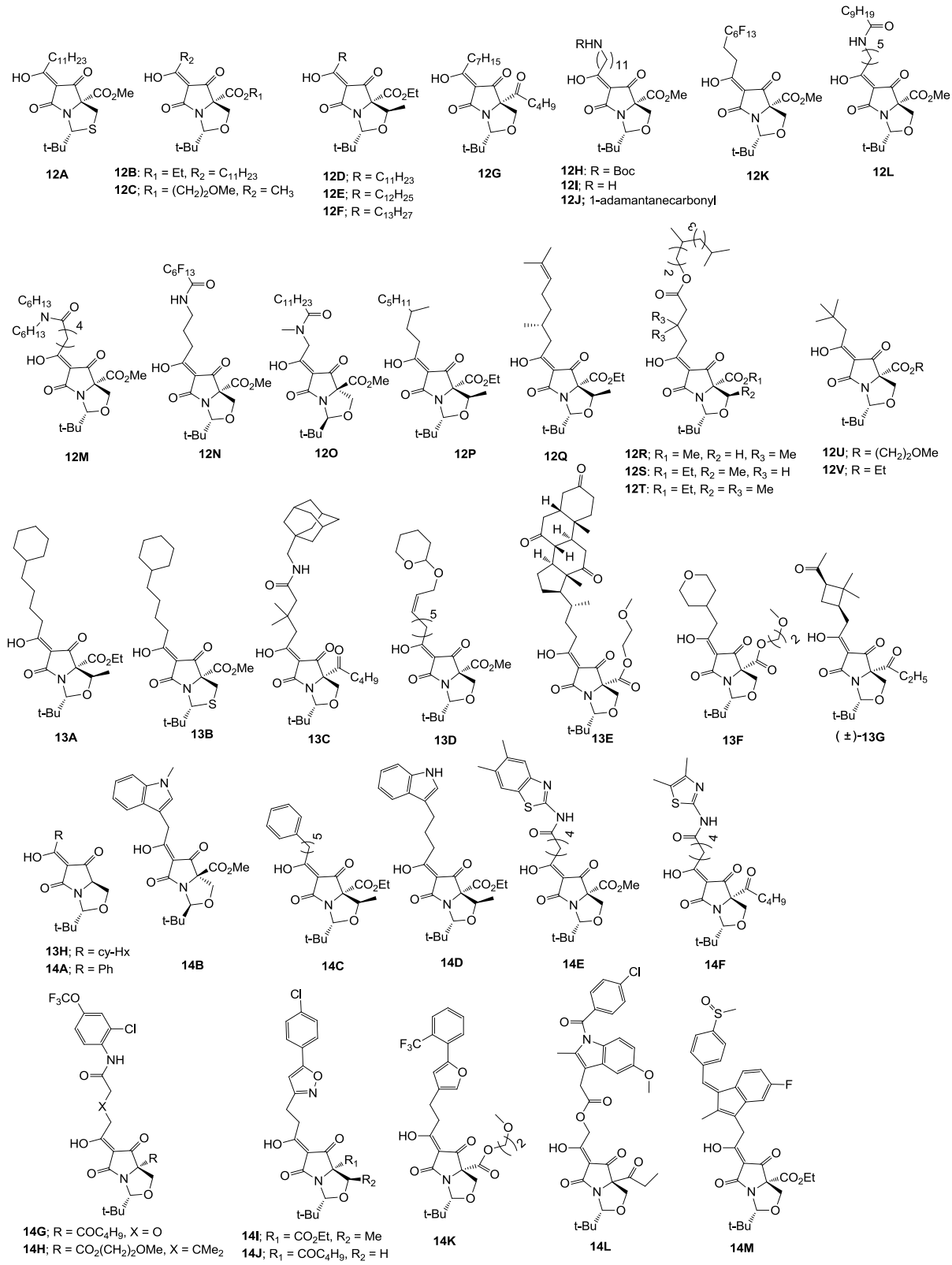


Figure S3. Bicyclic 3-acyl derivatives (43 analogues) synthesised and used for whole cell antibacterial assay

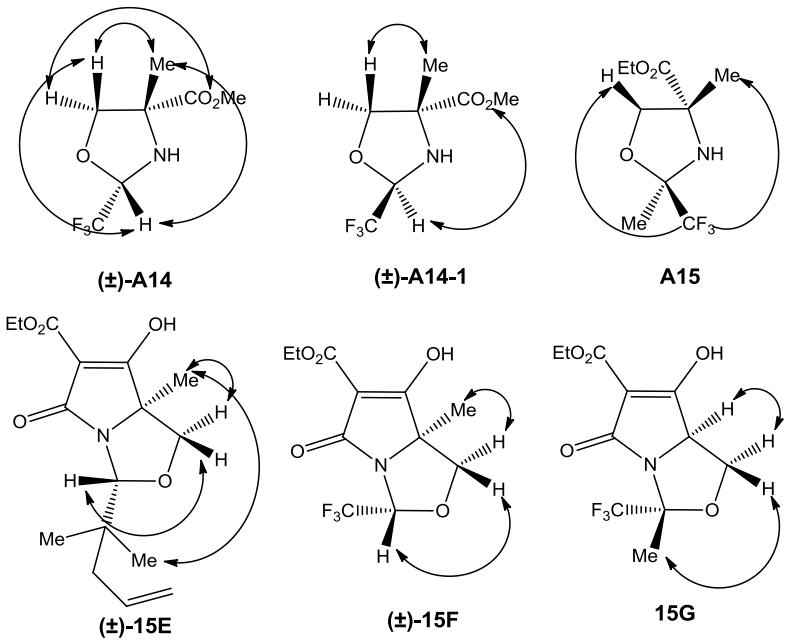


Figure S4. NOE correlation of intermediates and tetramic acid templates for stereochemical assignment

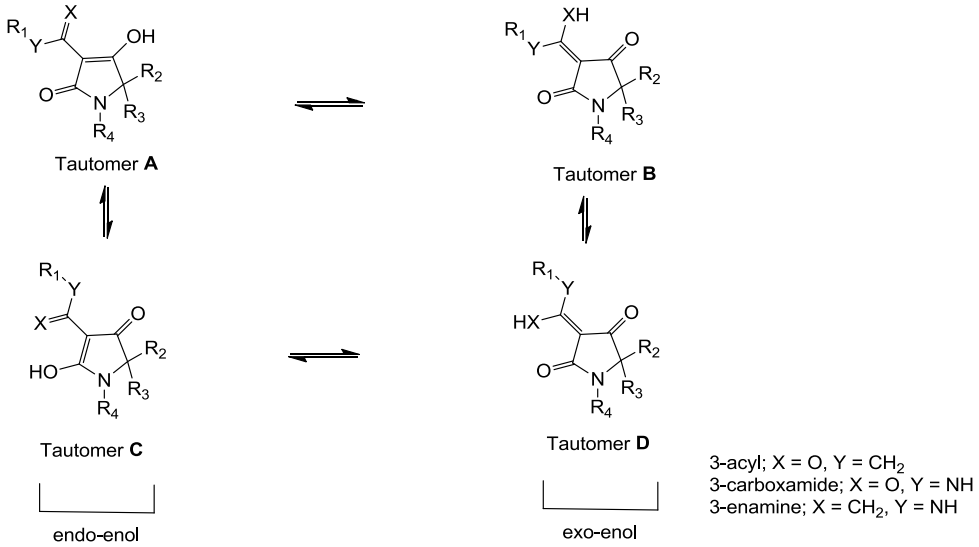


Figure S5. Tautomerisation in 3-carboxamide, 3-acyl and 3-enamine tetramic acids

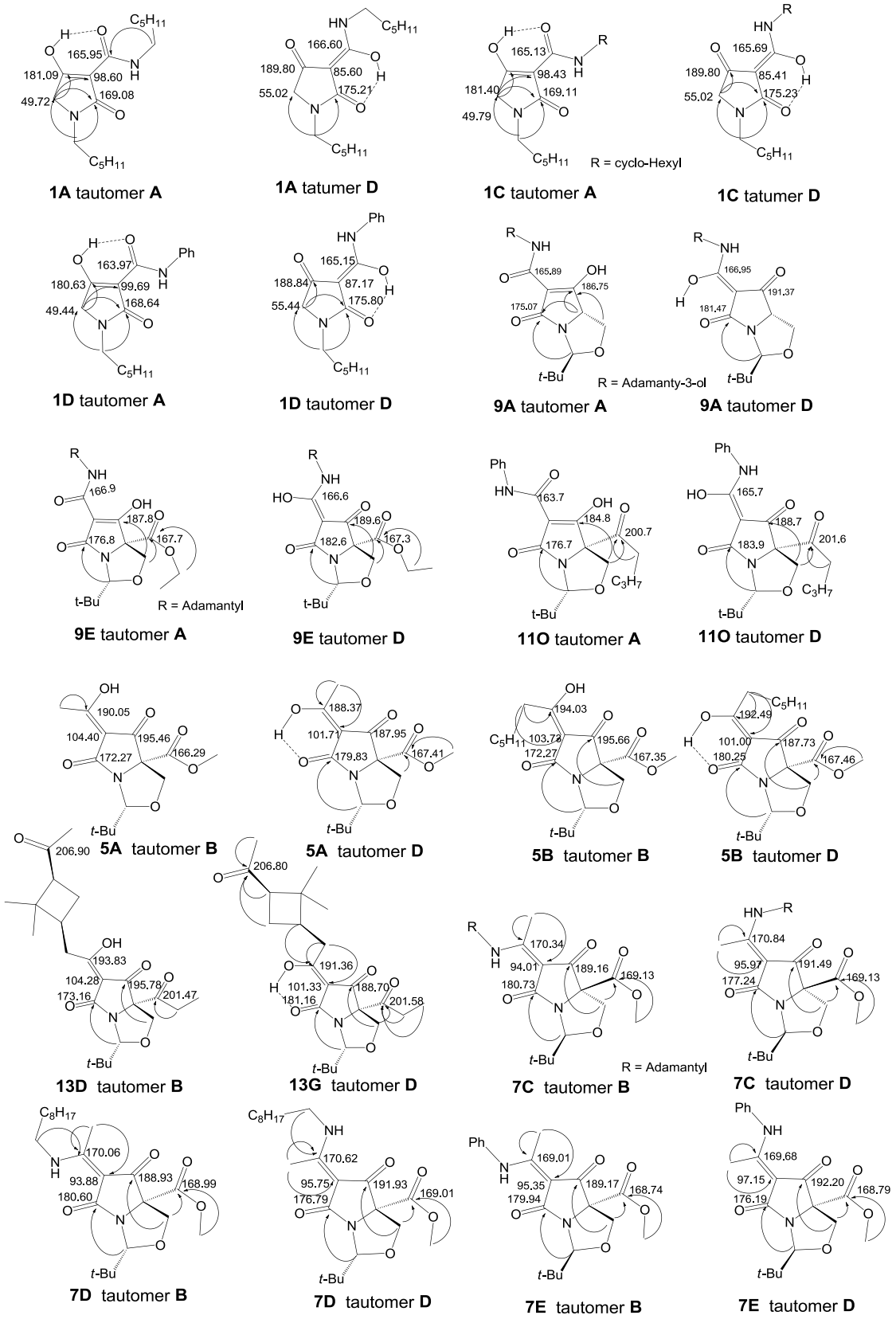
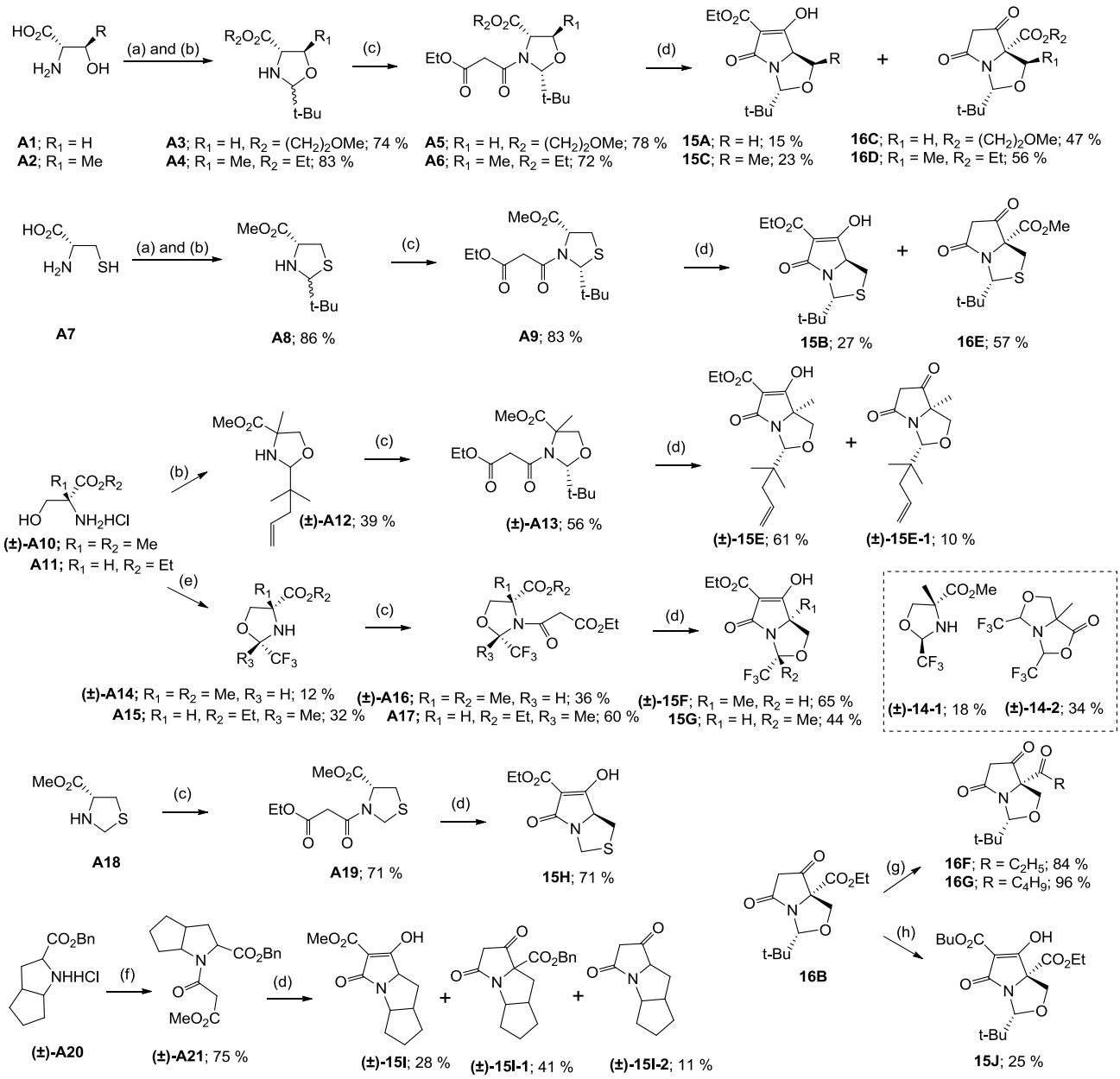
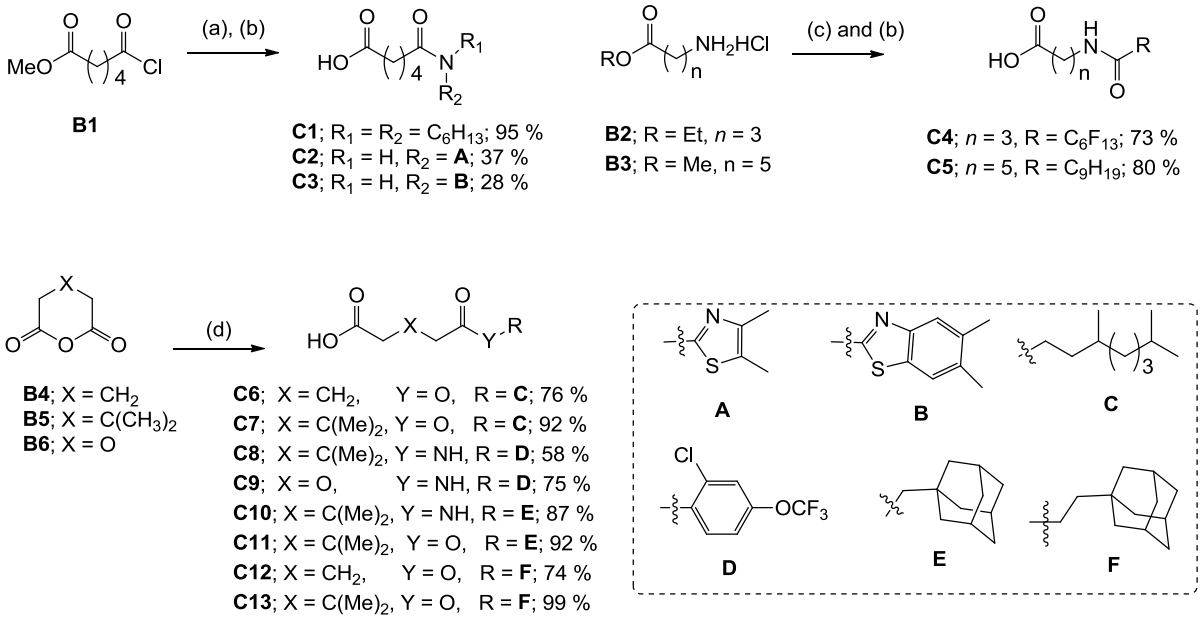


Figure S6. HMBC spectra of selected tetramic acids



(a) $SOCl_2$, ROH; (b) RCOH (1.3 eq), Et_3N (1.1 eq), petrol (40-60), relux; (c) mono-ethyl malonate (1.1 eq), DCC (1.1 eq), DMAP (0.05 eq), CH_2Cl_2, r.t; (d) KtBuO (1.1 eq), dry THF, reflux; (e) NaOAc (1.2 eq), trifluoroacetaldehyde ethyl hemiacetal (2.0 eq) for **(±)-A14** or trifluoroacetone (2.0 eq) for **A15,** toluene, r.t.-90 iÉ then Dean Stark; (f) methyl hydrogen malonate (1.05 eq), DCC (1.05 eq), DMAP (0.03 eq), CH_2Cl_2, r.t.; (g) EtLi (5.0 eq) for **T17** or *n*-BuLi (5.0 eq) for **T18**, THF, -78-r.t.; (h) butyl chloroformate (1.2 eq), DMAP (2.2 eq), CH_2Cl_2, r.t.

Scheme S1. Synthesis of tetramic acid templates



(a) amine (1.1 eq), triethylamine (1.2 eq), CH_2Cl_2, 0 °C-r.t.; (b) LiOH (3.0 eq), H_2O: CH_3OH: THF (2: 1:1), 0 °C-r.t.;
(c) acid chloride (1.1 eq), triethylamine (2.2 eq), CH_2Cl_2, 0 °C-r.t.; (d) amine or alcohol (1.1 eq), toluene, reflux;

Scheme S2. Synthesis of carboxylic acid templates

Supplementary discussions for detailed structure-enzyme activity relationships

In SAR of the enzyme inhibition activity of 3-carboxamide TAs, (±)-**2A**,**E**, in which the cyclic group was connected to the TA ring directly, and n-alkyl (±)-**2I**, all showed dual activity, while (±)-**2C**,**D** in which the cyclic group was connected to the TA scaffold by a methylene bridge showed only UPPS activity. However, the introduction of a hydroxyl group on the adamantyl pendant ((±)-**2A** versus (±)-**2B**) abolished RNAP activity, and polar cyclic (±)-**2F** and benzyl (±)-**2G**,**H** lost both the activities. On the other hand, phenyl (±)-**3A** had a lower UPPS potency compared with the corresponding monocyclic **1D**, which had weak RNAP potency. In the SAR of mono-substituted phenyl derivatives, bulky ((±)-**3D** < (±)-**3E** < (±)-**3F** and (±)-**3I** < (±)-**3J**) and non-polar ((±)-**3E** < (±)-**3C** < (±)-**3B**) groups tended to be more active, with diphenyl ether (±)-**3F** showing dual MOA. Disubstituted (±)-**3G**,**H** and methylindole (±)-**3K** showed improved enzyme activities compared with unsubstituted (±)-**3A**. Of interest is that the morpholinophenyl group of (±)-**3L** (which was highly effective in monocyclic **1E**) proved to be enzyme inactive, while the piperidinophenyl group ((±)-**3M**), which is effective in the Novartis' analogues, possessed only moderate IC_{50}s against both the enzymes, indicating that functionality of the pendant 3-carboxamide is critical. However, the replacement of oxygen by a sulphur atom at the 7-position (**4A** ⇔ **4H** and **4B** ⇔ **4K**) only weakly affected both activities, while the effect of the methyl group at the 5- or 6-position depended on the identity of the functional group in the carboxamide ((±)-**2A** < **4C**, (±)-**3A** < **4B** < **4E**, **4A** < **4D** ≤ (±)-**2C** and **4F** < (±)-**3H**).

In the SAR of 3-acyl TAs, longer chain **5C**-**E** and **5G**-**K** (*n* ≥9) were active whereas shorter chain **5A**,**B** and

This journal is © The Royal Society of Chemistry 2013

ent-**5A** (*n* ≤6) were inactive in the RNAP activity of *n*-alkyl derivatives, and stereoisomers **5C** and *ent*-**5C** showed similar efficiency. For substituents at the 5-position, ester derivatives were better than keto derivatives (eg. **5G** versus **5J**) and shorter ester and keto derivatives were better than the longer derivatives (eg. **5J** versus **5K** and **5G** versus **5I**). Furthermore, introduction of a methyl group at the 6-position (**5G** versus **5H**) gave improved activities against not only RNAP (1.6 μM) but also UPPS (3.0 uM), whereas all other *n*-alkylacyl derivatives without the 6-methyl did not show UPPS activity (>10 μM). In the SAR of adamantly (±)-**6A**-**D**, RNAP activity was high, and only weakly affected by the identity of the substituents R_2 of the adamantyl group and at the 5- and 6-positions in the TA scaffold, whereas UPPS activity was found only in **6C**. Interestingly, introduction of a methyl group at the 6-position of the adamantyl derivative gave a negative effect on UPPS/RNAP activity (**6C** versus **6D**), while a similar change in the nonyl **5G**,**H**, gave a similar positive effect as described above. In the SAR of **6E**-**H**, all inspired by the structure of streptolydigin, the substitution on R_2 was more sensitive (**6G** versus **6H**) than the presence of the methyl group on the 6-position (**6E** versus **6F**) and the chain-length (**6F** versus **6G**) for UPPS activity whereas RNAP activity was only weakly affected.

Table S1. *In vitro* enzyme activity (IC_{50}, μM) and antibiotic activity (MIC, μg/mL) of 3-carboxamide tetramic acids shown in Figure S1[a-d]

	RN	UP	S1	S26	S4	S2	E1	E2	P1	P9	P9B	HI3	HI4
1A	>100	0.30	2	2	2	2	2	2	4	1	4	1	0.12
1B	>100	0.50	2	16	16	16	8	0.5	4	1	4	>64	≤0.06
1C	>100	0.10	8	8	8	8	8	8	16	8	8	4	0.25
1D	>100	1.7	1	1	1	2	2	4	4	4	-[d]	2	0.5
1E	>100	0.50	4	8	8	8	8	8	16	8	32	16	4
(±)-**2A**	17	0.38	1	2	1	1	1	1	1	1	1	2	1
(±)-**2B**	>100	1.8	16	16	16	8	8	8	8	8	8	8	0.5
(±)-**2C**	>100	0.50	2	2	2	1	0.25	1	1	1	2	32	4
(±)-**2D**	>100	8.3	32	64	32	16	16	32	16	16	8	16	8
(±)-**2E**	31	0.68	4	4	4	2	2	1	2	1	1	4	0.12
(±)-**2F**	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	64
(±)-**2G**	>100	>10	32	32	32	64	16	32	16	16	16	8	2
(±)-**2H**	>100	>10	32	32	32	16	16	32	16	8	16	16	8
(±)-**2I**	20	0.75	0.25	0.5	0.25	0.25	0.25	0.25	0.12	0.25	4	>64	4
(±)-**3A**	64	>10	32	32	16	16	8	16	8	8	4	8	8
(±)-**3B**	13	>3.3	4	8	4	4	2	2	1	1	2	8	4
(±)-**3C**	35	>10	8	16	8	8	4	8	4	2	4	8	-[d]

This journal is © The Royal Society of Chemistry 2013

(±)-**3D**	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
(±)-**3E**	99	6.3	32	64	32	32	32	32	16	16	16	32	16
(±)-**3F**	7.3	0.78	1	4	1	0.5	0.5	0.5	0.5	0.5	2	1	0.5
(±)-**3G**	7.4	1.3	4	4	2	2	2	1	0.5	0.5	4	8	2
(±)-**3H**	18	0.88	4	4	4	2	2	1	2	1	4	16	4
(±)-**3I**	>100	>10	8	16	16	8	8	8	4	4	4	16	8
(±)-**3J**	20	3.1	2	8	4	4	2	4	2	2	2	16	8
(±)-**3K**	48	2.3	32	32	32	16	>64	32	>64	>64	>64	>64	8
(±)-**3L**	>100	>30	>64	>64	64	>64	32	32	32	16	16	32	32
(±)-**3M**	89	4.1	32	>64	16	16	32	16	8	4	16	16	2
4A	4.3	0.10	2	4	2	4	2	2	1	0.5	2	4	≤0.06
4B	>100	9.5	>64	>64	>64	64	64	64	32	16	32	16	8
4C	26	1.1	2	4	2	2	2	2	1	4	4	4	4
4D	>100	0.12	0.25	0.5	0.25	0.25	0.25	0.25	0.25	0.25	0.5	2	≤0.06
4E	88	8.4	32	64	16	16	8	16	8	8	8	8	8
4F	34	>10	16	16	8	8	8	4	2	2	8	32	8
4G	49	1.1	0.5	0.5	0.5	0.25	0.5	0.5	0.5	0.5	1	1	≤0.06
4H	5.5	0.20	0.25	0.5	0.25	0.12	0.12	0.12	0.5	0.5	1	1	≤0.06
4I	57	0.51	2	4	2	1	1	1	1	1	1	1	≤0.06
4J	16	0.17	0.5	1	1	1	0.5	1	0.5	0.5	8	>64	1
4K	69	9.2	32	64	16	16	16	16	8	8	8	8	4
4L	15	4.9	4	4	2	1	1	1	1	0.5	4	2	0.5
4M	52	>10	32	64	16	16	16	32	8	8	>64	16	2
4N	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Line	-[d]	-[d]	2	2	2	2	2	2	1	0.5	0.5	16	4
Cip	-[d]	-[d]	0.12	0.5	0.12	**16**	1	**32**	1	1	1	0.5	≤0.06

a; abbreviation; **RN**; *In vitro* activity against *E. Coli* RNAP, **UP**; *In vitro* activity against *S. pneumonia* UPPS, **S1**; *S. aureus* 1, ATCC13709 *in vivo* (methicillin sensitive), **S26**; *S. aureus* 26, ATCC25923 (vancomycin susceptible), **S4**; *S. aureus 4*, Oxford, **S2**; *S. aureus* 2 (MRSA *in vivo*), **E1**; *E. faecalis* 1, ATCC29212 VanS (vancomycin susceptible), **E2**; *E. faecium* 1, VanA (vancomycin resistant), **P1**; *S. pneumonia* 1, ATCC49619 (erythromycin susceptible), **P9**; *S. pneumonia* 9, (multi-drug resistant), **P9B**; *S. pneumonia* 9 in presence of 2.5 % horse blood, **H3**; *H. influenzae* 3, ATCC31517 MMSA, **H4**; *H. influenzae* 4, LS2 Efflux ko, **Line**; linezolid, **Cip**; ciprofloxacin; b; All analogues are inactive (MIC > 64 ug/ml) against *E. coli* 1, ATCC25922 (non Pathogenic strain), *E. coli* 50, Ec49 No Efflux and *P. aeruginosa* 1, ATCC27853. c; All analogues are antifungal inactive (MIC > 32 ug/ml) against *Candida albicans.* d; Not determined

This journal is © The Royal Society of Chemistry 2013

Table S2. *In vitro* enzyme activity (IC_{50}, µM) and antibiotic activity (MIC, µg/mL) of 3-acyl and 3-enamine tetramic acids shown in Figure S1[a-d]

	RN	UP	S1	S26	S4	S2	E1	E2	P1	P9	P9B	HI3	HI4
5A	>100	-[d]	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
ent-**5A**	>100	-[d]	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5B	>100	>10	>64	>64	>64	>64	64	>64	32	32	32	64	8
5C	10	-[d]	4	8	8	4	4	4	1	0.5	4	8	0.5
ent-**5C**	6.9	>10	4	8	8	8	2	2	1	1	4	8	2
5D	6.6	>10	0.5	1	1	0.5	0.5	0.5	0.25	0.25	2	4	0.5
5E	3.3	>10	0.5	0.5	0.5	0.5	0.12	0.12	0.25	0.12	1	>64	2
5F	-[d]	-[d]	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5G	6.4	>10	4	2	2	2	2	2	1	1	4	32	4
5H	1.6	3.0	0.5	2	1	1	0.5	0.5	0.12	0.25	2	16	0.25
5I	30	>10	2	4	4	2	2	2	2	1	8	16	4
5J	14	>10	2	4	4	2	1	1	0.5	0.5	1	8	1
5K	98	>10	1	4	2	1	0.5	1	0.5	0.5	4	>32	2
(±)-**5L**	-[d]	-[d]	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
(±)-**6A**	4.7	>10	0.5	1	1	1	0.5	1	2	1	2	4	≤0.06
6B	5.6	>10	8	8	4	8	4	4	2	2	2	32	0.5
6C	4.0	3.2	2	2	2	1	2	1	0.5	0.5	1	64	0.25
6D	6.1	>10	2	4	2	4	2	4	1	1	4	>64	0.5
6E	7.0	4.0	2	2	2	4	1	1	0.5	0.5	4	>64	1
6F	7.4	3.9	2	2	2	2	2	1	2	2	4	>64	1
6G	2.4	1.9	0.5	1	1	0.5	1	0.5	2	1	4	>64	2
6H	4.4	>10	64	>64	>64	64	32	16	2	4	>64	>64	4
6I	>100	>10	>64	>64	>64	>64	>64	>64	64	64	64	>64	16
(±)-**7A**	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	16
7B	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
7C	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	16
7D	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
7E	>100	>10	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
8A	>100	0.3	0.12	0.12	1	**64**	≤0.06	≤0.06	2	2	2	>64	0.5
8B	38	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]

a; abbreviation; see foot note in Table S1**,** b; All analogues are inactive (MIC > 64 ug/ml) against *E. coli* 1,

This journal is © The Royal Society of Chemistry 2013

ATCC25922 (non Pathogenic strain), *E. coli* 50, Ec49 No Efflux and *P. aeruginosa* 1, ATCC27853. c; All analogues are antifungal inactive (MIC > 32 ug/ml) against *Candida albicans.* d; Not determined

Table S3. *In vitro* antibiotic activity (MIC, µg/mL) of 3-carboxamide tetramic acids shown in Figure S2[a-d]

	S1	S26	S4	S2	E1	E2	P1	P9	P9B	HI3	HI4
9A	>64	>64	>64	>64	>64	>64	64	64	64	>64	8
(±)-**9B**	8	16	8	16	8	4	4	2	4	4	0.25
9C	>64	>64	>64	>64	>64	>64	64	64	64	>64	64
9D	8	4	8	8	2	4	2	2	2	2	0.25
9E	4	8	8	8	2	2	1	1	2	64	1
9F	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	16
(±)- **9G**	64	64	>64	64	>64	32	16	16	16	8	-[d]
9H	8	8	4	4	4	4	4	2	4	4	0.25
(±)-**19I**	1	0.5	1	1	0.25	0.5	0.25	0.25	2	2	≤0.06
(±)-**9J**	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
(±)-**9K**	>64	>64	>64	>64	>64	>64	64	64	64	>64	16
(±)-**9L**	32	32	32	64	16	32	16	16	16	16	8
(±)-**9M**	64	>64	>64	>64	64	64	32	32	32	16	4
(±)-**9N**	4	4	4	8	4	4	4	4	4	4	0.5
(±)-**9O**	>64	-[d]	>64	>64	>64	>64	64	64	64	64	16
(±)-**9P**	32	64	32	64	32	32	32	32	16	16	4
(±)-**9Q**	32	32	32	64	16	16	8	8	8	16	4
(±)-**9R**	>64	>64	64	>64	>64	>64	>64	64	64	>64	16
(±)-**9S**	>64	>64	64	>64	64	64	32	32	16	>64	64
(±)-**9T**	>64	>64	>64	>64	>64	>64	>64	64	64	>64	8
(±)-**9U**	>64	>64	64	64	64	32	16	16	8	>64	2
(±)-**9V**	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	16
(±)-**9W**	>64	>64	>64	>64	>64	64	32	32	32	>64	4
(±)-**9X**	>64	>64	64	>64	>64	32	64	32	32	>64	16
9Y	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
9Z	16	32	8	16	8	8	8	8	8	16	1
9AA	>64	>64	>64	>64	>64	>64	64	64	64	>64	64
(±)-**10A**	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	32
(±)-**10B**	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	64
(±)-**10C**	64	>64	>64	>64	>64	16	>64	>64	>64	>64	16

This journal is © The Royal Society of Chemistry 2013

(±)-**10D**	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
(±)-**10E**	>64	>64	>64	>64	>64	>64	>64	>64	>64	64	16
(±)-**10F**	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	32
(±)-**10G**	64	>64	>64	>64	>64	32	32	32	>64	>64	64
(±)-**10H**	64	>64	64	64	64	64	64	64	64	>64	16
(±)-**11A**	8	8	8	16	4	8	4	2	8	4	2
(±)-**11B**	16	32	16	8	8	8	4	4	4	16	4
(±)-**11C**	32	32	32	32	32	8	8	4	8	32	4
(±)-**11D**	4	4	2	4	2	1	1	0.5	8	16	0.2
(±)-**11E**	64	64	32	32	32	8	8	4	8	64	0.2
11F	>64	>64	>64	>64	>64	>64	>64	64	>64	>64	>64
11G	32	64	32	>64	8	16	8	8	8	8	4
11H	>64	>64	>64	>64	>64	>64	64	64	64	>64	64
11I	>64	>64	>64	>64	64	>64	>64	64	>64	>64	32
11J	>64	>64	>64	>64	64	64	32	32	32	>64	64
11K	>64	>64	>64	>64	>64	64	>64	>64	>64	>64	4
(±)-**11L**	64	>64	>64	64	>64	>64	>64	64	64	16	64
(±)-**11M**	>64	-[d]	>64	>64	>64	>64	>64	>64	>64	>64	64
11N	>64	>64	>64	>64	>64	64	>64	>64	64	>64	>64
11O	16	32	16	16	4	8	2	2	1	>64	4

a; abbreviation; see foot note in Table S1**,** b; All analogues are inactive (MIC > 64 ug/ml) against *E. coli* 1, ATCC25922 (non Pathogenic strain), *E. coli* 50, Ec49 No Efflux and *P. aeruginosa* 1, ATCC27853. c; All analogues are antifungal inactive (MIC > 32 ug/ml) against *Candida albicans.* d; Not determined

Table S4. *In vitro* antibiotic activity (MIC, µg/mL) of 3-acyltetramic acids shown in Figure S3[a-d]

	S1	**S26**	**S4**	**S2**	**E1**	**E2**	**P1**	**P9**	**P9B**	**HI3**	**HI4**
12A	4	16	4	8	4	4	2	2	32	>64	64
12B	1	2	1	0.5	1	0.5	0.5	0.25	4	>64	4
12C	64	64	64	64	64	32	64	64	64	>64	16
12D	0.5	2	2	1	0.5	0.5	0.12	0.25	32	>64	1
12E	2	4	4	2	2	1	1	0.5	32	>64	64
12F	1	8	4	4	2	2	4	2	8	>64	8
12G	2	8	4	2	2	2	1	1	4	64	1
12H	>64	>64	>64	>64	>64	>64	1	1	4	>64	32

This journal is © The Royal Society of Chemistry 2013

12I	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
12J	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
12K	>64	>64	>64	.>64	4	4	2	2	4	>64	4
12L	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
12M	>64	>64	>64	>64	>64	>64	2	4	8	>64	>64
12N	>64	>64	>64	>64	>64	>64	16	4	16	>64	>64
12O	>64	>64	>64	>64	>64	>64	4	8	16	>64	8
12P	16	32	16	16	16	16	8	8	16	>64	4
12Q	32	64	32	32	32	32	32	16	32	>64	16
12R	2	4	2	1	1	1	0.5	0.5	4	>64	2
12S	4	32	2	4	1	2	1	1	64	>64	2
12T	>64	>64	16	>64	16	8	16	8	32	>64	>64
12U	-[d]	>64	>64	>64	>64	>64	>64	>64	>64	>64	32
12V	64	>64	>64	>64	64	64	64	32	32	>64	16
13A	8	16	8	8	4	8	4	4	16	>64	4
13B	4	8	4	4	2	4	2	2	16	64	4
13C	>64	>64	>64	>64	>64	64	8	8	64	>64	4
13D	>64	>64	>64	>64	64	64	32	32	32	>64	64
13E	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
13F	-[d]	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
(±)-**13G**	64	64	64	64	64	64	32	32	>64	>64	-[d]
13H	>64	>64	>64	>64	>64	>64	>64	64	>64	64	8
14A	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
14B	>64	>64	>64	>64	>64	>64	64	64	64	>64	16
14C	16	64	64	16	16	16	8	8	16	>64	>64
14D	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	64
14E	>64	>64	>64	>64	>64	>64	>64	64	32	>64	8
14F	>64	>64	>64	>64	>64	>64	>64	64	32	>64	16
14G	>64	>64	>64	>64	>64	>64	16	8	16	>64	32
14H	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
14I	>64	>64	>64	.64	64	32	32	16	16	>64	>64
14J	>64	>64	>64	>64	8	8	4	4	8	>64	4
14K	>64	>64	>64	>64	32	16	8	4	8	>64	32
14L	>64	>64	>64	>64	>64	64	8	4	16	>64	8
14M	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	8

This journal is © The Royal Society of Chemistry 2013

a; abbreviation; see foot note in Table S1**,** b; All analogues are inactive (MIC > 64 ug/ml) against *E. coli* 1, ATCC25922 (non Pathogenic strain), *E. coli* 50, Ec49 No Efflux and *P. aeruginosa* 1, ATCC27853. c; All analogues are antifungal inactive (MIC > 32 ug/ml) against *Candida albicans.* d; Not determined

Table S5. Pharmacological properties of tetramic acids[a,b]

	DEP IC_{50}, µM	**RBC** IC_{50}, µM	**HEK** LD_{50}, µM	**PMB** LD_{50}, µM	**SOL** µM	**PPB** %
1A	>100	>100	>90.9	>90.9	-[b]	-[b]
1B	>100	>100	>90.9	>90.9	-[b]	-[b]
1C	>100	>100	>90.9	>90.9	-[b]	-[b]
1D	>100	>100	>90.9	>90.9	>200	99.8
1E	13.3	>100	>90.9	>90.9	>300	100
(±)-**2A**	10.8	>100	**30.3**	**30.3**	75-150	-[b]
(±)-**2C**	>100	>100	>90.9	>90.9	>300	-[b]
(±)-**2E**	84.3	>100	90.9	90.9	>300	96.6
(±)-**2I**	>100	>100	>90.9	>90.9	>300	-[b]
(±)-**3F**	>100	>100	**30.3**	90.9	150-300	-[c]
(±)-**3G**	21.9	>100	**10.1**	**30.3**	-[b]	-[b]
(±)-**3H**	49.3	>100	**30.3**	**30.3**	>300	-[b]
4C	31.3	>100	90.9	**30.3**	>300	99.5
4D	39.2	>100	>90.9	**30.3**	150-300	-[b]
4G	>100	>100	>90.9	>90.9	>300	-[b]
4H	>100	>100	**10.1**	90.9	150-300	99.9
4I	>100	>100	90.9	>90.9	>300	99.5
4J	>100	>100	90.9	90.9	>300	-[b]
4L	68.8	>100	**30.3**	**30.3**	>300	-[b]
5C	>100	>100	**30.3**	**30.3**	>200	100
ent-**5C**	>100	>100	**30.3**	90.9	>300	100
5D	43.4	>100	>90.9	>90.9	67-200	100
5E	>100	>100	>90.9	90.9	67-200	100
5G	>100	>100	**30.3**	90.9	>300	-[b]
5H	>100	>100	90.9	>90.9	>300	100
5I	>100	>100	90.9	>90.9	>300	-[b]
5K	>100	>100	>90.9	>90.9	>300	-[b]
6C	>100	>100	90.9	>90.9	>300	99.8

6F	>100	>100	**10.1**	>90.9	>300	-[b]
6G	>100	>100	**10.1**	>90.9	>300	-[b]

a; **DEP**; *In vitro* activity in depolarization of *S. aureus* membrane, **RBC**; *In vitro* mammalian red blood cell membrane lysis activity, **HEK;** *in vitro* toxicities against human embryonic kidney 293 cells, **PMB**; *in vitro* toxicities human peripheral blood cells, **SOL**; aqueous solubility at pH 7.4 (water with 2% DMSO), **PPB**; % ratio of plasma protein binding**;** b; not determined.

Table S6. *In vitro* antibiotic activity (MIC, µg/mL) of **1D** and **5C** against Gram-negative strains

Strain	E. coli Top10	E. coli TOP10 ΔTolC	K. pneumoniae JH1	K. pneumoniae JH1 ΔTolC	K. pneumoniae JH1 ΔAcrB
Phenotype	wt	efflux-	wt-	efflux-	efflux-
1D	>64	8	>64	>64	>64
5C	>64	8	>64	16	>64

Table S7. Summary of docking results

		UPPS (1V7U)		RNAP (1ZYR[a])		RNAP (3DXJ[b])	
Comp	Tautomer	docking energy (kcal/mol)	number of conformations	docking energy (kcal/mol)	number of conformations	docking energy (kcal/mol)	number of conformations
2A	A	-9.22	1	-6.59	2	-7.11	2
	B	-8.88	4	-6.94	1	-7.86	2
	C	-9.47	2	-6.53	2	-7.02	3
	D	-9.33	5	-7.34	2	-8.10	2
6C	A	-9.92	2	-8.14	1	-7.13	3
	B	-10.04	2	-8.23	1	-7.55	3
	C	-9.47	1	-7.61	2	-7.27	3
	D	-10.25	2	-7.13	2	-7.28	4

a; active site of streptolydigin, b; active site of myxopyronin.

This journal is © The Royal Society of Chemistry 2013

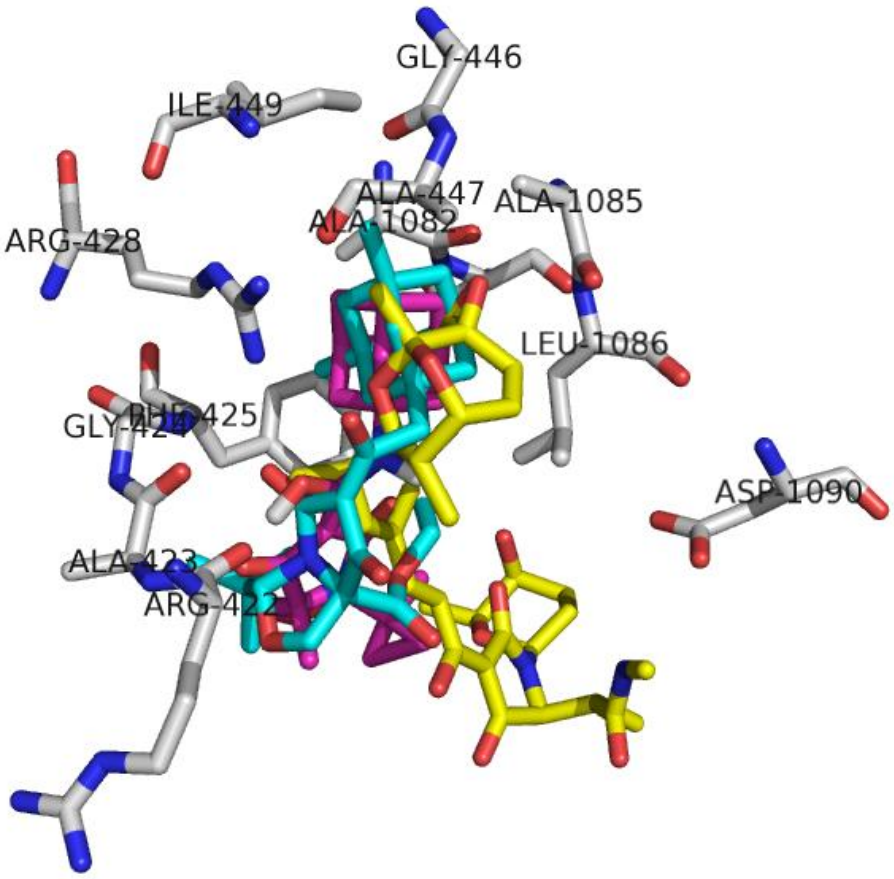


Figure S7. Docking model of **2A** (violet), **6C** (light blue) and streptolydigin (yellow) into active site of RNAP (1ZYR)

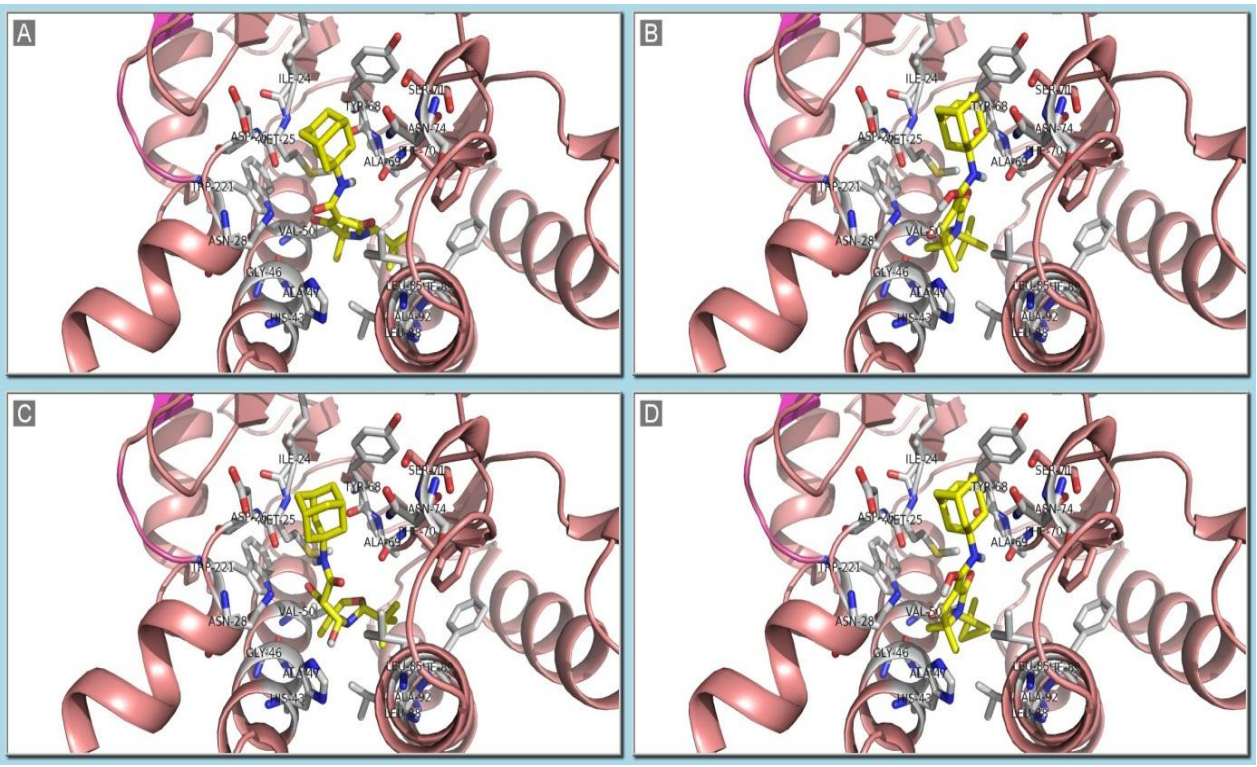


Figure S8. Docking model of **2A** in each tautomer into active site of UPPS (1V7U); (A) tautomer A, (B) tautomer B, (C) tautomer C and (D) tautomer D.

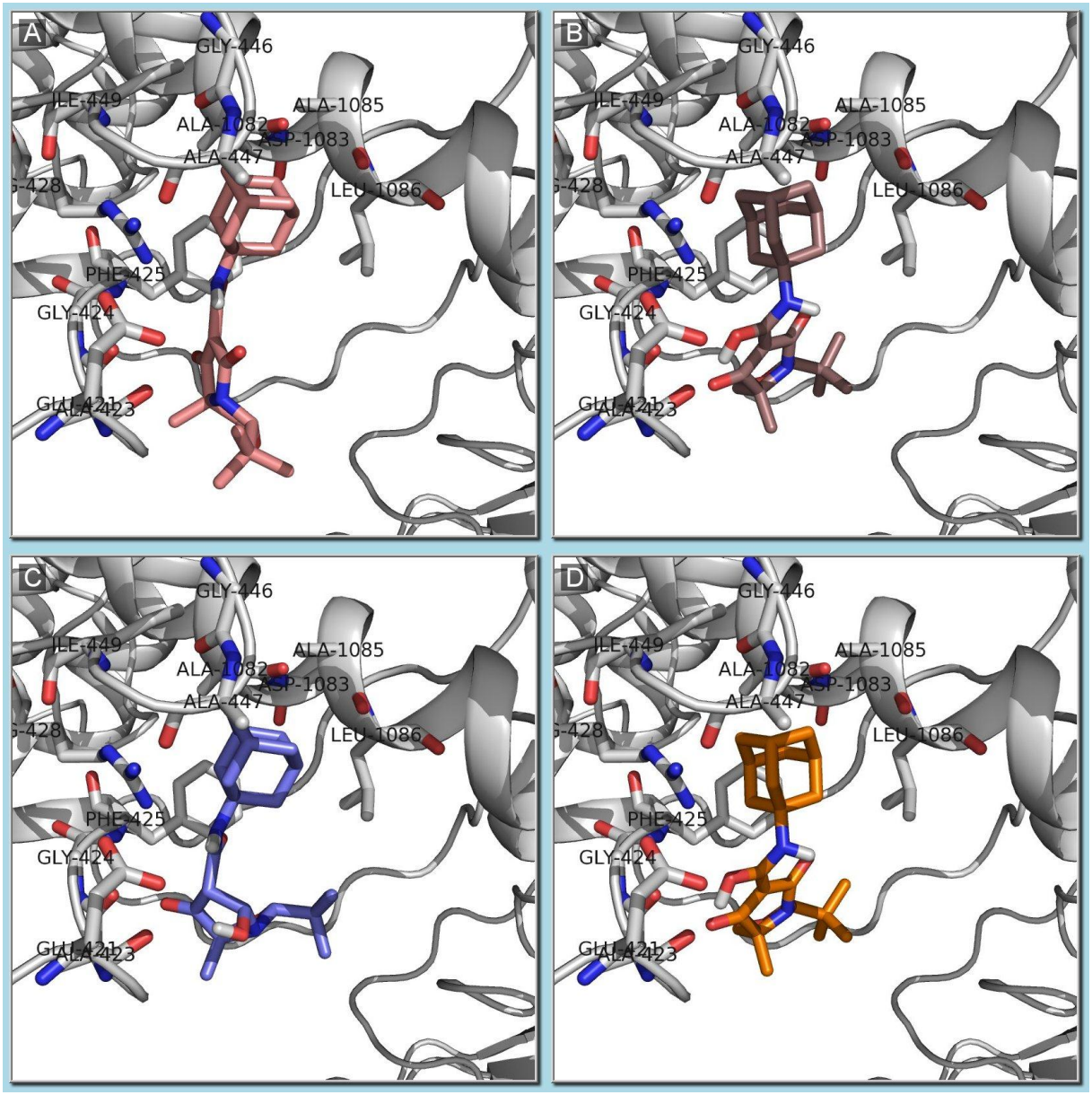


Figure S9. Docking model of **2A** in each tautomer into active site of RNAP (1ZYR, active site of streptolydigin); (A) tautomer A, (B) tautomer B, (C) tautomer C and (D) tautomer D.

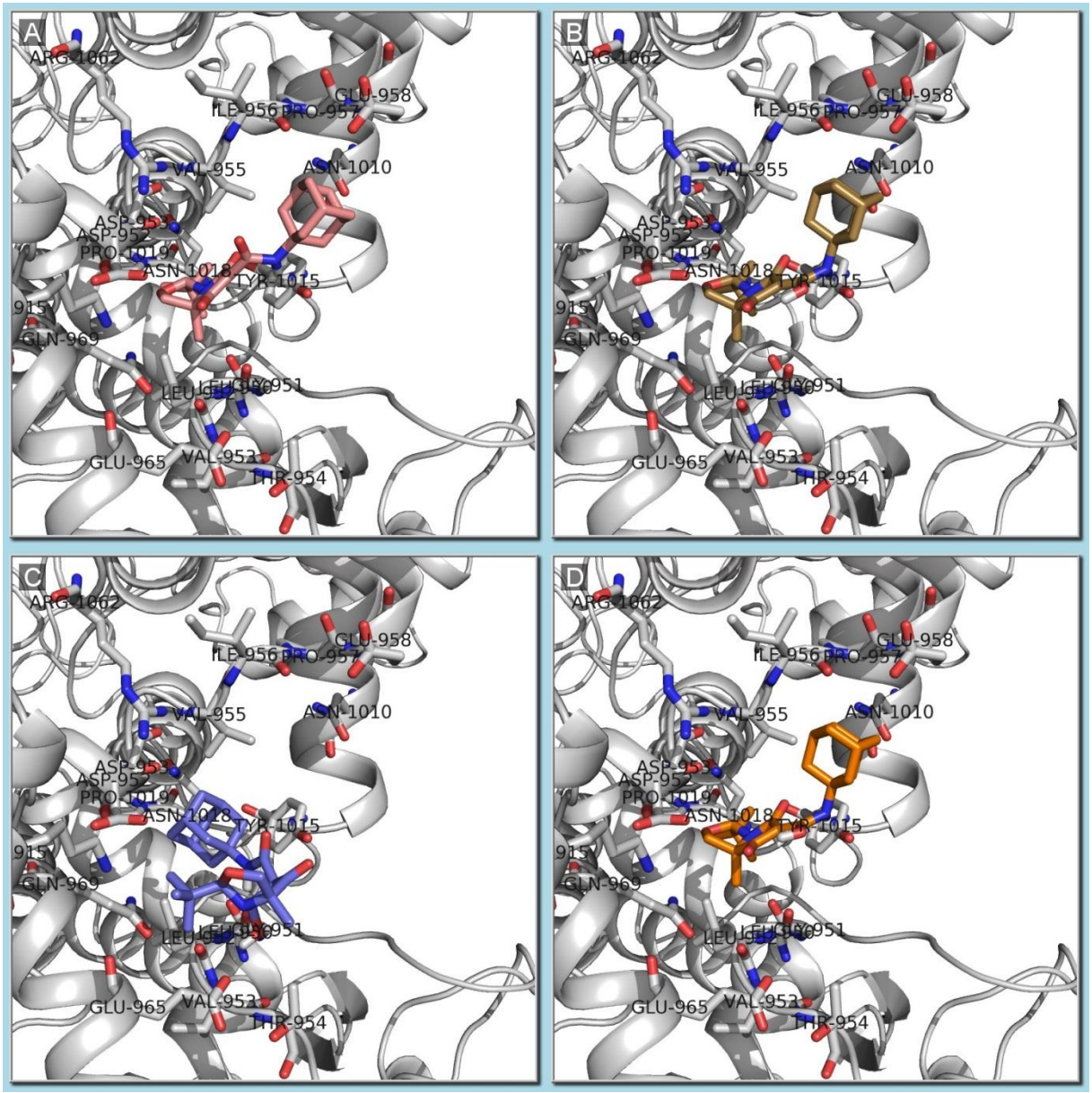


Figure S10. Docking model of **2A** in each tautomer into active site of RNAP (3DXJ, active site of myxopyronin); (A) tautomer A, (B) tautomer B, (C) tautomer C and (D) tautomer D.

This journal is © The Royal Society of Chemistry 2013

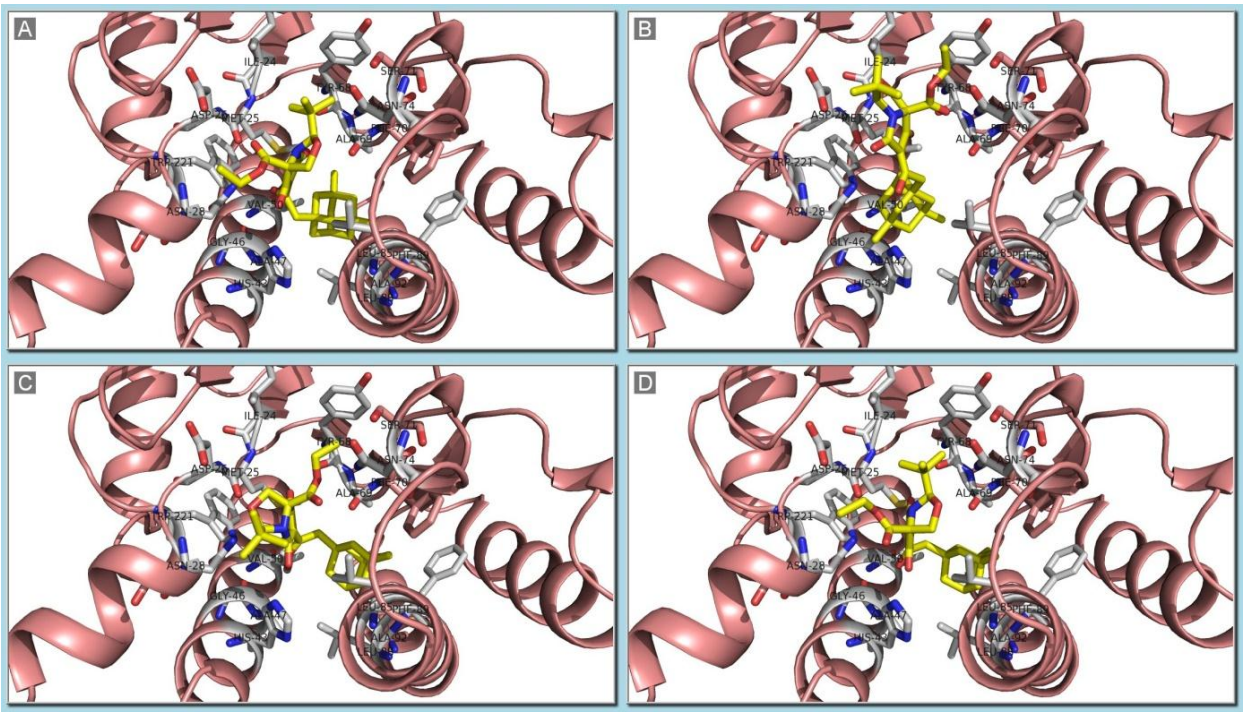


Figure S11. Docking model of **6C** in each tautomer into active site of UPPS (1V7U); (A) tautomer A, (B) tautomer B, (C) tautomer C and (D) tautomer D.

This journal is © The Royal Society of Chemistry 2013

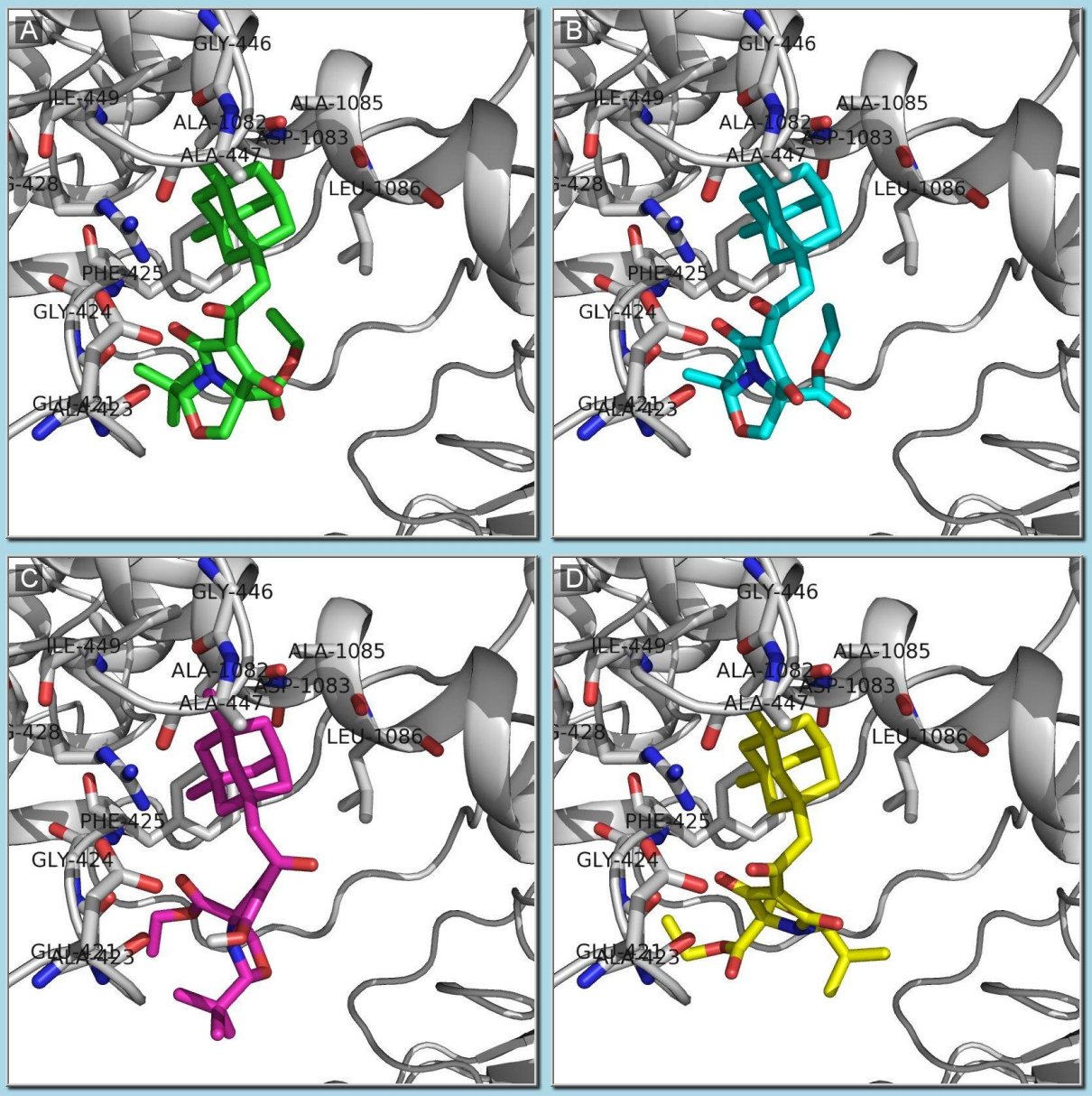


Figure S12. Docking model of **6C** in each tautomer into active site of RNAP (1ZYR, active site of streptolydigin); (A) tautomer A, (B) tautomer B, (C) tautomer C and (D) tautomer D.

This journal is © The Royal Society of Chemistry 2013

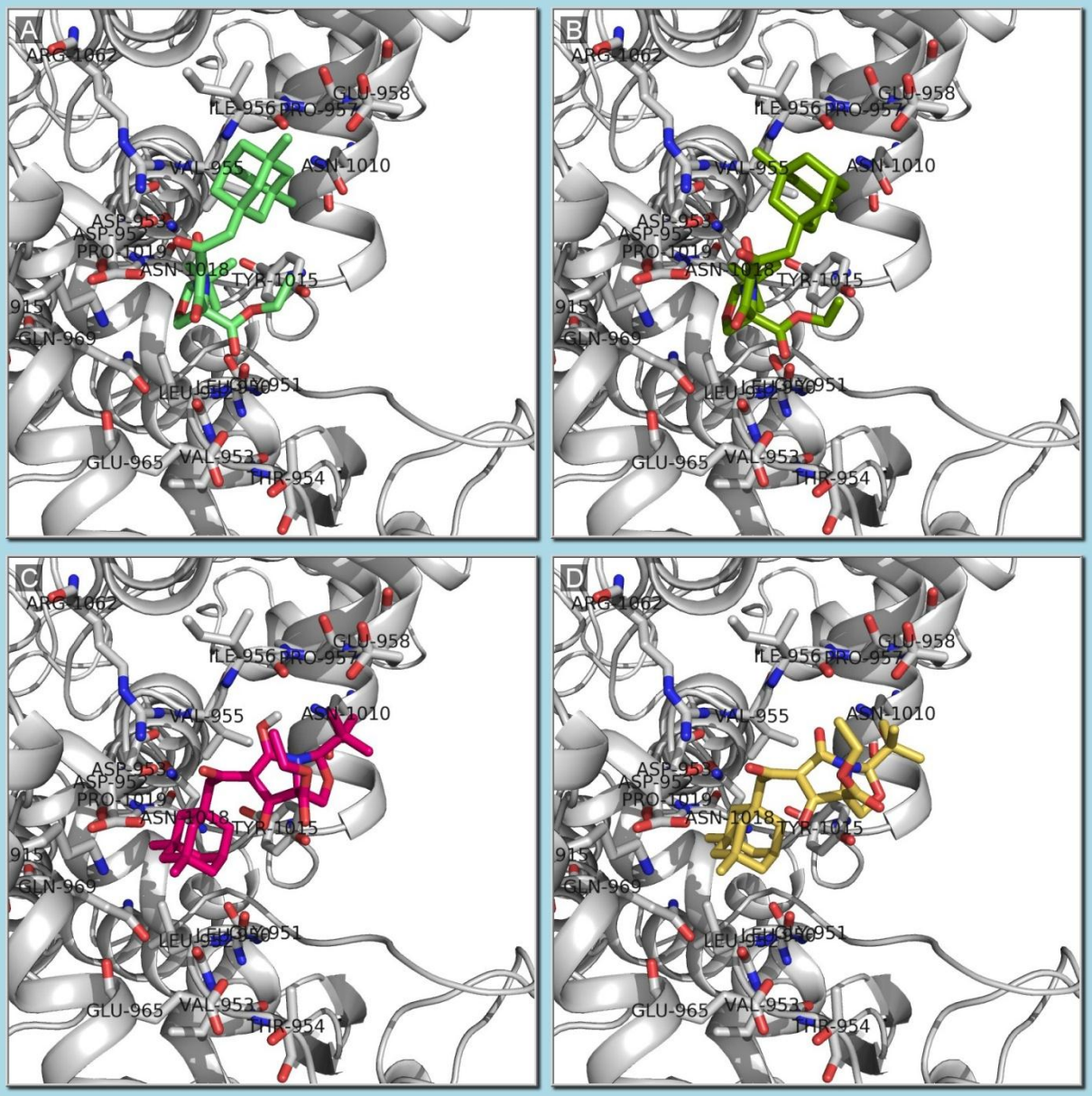


Figure S13. Docking model of **6C** in each tautomer into active site of RNAP (3DXJ, active site of myxopyronin); (A) tautomer A, (B) tautomer B, (C) tautomer C and (D) tautomer D.

This journal is © The Royal Society of Chemistry 2013

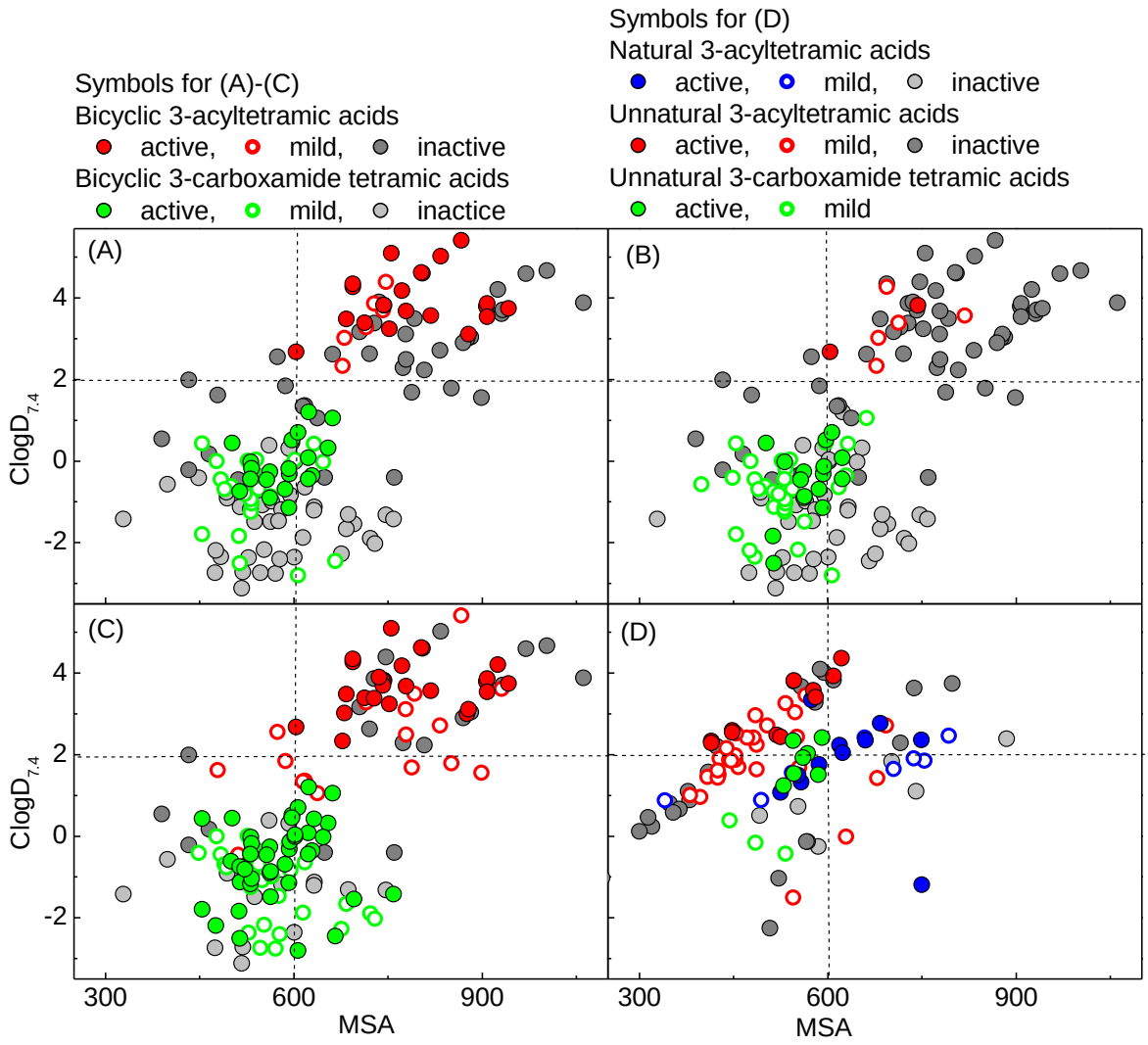


Figure S14. Plot of $ClogD_{7.4}$ against MSA of bicyclic 3-acyl (66 examples) and 3-carboxamide (86 examples) TAs prepared in this work against (A) MRSA, (B) *H. influenzae 3* and (C) efflux-negative *H. influenzae 4*. For comparison, (D) gives MICs against *S. aureus* without consideration of the species of strains of natural (34 analogues) and unnatural (66 analogues) 3-acyl TAs and Novartis' 3-carboxamide TAs (10 analogues) reported in the literatures. **"**Active", "mild" and "inactive" mean that the values are MIC ≤ 4 μg/mL, 4 μg/mL < MIC ≤ 32 μg/mL and MIC > 32 μg/mL, respectively. In order to compare with Figure A-C at increased resolution, Figure D has been cut off at 250< MSA <1100. See Figure S17 for the full version.

This journal is © The Royal Society of Chemistry 2013

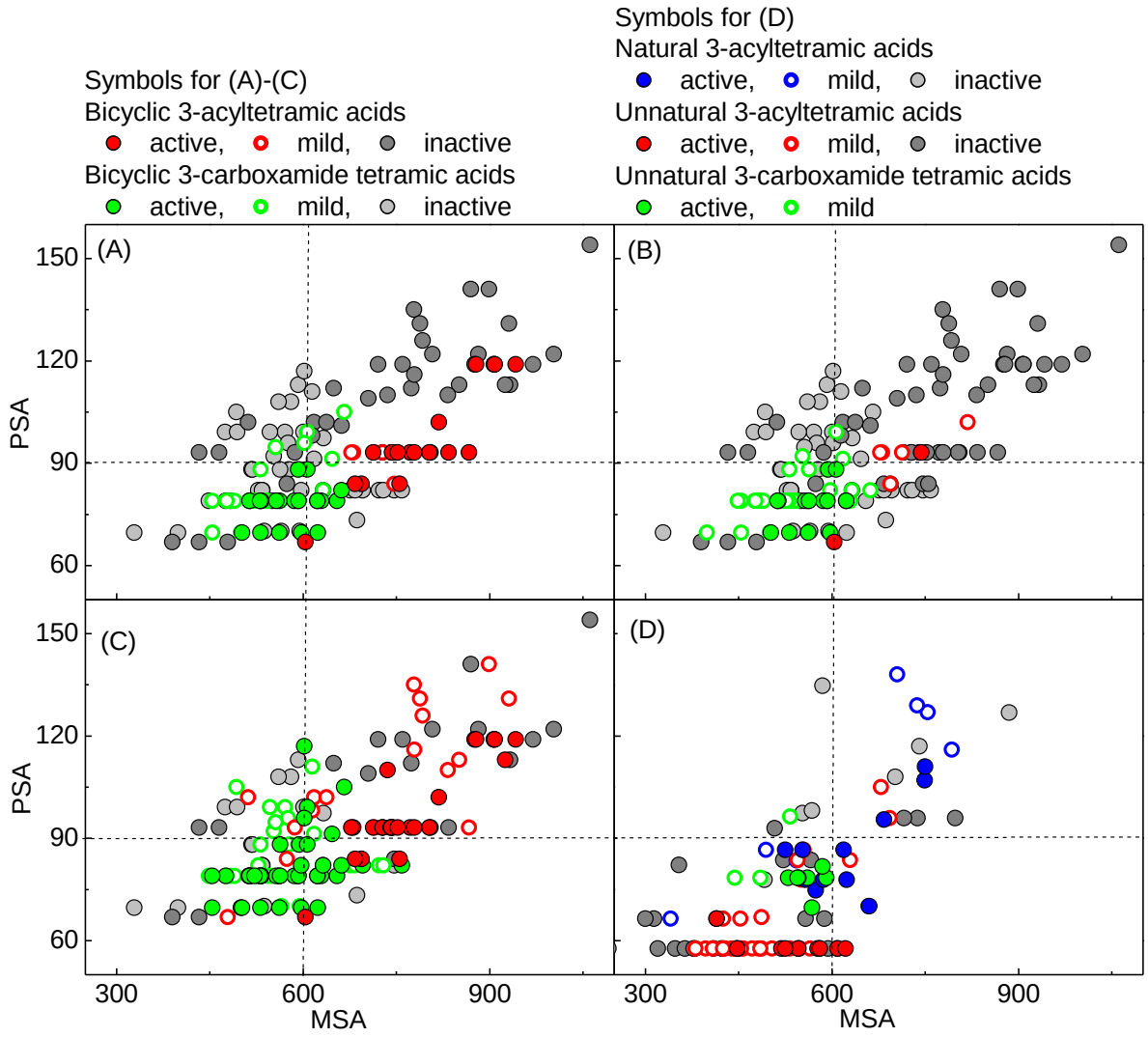


Figure S15. Plot of PSA against MSA of bicyclic 3-acyl (66 examples) and 3-carboxamide (86 examples) TAs prepared in this work against (A) MRSA, (B) *H. influenzae 3* and (C) efflux-negative *H. influenzae 4*. For comparison, (D) gives MICs against *S. aureus* without consideration of the species of strains of natural (34 analogues) and unnatural (66 analogues) 3-acyl TAs and Novartis' 3-carboxamide TAs (10 analogues) reported in the literatures. **"**Active", "mild" and "inactive" mean that the values are MIC ≤ 4 μg/mL, 4 μg/mL < MIC ≤ 32 μg/mL and MIC > 32 μg/mL, respectively. In order to compare with Figure A-C at increased resolution, Figure D has been cut off at 250< MSA <1100. See Figure S17 for the full version.

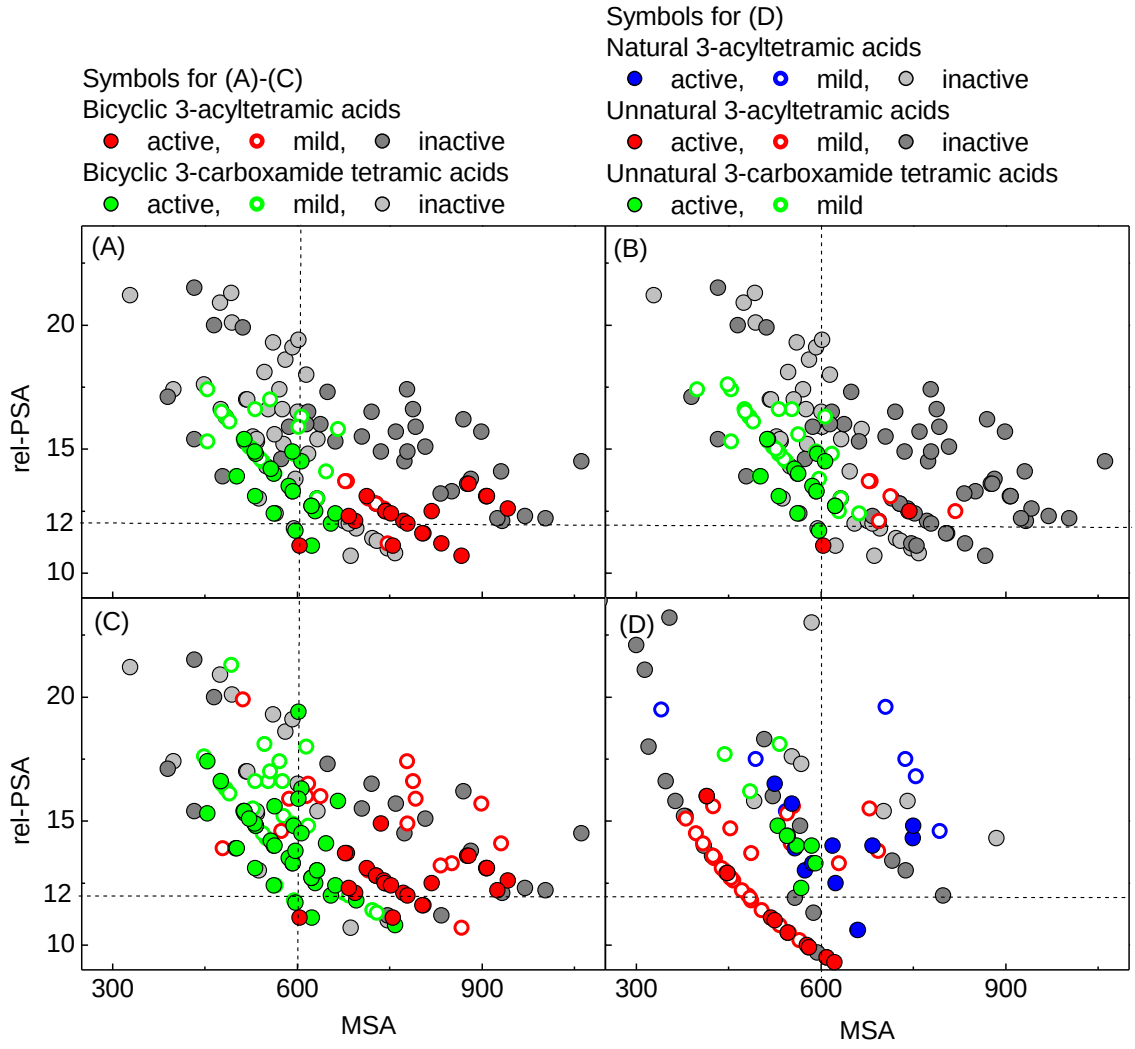


Figure S16. Plot of rel-PSA against MSA of bicyclic 3-acyl (66 examples) and 3-carboxamide (86 examples) TAs prepared in this work against (A) MRSA, (B) *H. influenzae 3* and (C) efflux-negative *H. influenzae 4*. For comparison, (D) gives MICs against *S. aureus* without consideration of the species of strains of natural (34 analogues) and unnatural (66 analogues) 3-acyl TAs and Novartis' 3-carboxamide TAs (10 analogues) reported in the literatures. **"**Active", "mild" and "inactive" mean that the values are MIC ≤ 4 μg/mL, 4 μg/mL < MIC ≤ 32 μg/mL and MIC > 32 μg/mL, respectively. In order to compare with Figure A-C in increased resolution, Figure D has been cut off at 250< MSA <1100. See Figure S17 for the full version.

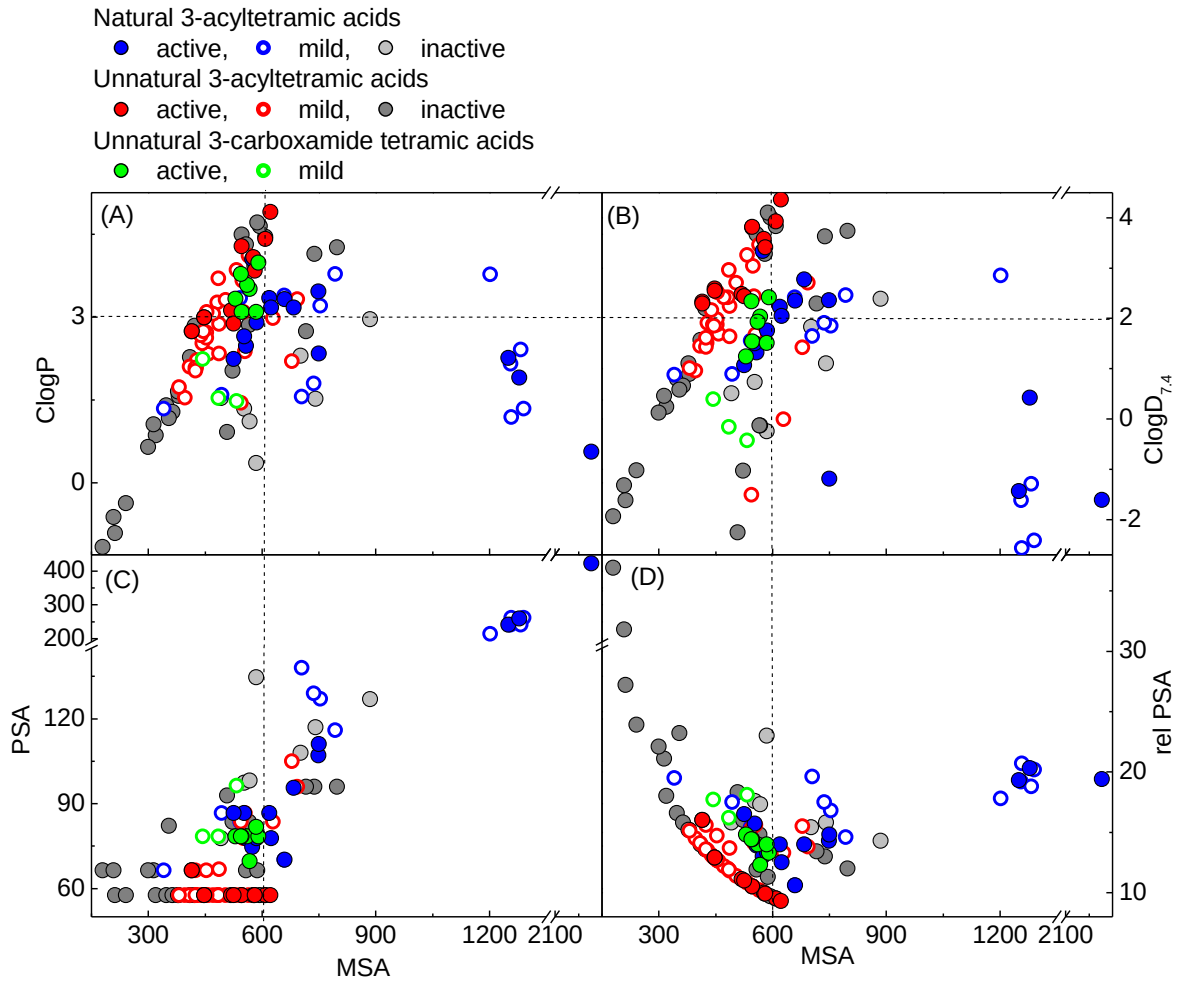


Figure S17. Plot of (A) ClogP, (B) $ClogD_{7.4,}$ (C) PSA and (D) rel-PSA against MSA of previously reported 3-acyl and 3-carboxamide TAs with MICs against *S. aureus* without consideration of the species of strains in the literatures. Active, mild and inactive mean that the values are MIC ≤ 4 μg/mL, 4 μg/mL < MIC ≤ 32 μg/mL and MIC > 32 μg/mL, respectively.

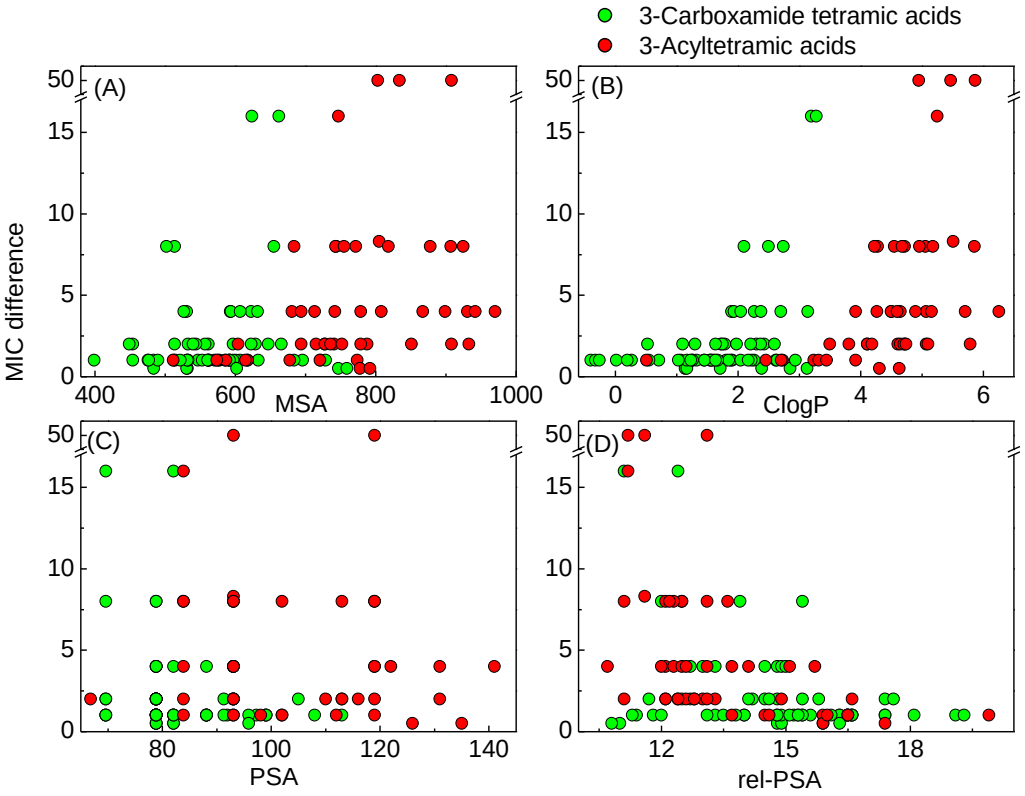


Figure S18. Correlation of blood effect against (A) MSA, (B) ClogP, (C) PSA and (D) rel-PSA. The MIC difference is defined as MIC with 2.5% blood/ MIC with 0% blood in the assay of *S. pneumonia* 9. 113 analogues were used after removing inactive analogues against any one of the bacterial panels.

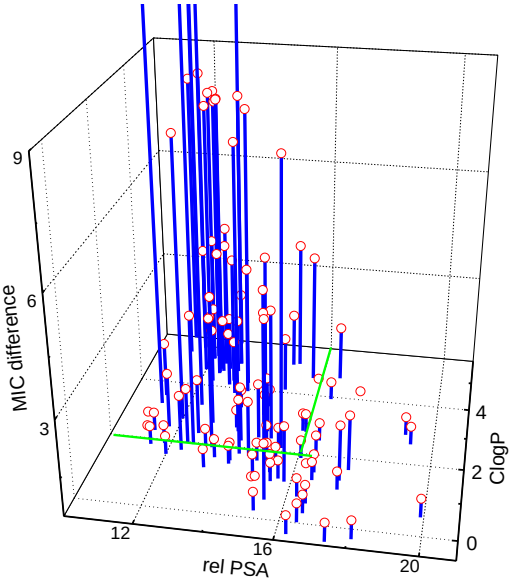


Figure S19. Correlation of blood effect against ClogP and rel-PSA. The MIC difference is defined as MIC with 2.5% blood/ MIC with 0% blood in the assay of *S. pneumonia* 9. 113 analogues are used after removing inactive analogues. The green line presents the thresholds for lowered blood effect. For increased resolution, the graph has been cut off at MIC difference >9.

This journal is © The Royal Society of Chemistry 2013

Table S8. Physical properties of the 3-carboxamide tetramic acids shown in Figure S1[a]

Entry	Name	Mw	MSA	PSA	%PSA	ClogP	$ClogD_{7.4}$	HD/ HA	RB
1	**1A**	310	540	69.6	12.9	1.69	0.23	2/3	11
2	**1B**	353	632	69.6	11.0	2.88	1.42	2/3	14
3	**1C**	308	509	69.6	13.7	1.28	-0.15	2/3	7
4	**1D**	302	462	69.6	15.1	1.85	0.64	2/3	7
5	**1E**	387	599	82.1	13.7	1.77	0.41	2/5	8
6	**(±)-2A**	389	592	78.9	13.3	1.27	-1.14	2/4	3
7	**(±)-2B**	404	607	99.1	16.3	-0.32	-2.80	3/5	3
8	**(±)-2C**	391	629	78.9	12.5	1.98	-0.36	2/4	4
9	**(±)-2D**	336	532	78.9	14.8	1.14	-1.25	2/4	3
10	**(±)-2E**	350	562	78.9	14.0	1.45	-0.90	2/4	4
11	**(±)-2F**	338	519	88.1	17.0	-0.21	-2.72	2/5	4
12	**(±)-2G**	344	516	78.9	15.3	1.33	-1.13	2/4	4
13	**(±)-2H**	358	544	78.9	14.5	1.75	-0.69	2/4	4
14	**(±)-2I**	381	655	78.9	12.0	2.74	0.32	2/4	10
15	**(±)-3A**	330	484	78.9	16.3	1.71	-0.45	2/4	3
16	**(±)-3B**	398	533	78.9	14.8	2.60	-0.18	2/4	4
17	**(±)-3C**	376	540	78.9	14.6	2.37	0.03	2/4	4
18	**(±)-3D**	346	494	99.1	20.1	1.43	-0.91	3/5	3
19	**(±)-3E**	360	532	88.1	16.6	1.46	-0.94	2/5	4
20	**(±)-3F**	422	607	88.1	14.5	3.14	0.70	2/4	5
21	**(±)-3G**	399	514	78.9	15.4	2.10	-0.75	2/4	3
22	**(±)-3H**	379	531	78.9	14.9	2.05	-0.44	2/4	3
23	**(±)-3I**	348	490	78.9	16.1	1.85	-0.69	2/4	3
24	**(±)-3J**	388	592	88.1	14.9	2.22	-0.19	2/5	5
25	**(±)-3K**	383	556	94.7	17.0	1.83	-0.34	3/4	3
26	**(±)-3L**	415	618	91.3	14.8	1.64	-0.64	2/6	4
27	**(±)-3M**	414	632	82.1	13.0	2.70	0.42	2/5	4
28	**4A**	376	593	78.9	13.3	1.90	-0.32	2/4	4
29	**4B**	316	449	78.9	17.6	1.64	-0.41	2/4	3
30	**4C**	389	586	78.9	13.5	1.61	-0.69	2/4	3
31	**4D**	391	623	78.9	12.7	2.31	0.08	2/4	4
32	**4E**	330	477	78.9	16.5	2.05	0.00	2/4	3
33	**4F**	379	527	78.9	15.0	2.38	0.01	2/4	3

34	**4G**	391	562	69.6	12.4	1.73	-0.26	2/3	3
35	**4H**	393	597	69.6	11.7	2.43	0.52	2/3	4
36	**4I**	352	532	69.6	13.1	1.91	-0.02	2/3	4
37	**4J**	383	624	69.6	11.1	3.20	1.20	2/3	10
38	**4K**	332	454	69.6	15.3	2.17	0.43	2/3	3
39	**4L**	381	502	69.6	13.9	2.50	0.44	2/3	3
40	**4M**	326	500	69.6	13.9	1.53	-0.62	2/3	9
41	**4N**	276	329	69.6	21.2	0.50	-1.42	2/3	2

[a]; **Mw**; molecular weight, **MSA**; molecular surface area, **PSA**; polar surface area, **rel-PAS**; relative polar surface area = (PSA/MSA) x 100, **ClogP**; calculated partition coefficient, **ClogD$_{7.4}$**; calculated distribution coefficient at pH 7.4, **HD**; hydrogen bond donor count, **HA**; hydrogen bond acceptor count, **RB**; rotatable bond count.

Table S9. Physical properties of the 3-enamine and 3-acyltetramic acids shown in Figure S1[a]

Entry	Name	Mw	MSA	PSA	%PSA	ClogP	ClogD$_{7.4}$	H-D/ H-A	RB
1	**5A**	297	433	93.1	21.5	0.68	-0.22	1/5	3
2	**5B**	367	587	93.1	15.9	2.73	1.84	1/5	8
3	**5C**	410	681	93.1	13.7	3.92	3.02	1/5	11
4	**5D**	438	744	93.1	12.5	4.72	3.82	1/5	13
5	**5E**	466	805	93.1	11.6	5.51	4.61	1/5	15
6	**5F**	311	465	93.1	20.0	1.02	0.17	1/5	4
7	**5G**	424	713	93.1	13.1	4.27	3.39	1/5	12
8	**5H**	438	743	93.1	12.5	4.68	3.83	1/5	12
9	**5I**	482	818	102	12.5	4.55	3.57	1/6	16
10	**5J**	408	694	83.9	12.1	5.07	4.27	1/5	11
11	**5K**	436	755	83.9	11.1	5.86	5.10	1/5	13
12	**(±)-5L**	253	390	66.8	17.1	1.20	0.54	1/4	1
13	**(±)-6A**	388	604	66.8	11.1	3.50	2.68	1/4	3
14	**6B**	446	678	93.1	13.7	3.32	2.33	1/5	6
15	**6C**	474	752	93.1	12.4	4.19	3.24	1/5	6
16	**6D**	488	779	93.1	12.0	4.60	3.68	1/5	6
17	**6E**	560	878	119	13.6	4.23	3.11	1/6	11
18	**6F**	574	908	119	13.1	4.65	3.54	1/6	11
19	**6G**	588	942	119	12.6	4.90	3.74	1/6	12
20	**6H**	559	876	119	13.6	4.14	3.00	1/6	12

21	**6I**	417	618	102	16.5	2.46	1.36	1/6	8
22	**(±)-7A**	387	616	58.6	9.5	2.63	2.63	1/4	3
23	**7B**	433	694	84.9	12.2	2.82	2.82	1/5	6
24	**7C**	431	659	84.9	12.9	2.11	2.11	1/5	5
25	**7D**	423	721	84.9	11.8	3.58	3.58	1/5	12
26	**7E**	372	550	84.9	15.4	2.22	2.22	1/5	5
[a]; see foot note in Table S8									

Table S10. Physical properties of the 3-carboxamide tetramic acids shown in Figure S2[a]

Entry	Name	Mw	MSA	PSA	%PSA	ClogP	$ClogD_{7.4}$	H-D/ H-A	RB
1	**9A**	390	571	99.1	17.4	-0.40	-2.76	3/5	3
2	**(±)-9B**	400	514	78.9	15.4	0.53	-2.51	2/4	3
3	**(±)-9C**	404	601	99.1	16.5	0.02	-2.36	3/5	3
4	**9D**	400	513	78.9	15.4	1.07	-1.84	2/4	3
5	**9E**	447	666	105	15.8	1.10	-2.45	2/5	6
6	**9F**	402	550	78.9	14.3	1.78	-1.08	2/4	4
7	**(±)-9G**	362	484	78.9	16.3	0.71	-2.35	2/4	4
8	**9H**	350	557	78.9	14.2	1.79	-0.46	2/4	4
9	**(±)-9I**	403	623	78.9	12.7	1.94	-0.44	2/4	4
10	**(±)-9J**	338	517	88.1	17.0	-0.61	-3.12	2/5	3
11	**(±)-9K**	352	547	99.1	18.1	-0.26	-2.74	3/5	4
12	**(±)-9L**	362	553	92.0	16.6	0.55	-2.17	2/4	4
13	**(±)-9M**	308	476	78.9	16.6	0.27	-2.19	2/4	4
14	**(±)-9N**	338	563	78.9	14.0	1.56	-0.87	2/4	7
15	**(±)-9O**	354	578	88.1	15.2	0.20	-2.41	2/5	7
16	**(±)-9P**	324	531	78.9	14.9	1.17	-1.17	2/4	5
17	**(±)-9Q**	374	563	88.1	15.6	1.17	-1.49	2/5	6
18	**(±)-9R**	422	722	82.1	11.4	1.81	-1.90	2/5	6
19	**(±)-9S**	448	747	82.1	11.0	2.39	-1.32	2/5	8
20	**(±)-9T**	456	729	82.1	11.3	2.27	-2.03	2/5	6
21	**(±)-9U**	482	759	82.1	10.8	2.85	-1.42	2/5	8
22	**(±)-9V**	448	676	82.1	12.1	1.55	-2.28	2/5	6
23	**(±)-9W**	454	696	82.1	11.8	1.89	-1.54	2/5	7
24	**(±)-9X**	432	684	82.1	12.0	1.55	-1.66	2/5	7

25	**9Y**	312	475	99.1	20.9	-0.38	-2.74	3/5	5
26	**9Z**	348	533	78.9	14.8	1.26	-1.04	2/4	5
27	**9AA**	418	633	97.3	15.4	1.57	-1.13	2/6	6
28	**(±)-10A**	350	565	70.1	12.4	1.39	-0.99	1/4	3
29	**(±)- 10B**	336	538	70.1	13.0	0.92	-1.49	1/4	2
30	**(±)- 10C**	376	595	70.1	11.8	1.55	-0.84	1/4	2
31	**(±)- 10D**	432	687	73.3	10.7	1.77	-1.31	1/5	5
32	**(±)- 10E**	337	528	82.1	15.5	0.15	-2.37	2/5	3
33	**(±)- 10F**	416	615	111	18.0	0.92	-1.88	3/6	5
34	**(±)- 10G**	379	581	108	18.6	1.36	-1.19	3/5	6
35	**(±)- 10H**	384	576	95.9	16.6	1.23	-1.47	2/5	5
36	**(±)-11A**	388	594	88.1	14.8	2.27	-0.13	2/5	6
37	**(±)-11B**	362	522	78.9	15.1	1.67	-0.81	2/4	3
38	**(±)-11C**	391	454	78.9	17.4	1.30	-1.79	2/4	3
39	**(±)-11D**	440	662	82.1	12.4	3.28	1.05	2/5	6
40	**(±)-11E**	442	647	91.3	14.1	2.21	-0.02	2/6	6
41	**11F**	359	535	82.1	15.3	1.90	-0.27	2/5	4
42	**11G**	399	597	82.1	13.8	2.62	0.45	2/5	4
43	**11H**	462	592	113	19.1	2.94	0.31	2/6	5
44	**11I**	345	493	105	21.3	1.27	-0.76	3/5	3
45	**11J**	438	561	108	19.3	2.64	0.39	3/5	4
46	**11K**	426	602	117	19.4	2.27	-0.01	3/6	5
47	**(±)-11L**	298	399	69.6	17.4	1.03	-0.57	2/3	2
48	**(±)-11M**	383	534	82.1	15.4	0.95	-0.77	2/5	3
49	**11N**	414	632	82.1	13.0	2.24	-1.21	2/5	5
50	**11O**	400	602	95.9	15.9	3.13	0.03	2/5	7
[a]; see foot note in Table S8									

Table S11. Physical properties of the 3-acyltetramic acids shown in Figure S3[a]

Entry	Name	Mw	MSA	PSA	%PSA	ClogP	$ClogD_{7.4}$	H-D/ H-A	RB
1	**12A**	454	747	83.9	11.2	5.25	4.39	1/4	13
2	**12B**	452	772	93.1	12.1	5.06	4.18	1/5	14
3	**12C**	341	512	102	19.9	0.51	-0.46	1/6	6
4	**12D**	466	803	93.1	11.6	5.47	4.62	1/5	14

5	**12E**	480	834	93.1	11.2	5.87	5.02	1/5	15
6	**12F**	494	867	93.1	10.7	6.26	5.41	1/5	16
7	**12G**	408	694	83.9	12.1	5.07	4.35	1/5	11
8	**12H**	553	931	131	14.1	4.51	3.61	2/6	17
9	**12I**	453	760	119	15.7	3.22	-0.40	2/6	14
10	**12J**	615	1003	122	12.2	5.57	4.67	2/6	16
11	**12K**	629	728	93.1	12.8	5.79	3.38	1/5	11
12	**12L**	523	882	122	13.8	4.07	3.04	2/6	17
13	**12M**	551	933	113	12.1	4.73	3.71	1/6	18
14	**12N**	686	808	122	15.1	5.16	2.23	2/6	13
15	**12O**	509	851	113	13.3	3.81	1.79	1/6	15
16	**12P**	438	741	93.1	12.6	4.61	3.84	1/5	11
17	**12Q**	436	715	93.1	13.0	4.11	3.28	1/5	9
18	**12R**	538	907	119	13.1	4.96	3.79	1/6	15
19	**12S**	538	908	119	13.1	4.95	3.86	1/6	16
20	**12T**	566	970	119	12.3	5.71	4.60	1/6	16
21	**12U**	397	638	102	16.0	2.14	1.05	1/6	8
22	**12V**	351	574	83.9	14.6	3.45	2.56	1/5	5
23	**13A**	450	742	93.1	12.5	4.50	3.70	1/5	9
24	**13B**	438	684	83.9	12.3	4.28	3.48	1/4	8
25	**13C**	571	925	113	12.2	5.18	4.21	2/6	11
26	**13D**	494	774	112	14.5	3.24	2.29	1/7	12
27	**13E**	684	1061	154	14.5	4.98	3.88	1/9	10
28	**13F**	425	649	112	17.3	0.75	-0.40	1/7	8
29	**(±)-13G**	420	662	101	15.3	3.55	2.62	1/6	6
30	**13H**	307	479	66.8	13.9	2.55	1.62	1/4	2
31	**14A**	301	433	66.8	15.4	2.43	1.99	1/4	2
32	**14B**	426	615	98.1	16.0	2.71	1.34	1/5	5
33	**14C**	458	728	93.1	12.8	4.71	3.86	1/5	10
34	**14D**	469	705	109	15.5	4.02	3.17	2/5	8
35	**14E**	544	778	135	17.4	4.31	3.11	2/7	9
36	**14F**	520	792	126	15.9	4.63	3.49	2/7	11
37	**14G**	591	788	131	16.6	4.74	1.68	2/8	12
38	**14H**	635	870	141	16.2	4.40	2.90	2/8	13
39	**14I**	517	721	119	16.5	3.92	2.63	1/6	8

40	**14J**	515	736	110	14.9	5.10	3.90	1/6	9
41	**14K**	566	779	116	14.9	4.11	2.49	1/6	11
42	**14L**	651	899	141	15.7	4.65	1.55	1/8	10
43	**14M**	608	833	110	13.2	4.42	2.71	1/6	8
[a]; see footnote in Table S8									

Table S12. *In vitro* antibiotic activity against *S. aureus* (MIC, μg/mL) and physical properties of natural 3-acyltetramic acid analogues[a,b]

Entry	Name	MIC[c]	Mw	MSA	PSA	%PSA	ClogP	$ClogD_{7.4}$	H-D/ H-A	RB
Active (MIC ≤ 4)										
1	TPU-0037-C	3.53	825	1250	241	19.3	2.26	-1.44	10/12	19
2	Vancoresmycin	0.04	1344	2177	423	19.4	0.56	-1.61	17/22	43
3	Kibdelomycin	0.5-4	940	1279	259	20.3	1.90	0.42	6/12	13
4	Delaminomycin C	3.12	486	749	107	14.3	3.46	2.36	4/5	8
5	Equisetin	1.0	373	558	77.8	13.9	2.48	1.32	2/4	3
6	Vermisporin	0.5	416	660	70.1	10.6	3.32	2.35	1/4	3
7	Coniosetin	0.3	414	619	86.6	14.0	3.34	2.23	3/4	4
8	BU-4514N	3.1	475	750	111	14.8	2.34	-1.19	3/6	5
9	49F233α	1.0	414	624	77.8	12.5	3.17	2.05	2/4	4
10	Paecilosetin	4.0	373	553	86.6	15.7	2.65	1.50	3/4	3
11	Reutericyclin	0.2	349	574	74.7	13.0	4.05	3.34	1/4	9
12	Trichosetin	2-4	359	525	86.6	16.5	2.24	1.07	3/4	3
13	Cissetin	2-4	388	586	77.8	13.3	2.90	1.76	2/4	3
14	Ikarugamycin	1	479	684	95.5	14.0	3.17	2.77	3/4	1
Mild (4 < MIC ≤ 32)										
15	TPU-0037-A	12.5	841	1258	261	20.7	1.19	-2.57	11/13	19
16	TPU-0037-B	12.5	837	1256	241	19.2	2.15	-1.62	10/12	18
17	Lydicamycin	6.25	855	1290	261	20.2	1.34	-2.42	11/13	19
18	TPU-0037-D	12.5	839	1283	241	18.8	2.41	-1.29	10/12	19
19	Virgineone	16	748	1202	214	17.8	3.77	2.85	8/11	26
20	Delaminomycin B	6.25	516	793	116	14.6	3.78	2.46	4/6	9
21	Delaminomycin A	25	502	754	127	16.8	3.20	1.85	5/6	8
22	PF1052	10	416	659	70.1	10.6	3.39	2.42	1/4	4
23	Oxasetin	16	359	543	83.5	15.4	3.34	1.55	2/4	3

This journal is © The Royal Society of Chemistry 2013

24	Ravenic acid	25	259	341	66.4	19.5	1.34	0.88	2/3	4
25	C12-TA	25	297	494	86.6	17.5	1.59	0.89	3/4	10
26	Bu-2313 A	12-25	518	737	129	17.5	1.80	1.91	1/8	6
27	Bu-2313 B	12-25	504	705	138	19.6	1.56	1.65	2/8	6
Inactive (MIC > 32)										
28	Methiosetin	256	333	492	77.8	15.8	1.53	0.51	2/4	2
29	Tirandalydigin	>64	401	553	97.4	17.6	1.34	0.73	2/6	4
30	Streptolygin	>64	599	885	126.9	14.3	2.96	2.39	2/8	7
31	Tirandamycin A	>64	433	585	134.7	23.0	0.36	-0.25	3/8	5
32	Ophiosetin	>128	389	568	98.1	17.3	1.11	-0.13	3/5	4
33	Ikarugamycin epoxide	100	495	702	108	15.4	2.30	1.83	3/5	1
34	Ripromycin	100	525	741	117	15.8	1.52	1.10	3/6	2
a; see foot note in Table S8 for the abbreviation, b; see references **S-1**; c; MIC values against *S. aureus* without consideration of the species of strain.										

Table S13. *In vitro* antibiotic activity against *S. aureus* (MIC, μg/mL) and physical properties of previously reported unnatural 3-acyltetramic acid analogues[a]

Entry	Name[b]	MIC[C]	Mw	MSA	PSA	%PSA	ClogP	$ClogD_{7.4}$	H-D/ H-A	R-B
Active (MIC ≤ 4)										
1	CPB-11	1.56	295	519	57.6	11.1	3.12	2.48	1/3	10
2	JMC-B	0.8	337	609	57.6	9.5	4.41	3.93	1/3	11
3	JMC-I	0.8	323	577	57.6	10.0	4.08	3.58	1/3	10
4	JMC-K	0.8	363	546	57.6	10.5	4.28	3.82	1/3	5
5	JMC-L	1.6	331	525	57.6	11.0	2.88	2.44	1/3	4
6	JMC-M	0.8	335	581	57.6	9.9	3.84	3.41	1/3	8
7	JMC-N	0.8	372	622	57.6	9.3	4.90	4.36	1/3	11
8	JMC-T	3.1	319	415	66.4	16.0	2.74	2.33	2/3	3
9	JMC-U	3.1	333	448	57.6	12.9	2.99	2.59	1/3	3
10	JMC-V	1.56	319	415	66.4	16.0	2.74	2.29	2/3	3
11	JMC-W	1.56	333	448	57.6	12.9	2.99	2.55	1/3	3
Mild (4 < MIC ≤ 32)										
12	CPB-9	25	239	397	57.6	14.5	1.54	0.96	1/3	6
13	CPB-10	6.25	267	458	57.6	12.6	2.33	1.69	1/3	8

This journal is © The Royal Society of Chemistry 2013

14	CPB-13	12.5	265	428	57.6	13.5	2.22	1.91	1/3	7
15	CPB-15	6.25	321	453	57.6	12.7	2.72	1.87	1/3	4
16	CPB-17	12.5	253	426	57.6	13.5	2.08	1.51	1/3	6
17	CPB-18	6.25	281	487	57.6	11.8	2.87	2.24	1/3	8
18	CPB-19	12.5	309	548	57.6	10.5	3.66	3.04	1/3	10
19	CPB-21	25	273	409	57.6	14.1	2.10	1.45	1/3	4
20	CPB-22	12.5	335	482	57.6	12.0	3.26	2.42	1/3	4
21	CPB-23	25	259	381	57.6	15.1	1.73	1.01	1/3	4
22	CPB-24	6.25	287	443	57.6	13.0	2.52	1.87	1/3	6
23	CPB-25	6.25	315	504	57.6	11.4	3.31	2.71	1/3	8
24	CPB-26	12.5	343	565	57.6	10.2	4.11	3.46	1/3	10
25	CPB-28	25	301	472	57.6	12.2	3.06	2.42	1/3	6
26	CPB-29	6.25	329	533	57.6	10.8	3.85	3.26	1/3	8
27	CPB-31	25	335	485	57.6	11.9	3.70	2.96	1/3	5
28	CPB2-14	6.25	253	425	66.4	15.6	2.08	1.43	2/3	8
29	CPB2-15	6.25	267	453	66.4	14.7	2.62	1.98	2/3	8
30	JMC-A	6.25	287	439	57.6	13.1	2.67	2.16	1/3	4
31	JMC-C	25	321	454	57.6	12.7	3.09	2.52	1/3	4
32	JMC-D	25	317	487	66.8	13.7	2.34	1.64	1/4	5
33	JMC-E	25	305	446	57.6	12.9	2.74	1.85	1/3	4
34	JMC-J	6.25	253	425	57.6	13.6	2.03	1.61	1/3	5
35	C14-TA	6.25	325	555	86.6	15.6	2.38	1.68	3/4	12
36	T-4d	25	431	693	95.9	13.8	3.32	2.71	2/4	10
37	T-4e	12.5	433	679	105	15.5	2.20	1.42	2/5	10
38	T-5b	25	346	545	83.6	15.3	1.45	-1.51	2/4	6
39	T-5c	25	353	629	83.6	13.3	2.98	-0.01	2/4	13
40	T-6	25	381	551	77.8	14.1	3.09	2.44	2/4	4
Inactive (MIC > 32)										
41	CPB-2	>64	155	212	57.6	27.2	-0.91	-1.62	1/3	0
42	CPB-3	>64	169	241	57.6	23.9	-0.37	-1.02	1/3	0
43	CPB-4	>64	231	320	57.6	18.0	0.86	0.24	1/3	2
44	CPB-5	>64	245	348	57.6	16.6	1.40	0.80	1/3	2
45	CPB-6	50	307	423	57.6	13.6	2.84	2.20	1/3	3
46	CPB-12	>64	323	580	57.6	9.9	3.92	3.28	1/3	12
47	CPB-14	50	259	380	57.6	15.2	1.57	0.89	1/3	4

This journal is © The Royal Society of Chemistry 2013

48	CPB-16	50	225	364	57.6	15.8	1.28	0.66	1/3	4
49	CPB-20	>64	337	609	57.6	9.5	4.45	3.83	1/3	12
50	CPB-27	50	273	410	57.6	14.0	2.27	1.57	1/3	4
51	CPB-30	50	357	594	57.6	9.7	4.64	4.01	1/3	10
52	CPB-32	50	363	546	57.6	10.5	4.49	3.80	1/3	7
53	CPB2-16	>64	343	558	66.4	11.9	4.31	3.67	2/3	10
54	CBP2-17	50	357	588	66.4	11.3	4.71	4.10	2/3	10
55	JMC-H	>64	259	378	57.6	15.2	1.65	1.10	1/3	3
56	T-4a	200	479	738	95.9	13.0	4.14	3.63	2/4	10
57	T-4b	>200	447	716	95.9	13.4	2.74	2.29	2/4	9
58	T-4c	50	453	798	95.9	12.0	4.26	3.74	2/4	16
59	T-5a	100	378	566	83.6	14.8	2.85	-0.13	2/4	7
60	T-5d	>200	330	522	83.6	16.0	2.03	-1.03	2/4	7
61	T-5e	200	332	508	92.9	18.3	0.92	-2.26	2/5	7
62	CPB2-3	>100	141	180	66.4	36.9	-1.16	-1.94	2/3	0
63	CPB2-4	>100	155	209	66.4	31.8	-0.62	-1.32	2/3	0
64	CPB2-5	>100	231	314	66.4	21.1	1.06	0.46	2/3	2
65	CPB2-6	>100	197	300	66.4	22.1	0.65	0.12	2/3	2
66	CPB2-7	>100	270	354	82.2	23.2	1.17	0.58	3/3	2

a; see foot note in Table S8 for the abbreviation, b; see references **S-2**; c; MIC values against *S. aureus* without consideration of the species of strain.

Table S14. *In vitro* antibiotic activity against *S. aureus* (MIC, μg/mL) and physical properties of previously reported unnatural 3-carboxamide tetramic acid analogues[a]

Entry	Name	MIC[b]	Mw	MSA	PSA	%PSA	ClogP	$ClogD_{7.4}$	H-D/ H-A	R-B
Active (MIC ≤ 4)										
1	BMC-2	0.5	390	568	69.6	12.3	3.51	2.03	2/3	5
2	BMC-B	0.5	390	561	78.4	14.0	3.58	1.93	3/3	5
3	BMC-D	2	376	530	78.4	14.8	3.33	1.24	3/3	4
4	BMC-E	4	405	591	78.4	13.3	3.98	2.42	3/3	6
5	BMC-F	0.5	356	546	78.4	14.4	3.09	1.54	3/3	5
6	BMC-I	4	398	545	78.4	14.4	3.78	2.34	3/3	6
7	BMC-J	4	405	585	81.7	14.0	3.09	1.51	3/4	6
Mild (4 < MIC ≤ 32)										

8	BMC-G	16	380	533	96.3	18.1	1.48	-0.43	3/4	4
9	BMC-K	16	340	444	78.4	17.7	2.24	0.39	3/3	5
10	BMC-L	32	328	485	78.4	16.2	1.53	-0.16	3/3	5
a; see foot note in Table S8 for the abbreviation, b; see reference **S-3**; c; MIC values against *S. aureus* without consideration of the species of strain.										

Table S15. Physical properties of fluoroquinolones

Entry	Name	Mw	MSA	PSA	%PSA	ClogP	$ClogD_{7.4}$	HD/HA	RB
1	Piromidic acid	288	394	86.6	22.0	1.50	-0.29	1/7	3
2	Pipemidic acid	303	415	98.7	23.8	0.62	-2.66	2/8	3
3	Rosoxacin	294	388	70.5	18.2	2.04	0.77	1/5	3
4	Ciprofloxacin	331	441	72.9	16.5	1.57	-1.38	2/6	3
5	Enoxacin	320	429	85.8	20.0	1.60	-1.51	2/7	3
6	Fleroxacin	369	478	64.1	13.4	1.83	0.11	1/6	4
7	Lomefloxacin	365	501	72.9	14.6	2.53	-0.42	2/6	3
8	Nadifloxacin	360	483	81.1	16.8	1.77	0.48	2/6	2
9	Norfloxacin	319	436	72.9	16.7	1.51	-1.42	2/6	3
10	Ofloxacin	361	485	73.3	15.1	1.51	-0.33	1/7	2
11	Rufloxacin	363	462	64.1	13.9	1.76	-0.10	1/6	2
12	Pefloxacin	333	468	64.1	13.7	1.87	0.20	1/6	3
13	Balofloxacin	389	548	82.1	15.0	1.89	-1.97	2/7	5
14	Grepafloxacin	359	500	72.9	14.6	2.45	-0.47	2/6	3
15	Pazufloxacin	318	405	92.9	22.9	0.70	-2.09	2/6	2
16	Sparfloxacin	392	517	98.9	19.1	2.40	-0.66	3/7	3
17	Temafloxacin	417	523	72.9	13.9	3.54	0.37	2/6	3
18	Tosufloxacin	404	483	99.8	20.7	2.93	-1.23	2/7	3
19	Clinafloxacin	365	452	86.9	19.2	1.80	-2.15	2/6	3
20	Gatifloxacin	375	517	82.1	15.9	1.73	-1.33	2/7	4
21	Gemifloxacin	389	510	121	23.8	2.09	-1.89	2/9	5
22	Moxifloxacin	401	549	82.1	15.0	1.85	-1.88	2/7	4
23	Sitafloxacin	410	497	86.9	17.5	2.18	-1.48	2/6	3
24	Danofloxacin	357	474	64.1	13.5	1.94	0.27	1/6	3
25	Garenoxacin	426	543	78.9	14.5	3.68	0.26	2/6	5
26	Trovafloxacin	416	487	99.8	20.5	2.69	-1.32	2/7	3
27	Difloxacin	399	519	64.1	12.4	3.35	1.65	1/6	3

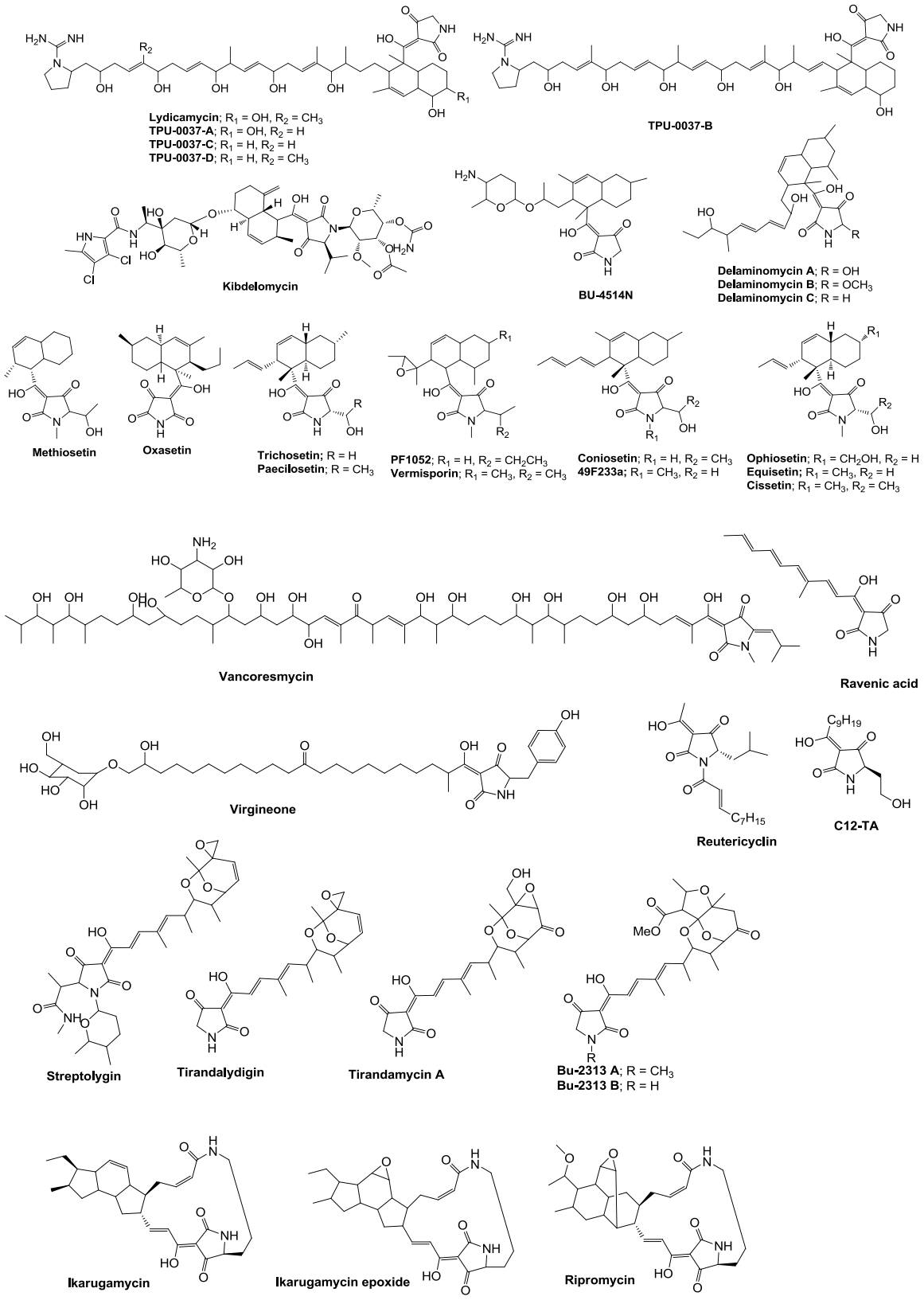


Figure S20. Natural 3-acyl tetramic acids reported antibiotic activity against *S. aureus*.

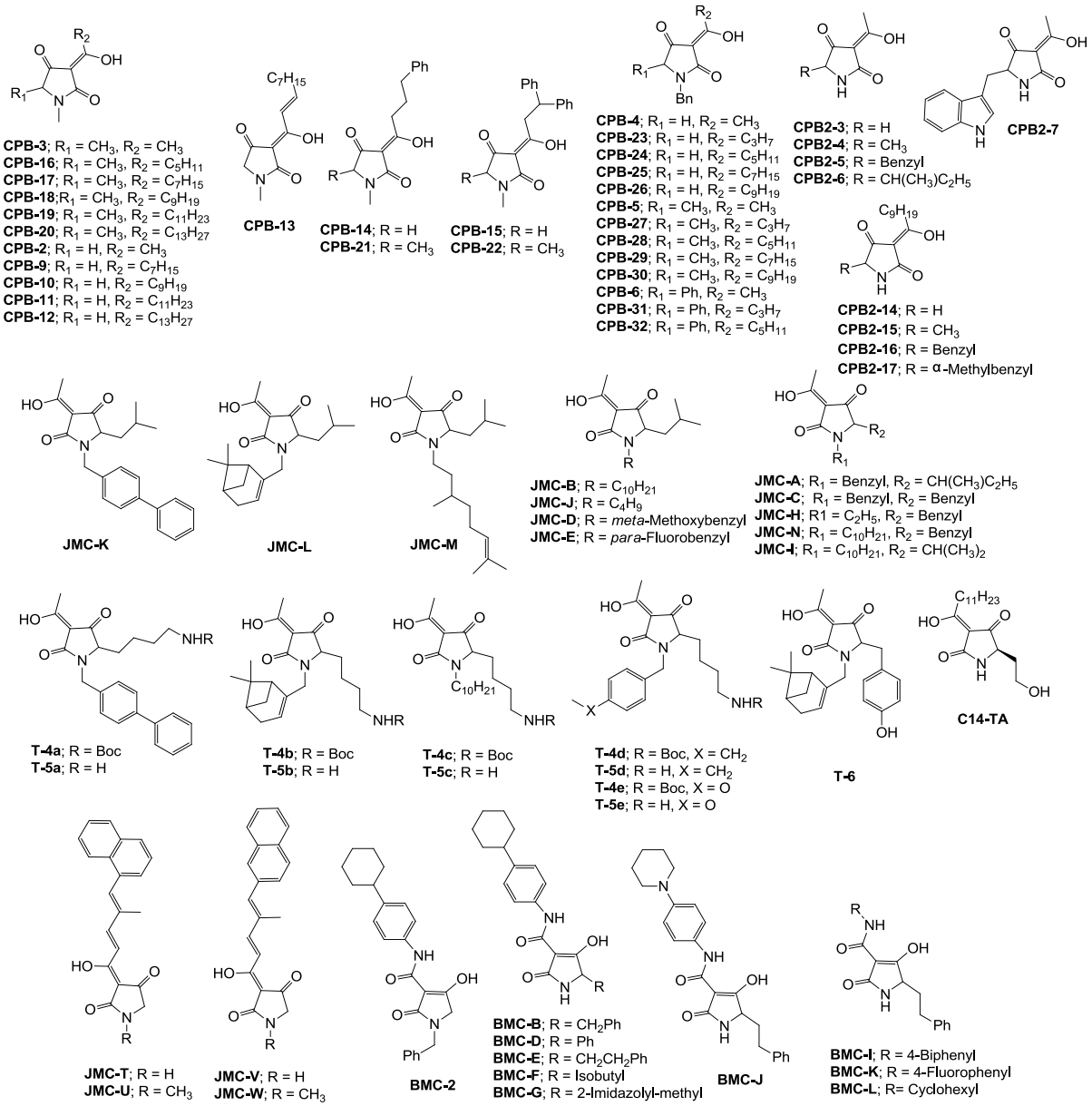


Figure S21. Unnatural 3-acyl and 3-carboxamide tetramic acids with reported antibiotic activity against *S. aureus*

Experimental Section

1. General

1.1. Synthesis

The ^{1}H, ^{13}C, DEPT, COSY, HSQC and HMBC NMR spectra were obtained using a Bruker AVB500 (500 MHz, 125 MHz respectively) or DPX400 (400 MHz, 100 MHz, respectively) with residual solvent peaks or tetramethylsilane as the internal reference. Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained with Micro Mass LCT and GCT spectrometers under the conditions of electrospray ionization (ESI) and chemical ionization (CI) respectively, and values were reported in Daltons. Optical rotations were read on a Perkin Elmer 241 polarimeter using the sodium D line (589 nm) and $[\alpha]_D$ were given in units of 10^{-1}

deg dm^2g^{-1}.

1.2. Calculation

Docking study; Docking calculations were carried out according to the DockingServer methodology.[S-4a] The MMFF94 force field[S-4b] was used for energy minimization of ligand molecules 2A and 6C tautomers using DockingServer. PM6 semiempirical charges calcuted by MOPAC2009[S-4c] were added to the ligand atoms. Non-polar hydrogen atoms were merged and rotatable bonds were defined. Docking calculations were carried out on RNA polymerase of Thermus thermophilus (PDB code: 3DXJ and 1ZYR) and Undecaprenyl Pyrophosphate Synthase (PDB code: 1V7U). Essential hydrogen atoms, Kollman united atom type charges and solvation parameters were added with the aid of AutoDock tools.[S-4d] Affinity (grid) maps of 25×25×25 Å grid points and 0.375 Å spacing were generated using the Autogrid program.[S-4d] AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method.[S-4e] Initial position, orientation and torsions of the ligand molecules were set randomly. Alternative conformations from 100 independent dockings were considered when the frequency of the conformation was above 10% and the docking energy was within 1 kcal/mol as compared to the lowest energy hit. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 2500000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

Calculation of physicochemical properties; Molecular surface area (MSA), polar surface area (PSA), calculated partition coefficient (ClogP), calculated distribution coefficient at $pH_{7.4}$ ($ClogD_{7.4}$), hydrogen bond donor count, hydrogen bond acceptor count and rotatable bond count were calculated by using MarvinSketch version 5.3.8. (www.chemaxon.org). Van der Waals for MSA and VG method for ClogP and $ClogD_{7.4}$ were selected for the calculations. Sulfur atoms were excluded from the calculation of PSA. rel-PSA were obtained from (PSA/MSA) x 100. In the calculation, the major tautomer only was selected.

Set of previously reported 3-acyl and 3-carboxamide tetramic acids; 34 of natural and 66 of unnatural 3-acyltetramic acids and 10 of 3-carboxamide tetramic acids and their reported MIC values against *S. aureus* without consideration of species of strain in the literature were selected in the bins for each family, with activity defined as “active” in which MIC values are ≤ 4 µg/ml, “mild active” in which MIC values are 4 < MIC ≤ 32 µg/ml and “inactive” in which MIC values are >32 µg/ml.

1.3. Biological tests

RNAP enzyme assay; The activities of the compounds against *Escherichia coli* RNA Polymerase *in vitro* were compared using the Kool NC-45 universal RNAP template (Epicentre, Madison, WI). A dilution series of each compound, starting from 100µM highest concentration, 2/5 dilution, was added to the reaction volume. Data were converted to percent inhibition with respect to positive and negative controls.

This journal is © The Royal Society of Chemistry 2013

UPPS enzyme assay; UPPS from *Streptococcus pneumoniae* R6 was purified from a recombinant *E.coli* strain, containing a pQTEV-*UPPS*(FL) fusion construct with a TEV cleavable N-terminal H_7 tag. The *E.coli* strain BL21(DE3) was transformed with the pQTEV-*UPPS*(FL) construct and was grown in Terrific Broth (TB) medium under 200 rpm shaking at 37°C. When OD_{600} reached 0.8, bacteria were induced with 0.5 mM isopropyl β-D-1-thiogalactopyranoside and left at 37°C for 3 hours under 200 rpm shaking. Cells were harvested by centrifugation at 6,000 x *g* and frozen at -20°C before use. Expression yield was determined after lysis using B-PER® Bacterial Protein Extraction Reagent (Thermo Scientific, #78248) as described by the manufacturer, giving 300 mg/ L of soluble protein. A total of 6 g (wet weight) of *E.coli* BL21(DE3) paste was suspended in 10 volumes of lysis buffer (20 mM Tris pH 8, 10% Glycerol, 1 mM $MgSO_4$, 150 mM NaCl, 0.1% TritonX-100, 100 mM lysozyme and protease cocktail inhibitor (Roche Diagnostics, # 11873580001)). The pellet was homogenized at 4°C by magnetic stirring for 15 min. Cells were broken by sonication (180 pulses of 5 sec (9.9 sec off) using a 13 mm diameter probe, in icy bath). To hydrolyze DNA and RNA, 25 U/ mL of Benzonase® nuclease (Novagen, #70746-3) was added before ultracentrifugation at 142,400 x *g* for one hour at 4°C. Supernatant was recovered and loaded on a 5 mL Histrap™ column HP (GE Healthcare, 17-5248-02) preequilibrated in buffer A (20 mM Tris pH 8, 500 mM NaCl, 10% Glycerol, 10 mM Imidazole). The column was washed with buffer A until baseline return to zero. Bound proteins were first eluted with 4 column-volumes of buffer A + 30 mM Imidazole then 4 column-volumes of buffer A + 70 mM Imidazole to remove unspecific binding and finally with a 4-column-volume linear gradient buffer A + 70 mM Imidazole to 100 % buffer B (20 mM Tris pH 8, 500 mM NaCl, 10% Glycerol, 0.5 M Imidazole). Fractions containing UPPS, as determined by SDS-PAGE analysis, were pooled giving 90 mg of 85% pure target protein (yield of affinity chromatography: 225 mg/ L). To remove the H7 tag, 20 mg of the pool were then incubated overnight at room temperature with 75 units of AcTev™ protease (Invitrogen, #12575-015) per milligram of UPPS protein. Sample was ultracentrifuged at 142,400 x *g* for one hour at 4°C before being loaded on a 5 mL Histrap™ column HP (GE Healthcare, 17-5248-02). 20 mg of UPPS were recovered into flow through and wash fractions and concentrated 2.5 times using Amicon®Ultra centrifugal filter 10K (Millipore, UFC 901024) giving 10 mL at 1.9 mg/ mL. The solution was ultracentrifuged at 142,400 x *g* for one hour at 4°C and submitted to size exclusion chromatography on a HRX 16/20 Superdex 200, 184 mL (GE Healthcare) running at 2 mL/ min with GF buffer (Tris HCl pH 8, 250 mM NaCl, 1 mM $MgCl_2$, 0.01% Triton X-100). Fractions containing UPPS, as determined by SDS-PAGE analysis, were pooled and concentrated using Amicon®Ultra centrifugal filter 10K (Millipore, UFC 901024) giving 10 mg of 95% pure target protein. (Final yield: 50 mg/L). Five µl of a dilution series of compound, starting from 180 µM highest concentration, 1/3 dilution, was added to the wells of a 96 well plate. Purified UPPS enzyme, without tags, was diluted to 0.002µg/ml in a buffer containing 100mM Tris-HCl pH 7.3, 50mM KCl, 1mM $MgCl_2$, 0,01% Triton-x100 and 20µg/ml BSA and 15µl thereof was added to the compound dilutions. The reaction was started by the addition of 10µl substrate in the same buffer, containing 45µM IPP (Sigma Aldrich, I0503), 1.5µM FPP (Sigma Aldrich, F6892) and 2U/ml *E.coli* inorganic pyrophosphatase (Sigma Aldrich, I5907). The mixture was incubated at 37°C for 30 minutes and terminated by the addition of

30µl Biomol Green Reagent (Enzo Life Science). After 60 minutes, the inorganic phosphate generated in the reaction was detected by measurement absorbance at 615 nm. Data were converted to percent inhibition with respect to positive and negative controls and IC_{50} values calculated using GraphPrism™ software.

Bacterial cell membrane depolarization; To measure the effect of compounds on membrane potential i n *S. aureus* a method based on the cationic dye 3,3′-Diethyloxacarbocyanine iodide, DiOC2(3) was us ed. A rapid microtiter plate assay for measuring the effect of compounds on S. aureus membrane potential.[S-5a]

Red blood cell lysis; Freshly isolated erythrocytes were resuspended to obtain a 2% erythrocyte suspension (1/50 dilution) in PBS. 2 µl of compound diluted to give the appropriate test concentration was added to 198 µl of the erythrocyte suspension in a V-bottom microtitre plate. This was incubated at 37C for 1 hour with shaking at 200rpm. The plate was then centrifuged at 600 rpm for 10 minutes and the supernatant collected. 100uL was transferred to a flat bottom microtitre plate and the OD read at 415nm. The % haemolysis elicited by the test compound was calculated compared to a positive control using Triton detergent.

MIC determination (bacteria); MICs were determined based on Clinical and Laboratory Standards Institute (CLSI) methodology[S-5b] by a 2-fold broth dilution technique in Mueller Hinton (pH7.4 Biorad). For *S. pneumoniae*, the medium was supplemented with 2.5% laked horse blood. For *H. influenzae,* the medium was haemophilus test medium (H.T.M.). Overnight cultures were diluted to obtain the final inoculum of 105 cfu/well. Incubation was 37°C overnight in ambient air. The MIC was defined as the lowest concentration which inhibited all visual growth and was expressed in µg/ml. For each bacterial species, all of the molecules were tested in the same experiment in order to give a head-to-head comparison.

MIC determination (*Candida albicans*); MICs were determined for the antifungus by microdilution methods using RPMI 1640 medium buffered with morpholinopropanesulfonic acid (MOPS) and supplemented with L-glutamine as described by CLSI procedures (M27-A method).[S-5c] After incubation for 24-48 hours at 35°C, the lowest concentration of drug which produced 80% reduction in visible growth compared with control was considered as the MIC.

Cytotoxicity test; Cytotoxicity in Hek293 and PBMC cell cultures, was analysed by ATP content of the cells using ATP-lite (luminescence readout) after 24 hours of incubation of the cells with the compounds. Three concentrations are tested (90.9, 30.3 and 10.1 µM) and results are expressed as the lowest concentration leading to 50% cell viability (LD_{50})

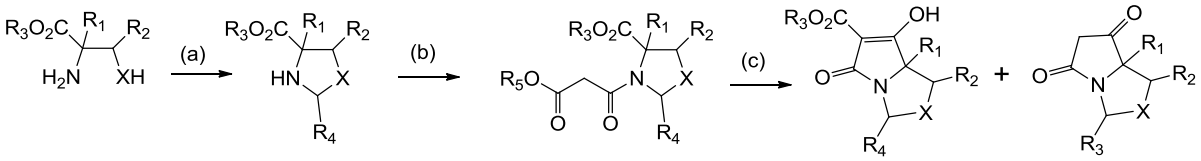
Solubility assay; Starting from a 10mM stock solution of compound in DMSO, a dose-response in DMSO was made by using ½ dilutions: 10, 5, 2.5, 1.25 and 0.63 mM. This dose-response in DMSO was further diluted 1/32.5 in 0.1M phosphate buffer pH 7.4 or 0.1M citrate buffer pH 3.0. This was done by adding 4µl of compound to 130µl buffer. Final compound concentrations are 300, 150, 75, 37.5 and 18.75 µM. The final DMSO concentration was 3%. The assay plates were sealed and incubated for 1 hour at 37°C while shaking at 230 rpm. The plates were then scanned under a white light microscope, yielding individual pictures of the precipitate per concentration. The precipitate was analyzed by image analysis software from SISNCOM. The

first concentration at which the compound appears completely dissolved is the concentration reported. Solubility values are reported in µM and µg/ml.

Plasma protein binding assay; A 10 mM stock solution of compound in DMSO was diluted with a factor 10 in DMSO. This solution was further diluted in freshly thawed human, rat, mouse or dog plasma (BioReclamation INC) with a final concentration of 5 µM and final DMSO concentration of 0.5%. A Pierce Red Device plate with inserts (ThermoScientific, Cat no. 89809) was filled with 450 µL PBS in the buffer chamber and 300 µL of the spiked plasma in the plasma chamber. The plate was incubated for 4 hours at 37°C while shaking at 100 rpm. After incubation, 120 µL of both chambers was transferred to 480 µL methanol in a 96-well round bottom, deep-well plates (Nunc, Cat no. 278743) and sealed with an aluminum foil lid. The samples were mixed and immediately centrifuged 30 min at 1400 rcf at 4°C and the supernatant was transferred to a 96 v-bottom PP plate (Greiner, 651201) for analysis on LC-MS/MS (API2000 from Applied Biosystems, see appendix). Peak area from the compound in the buffer chamber and the plasma chamber were considered to be 100% compound, thus non-specific binding to plastic was skipped. The percentage bound to plasma proteins was derived from these results. Acebutolol and Nicardipine are included in the assay design as low and high binding controls.

2. Synthesis of tetramic acid templates and carboxylic acids

2.1. Synthesis of tetramic acids via Dieckmann cyclisation



(a) RCOH (1.3 eq), Et_3N (1.1 eq), petrol (40-60), relux;
(b) mono-alkyl malonate (1.1 eq), DCC (1.1 eq), DMAP (0.05 eq), CH_2Cl_2, r.t;
(c) KtBuO (1.1 eq), dry THF, reflux.

Synthesis and analytical data of tetramic acid templates *ent*-**15A**, **15A**, (±)-**15D**, **15K**, *ent*-**16A**, **16A**,**B**,**I** and (±)-**16H** have been reported in previous papers.[S-6]

General procedure for synthesis of oxazolidine (step (a)): To ester hydrochloride (1.0 eq) in petrol was added triethylamine (1.5 eq) and pivaldehyde (1.2 eq). The mixture was heated at reflux for 20 h with continuous removal of water using Dean Stark head then filtered and washed with ether (20 ml). The combined filtrates were concentrated *in vacuo* to give oxazolidine. (see below for compounds (±)-**A12**, (±)-**A14** and **A15**)

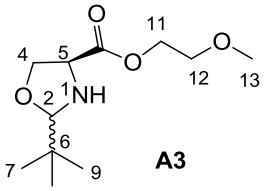
General procedure for N-acylation of oxazolidine (step (b)): To a solution of oxaolidine (1.0 eq), DCC (1.1 eq) and DMAP (0.05 eq) in DCM at 0 ℃ was added ethyl hydrogen malonate (1.05 eq) in DCM. The mixture was stirred at 0 ℃ for 15 min and then at room temperature for 4 h. The reaction mixture was filtered, the residue was washed with DCM. The combined filtrates were evaporated *in vacuo* and purified by flash column chromatography to give N-acyl oxazolidine.

General procedure for Dieckmann cyclisation (step (c)): To a solution of N-acyl oxazolidine (1.0 eq) in dry

THF was added KO^{t}Bu (1.1 eq) and solution was heated at reflux for 3 h, cooled to room temperature and partitioned between ether and water. The aqueous layer was acidified with 2M HCl and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography giving tetramic acid and 3-ester tetramic acid.

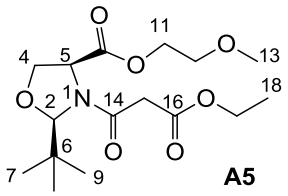
2.1.1. Synthesis of 16C

2.1.1.1. Synthesis of **A3** and **A5**



A3

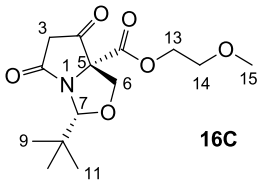
A3; Yield; 74 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$); 4.30-4.22 (m, 3H, C2 and C11), 4.09-3.94 (m, 1H, C5), 3.91-3.81 (m, 1H, C4), 3.73-3.62 (m, 1H, C4), 3.55 (t, 2H, *J* = 4.8 Hz, C12), 3.33 (s, 3H, C13), 2.45 (br s, 1H, NH), 0.95 (s, 9H, C9-C11 *cis* or *trans*), 0.87 (s, 9H, C9-C11 *cis* or *trans*). **^{13}C NMR** (100 MHz, $CDCl_3$); 172.6 and 172.5, (C10), 99.9 and 99.2 (C2), 70.2 and 70.1 (C4), 68.9 and 68.3 (C12), 64.3 and 64.1 (C11), 59.5 and 58.9 (C13) 34.6 and 33.1 (C6), 25.2 and 24.8 (C9-C11). **MS** (ES^+); 232.17 ($M+H^+$); **HRMS** ($M+Na^+$); calculated for $C_{11}H_2NNaO_4$; 254.1363; found; 254.1370.



A5

A5; Yield; 78 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of conformers; major A and minor B); 5.21 (s, 1H, C2 B), 5.18 (s, 1H, C2 A), 4.64 (d, 1H, *J* = 5.3 Hz, C5 B), 4.41 (d, 1H, *J* = 8.3 Hz, C5 A), 4.26-4.20 (m, 1H, C4), 4.19-4.12 (m, 2H, C11), 4.11-4.02 (m, 2H, C17), 3.96-3.89 (m, 1H, C4), 3.56-3.39 (m, 4H, C12 and C15), 3.23 (s, 3H, C13), 1.15 (t, 3H, *J* = 6.7 Hz, C18), 0.85 (s, 9H, C7-C9 B), 0.78 (s, 9H, C7-C9 A). **^{13}C NMR** (100 MHz, $CDCl_3$); 169.4 (C=O), 167.5 (C=O), 167.3 (C=O), 96.6 (C2), 69.8 (C12), 67.7 (C11), 64.4 (C4), 61.4 (C17), 58.7 (C13), 42.8 (C15), 37.3 (C6), 25.5 (C7-C9), 13.9 (C18). **MS** (ES^+); 346.21 ($M+H^+$); **HRMS** ($M+Na^+$); calculated for $C_{16}H_{27}NNaO_7$; 368.1680; found; 368.1683.

2.1.1.2. Synthesis of **16C**

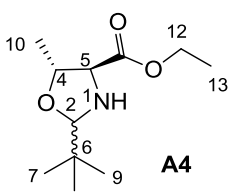


16C

Yield: 47 %; M.P.; 107 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 5.04 (s, 1H, C7), 4.75 (d, 1H, *J* = 8.8 Hz, C6), 4.39-4.25 (m, 2H, C13), 3.72 (d, 1H, *J* = 21.5 Hz, C3), 3.65 (d, 1H, *J* = 8.8 Hz, C6), 3.58-3.54 (m, 2H, C14), 3.00 (s, 3H, C15), 3.14 (d, 1H, *J* = 21.5 Hz, C3), 0.87 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$); 198.2 (C4), 172.7 (C2), 166.3 (C12), 98.2 (C7), 80.6 (C5), 69.9 (C6), 67.8 (C14), 65.7 (C13), 58.8 (C15), 44.8 (C3), 35.6 (C8), 24.6 (C9-C11). **MS** (ES^+); 300.16 (M+H); **HRMS** (M+Na); calculated for $C_{14}H_{21}NNaO_6$; 322.1261; found; 322.1270.

2.1.2. Synthesis of 15C and 16D

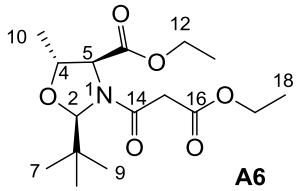
2.1.2.1. Synthesis of **A4** and **A6**



A4

A4; Yield; 83 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$); 4.33 (d, 1H, *J* = 7.6 H, C2 *trans*), 4.27-

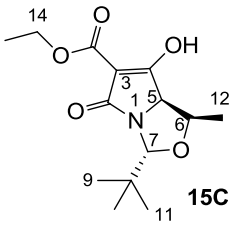
4.21 (m, 1H, C2 *cis*), 4.16 (q, 2H, *J* = 7.3 Hz, C12), 3.80-3.68 (m, 1H, C4), 3.38 (brs, 1H, C5 *cis*), 3.26 (t, 1H, *J* = 7.7 Hz, C5 *trans*), 2.59 (brs, NH), 1.36-1.17 (m, 6H, C10 and C13), 0.92 (d, 9H, *J* = 7.7 Hz, C7-C9 *cis*), 0.84 (d, 9H, *J* = 7.8 Hz, C7-C9 *trans*); **^{13}C NMR** (400 MHz, $CDCl_3$); 172.0 (C11 *trans*), 171.4 (C11 *cis*), 98.7 (C2 *trans*), 98.1 (C2 *cis*), 76.7 (C4 *trans*), 76.3 (C4 *cis*), 67.1 (C5 *cis*), 65.7 (C5 *trans*), 61.3 (C12 *cis*), 61.2 (C12 *trans*), 34.7 (C6 *trans*), 33.5 (C6 *cis*), 25.1 (C7-C9 *cis*), 24.7 (C7-C9 *trans*), 19.8 (C13 *cis*), 18.7 (C13 *trans*), 14.1 (C10). **MS** (ES^+); 216.17 (M+H), 238.15 (M+Na); **HRMS** (M+Na); calculated for $C_{11}H_{21}NNaO_3$ 238.1414; found 238.1421.



A6

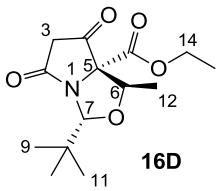
A6; Yield; 72 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$); 5.42 (s, 1H, C2), 4.29-4.14 (m, 6H, C4, C5, C12 and C17), 3.55 (d, 1H, *J* = 15.2 Hz, C15), 3.42 (d, 1H, *J* = 15.2 Hz, C15), 1.36-1.23 (m, 9H, C10, C13 and C18), 0.90 (s, 9H, C7-C9). **^{13}C NMR** (400 MHz, $CDCl_3$); 169.4 (C=O), 167.3 (C=O), 167.2 (C=O), 96.2 (C2), 76.2 (C4), 65.5 (C5), 61.6 (C12 and C17), 42.7 (C15), 37.8 (C6), 25.8 (C7-C9), 20.2 (C13 and C18), 14.0 (C10). **MS** (ES^+); 352.18 (M+Na); **HRMS** (M+Na); calculated for $C_{16}H_{27}NNaO_6$; 352.1731; found 352.1724.

2.1.2.2. Synthesis of **15C** and **16D**



15C

15C; Yield: 23 %; M.P.; 113 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 4.82 (s, 1H, C7), 4.37 (q, 2H, *J* = 7.1 Hz, C14), 3.91-3.86 (m, 1H, C5), 3.64 (dq, 1H, J_1 = 8.5 Hz, J_2 = 6.1 Hz, C6), 1.45 (d, 3H, *J* = 6.1, C12), 1.38 (t, 3H, *J* = 7.1 Hz, C15), 0.95 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 185.6 (C4), 172.9 (C2), 167.3 (C13), 95.0 (C7), 83.7 (C3), 75.9 (C5), 67.4 (C6), 61.6 (C14), 35.6 (C8), 24.6 (C9-C11), 17.2 (C12), 14.1 (C15). **MS** (ES^+); 306.16 (M+Na); **HRMS** (M+Na); calculated for $C_{14}H_{21}N_2NaO_5$; 306.1312; found; 306.1316.

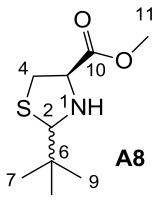


16D

16D; Yield: 56 %; M.P.; 98 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 5.10 (s, 1H, C7), 5.06 (q, 1H, *J* = 6.7 Hz, C6), 4.24 (q, 2H, *J* = 7.1 Hz, C14), 3.62 (d, 1H, *J* = 21.7, C3), 3.12 (d, 1H, *J* = 21.7, C3), 1.28 (t, 3H, *J* = 7.1 Hz, C15), 1.03 (d, 3H, *J* = 6.7 Hz, C12), 0.89 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$); 199.6 (C4), 172.9 (C2), 166.1 (C13), 95.8 (C7), 83.7 (C5), 74.9 (C6), 63.0 (C14), 45.1 (C3), 35.4 (C8), 24.7 (C9-C11), 15.1 (C12), 13.9 (C15). **MS** (ES^+); 306.15 (M+Na); **HRMS** (M+Na); calculated for $C_{14}H_{21}N_2NaO_5$; 306.1312; found; 306.1316.

2.1.3. Synthesis of 15B and 16E

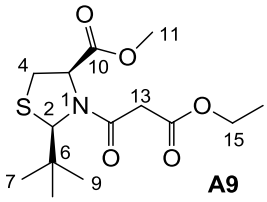
2.1.3.1. Synthesis of **A8** and **A9**



A8

A8; Yield; 86 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$); 4.51 (s, 1H, C2 *trans*), 4.44 (d, 1H, *J* = 5.9 Hz, C2 cis), 4.12 (*t*, 1H, *J* = 5.9 Hz, C5 *trans*), 3.78-3.73 (m, 1H, C5 *cis*), 3.76 (s, 3H, C11 *cis*), 3.73 (s, 3H, C11 *trans*), 3.24 (dd, 1H, J_1 = 10.2 Hz, J_2 = 6.7 Hz, C4 *cis*), 3.10 (dd, 1H, J_1 = 10.6 Hz, J_2 = 6.3 Hz, C4 *trans*), 3.00 (dd, 1H, J_1 = 10.6 Hz, J_2 = 5.7 Hz, C4 *trans*), 2.66 (t, 1H, *J* =

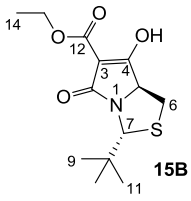
10.0 Hz, C4 *cis*), 2.40 (brs, 1H, NH *trans*), 2.18 (t, 1H, *J* = 12.8 Hz, NH *cis*), 1.05 (s, 9H, C7-C9 *cis*), 0.96 (s, 9H, C7-C9 *trans*). **^{13}C NMR** (100 MHz, $CDCl_3$); 172.4 (C10 *trans*), 171.8 (C10 *cis*), 81.8 (C2 *cis*), 79.8 (C2 *trans*), 65.4 (C5 *cis*), 65.0 (C5 *trans*), 52.4 (C11), 37.4 (C4 *cis*), 37.0 (C4 *trans*), 35.9 (C6 *trans*), 33.9 (C6 *cis*), 26.9 (C7-C9 *cis*), 26.5 (C7-C9 *trans*). **MS** (ES^+); 226.10 (M+Na); **HRMS** (M+Na); calculated for $C_9H_{17}NNaO_2S$; 226.0872; found; 226.0879.



A9

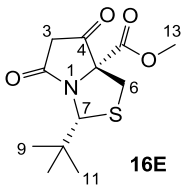
A9; Yield; 83 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$, 1.5:1 mixture of conformers; major A and minor B); 5.46 (s, 1H, C2), 5.37 (s, 1H, C2 B), 5.04-4.97 (m, 1H, C5 B), 4.92-4.78 (m, 1H, C5 A), 4.12-4.07 (m, 2H, C15), 3.77-3.63 (m, 2H, C13 and C4 B), 3.53-3.41 (m, 1H, C4 A), 3.37-3.18 (m, 1H, C4), 1.21 (t, 3H, *J* = 7.2 Hz, C16), 0.92 (9H, s, C7-C9 B), 0.91 (9H, s, C7-C9 A). **^{13}C NMR** (100 MHz, $CDCl_3$); 170.8 (C=O A), 170.5 (C=O B), 166.9 (C=O), 166.7 (C=O), 74.8 (C2 B), 73.1 (C2 A), 65.3 (C5 B), 64.1 (C5 A), 61.5 (C15 A), 61.4 (C15 B), 52.9 (C11 A), 52.4 (C11 B), 42.3 (C13 A), 41.0 (C13 B), 40.0 (C6 B), 39.3 (C6 A), 34.1 (C4 A), 32.8 (C4 B), 27.1 (C7-C9 A), 26.8 (C7-C9 B), 14.0 (C16). **MS** (ES^+); 318.16 (M+H); **HRMS** (M+Na) calculated for $C_{14}H_{23}NNaO_5S$ 340.1189, found 340.1198.

2.1.3.2. Synthesis of **15B** and **16E**



15B

15B; Yield: 27 %; M.P.; 117 ℃; $[\alpha]_D^{22}$ = -106 (c = 0.025 in MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$); 4.98 (s, 1H, C7), 4.56 (dd, 1H, J_1 = 9.5 Hz, J_2 = 6.4 Hz, C5), 4.34 (q, 2H, *J* = 6.9 Hz, C13), 3.86 (s, 1H, C7), 3.14 (dd, 1H, J_1 = 10.1 Hz, J_2 = 6.8 Hz, C5), 2.69 (t, 1H, *J* = 10.1 Hz, C4), 1.34 (t, 3H, *J* = 6.9 Hz, C14), 0.96 (s, 9H, C9-C11). **MS** (ES^+); 308.11 (M+Na); **HRMS** (M+Na); calculated for $C_{13}H_{19}NNaO_4S$; 308.0927; found; 308.0932.



16E

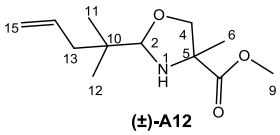
16E; Yield: 57 %; M.P.; 109 ℃; $[\alpha]_D^{22}$ = +112 (c = 0.017 in MeOH)**; ^{1}H NMR** (400 MHz, $CDCl_3$); 5.78 (s, 1H, C7), 3.79 (s, 3H, C13), 3.74 (d, 1H, *J* = 11.4 Hz, C6), 3.58 (d, 1H, *J* = 21.5 Hz, C3), 3.12 (d, 1H, *J* = 21.5 Hz, C3), 3.01 (d, 1H, *J* = 11.4 Hz, C6), 0.92 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$); 199.4 (C4), 170.7 (C2), 167.1 (C12), 84.9 (C5), 73.6 (C7), 53.8 (C13), 42.8 (C3), 37.1 (C8), 33.7 (C6), 26.4 (C9-C11). **MS** (ES^+); 272.12 (M+H); **HRMS** (M+H); calculated for $C_{12}H_{18}NO_4S$; 272.0951; found; 272.0954.

2.1.4. Synthesis of (±)-15E and (±)-15E-1

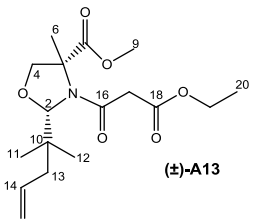
2.1.4.1. Synthesis of (±)-**A12 and** (±)-**A13**

(±)-**A12;** To α-methyl serine methylester hydrochloride **(±)-A10** (3.0 g, 17.6 mmol) in toluene (80 ml) was added triethylamine (3.6 ml, 26.4 mmol) and 2,2-dimethyl-4-pentenal (2.96 g, 24.6 mmol). The mixture was heated at reflux, with continuous removal of water using Dean Stark, for 20 h then filtered and washed with ether (25 ml). The combined filtrates were concentrated *in vacuo* and residue was purified by flash column

chromatography to give mixture of the *cis* and *trans* oxazolidine in 3:2 ratio (1.56 g, 39 % yield) as a colourless oil.

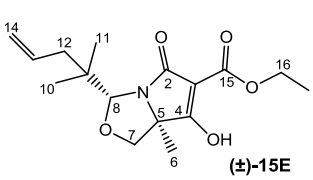


^{1}H NMR (400 MHz, $CDCl_3$, cis/trans mixture, a; major, b; minor); 5.88-5.77 (m, 1H, C14), 5.06-5.01 (m, 2H, C15), 4.32 (s, 1H, C2b), 4.17 (s, 1H, C2a), 4.08 (d, 1H, *J* = 8.1 Hz, C4b), 3.93 (d, 1H, *J* = 8.5 Hz, C4a), 3.75 (s, 3H, C9a), 3.74 (s, 3H, C9b), 3.54 (d, 1H, *J* = 8.5 Hz, C4b), 3.47 (d, 1H, *J* = 8.5 Hz, C4a), 2.10-2.00 (m, 2H, C13), 1.43 (s, 3H, C6b), 1.41 (s, 3H, C6a), 0.94 (s, 3H, C11a), 0.93 (s, 3H, C12a), 0.89 (s, 3H, C11b), 0.88 (s, 3H, C12b). **^{13}C NMR** (100 MHz, $CDCl_3$): 175.7 (C7b), 175.4 (C7a), 134.9 (C14b), 134.4 (C14a), 117.6 (C15a), 117.3 (C15b), 98.2 (C2b), 98.1 (C2a), 75.1 (C4a), 74.8 (C4b), 65.4 (C5b), 65.2 (C5a), 52.7 (C9a), 52.5 (C9b), 43.2 (C13a), 42.5 (C13b), 37.1 (C10b), 36.1 (C10a), 23.5 (C6a), 23.3 (C6b), 22.2 (C11a), 22.0 (C12a), 21.9 (C11b), 21.8 (C12b). **MS** (ES^+); 228.17 (M+H), 250.14 (M+Na); **HRMS** (M+Na); calculated for $C_{12}H_{21}NNaO_3$; 250.1414; found; 250.1416.

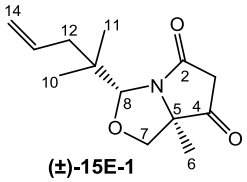


(±)-A13; Yield; 56 % (oil)**; ^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers, a; major, b; minor, a: b = 3: 1) 5.88-5.78 (m, 1H, C14), 5.65 (brs, 1H, C2a), 5.29 (brs, 1H, C2b), 5.05-5.01 (m, 2H, C15), 4.42 (d, 1H, *J* = 8.5 Hz, C4), 4.18 (q, 2H, *J* = 6.9 Hz, C19), 4.13-4.02 (m, 2H, C4b), 3.84-3.69 (m, 4H, C4a and C9), 3.49 (d, 1H, *J* = 15.4 Hz, C17a), 3.38 (d, 1H, *J* = 15.4 Hz, C17a), 3.22 (brs, 2H, C17b), 2.25-2.00 (m, 2H, C13), 1.70 (s, 3H, C6), 1.26 (t, 3H, *J* = 7.2 Hz, C20), 0.93 (brs, 6H, C11 and C12). **^{13}C NMR** (100 MHz, mixture of rotamers, a; major, b; minor) 172.1 (C7), 167.5 (C12), 166.9 (C10), 134.6 (C14), 117.7 (C15), 98.2 (C2a), 97.1 (C2b), 78.7 (C4), 65.9 (C5), 61.5 (C19b), 61.4 (C19a), 53.5 (C9a), 53.0 (C9b), 43.6 (C17a), 43.2 (C17b), 41.8 (C13), 30.6 (C10), 23.6 (C11a), 23.3 (C11b), 22.9 (C6), 21.6 (C12), 14.0 (C20). **MS** (ES^+); 364.17 (M+Na); **HRMS** (M+Na); calculated for $C_{17}H_{27}NNaO_6$; 364.1731; found; 364.1722.

2.1.4.2. Synthesis of **(±)-15E** and **(±)-15E-1**



(±)-15E; Yield; 61 %; m.p.; 198 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) 5.86-5.76 (m, 1H, C13), 5.04-4.98 (m, 2H, C14), 4.68 (s,1 H, C8), 4.32 (q, 2H, *J* = 6.9 Hz, C16), 3.86 (d, 1H, *J* = 8.3 Hz, C7), 3.38 (d, 1H, *J* = 8.3 Hz, C7), 2.09 (d, 2H, *J* = 7.3 Hz, C12), 1.54 (s, 3H, C6), 1.33 (t, 3H, *J* = 7.1 Hz, C17), 0.93 (s, 3H, C10), 0.90 (s, 3H, C11). **^{13}C NMR** (100 MHz, $CDCl_3$): 189.3 (C4), 167.3 (C2 and C15), 134.6 (C13), 117.5 (C14), 97.0 (C8), 72.1 (C7), 61.6 (C16), 42.5 (C12), 37.5 (C9), 22.5 (C10), 22.2 (C11), 20.8 (C6), 14.1 (C17). **MS** (ES^+); 310.17 (M+H), 332.15 (M+Na); **HRMS** (M+Na); calculated for $C_{16}H_{23}NNaO_5$; 332.1468; found; 332.1473.



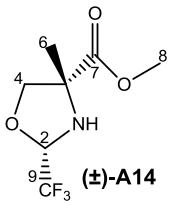
(±)-15E-1; Yield; 10 %; m.p.; 143 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) 5.92-5.82 (m, 1H, C13), 5.13-5.00 (m, 3H, C8 and C14), 3.86 (d, 1H, *J* = 8.3 Hz, C7), 3.56 (d, 1H, *J* = 21.5 Hz, C3), 3.55 (d, 1H, *J* = 8.3 Hz, C7), 3.14 (d, 1H, *J* = 21.5 Hz, C3), 2.15-2.12 (m,

2H, C12), 1.58 (s, 3H, C6), 0.99 (s, 3H, C10), 0.96 (s, 3H, C11). **^{13}C NMR** (100 MHz, $CDCl_3$): 206.1 (C4), 173.0 (C2), 134.3 (C13), 117.9 (C14), 97.9 (C8), 75.1 (C5), 71.4 (C7), 44.7 (C3), 42.6 (C12), 37.8 (C9), 22.7 (CH_3), 22.3 (CH_3), 22.1 (CH_3). **MS** (ES^+); 238.14 (M+H), 260.13 (M+Na); **HRMS** (M+Na); calculated for $C_{13}H_{19}NNaO_3$; 260.1257; found; 260.1256.

2.1.5. Synthesis of (±)-15F

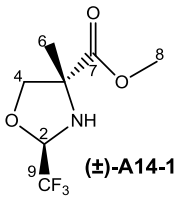
2.1.5.1. Synthesis of (±)-**A14**, (±)-**A14-1,** (±)-**A14-2** and (±)-**A16**

(±)-**A14**, (±)-**A14-1** and (±)-**A14-2;** To a solution of α-methyl serine methyl ester hydrochloride (±)-**A10** (1.0 g, 5.92 mmol) in toluene (10 ml) at 0 ^oC was added NaOAc (0.58 g, 6.90 mmol) and trifluoroacetaldehyde ethyl hemiacetal (1.37 ml, 11.82 mmol). The resulting mixture was stirred at room temperature for 30 mins and warmed to 90 ^oC for 2h. Toluene (30 ml) was then added to reaction mixture which was warmed to reflux using a Dean Stark apparatus for 10 h. The reaction mixture was then cooled to 0 ^oC with an ice bath and filtered and toluene was evaporated. Purification by flash column chromatography gave (±)-**A14** (0.15 g, 12 %, oil), (±)-**A14-1** (0.23 g, 18 %, oil) and (±)-**A14-2** (0.56 g, 34 %, M.P. 132 °C).



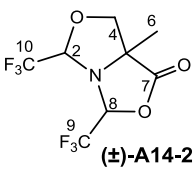
(±)-**A14**

(±)-**A14: ^{1}H NMR** (400 MHz, $CDCl_3$) 4.99 (q, 1H, $J_{H\text{-}F}$ = 5.5 Hz, C2), 4.28 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.3 Hz, C4), 3.80 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.4 Hz, C4), 3.76 (s, 3H, C8), 3.60 (brs, 1H, NH), 1.44 (s, 3H, C6). **^{13}C NMR** (100 MHz, $CDCl_3$): 175.6 (C7), 123.3 (q, $J_{C\text{-}F}$ = 282 Hz, C9), 87.0 (q, $J_{C\text{-}F}$ = 34.1 Hz, C2), 75.6 (C4), 65.6 (C5), 53.0 (C8), 22.4 (C6). **MS** (ES^+); 214.07 (M+H); **HRMS** (M+H); calculated for $C_7H_{11}F_3NO_3$; 214.0686; found; 214.0689.



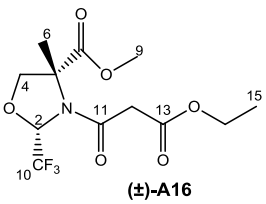
(±)-**A14-1**

(±)-**A14-1: ^{1}H NMR** (400 MHz, $CDCl_3$) 4.97 (q, 1H, $J_{H\text{-}F}$ = 5.1 Hz, C2), 4.35 (d, 1H, J = 8.3 Hz, C4), 3.77 (s, 3H, C8), 3.70 (d, 1H, J = 8.3 Hz, C4), 1.51 (s, 3H, C6). **^{13}C NMR** (100 MHz, $CDCl_3$): 173.6 (C7), 122.9 (q, $J_{C\text{-}F}$ = 281 Hz, C9), 87.6 (q, $J_{C\text{-}F}$ = 34.1 Hz, C2), 75.1 (C4), 65.4 (C5), 52.9 (C8), 23.6 (C6). **MS** (ES^+); 214.07 (M+H); **HRMS** (M+H); calculated for $C_7H_{11}F_3NO_3$; 214.0686; found; 214.0687.



(±)-**A14-2**

(±)-**A14-2: ^{1}H NMR** (400 MHz, $CDCl_3$) 5.25 (q, 1H, $J_{H\text{-}F}$ = 4.6 Hz, C8), 5.03 (q, 1H, $J_{H\text{-}F}$ = 5.8 Hz, C2), 4.45 (d, 1H, J = 22.0 Hz, C4), 4.02 (d, 1H, J = 22.0 Hz, C4), 1.60 (s, 3H, C6). **^{13}C NMR** (100 MHz, $CDCl_3$): 173.9 (C7), 126.2-119.3 (m, C9 and C10), 96.3 (q, $J_{C\text{-}F}$ = 35.7 Hz, C2), 91.0 (q, $J_{C\text{-}F}$ = 35.7 Hz, C8), 76.6 (C4), 67.4 (C5), 20.8 (C2). **MS** (ES^+); 280.04 (M+H); **HRMS** (M+H); calculated for $C_8H_8F_6NO_3$; 280.0403; found; 280.0407.

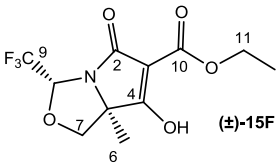


(±)-**A16**

(±)-**A16;** Yield; 36 % (oil)**; ^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers, a; major, b; minor, a: b = 3: 1) 5.62 (brs, 1H, C2a), 4.95 (q, 1H, $J_{H\text{-}F}$ = 5.1 Hz, C2b), 4.47-4.27 (m, 1H, C4), 4.18 (q, 2H, J = 7.1 Hz, C14), 4.07 (d, 1H, J = 8.3 Hz, C4), 3.75 (s, 3H,

C9), 3.49 (d, 1H, *J* = 16.0 Hz, C12), 3.38 (d, 1H, *J* = 16.0 Hz, C12), 1.72 (s, 3H, C6), 1.49 (s, 3H, C6, minor), 1.26 (t, 3H, *J* = 7.2 Hz, C15). **^{13}C NMR** (100 MHz, $CDCl_3$): 173.6 (C7), 170.2 (C13), 163.4 (C11), 123.3 (q, $J_{C\text{-}F}$ = 282 Hz, C10), 87.6 (q, $J_{C\text{-}F}$ = 34.1 Hz, C2), 75.0 (C4), 65.4 (C5), 61.8 (C14), 52.8 (C9), 42.3 (C12), 23.5 (C6), 13.9 (C15). **MS** (ES^+); 350.09 (M+H); **HRMS** (M+Na); calculated for $C_{12}H_{16}F_3NNaO_6$; 350.0822; found; 350.0814.

2.1.5.2. Synthesis of (±)-**15F**



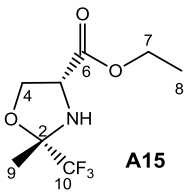
(±)-15F

Yield; 65 % (oil); **^{1}H NMR** (400 MHz, CD_3OD); 5.41 (q, 1H, *J* = 5.4 Hz, C8), 4.31-4.23 (m, 2H, C11), 3.97 (d, 1H, *J* = 8.3 Hz, C7), 3.77 (d, 1H, *J* = 8.3 Hz, C7), 1.52 (s, 3H, C6), 1.30 (t, 3H, *J* = 7.1 Hz, C12). **^{13}C NMR** (125 MHz, CD_3OD); 193.7 (C4), 178.5 (C2), 166.6 (C10), 123.3 (q, $J_{C\text{-}F}$ = 279 Hz, C9), 94.0 (C3), 86.5 (q, $J_{C\text{-}F}$ = 36.0 Hz, C8), 74.5 (C7), 70.5 (C5), 60.9 (C11), 21.4 (C6), 14.8 (C12). **MS** (ES^+); 296.07 (M+H); **HRMS** (M+Na); calculated for $C_{11}H_{12}F_3NNaO_5$; 318.0560; found; 318.0546.

2.1.6. Synthesis of 15G

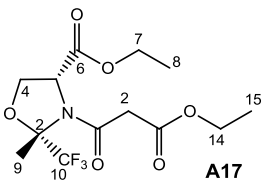
2.1.6.1. Synthesis of **A15** and **A17**

A15; To serine ethyl ester salt **A11** (1.0 g, 5.9 mmol) was added NaOAc and toluene (3 ml). Then trifluoroacetone (1.05 ml, 11.8 mmol) was added and resulting mixture was stirred at room temperature for 6h. Then more toluene (40 ml) was added and resulting solution was heated to reflux for 16 h. The mixture was filtered, evaporated and purified by flash column chromatography to give oxazolidine in 32% yield (0.43 g, oil).



A15

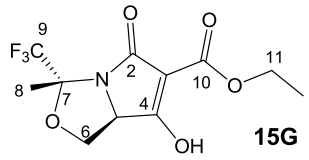
^{1}H NMR (400 MHz, $CDCl_3$); 4.33-4.27 (m, 1H, C4), 4.24 (q, 2H, *J* = 7.1 Hz, C7), 4.07 (q, 1H, *J* = 7.1 Hz, C5), 3.92-3.85 (m, 1H, C4), 2.97 (d, 1H, *J* = 6.3 Hz, NH), 1.58 (s, 3H, C9), 1.29 (t, 3H, *J* = 7.1 Hz, C12). **^{13}C NMR** (100 MHz, $CDCl_3$); 171.9 (C6), 124.6 (q, $J_{C\text{-}F}$ = 285 Hz, C10), 94.7 (q, $J_{C\text{-}F}$ = 30.2 Hz, C2), 70.3 (C4), 62.1 (C7), 59.7 (C5), 19.8 (C9), 14.1 (C8). **MS** (ES^+); 250.05 (M+Na); **HRMS** (M+Na); calculated for $C_8H_{12}F_3NNaO_3$; 250.0661; found; 250.0663.



A17

A17; Yield; 60 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers, a; major, b; minor, a: b = 5: 1); 4.76 (d, 1H, *J* = 6.6 Hz, C5b), 4.68 (d, 1H, *J* = 6.6 Hz, C5a), 4.43-4.35 (m, 1H, C4a), 4.30-4.16 (m, 4H, C7 and C14 and 1H of C4b), 3.55 (s, 2H, C12b), 3.31 (s, 2H, C12a), 1.90 (s, 3H, C9b), 1.87 (s, 3H, C9a), 1.31 (t, 3H, *J* = 7.1 Hz, CH_3), 1.25 (t, 3H, *J* = 7.1 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$,major rotamer): 169.9 (C=O), 166.3 (C=O), 163.9 (C=O), 123.8 (q, $J_{C\text{-}F}$ = 290 Hz, C10), 94.2 (q, $J_{C\text{-}F}$ = 31.8 Hz, C2), 69.3 (C5), 62.8 (CH_2), 61.7 (CH_2), 60.1 (CH_2), 43.9 (C2), 18.5 (C9), 14.0 (CH_3), 13.9 (CH_3). **MS** (ES^+); 342.12 (M+H), 364.10 (M+Na); **HRMS** (M+Na); calculated for $C_{13}H_{18}F_3NNaO_6$; 364.0978; found; 364.0973.

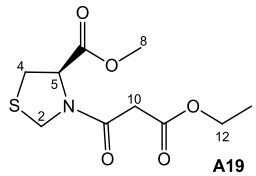
2.1.6.2. Synthesis of **15G**



Yield; 44 % (oil)**; ^{1}H NMR** (400 MHz, DMSO): 4.64 (t, 1H, *J* = 7.7 Hz, C6), 4.29 (t, 1H, *J* = 7.7 Hz, C5), 4.18-4.07 (m, 2H, C11), 3.81-3.72 (m, 1H, C6), 1.68 (s, 3H, C8), 1.20 (t, 3H, *J* = 7.1 Hz, C12). **^{13}C NMR** (100 MHz, $CDCl_3$); 185.5 (C4), 167.4 (C=O), 166.8 (C=O), 123.2 (q, $J_{C\text{-}F}$ = 284 Hz, C9), 100.0 (C3), 91.8 (q, $J_{C\text{-}F}$ = 32.6 Hz, C7), 66.3 (C6), 62.3 (C5), 61.9 (C11), 16.2 (C8), 14.0 (C12). **MS** (ES^+); 296.07 (M+H), 318.06 (M+Na); **HRMS** (M+Na); calculated for $C_{11}H_{12}F_3NNaO_5$; 318.0560; found; 318.0546.

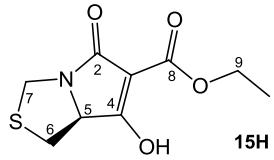
2.1.7. Synthesis of 15H

2.1.7.1. Synthesis of **A19**



Yield; 71 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers, a; major, b; minor, a: b = 2: 1); 5.10 (dd, 1H, J_1 = 6.9 Hz, J_2 = 3.7 Hz, C5a), 4.91 (dd, 1H, J_1 = 6.1 Hz, J_2 = 1.8 Hz, C5b), 4.76 (d, 1H, *J* = 9.9 Hz, C2b), 4.63 (d, 1H, *J* = 8.0 Hz, C2a), 4.57 (d, 1H, *J* = 8.0 Hz, C2a), 4.47 (d, 1H, *J* = 9.9 Hz, C2b), 4.24-4.09 (m, 2H, C12), 3.77 (s, 3H, C8b), 3.73 (s, 3H, C8a), 3.49-3.17 (m, 4H, C4 and C10), 1.30-1.21 (m, 3H, C13). **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of rotamers, a; major, b; minor); 169.9 (C=O a), 169.8 (C=O b), 166.9 (C=O b), 166.6 (C=O a), 164.5 (C=O b), 164.1 (C=O a), 62.3 (C5b), 61.7 (C5a), 61.3 (C12), 53.2 (C8b), 52.8 (C8a), 48.8 (C2a), 48.6 (C2b), 42.8 (C10b), 42.4 (C10a), 34.3 (C4b), 32.8 (C4a), 14.1 (C13). **MS** (ES^+); 284.06 (M+Na); **HRMS** (M+Na); calcd for $C_{10}H_{15}N_1Na_1O_5S_1$; 284.0563; found; 284.0562.

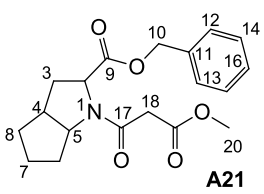
2.1.4.2. Synthesis of **15H**



Yield; 71 % (light yellow solid) $[\alpha]_D^{22}$ = -126 (c = 0.027 in MeOH)**; ^{1}H NMR** (500 MHz, DMSO, mixture of rotamers, a; major, b; minor, a: b = 3: 1);4.70 (d, 1H, *J* = 9.8 Hz, C7b), 4.76 (d, 1H, *J* = 9.8 Hz, C7a), 4.50 (dd, 1H, J_1 = 8.2 Hz, J_2 = 5.9 Hz, C5a), 4.41 (dd, 1H, J_1 = 8.2 Hz, J_2 = 5.4 Hz, C5b), 4.14 (q, 2H, *J* = 7.1 Hz, C9a), 4.01 (d, 1H, *J* = 9.8 Hz, C7a), 3.97 (d, 1H, *J* = 9.8 Hz, C7b), 3.44 (q, 2H, *J* = 7.2 Hz, C9b), 3.28 (dd, J_1 = 11.4 Hz, J_2 = 8.2 Hz, C6a), 3.22 (dd, J_1 = 11.2 Hz, J_2 = 8.2 Hz, C6b), 2.92 (dd, J_1 = 11.2 Hz, J_2 = 5.9 Hz, C6a), 2.85 (dd, J_1 = 11.2 Hz, J_2 = 5.4 Hz, C6b), 1.21 (t, 3H, *J* = 7.1 Hz, C10a), 1.06 (t, 3H, *J* = 7.1 Hz, C10b). **^{13}C NMR** (125 MHz, DMSO, mixture of rotamers, a; major, b; minor): 182.2 (C4), 177.4 (C2b), 172.0 (C2a), 161.4 (C8), 97.7 (C3a), 93.7 (C3b), 65.7 (C9b), 64.2 (C9a), 59.2 (C5a), 56.0 (C5b), 46.3 (C7b), 47.0 (C7a), 32.6 (C6a), 31.6 (C6b), 18.5 (C10b), 15.1 (C10a). **MS** (ES^-); 228.04 (M-H); **HRMS** (M+-H); calcd for $C_9H_{10}N_1O_4S_1$; 228.0336; found; 228.0343.

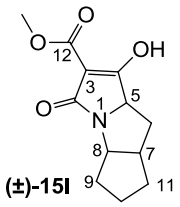
2.1.8. Synthesis of (±)-15I, (±)-15I-1 and (±)-15I-2

2.1.8.1. Synthesis of **A21**

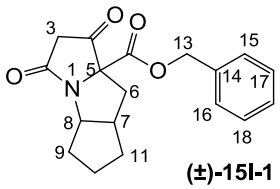


Yield; 75 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamer A (major) and B (minor)); 7.39-7.26 (m, 5H, C12-C16), 5.17 (s, 2H, C10 B), 5.15 (s, 2H, C10 A), 4.66 (dd, 1H, J_1 = 9.5 Hz, J_2 = 5.8 Hz, C2 A), 4.53 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.3 Hz, C2 B), 4.45 (td, 1H, J_1 = 7.8 Hz, J_2 = 4.6 Hz, C5 B), 4.25 (td, 1H, J_1 = 8.0 Hz, J_2 = 5.4 Hz, C5 A), 3.72 (s, 3H, C20 A), 3.70 (s, 3H, C20 B), 3.51 (d, 1H, J = 15.3 Hz, C18 A), 3.41 (d, 1H, J = 15.3 Hz, C18 A), 3.31 (d, 1H, J = 15.1 Hz, C18 B), 3.27 (d, 1H, J = 15.1 Hz, C18 B), 2.85-2.73 (m, 1H, C4 A), 2.63-2.56 (m, 1H, C4 B), 2.45-2.32 (m, 1H, C3), 2.17-1.99 (m, 1H, C6), 1.90-1.03 (m, 6H, C3, C6-C8). **^{13}C NMR** (100 MHz, $CDCl_3$); 172.1 (C9 B), 171.9 (C9 A), 167.9 (C17 B), 167.8 (C17 A), 164.8 (C19 A), 164.7 (C19 B), 135.6 (C11 A), 134.9 (C11 B), 128.7 (tert-ArC), 128.5 (tert-ArC), 128.2 (tert-ArC), 67.6 (C10 B), 66.9 (C10 A), 64.8 (C5 B), 64.4 (C5 A), 60.9 (C2 B), 60.7 (C2 A), 52.4 (C20), 44.1 (C4 A), 42.0 (C4 B), 41.5 (C18 A), 41.4 (C18 B), 34.9 (C3 B), 33.7 (C3 A), 33.6 (C8 A), 33.5 (C8 B), 32.1 (C6 B), 31.4 (C6 A), 25.7 (C7 B), 25.3 (C7 A). **MS** (ES^+); 346.17 (M+H), 368.16 (M+Na); **HRMS** (M+Na); calculated for $C_{19}H_{23}NNaO_5$; 368.1468; found; 368.1477.

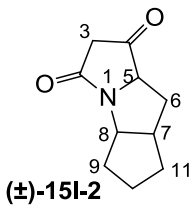
2.1.8.2. Synthesis of (±)-**15l**, (±)-**15l-1** and (±)-**15l-2**



(±)-**15l;** Yield: 41 %; **^{1}H NMR** (400 MHz, $CDCl_3$); 4.36-4.23 (m, 2H, C5 and C8), 3.87 (s, 3H, C13), 3.05-2.92 (m, 1H, C7), 2.04-1.96 (m, 1H, C9), 1.88-1.81 (m, 2H, C6 and C11), 1.79-1.71 (m, 1H, C9), 1.66-1.58 (m, 3H, C6 and C10), 1.50-1.41 (m, 1H, C11). **MS** (ES^+); 238.12 (M+H); **HRMS** (M+Na); calculated for $C_{12}H_{15}NNaO_4$; 260.0893; found; 260.0897.



(±)-**15l-1;** Yield: 28 %; M.P.; 134 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 7.40-7.28 (m, 5H, C15-C19), 5.22 (s, 2H, C13), 4.62 (dt, 1H, J_1 = 7.9 Hz, J_2 = 4.8 Hz, C8), 3.47 (d, 1H, J = 21.0 Hz, C3), 2.97 (d, 1H, J = 21.0 Hz, C3), 2.80 (quin. 1H, J = 7.6 Hz, C7), 2.56 (d, 1H, J = 13.7 Hz, C6), 2.05 (dd, 1H, J_1 = 13.7 Hz, J_2 = 9.6 Hz, C6), 1.94 (dt, 1H, J_1 = 13.7 Hz, J_2 = 9.6 Hz, CH_2), 1.82-1.60 (m, 1H, CH_2), 1.56-1.43 (m, 1H, CH_2), 1.41-1.29 (m, 2H, CH_2), 1.28-1.17 (m, 1H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$); 200.8 (C4), 169.5 (C2), 168.0 (C12), 134.5 (C14), 128.8 (Ar-C), 128.7 (Ar-C), 128.5, (Ar-C), 82.6 (C5), 68.6 (C13), 62.0 (C8), 44.4 (C3), 43.5 (C7), 36.1 (CH_2), 33.2 (CH_2), 32.5 (CH_2), 25.9 (C10). **MS** (ES^+); 336.14 (M+Na); **HRMS** ($M+Na^+$); calculated for $C_{18}H_{19}NNaO_4$; 336.1206; found; 336.1202.

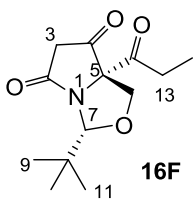


(±)-**15l-2;** Yield: 11 %; M.P.; 121 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 4.51-4.64 (m, 1H, C8), 4.23 (dd, 1H, J_1 = 10.9 Hz, J_2 = 6.8 Hz, C5), 3.30 (d, 1H, J = 21.5 Hz, C3), 3.00 (d, 1H, J = 21.5 Hz, C3), 2.86 (quin. 1H, J = 7.6 Hz, C7), 2.08-1.84 (m, 3H, CH_2), 1.77 (td, 1H, J_1 = 11.6 Hz, J_2 = 8.8 Hz, CH_2), 1.68-1.51 (m, 3H, CH_2), 1.40 (dq, 1H, J_1 = 12.9 Hz, J_2 = 6.8 Hz, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$); 206.3 (C4), 169.3 (C2), 69.4 (C5), 60.7 (C8), 44.5 (C3), 44.4 (C7), 34.2 (CH_2), 34.1 (CH_2), 33.7 (CH_2), 26.4 (C10). **MS** (ES^+); 180.13 (M+H); **HRMS** (M+H); calculated

for $C_{10}H_{14}NO_2$; 180.1019; found; 180.1021.

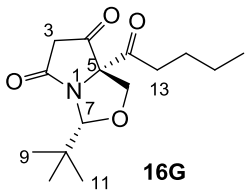
2.2. Synthesis of keto tetramic acids 16F,G

General procedure; To a solution of ester tetramic acid (1.0 eq) in dry THF was slowly added alkyllithium (5.0 eq) at -78 ℃. The solution was stirred at -78℃ to room temperature for 3 hours and the reaction was quenched by the cautious addition of water. The mixture was partitioned between ether and water. The aqueous layer was acidified with 2 M HCl and extracted with ether. The combined ether extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography giving keto tetramic acid.



16F

16F; Yield; 84 %; M.P. 185 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 5.08 (s, 1H, C7), 4.81 (d, 1H, *J* = 9.2 Hz, C6), 3.67 (d, 1H, *J* = 9.2 Hz, C6), 3.63 (d, 1H, *J* = 17.6 Hz, C3), 3.18 (d, 1H, *J* = 17.6 Hz, C3), 2.95 (dq, 1H, J_1 = 18.8 Hz, J_2 = 7.2 Hz, C13), 2.45 (dq, 1H, J_1 = 18.8 Hz, J_2 = 7.2 Hz, C13), 1.11 (t, 3H, *J* = 7.2 Hz, C14), 0.88 (s, 9H, C9-11). **^{13}C NMR** (100 MHz, $CDCl_3$); 201.5 (Carbonyl), 199.4 (Carbonyl), 173.2 (C2), 98.7 (C7), 86.7 (C5), 67.4 (C6), 44.7 (C3), 35.4 (C8), 31.9 (C13), 25.0 (C9-11), 7.3 (C14). **MS** (ES^-); 252.10 (M-H); MS (ES^+); 276.14 (M+Na); **HRMS** (M+Na); calcd for $C_{13}H_{19}N_1Na_1O_4$; 276.1206; found; 276.1214.

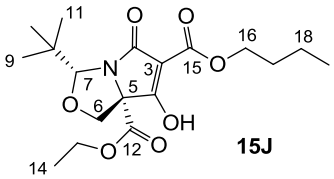


16G

16G; Yield; 96 %; M.P. 168 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 5.09 (s, 1H, C7), 4.80 (d, 1H, *J* = 8.8 Hz, C6), 3.68 (d, 1H, *J* = 9.2 Hz, C6), 3.63 (d, 1H, *J* = 21.2 Hz, C3), 3.18 (d, 1H, *J* = 21.2 Hz, C3), 2.91-2.82 (m, 1H, C13), 2.50-2.41 (m, 1H, C13), 1.68-1.49 (m, 2H, C14), 1.36-1.27 (m, 2H, C15), 0.93-0.89 (m, 12H, C9-11 and C16). **^{13}C NMR** (100 MHz, $CDCl_3$); 201.0 (Carbonyl), 199.4 (Carbonyl), 173.1 (C2), 98.7 (C7), 86.9 (C5), 67.5 (C6), 44.8 (C3), 38.4 (C13), 35.5 (C8), 25.2 (C14), 25.0 (C9-11), 22.0 (C15), 13.8 (C16). **MS** (ES^-); 280.16 (M-H); **HRMS** (M-H); calcd for $C_{15}H_{22}N_1O_4$; 280.1554; found; 280.1560.

2.3. Synthesis of tetramic acid 15J

To the solution of tetramic acid **16B** (400 mg, 1.49 mmol) and DMAP (400 mg, 3.28 mmol) in dichloromethane (30 ml) was added butyl chloroformate (250 mg, 1.78 mmol) under nitrogen atmosphere. After strring the solution overnight, the mixture was washed with acidic water (2 M HCl). The organic layer were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography giving tetramic acid **T10** (140 mg, 0.379 mmol, 25 % yield, oil).



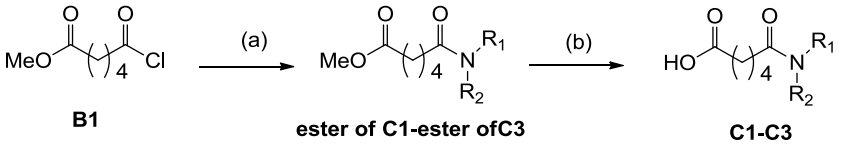
15J

^{1}H NMR (500 MHz, $CDCl_3$); 4.84 (d, 1H, *J* = 9.0 Hz, C6), 4.72 (s, 1H, C7), 4.32-4.22 (m, 4H, C13 and C16), 3.47 (d, 1H, *J* = 9.0 Hz, C6), 1.75-1.69 (m, 2H, C17), 1.46-1.39 (m, 2H, C18), 1.27 (t, 3H, *J* = 7.5 Hz, C14), 0.92 (t, 3H, *J* = 7.5

Hz, C19), 0.90 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 184.0 (C4), 171.9 (C2), 167.0 (C15), 166.2 (C12), 99.6 (C3), 97.4 (C7), 73.4 (C5), 68.8 (C6), 65.6 (OCH_2), 62.9 (OCH_2), 35.0 (C8), 30.3 (C17), 24.6 (C9-C11), 18.9 (C18), 13.9 (CH_3), 13.6 (CH_3). **MS** (ES^-); 368.17 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{26}N_1O_7$; 368.1715; found; 368.1712.

2.4. Synthesis of carboxylic acids

2.4.1. Synthesis of carboxylic acids C1-C3

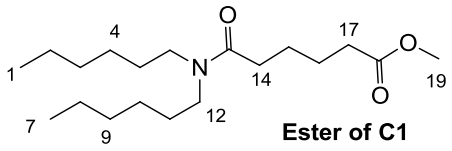


(a) amine (1.1 eq), triethylamine (1.2 eq), CH_2Cl_2, 0 °C-r.t.;
(b) LiOH (3.0 eq), H_2O: CH_3OH: THF (2: 1:1), 0 °C-r.t.;

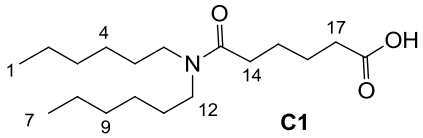
General procedure for synthesis of ester compounds (step (a)); To a stirred solution of the corresponding amine (1.1 eq) and triethylamine (1.2 eq) in dichloromethane was slowly added methyl adipoyl chloride **B1** (1.0 eq) under nitrogen atmosphere at 0 ℃. The reaction mixture was stirred for 3 hours at room temperature. After completion of the reaction, the organic layer was washed with aques HCl. Concentration in *vacuo* followed by flash column chromatography gave the ester compounds.

General procedure for carboxylic acids (step (b)); Lithium hydroxide (3.0 eq) in water was slowly added to the solution of the ester compound (1.0 eq) obtained above in 1:1 mixture of THF and methanol at 0 ℃. Then the mixture was stirred for 3 hours at room temperature. After completion of the reaction, THF and methanol were removed in *vacuo* and extracted with dichloromethane and aques HCl (pH ≒ 1~2). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to afford crude product. Further purification by precipitation in ethyl acetate and petroleum ether solution gave desired product.

2.4.1.1. Synthesis of **ester of C1** and **C1**



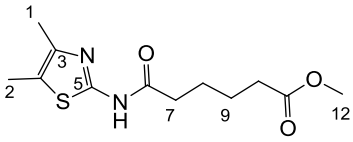
Ester of C1; Yield; 99 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers); 3.58 (s, 3H, C19), 3.20 (t, 2H, *J* = 7.2 Hz, rotamer a of C6 and C12), 3.12 (t, 2H, *J* = 7.6 Hz, rotamer b of C6 and C12), 2.26-2.23 (m, 4H, C14 and C17), 1.59 (brs, 4H, C15 and C16), 1.45-1.42 (m, 4H, C5 and C11), 1.22-1.20 (m, 12H, C2-4 and C8-10), 0.82-0.78 (m, 6H, C1 and C7). **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of rotamers); 173.69 (quart C), 171.69 (quart C), 51.22 (C19), 47.74 (rotamer a of C6 and C12), 45.72 (rotamer b of C6 and C12), 33.69 (C14), 32.47 (C17), 31.40 (rotamer a of C5 and 11), 31.32 (rotamer b of C5 and 11), 28.91 ($\underline{C}H_2$), 27.55 ($\underline{C}H_2$), 26.50 ($\underline{C}H_2$), 26.37 ($\underline{C}H_2$), 24.69 ($\underline{C}H_2$), 24.53 ($\underline{C}H_2$), 22.37 ($\underline{C}H_2$), 13.77 (C1 and C7). **MS** (ES^+); 328.30 (M+H), 350.27 (M+Na); **HRMS** (M+Na); calcd for $C_{19}H_{37}N_1Na_1O_3$; 350.2666; found; 350.2665.



C1

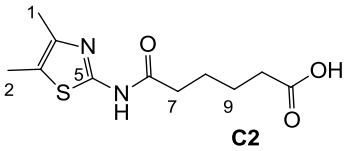
C1; Yield; 96 % (Oil); **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers); 3.27 (t, 2H, *J* = 7.6 Hz, rotamer a of C6 and C12), 3.18 (t, 2H, *J* = 8.0 Hz, rotamer b of C6 and C12), 2.37-2.30 (m, 4H, C14 and C17), 1.71-1.62 (m, 4H, C15 and C16), 1.52-1.46 (m, 4H, C5 and C11), 1.28-1.26 (m, 12H, C2-4 and C8-10), 0.90-0.84 (m, 6H, C1 and C7). **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of rotamers); 177.91 (C18), 172.50 (C13), 48.06 (rotamer a of C6 and C12), 46.07 (rotamer b of C6 and C12), 33.85 (C14), 32.63 (C17), 31.50 (rotamer a of C5 and 11), 31.42 (rotamer b of C5 and 11), 28.98 ($\underline{C}H_2$), 27.59 ($\underline{C}H_2$), 26.61 ($\underline{C}H_2$), 26.48 ($\underline{C}H_2$), 24.75 ($\underline{C}H_2$), 24.50 ($\underline{C}H_2$), 22.50 ($\underline{C}H_2$), 13.94 (rotamer a of C1 and C7), 13.91 (rotamer b of C1 and C7). **MS** (ES^-); 312.26 (M-H); MS (ES^+); 314.29 (M+H), 336.26 (M+Na); **HRMS** (M+Na); calcd for $C_{18}H_{35}N_1Na_1O_3$; 336.2509; found; 336.2510.

2.4.1.2. Synthesis of **ester of C2** and **C2**



ester of C2

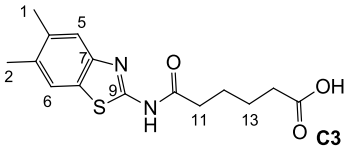
Ester of C2; Yield; 46 %; M.P.; 79 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 12,22 (brs, 1H, NH), 3.60 (s, 3H, C12), 2.63 (t, 2H, *J* = 7.2 Hz, C7), 2.32-2.27 (m, 8H, C1, C2 and C10), 1.77-1.70 (m, 2H, C8), 1.67-1.60 (m, 2H, C9). **^{13}C NMR** (100 MHz, $CDCl_3$); 173.3 (quart C), 171.1 (quart C), 158.7 (C5), 131.5 (C3), 119.9 (C4), 51.4 (C12), 35.6 (C7), 33.3 (C10), 23.9 (CH_2), 23.6 (CH_2), 11.6 (C1), 10.5 (C2). **MS** (ES^-); 269.12 (M-H); MS (ES^+); 271.12 (M+H), 293.11 (M+Na); **HRMS** (M+H); calcd for $C_{12}H_{19}N_2O_3S_1$; 271.1111; found; 271.1114.



C2

C2; Yield; 80 %; M.P.; 215 ℃; **^{1}H NMR** (400 MHz, DMSO); 2.39 (t, 2H, *J* = 7.6 Hz, C7), 2.23-2.20 (m, 5H, C1 and C10), 2.14 (s, 3H, C2), 1.61-1.45 (m, 4H, C8 and C9). **^{13}C NMR** (100 MHz, DMSO); 174.4 (C=O), 170.8 (C=O), 154.0 (C5), 140.7 (C3), 118.5 (C4), 34.6 (CH_2), 33.4 (CH_2), 24.3 (CH_2), 24.0 (CH_2), 14.1 (C1), 10.4 (C2). **MS** (ES^-); 255.09 (M-H); MS (ES^+); 257.10 (M+H), 279.08 (M+Na); **HRMS** (M-H); calcd for $C_{11}H_{15}N_2O_3S_1$; 255.0809; found; 255.0809.

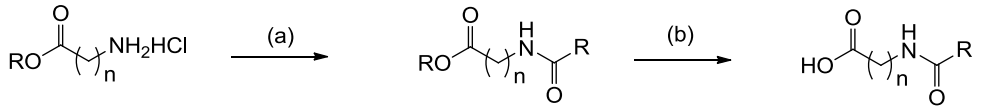
2.4.1.3.. Synthesis of **C3**



C3

C3; Yield; 55 %, M.P.; 244 ℃; **^{1}H NMR** (400 MHz, DMSO); 7.66 (s. 1H, C5), 7.51 (s. 1H, C6), 2.48 (t, 2H, *J* = 7.2 Hz, C11), 2.30 (s, 3H, C2), 2.29 (s, 3H, C1), 2.24 (t, 2H, *J* = 6.8 Hz, C14), 1.66-1.58 (m, 2H, C12), 1.56-1.49 (m, 2H, C13). **^{13}C NMR** (100 MHz, DMSO); 174.36 (C15), 171.92 (C10), 157.03 (C9), 147.02 (C7), 134.75 (C3), 132.32 (C4), 128.78 (C8), 121.45 (C6), 120.84 (C5), 34.87 (C11), 33.40 (C14), 24.19 (C12), 24.06 (C13), 19.76 (C1), 19.59 (C2). **MS** (ES^-); 305.11 (M-H); MS (ES^+); 329.09 (M+Na).

2.4.2. Synthesis of carboxylic acids C4 and C5



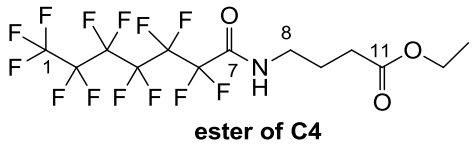
B2; R = Et, *n* = 3
B3; R = Me, n = 5

(a) acid chloride (1.1 eq), triethylamine (2.2 eq), CH_2Cl_2, 0 ℃-r.t.;
(b) LiOH (3.0 eq), H_2O: CH_3OH: THF (2: 1:1), 0 ℃-r.t.;

General procedure for synthesis of ester compounds; To a stirred solution of the corresponding amine HCl **B2** or **B3** (1.1 eq) and triethylamine (2.2 eq) in dichloromethane was slowly added acid chloride (1.0 eq) under nitrogen atmosphere at 0 ℃. The reaction mixture was stirred for 3 hours at room temperature. After completion of the reaction, the organic layer was washed with aques HCl. Concentration in *vacuo* followed by flash column chromatography gave the ester compounds.

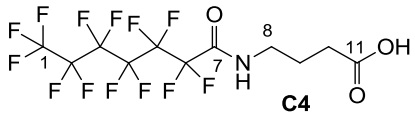
General procedure for carboxylic acids: Same as synthesis of **C1**-**C3**

2.4.2.1. Synthesis of **ester of C4** and **C4**



ester of C4

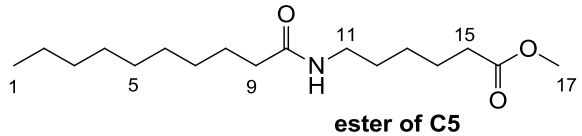
Ester of C4; Yield; 97 % (oil); **^{1}H NMR** (400 MHz, $CDCl_3$); 7.41 (brs, 1H, NH), 4.13 (q, 2H, *J* = 6.8 Hz, C12), 3.42 (q, 2H, *J* = 6.4 Hz, C8), 2.40 (t, 2H, *J* = 6.8 Hz, C10), 1.95-1.88 (m, 2H, C9), 1.24 (t, 3H, *J* = 6.8 Hz, C13). **MS** (ES^-); 476.07 (M-H); MS (ES^+); 500.08 (M+Na); **HRMS** (M+Na); calcd for $C_{13}H_{12}F_{13}N_1Na_1O_3$; 500.0502; found; 500.0509.



C4

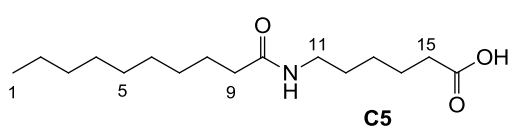
C4; Yield; 74 %; M.P.; 128 ℃; **^{1}H NMR** (400 MHz, MeOD); 3.35 (t, 2H, *J* = 6.8 Hz, C8), 2.39-2.32 (m, 2H, C10), 1.89-1.82 (m, 2H, C9). **MS** (ES^-); 448.02 (M-H); MS (ES^+); 472.04 (M+Na); **HRMS** (M-H); calcd for $C_{11}H_7F_{13}N_1O_3$; 448.0224; found; 448.0223.

2.4.2.2. Synthesis of **ester of C5** and **C5**



ester of C5

Ester of C5; Yield; 87 %, M.P.; 61 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 5.54 (brs, 1H, NH), 3.67 (s, 3H, C17), 3.25 (q, 2H, *J* = 6.8 Hz, C11), 2.32 (t, 2H, *J* = 7.6 Hz, C15), 2.15 (t, 2H, *J* = 7.2 Hz, C9), 1.68-1.63 (m, 4H, C8, C140), 1.55-1.48 (m, 2H, C12), 1.39-1.26 (m, 14H, C2-C7, C13), 0.88 (t, 3H, *J* = 7.6 Hz, C1). **^{13}C NMR** (100 MHz, $CDCl_3$); 174.0 (C=O), 173.1(C=O), 51.5 (C17), 39.1 (CH_2), 36.9 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 24.4 (CH_2), 22.6 (CH_2), 14.1 (C1). **MS** (ES^-); 298.25 (M-H); MS (ES^+); 300.25 (M+H), 322.23 (M+Na); **HRMS** (M+Na); calcd for $C_{17}H_{33}N_1Na_1O_3$; 322.2353; found; 322.2349.

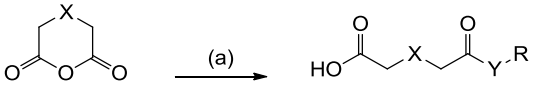


C5

C5; Yield; 92 %, M.P.; 89 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$); 11.10 (brs, 1H, OH), 5.82 (brs, 1H, NH), 3.24 (q, 2H, *J* = 6.4 Hz, C11),

2.34 (t, 2H, *J* = 7.2 Hz, C15), 2.17 (t, 2H, *J* = 7.6 Hz, C9), 1.68-1.57 (m, 4H, C8 and C14), 1.55-1.48 (m, 2H, C12), 1.40-1.34 (m, 2H, C2), 1.26-1.25 (m, 12H, C3-7 and C13), 0.87 (t, 3H, *J* = 6.8 Hz, C1). **^{13}C NMR** (100 MHz, $CDCl_3$); 178.4 (C=O), 173.7 (C=O), 39.2 (C11), 36.8 (C9), 33.8 (C15), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 24.2 (CH_2), 22.6 (CH_2), 14.1 (C1). **MS** (ES^-); 284.22 (M-H); MS (ES^+); 286.25 (M+H), 308.21 (M+Na); **HRMS** (M-H); calcd for $C_{16}H_{30}N_1O_3$; 284.2231; found; 284.2237.

2.4.3. Synthesis of carboxylic acids C6-C13



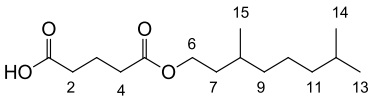
B4; X = CH_2
B5; X = $C(CH_3)_2$
B6; X = O

C6-C13

(a) amine or alcohol (1.1 eq), toluene, reflux;

General procedure; A mixture of alcohol or amine (1.0 eq) with glutaric anhydride derivative (1.0 eq) in toluene was refluxed for 3 hours. After completion of the reaction, toluene was removed and the residue was purified by flash column chromatography giving carboxylic acid.

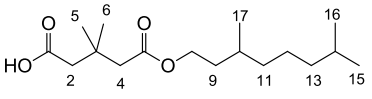
2.4.3.1. Synthesis of **C6**



C6

Yield; 76 % (Oil)**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.17-4.06 (m, 2H, C6), 2.44 (t, 2H, *J* = 7.2 Hz, C4), 2.39 (t, 2H, *J* = 7.2 Hz, C2), 2.01-1.92 (m, 2H, C3), 1.70-1.62 (m, 1H, C8), 1.56-1.49 (m, 2H, C7), 1.47-1.40 (m, 1H, C12), 1.33-1.09 (m, 6H, C9-C11), 0.90 (d, 3H, *J* = 6.8 Hz, C15), 0.87 (d, 6H, *J* = 6.8 Hz, C13 and C14). **^{13}C NMR** (100 MHz, $CDCl_3$); 179.05 (carbonyl), 172.98 (carbonyl), 63.16 (C6), 39.16, 37.09, 35.47, 33.21, 32.98, 29.82, 27.92, 24.58, 22.66, 22.56, 19.81, 19.48. **MS** (ES^-); 271.18 (M-H); MS (ES^+); 295.20 (M+Na); **HRMS** (M-H); calcd for $C_{15}H_{27}O_4$; 271.1915; found; 271.1908.

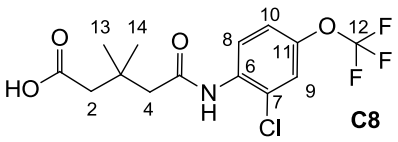
2.4.3.2. Synthesis of **C7**



C7

Yield; 92 % (Oil)**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.15-4.05 (m, 2H, C8), 2.47 (s, 2H, C4), 2.43 (s, 2H, C2), 1.69-1.61 (m, 1H, C10), 1.56-1.48 (m, 2H, C9), 1.46-1.39 (m, 1H, C14), 1.32-1.08 (m, 12H, C5, C6 and C11-C13), 0.89 (d, 3H, *J* = 6.4 Hz, C17), 0.86 (d, 6H, *J* = 6.4 Hz, C15 and C16). **^{13}C NMR** (100 MHz, $CDCl_3$); 177.78 (carbonyl), 172.20 (carbonyl), 62.89 (C8), 45.14 (C4), 45.01 (C2), 39.13 ($\underline{C}H_2$), 37.04 ($\underline{C}H_2$), 35.50 ($\underline{C}H_2$), 32.48 (C3), 29.78 (C14), 27.88 ($\underline{C}H$), 27.68 ($\underline{C}H$), 24.56 ($\underline{C}H_2$), 22.64 (C16), 22.55 (C15), 19.43 (C17). **MS** (ES^-); 299.19 (M-H); MS (ES^+); 301.25 (M+H), 323.20 (M+Na); **HRMS** (M+Na); calcd for $C_{17}H_{32}Na_1O_4$; 323.2193; found; 323.2194.

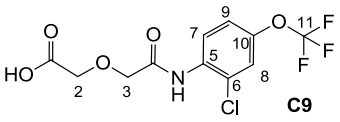
2.4.3.3. Synthesis of **C8**



C8

Yield; 58 %; M.P.; 112 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$); 8.41 (brs, 1H, NH), 8.39 (d, 1H, *J* = 9.6 Hz, C8), 7.28 (d, 1H, *J* = 2.4 Hz, C9), 7.16 (dd, 2H, J_1 =9.6 Hz, J_2 = 2.4 Hz, C10), 2.58 (s, 2H, CH_2), 2.51 (s, 2H, CH_2), 1.21 (s, 6H, C13 and C14). **^{13}C NMR** (100 MHz, $CDCl_3$); 177.36 (C=O), 170.33 (C=O), 144.91 (Ar-quart C), 133.38, (Ar-quart C) 123.79 (Ar-quart C), 123.00 (Ar-*tert* C), 122.11 (Ar-*tert* C), 120.39 (Ar-*tert* C), 47.96 (CH_2), 44.72 (CH_2), 33.73 (C3), 28.80 (C13 and C14). **MS** (ES^-); 352.58 (M-H); **HRMS** (M-H); calcd for $C_{14}H_{14}Cl_1F_3N_1O_4$; 326.0049; found; 326.0043.

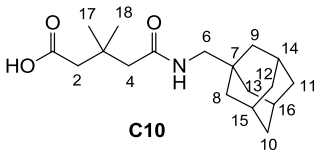
2.4.3.4. Synthesis of **C9**



C9

Yield; 75 %; M.P.; 107 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$); 9.08 (brs, 1H, NH), 8.46 (d, 1H, *J* = 9.2 Hz, C7), 7.30 (d, 1H, *J* = 2.8 Hz, C8), 7.18 (dd, 2H, J_1 =9.2 Hz, J_2 = 2.8 Hz, C9), 4.35 (s, 2H, CH_2), 4.30 (s, 2H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$); 174.12 (C=O), 167.37 (C=O), 145.02 (Ar-quart C), 132.70, (Ar-quart C) 123.85 (Ar-quart C), 122.23 (Ar-*tert* C), 122.12 (Ar-*tert* C), 120.47 (Ar-*tert* C), 71.08 (CH_2), 68.06 (CH_2). **MS** (ES^-); 326.00 (M-H); **HRMS** (M+Na); calcd for $C_{11}H_8Cl_1F_3N_1O_5$; 326.0049; found; 326.0043.

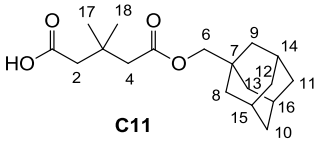
2.4.3.5. Synthesis of **C10**



C10

Yield; 87 %; M.P.; 151 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$); 6.61 (brs, 1H, NH), 3.02 (s, 2H, C6 rotamer A), 3.00 (s, 2H, C6 rotamer A), 2.42 (s, 2H, C2 or C4), 2.35 (s, 2H, C2 or C4), 1.99 (brs, 3H, C14-C16), 1.74-1.60 (m, 6H, adamantly CH_2), 1.50 (brs, 6H, adamantly CH_2), 1.12 (s, 6H, C17 and C18). **^{13}C NMR** (100 MHz, $CDCl_3$); 173.76 (C=O), 173.32 (C=O), 51.58 (C6), 47.05 (C2 or C4), 46.95 (C2 or C4), 40.19 (adamantyl CH_2), 36.76 (adamantyl CH_2), 33.65 (quart C), 33.62 (quart C), 29.36 (C17 and C18), 28.07 (C14-C16). **MS** (ES^-); 306.19 (M-H); MS (ES^+); 308.25 (M+H), 330.21 (M+Na); **HRMS** (M+Na); calcd for $C_{18}H_{29}N_1Na_1O_3$; 330.2040; found; 330.2040.

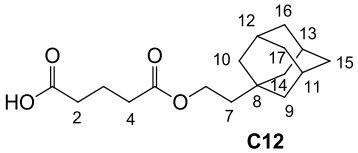
2.4.3.6. Synthesis of **C11**



C11

Yield; 60 %; M.P.; 89 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$); 3.68 (s, 2H, C6), 2.48 (s, 2H, C2 or C4), 2.47 (s, 2H, C2 or C4), 1.99 (brs, 3H, C14-C16), 1.75-1.64 (m, 6H, adamantly CH_2), 1.54 (brs, 6H, adamantly CH_2), 1.15 (s, 6H, C17 and C18). **^{13}C NMR** (100 MHz, $CDCl_3$); 176.8 (C=O), 172.7 (C=O), 74.3 (C6), 45.2 (C2 or C4), 45.1 (C2 or C4), 39.3 (adamantyl CH_2), 36.9 (adamantyl CH_2), 33.0 (quart C), 32.6 (quart C), 28.0 (C15-C17), 27.9 (C17 and C18). **MS** (ES^-); 307.21 (M-H); MS (ES^+); 331.21 (M+Na); **HRMS** (M-H); calcd for $C_{18}H_{27}O_4$; 307.1915; found; 307.1911.

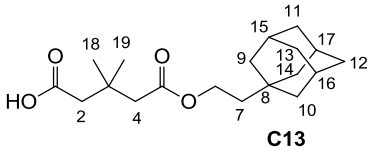
2.4.3.7. Synthesis of **C12**



C12

Yield; 74% (Oil); **^{1}H NMR** (400 MHz, $CDCl_3$); 4.14 (t, 2H, *J* = 7.6 Hz, C6), 2.44 (t, 2H, *J* = 7.2 Hz, C4), 2.38 (t, 2H, *J* = 7.2 Hz, C2), 1.99-1.92 (m, 5H, C3, C11-C13), 1.72-1.52 (m, 12H, C9, C10, C14-C17), 1.49 (t, 3H, *J* = 7.6 Hz, C7). **^{13}C NMR** (100 MHz, $CDCl_3$); 179.0 (C=O), 173.0 (C=O), 61.0 (C6), 42.4 (CH_2), 42.3 (CH_2), 37.0 (CH_2), 33.3 (C4), 33.0 (C2), 31.7 (CH_2), 28.5 (C11-C13), 19.8 (C3 and C8). **MS** (ES^-); 293.18 (M-H); MS (ES^+); 295.22 (M+H), 317.18 (M+Na); **HRMS** (M-H); calcd for $C_{17}H_{25}O_4$; 293.1758; found; 293.1758.

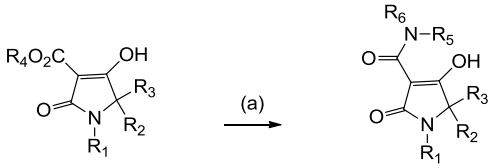
2.4.3.8. Synthesis of **C13**



C13

Yield; 99 % (Oil); **^{1}H NMR** (400 MHz, $CDCl_3$); 4.14 (t, 2H, *J* = 7.6 Hz, C6), 2.48 (s, 2H, C2 or C4), 2.43 (s, 2H, C2 or C4), 1.95 (brs, 3H, C15-C17), 1.72-1.61 (m, 6H, adamantly CH_2), 1.53 (brs, 6H, adamantly CH_2), 1.42 (t, 2H, *J* = 7.6 Hz, C7), 1.14 (s, 6H, C18 and C19). **^{13}C NMR** (100 MHz, $CDCl_3$); 177.2 (C=O), 172.4 (C=O), 60.9 (C6), 45.2 (C2 or C4), 45.0 (C2 or C4), 42.5 (adamantyl CH_2), 42.3 (adamantyl CH_2), 37.0 (CH_2), 32.6 (quart C), 31.7 (quart C), 28.5 (C15-C17), 27.8 (C18 and C19). **MS** (ES^-); 321.16 (M-H); MS (ES^+); 323.25 (M+H), 345.21 (M+Na); **HRMS** (M+Na); calcd for $C_{19}H_{30}Na_1O_4$; 345.2036; found; 345.2035.

3. Synthesis of 3-carboximide tetramic acids

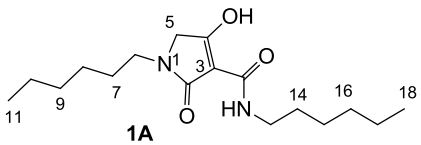


(a) amine (1.0 eq), toluene, reflux;

General procedure: To the solution of 3-alkoxycarbonyl tetramic acid (1.0 eq) in toluene was added amine (1.1 eq) and the mixture was refluxed for 4 hr. After completion of reaction as checked by TLC, concentration *in vacuo* followed by flash column chromatography gave metal-chelated 3-carboxamide tetramic acid. The compound was dissolved in dichloromethane (50 mL) and washed with aqueous HCl (3< pH <5, 50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give the metal free form of 3-carboxamide tetramic acid.

3.1. Synthesis of mono 3-carboximide tetramic acids

3.1.1. Synthesis of **1A**

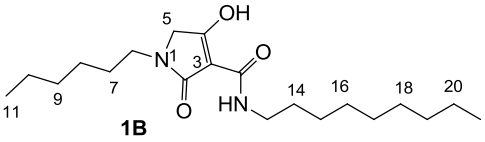


1A

Yield; 41 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (400 MHz, $CDCl_3$); 9.14 (brs, 1H, OH), 7.70 (brs, 1H, NH), 3.90 (s, 2H, C5 AB), 3.68 (s, 2H, C5 CD), 3.39-3.16 (m, 4H, C6 and C13), 1.56-1.51 (m, 4H, C7 and C14), 1.37-1.28 (m, 12H, C8-10 and C15-17), 0.87 (t, 6H, *J* = 6.8 Hz, C11 and C18). **^{13}C NMR** (125 MHz, $CDCl_3$);

189.8 (C4 CD), 181.1 (C4 AB), 175.2 (C2 CD), 169.1 (C2 AB), 166.6 (C12 AB), 166.0 (C12 AB), 98.6 (C3 AB), 85.6 (C3 CD), 55.0 (C5 CD), 49.7 (C5 AB), 41.5 (CH_2), 41.2 (CH_2), 39.6 (CH_2), 38.4 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 29.4 (CH_2), 28.4 (CH_2), 28.0 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 22.5 (CH_2), 13.9 (C11 and C18). **MS** (ES^-); 309.2, **HRMS** (M-H); calcd for $C_{17}H_{29}N_2O_3$; 309.2184; found; 309.2178.

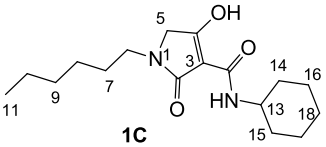
3.1.2. Synthesis of **1B**



1B

Yield; 58 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (400 MHz, $CDCl_3$); 9.44 (brs, 1H, OH), 7.70 (brs, 1H, NH), 3.91 (s, 2H, C5 AB), 3.68 (s, 2H, C5 CD), 3.40-3.30 (m, 4H, C6 and C13), 1.59-1.52 (m, 4H, C7 and C14), 1.35-1.25 (m, 18H, C8-10 and C15-20), 0.89-0.85 (m, 6H, C11 and C21). **^{13}C NMR** (100 MHz, $CDCl_3$, Only AB tautomer); 181.1 (C4), 169.1 (C2), 166.0 (C12), 98.6 (C3), 49.7 (C5), 41.3 (CH_2), 38.4 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 22.5 (CH_2),14.1 (CH_3), 14.0 (CH_3). **MS** (ES^-); 351.3, **HRMS** (M-H); calcd for $C_{20}H_{35}N_2O_3$; 351.2653; found; 351.2657.

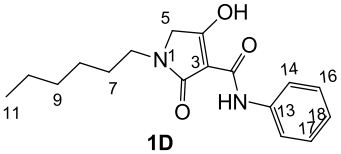
3.1.3. Synthesis of **1C**



1C

Yield; 88 % (oil); Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, $CDCl_3$); 8.88 (brs, 1H, OH), 7.65 (brs, 1H, NH), 3.90 (s, 2H, C5 AB), 3.85-3.81 (m, 1H, C13), 3.67 (s, 2H, C5 CD), 3.38 (t, 2H, *J* = 7.2 Hz, C6), 1.91-1.88 (m, 2H, CH_2), 1.74-1.71 (m, 2H, CH_2), 1.60-1.52 (m, 3H, CH_2), 1.42-1.17 (m, 11H, CH_2), 0.88 (t, 3H, *J* = 6.4 Hz, C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 189.8 (C4 CD), 181.4 (C4 AB), 175.2 (C2 CD), 169.1 (C2 AB), 165.7 (C12 CD), 165.1 (C12 AB), 98.4 (C3 AB), 85.4 (C3 CD), 55.0 (C5 CD), 49.8 (C5 AB), 48.9 (C13 CD), 47.3 (C13 AB), 41.5 (C6 CD), 41.3 (C6 AB), 32.8 (CH_2), 32.7 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 28.4 (CH_2), 28.0 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 24.5 (CH_2), 22.5 (CH_2), 13.9 (C11). **MS** (ES^-); 307.2 (M-H); **HRMS** (M+Na); calcd for $C_{17}H_{28}N_2Na_1O_3$; 331.1992; found; 331.1993.

3.1.4. Synthesis of **1D**

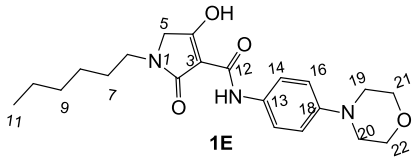


1D

Yield; 90 %; M.P.; 67℃; Form AB: CD = 90: 10**; ^{1}H NMR** (500 MHz, $CDCl_3$); 11.10 (s, 1H, NH), 9.70 (s, 1H, OH AB), 9.30 (s, 1H, OH CD), 7.61 (d, 2H, *J* = 8.0 Hz, C14 and C15 AB), 7.51 (d, 2H, *J* = 7.6 Hz, C14 and C15 CD), 7.34 (dd, 2H, J_1 = 8.0 Hz, J_2 = 7.6 Hz, C16 and C17), 7.34 (dd, 1H, J_1 = 7.6 Hz, J_2 = 7.6 Hz, C18), 3.97 (s, 2H, C5 AB), 3.79 (s, 2H, C5 CD), 3.43 (t, 2H, *J* = 7.2 Hz, C6), 1.58-1.53 (m, 2H, C7), 1.36-1.26 (m, 6H, C8-10), 0.89 (t, 3H, *J* = 6.8 Hz, C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 188.8 (C4 CD), 180.6 (C4 AB), 175.8 (C2 CD), 168.6 (C2 AB), 165.2 (C12 CD), 164.0 (C12 AB), 136.9 (C13 AB), 136.3 (C13 CD), 129.0 (C16 and C17 CD), 128.9 (C16 and C17 AB), 124.7 (C18 CD), 124.4 (C18 AB), 120.5 (C14 and C15 CD), 120.0 (C14 and C15 AB), 99.7 (C3 AB), 87.2 (C3 CD), 55.4 (C5 CD), 49.4 (C5 AB), 42.2 (C6 CD), 41.3 (C6 AB),

31.3 (C9 AB), 31.2 (C9 CD), 28.3 (C7 AB), 27.9 (C7 CD), 26.3 (C8 AB), 26.2 (C8 CD), 22.4 (C10), 13.9 (C11). **MS** (ES^-); 301.1, **HRMS** (M+H); calcd for $C_{17}H_{23}N_2O_3$; 303.1703; found; 303.1700.

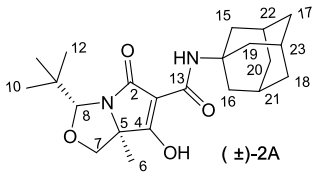
3.1.5. Synthesis of **1E**



Yield; 66 %; M.P.; 97 ℃; Form AB: CD = 90: 10**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.81 (brs, 1H, NH or OH), 9.55 (brs, 1H, NH or OH AB), 9.25 (brs, 1H, NH or OH AB), 7.51 (d, 2H, *J* = 8.8 Hz, C14 and C15 AB), 7.39 (d, 2H, *J* = 8.8 Hz, C14 and C15 CD), 6.91 (d, 2H, *J* = 8.8 Hz, C16 and C17), 3.98 (s, 2H, C5 AB), 3.87 (t, 4H, *J* = 4.8 Hz, C21 and C22), 3.77 (s, 2H, C5 CD), 3.43 (t, 2H, *J* = 7.2 Hz, C6), 3.13 (t, 4H, *J* = 4.8 Hz, C19 and C20), 1.59-1.54 (m, 2H, C7), 1.34-1.25 (m, 6H, C8-10), 0.89 (t, 3H, *J* = 6.8 Hz, C11). **^{13}C NMR** (100 MHz, $CDCl_3$, Only AB tautomer); 180.5 (C4), 168.8 (C2), 163.7 (C12), 148.2 (C18), 129.7 (C13), 121.4 (C14 and C15), 116.3 (C16 and C17), 99.6 (C3), 66.7 (C21 and C22), 49.7 (C5), 49.5 (C19 and C20), 41.4 (C6), 31.4 (CH_2), 28.4 (CH_2), 26.4 (CH_2), 22.5 (CH_2), 14.0 (C11). **MS** (ES^-); 386.22, **HRMS** (M-H); calcd for $C_{21}H_{28}N_3O_4$; 386.2085; found; 386.2092.

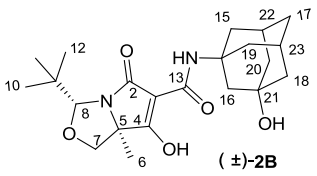
3.2. Synthesis of bicyclic 3-carboximide tetramic acid

3.2.1. Synthesis of (±)-**2A**



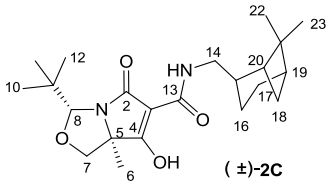
Yield; 31 % (oil); Form AB: CD = 75: 25**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.90 (brs, 1H, NH or OH CD), 7.42 (brs, 1H, NH or OH AB), 4.62 (s, 1H, C8), 3.86 (d, 1H, *J* = 8.3 Hz, C7), 3.41 (d, 1H, *J* = 8.3 Hz, C7), 2.11 (brs, 3H, C21-C23), 2.05 (brs, 6H, C15-C16 and C19), 1.69 (brs, 6H, C17-C18 and C20), 1.55 (s, 3H, C6 AB), 1.49 (s, 3H, C6 CD), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 190.5 (C4), 176.0 (C2), 166.2 (C13), 97.2 (C8), 95.6 (C3), 72.1 (C7), 69.7 (C5), 52.9 (C14), 41.6 (CH_2), 36.1 (CH_2), 34.6 (C9), 29.3 (C21-C23), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 387.24 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{31}N_2O_4$; 387.2289; found; 387.2291.

3.2.2. Synthesis of (±)-**2B**



Yield; 64 %; M.P.; 139 ℃; Form AB: CD = 75: 25; **^{1}H NMR** (500 MHz, $CDCl_3$); 7.46 (brs, 1H, NH or OH), 4.63 (s, 1H, C8 CD), 4.61 (s, 1H, C8 AB), 3.87 (d, 1H, *J* = 8.2 Hz, C7), 3.41 (d, 1H, *J* = 8.2 Hz, C7), 2.29 (brs, 2H, C22 and C23), 2.05-1.91 (m, 6H, CH_2), 1.70-1.49 (m, 9H, C6 and CH_2), 1.00 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 189.5 (C4), 175.9 (C2), 166.0 (C13), 97.2 (C8), 96.5 (C3), 72.2 (C7), 69.5 (quart C), 69.1 (quart C), 54.8 (C14), 48.9 (CH_2), 43.9 (CH_2), 40.3 (CH_2), 34.7 (CH_2), 34.6 (C9), 30.5 (C22 and C23), 25.5 (C10-C12), 20.5 (C6). **MS** (ES^-); 403.24 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{31}N_2O_5$; 403.2238; found; 403.2237.

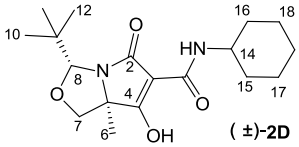
3.2.3. Synthesis of (±)-**2C**



(±)-**2C**

Yield; 44 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (500 MHz, $CDCl_3$); 9.20 (brs, 1H, NH or OH), 7.62 (brs, 1H, NH or OH), 4.64 (s, 1H, C8), 3.88 (d, 1H, *J* = 8.5 Hz, C7 AB), 3.80 (d, 1H, *J* = 8.5 Hz, C7 CD), 3.43 (d, 1H, *J* = 8.5 Hz, C7), 3.35-3.33 (m, 2H, C14), 2.38-2.41 (m, 1H), 2.28-2.22 (m, 1H), 2.00-1.85 (m, 5H), 1.57 (s, 3H, C6), 1.50 (brs, 1H), 1.19 (s, 3H, C22), 1.04-1.02 (m, 12H, C10-C12 and C23), 0.88 (d, 1H, *J* = 10.0 Hz). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 189.2 (C4), 175.8 (C2), 166.2 (C13), 97.2 (C8), 97.0 (C3), 72.2 (C7), 69.7 (C5), 44.3 and 44.2 (C14), 43.6 and 43.5 (C15), 41.2 (C19 and C20), 38.6 (C21), 34.7 (C9), 33.2 (CH_2), 27.9 (C22), 25.9 (CH_2), 25.5 (C10-C12), 23.1 (C23), 20.6 (C6), 19.7 (CH_2). **MS** (ES^-); 387.26 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{33}N_2O_4$; 389.2446; found; 389.2447.

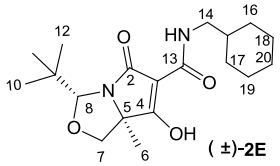
3.2.4. Synthesis of (±)-**2D**



(±)-**2D**

Yield; 39 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (400 MHz, $CDCl_3$); 8.99 (brs, 1H, OH), 7.84 (d, 1H, *J* = 8.0 Hz, NH CD), 7.48 (d, 1H, *J* = 8.0 Hz, NH AB), 4.66 (s, 1H, C8 CD), 4.64 (s, 1H, C8 AB), 3.88 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.84-3.76 (m, 1H, C14 and 1H C7 CD), 3.43 (d, 1H, *J* = 8.3 Hz, C7), 1.94-1.91 (m, 2H, CH_2), 1.78-1.72 (m, 2H, CH_2), 1.64-1.59 (m, 1H, CH_2), 1.58 (s, 3H, C6 AB), 1.51 (s, 3H, C6 CD), 1.44-1.16 (m, 5H, CH_2), 1.02 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 189.8 (C4), 175.8 (C2), 165.5 (C13), 97.2 (C8), 95.8 (C3), 72.2 (C7), 69.7 (C5), 47.9 (C14), 34.7 (C9), 32.8 (CH_2), 32.6 (CH_2), 25.5 (C10-C12), 25.3 (CH_2), 24.6 (CH_2), 20.6 (C6). **MS** (ES^-); 335.21 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{27}N_2O_4$; 335.1976; found; 335.1967.

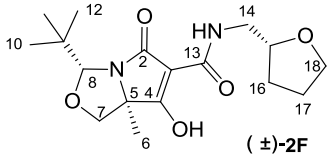
3.2.5. Synthesis of (±)-**2E**



(±)-**2E**

Yield; 39 %; M.P.; 139℃; Form AB: CD = 99: 1**;** **^{1}H NMR** (400 MHz, acetone-d_6); 6.07 (brs, 2H, NH and OH), 4.58 (s, 1H, C8), 3.95 (d, 1H, *J* = 8.1 Hz, C7), 3.50 (d, 1H, *J* = 8.1 Hz, C7), 3.25 (brs, 2H, C14), 1.76-1.65 (m, 6H, C15 and CH_2), 1.54 (s, 3H, C6), 1.32-1.18 (m, 5H, CH_2), 1.00 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, acetone-d_6); 191.0 (C4), 176.1 (C2), 167.2 (C13), 97.8 (C8), 96.9 (C3), 72.8 (C7), 70.3 (C5), 45.2 (C14), 38.8 (C15), 35.2 (C9), 31.4 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 25.9 (C10-C12), 21.1 (C6). **MS** (ES^-); 349.21 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{29}N_2O_4$; 349.2133; found; 349.2134.

3.2.6. Synthesis of (±)-**2F**

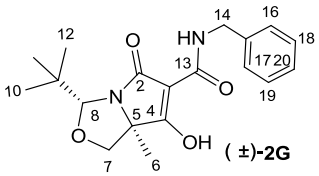


(±)-**2F**

Yield; 42 %; M.P.; 81 ℃; Form AB: CD = 99: 1**;** **^{1}H NMR** (400 MHz, $CDCl_3$,); 7.75 (br s, 1H, NH or OH), 4.63 (s, 1H, C8), 4.05-4.00 (m, 1H, C15), 3.90-3.86 (m, 2H, C7 and C18), 3.78-3.73 (m, 1H, C18), 3.60-3.51 (m, 1H, C14), 3.42 (d, *J* = 8.2 Hz) and 3.40 (d, 1H, *J* = 8.2 Hz, C7), 3.38-3.30 (m, 1H, C14), 2.04-1.53

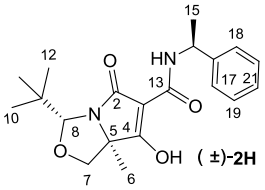
(m, 7H, C6, C16 and C17), 1.00 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$,); 188.5 (C4), 175.4 and 175.3 (C2), 166.3 (C13), 97.1 and 97.2 (C8), 97.0 and 97.1 (C3), 77.0 (C), 72.3 and 72.2 (C7), 69.4 (C5), 68.2 (C18), 42.4 (C14), 34.7 (C9), 28.8 (C16), 25.8 (C17), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 337.19 (M-H); **HRMS** (M-H); calcd for $C_{17}H_{25}N_2O_5$; 337.1769; found; 337.1770.

3.2.7. Synthesis of (±)-**2G**



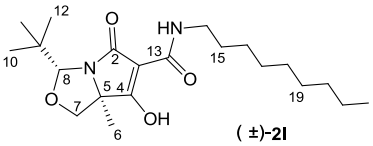
Yield; 39 % (oil); Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, $CDCl_3$); 8.11 (brs, 1H, NH or OH CD), 7.88 (brs, 1H, NH or OH AB), 7.40-7.27 (m, 5H, C16-C20), 4.67 (s, 1H, C8 CD), 4.63 (s, 1H, C8 AB), 4.59 (dd, 2H, J_1 = 10.0 Hz, J_2 = 6.3 Hz, C14 CD), 4.53 (d, 2H, J = 6.3 Hz, C14 AB), 3.91 (d, 1H, J = 8.1 Hz, C7 AB), 3.81 (d, 1H, J = 8.1 Hz, C7 CD), 3.45 (d, 1H, J = 8.1 Hz, C7 AB), 3.42 (d, 1H, J = 8.1 Hz, C7 CD), 1.60 (s, 3H, C6 AB), 1.51 (s, 3H, C6 AB), 1.03 (s, 9H, C10-C12 CD), 1.01 (s, 9H, C10-C12 AB). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 188.3 (C4), 175.4 (C2), 165.9 (C13), 137.1 (C15), 128.8 (C18 and C19), 127.8 (C16 and C17), 127.7 (C20), 97.3 (C3), 97.1 (C8), 72.3 (C7), 69.4 (C5), 42.6 (C14), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 343.17 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{23}N_2O_4$; 343.1663; found; 343.1667.

3.2.8. Synthesis of (±)-**2H**



Yield; 40 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$, two set of signals in some case caused by two diastereomers); 7.87 (brs, 1H, NH or OH), 7.42-7.28 (m, 5H, C17-C21), 5.22-5.13 (m, 1H, C14), 4.66 (s) and 4.64 (s, 1H, C8), 3.90 (d, J = 8.2 Hz) and 3.88 (d, 1H, J = 8.2 Hz, C7), 3.45 (d, J = 8.2 Hz) and 3.42 (d, 1H, J = 8.2 Hz, C7), 1.59-1.55 (m, 6H, C6 and C15), 1.03 (s) and 1.02 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, two set of signals in some case caused by two diastereomers); 187.7 and 187.6 (C4), 174.6 and 174.5 (C2), 164.3 and 164.2 (C13), 141.5 and 141.4 (C16), 127.8 and 127.7 (C19 and C20), 126.6 (C21), 125.0 and 124.9 (C17 and C18), 96.2 and 96.1 (C8), 96.0 and 95.9 (C3), 71.2 and 71.1 (C7), 68.5 and 68.4 (C5), 47.5 and 47.4 (C14), 33.7 (C9), 24.7 (C10-C12), 21.4 and 21.2 (C15), 19.6 and 19.5 (C6). **MS** (ES^+); 359.20 (M+H), 381.19 (M+Na); **HRMS** (M+Na); calcd for $C_{20}H_{26}N_2Na_1O_4$; 381.1785; found; 381.1775.

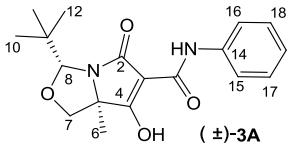
3.2.9. Synthesis of (±)-**2I**



Yield; 19 %; M.P.;163 ℃; Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, $CDCl_3$); 8.92 (brs, 1H, NH or OH), 7.55 (brs, 1H, NH or OH CD), 4.66 (s, 1H, C8 CD), 4.64 (s, 1H, C8 AB), 3.89 (d, 1H, J = 8.3 Hz, C7 AB), 3.81 (d, 1H, J = 8.3 Hz, C7 CD), 3.45-3.32 (m, 3H, C7 and C14), 1.63-1.51 (m, 5H, C6 and C15), 1.30-1.22 (m, 12H, C16-C21), 1.02 (s, 9H, C10-C12), 0.88 (t, 3H, J = 6.1 Hz, C22). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 189.2 (C4), 175.7 (C2), 166.2 (C13), 97.1 (C8), 96.2 (C3), 72.2 (C7), 69.6 (C5), 38.8 (C14), 34.7 (C9), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 25.5 (C10-C12), 22.6 (CH_2), 20.6 (C6), 14.1 (C22). **MS**

(ES$^-$); 379.26 (M-H), **HRMS** (M-H); calcd for $C_{21}H_{35}N_2O_4$; 379.2602; found; 379.2607.

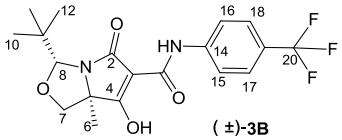
3.2.10. Synthesis of (±)-**3A**



(±)-**3A**

Yield; 31 % (oil); Form AB: CD = 95: 5**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.42 (brs, 2H, NH & OH), 7.59 (d, 2H, *J* = 8.3 Hz, C15 and C16), 7.36 (dd, 2H, J_1 = 8.3 Hz, J_2 = 7.7 Hz, C17 and C18), 7.16 (t, 1H, *J* = 7.7 Hz, C19), 4.69 (s, 1H, C8), 3.95 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.87 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.49 (d, 1H, *J* = 8.3 Hz, C7), 1.64 (s, 3H, C6 AB), 1.58 (s, 3H, C6 CD),1.06 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 187.8 (C4), 175.4 (C2), 164.1 (C13), 136.5 (C14), 129.1 (C17 and C18), 124.9 (C19), 120.3 (C15 and C16), 98.4 (C3), 97.2 (C8), 72.3 (C7), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES$^-$); 329.15 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{21}N_2O_4$; 329.1507; found; 329.1506.

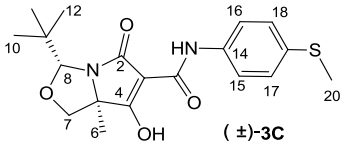
3.2.11. Synthesis of (±)-**3B**



(±)-**3B**

Yield; 42 %; M.P.; 157 ℃; Form AB: CD =99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.64 (brs, 1H, NH or OH), 7.73 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.60 (d, 2H, *J* = 8.6 Hz, Ar-H), 4.69 (s, 1H, C8), 3.96 (d, 1H, *J* = 8.3 Hz, C7), 3.49 (d, 1H, *J* = 8.3 Hz, C7), 1.65 (s, 3H, C6), 1.06 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$); 187.7 (C4), 175.2 (C2), 164.3 (C13), 139.7 (C14), 126.3 (C17 and C18), 119.9 (C15 and C16), 98.6 (C3), 97.3 (C8), 72.3 (C7), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES$^-$); 397.14 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{20}F_3N_2O_4$; 397.1381; found; 397.1382.

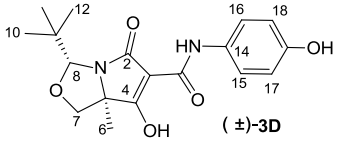
3.2.12. Synthesis of (±)-**3C**



(±)-**3C**

Yield; 45 %; M.P.; 132 ℃; Form AB: CD = 90: 10**; ^{1}H NMR** (400 MHz, $CDCl_3$); 10.95 (brs, 1H, NH or OH), 9.65 (brs, 1H, NH or OH CD), 9.39 (brs, 1H, NH or OH AB), 7.78 (d, 2H, *J* = 8.3 Hz, C17 and C18 CD), 7.63 (d, 2H, *J* = 8.3 Hz, C15 and C16 CD), 7.51 (d, 2H, *J* = 8.3 Hz, C17 and C18 AB), 7.24 (d, 2H, *J* = 8.3 Hz, C15 and C16 AB), 4.67 (s, 1H, C8), 3.93 (d, 1H, *J* = 8.3 Hz, C7), 3.47 (d, 1H, *J* = 8.3 Hz, C7), 2.72 (s, 3H, C20 CD), 2.47 (s, 3H, C20 AB), 1.62 (s, 3H, C6), 1.04 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 187.7 (C4), 175.3 (C2), 163.9 (C13), 134.6 (quart Ar-C), 134.0 (quart Ar-C), 127.7 (C17 and C18), 120.8 (C15 and C16), 98.4 (C3), 97.2 (C8), 72.3 (C7), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6), 16.4 (C20). **MS** (ES$^-$); 375.14 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{23}N_2O_4S_1$; 375.1384; found; 375.1374.

3.2.13. Synthesis of (±)-**3D**

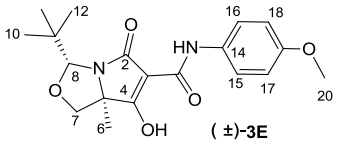


(±)-**3D**

Yield; 43 % (oil); Form AB: CD = 95: 5**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.27 (brs, 1H, NH or OH CD), 9.27 (brs, 1H, NH or OH AB), 7.39 (d, 2H, *J* = 8.2 Hz, C15 and C16 AB), 7.30 (d, 2H, *J* = 8.2 Hz, C15 and C16 CD), 6.98 (brs, 1H, NH or

OH), 6.80 (d, 2H, *J* = 8.2 Hz, C17 and C18), 4.69 (s, 1H, C8), 3.94 (d, 1H, *J* = 8.2 Hz, C7 AB), 3.87 (d, 1H, *J* = 8.2 Hz, C7 AB), 3.48 (d, 1H, *J* = 8.2 Hz, C7), 1.63 (s, 3H, C6 AB), 1.57 (s, 3H, C6 CD), 1.05 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 187.9 (C4), 175.5 (C2), 163.9 (C13), 153.1 (C19), 129.3 (C14), 122.4 (C15 and C16), 115.8 (C17 and C18), 98.1 (C3), 97.2 (C8), 72.3 (C7), 69.4 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 345.16 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{21}N_2O_5$; 345.1456; found; 345.1444.

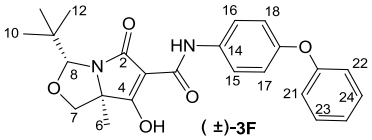
3.2.14. Synthesis of (±)-**3E**



(±)-3E

Yield; 38 %; M.P.; 129 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.30 (br s, 1H, NH or OH), 7.49 (d, 2H, *J* = 8.6 Hz, C17 and C18), 6.89 (d, 2H, *J* = 8.6 Hz, C15 and C16), 4.68 (s, 1H, C8), 3.94 (d, 1H, *J* = 8.3 Hz, C7), 3.81 (s, 3H, C20), 3.48 (d, 1H, *J* = 8.3 Hz, C7), 1.63 (s, 3H, C6), 1.05 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 187.6 (C4), 175.5 (C2), 163.8 (C13), 156.9 (C19), 129.5 (C14), 121.9 (C15 and C16), 114.3 (C17 and C18), 98.1 (C3), 97.2 (C8), 72.3 (C7), 69.3 (C5), 55.4 (C20), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 359.16 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{23}N_2O_5$; 359.1612; found; 359.1617.

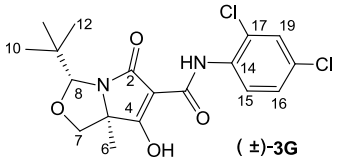
3.2.15. Synthesis of (±)-**3F**



(±)-3F

Yield; 51 %; M.P.; 188 ℃; Form AB: CD = 90: 10**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.39 (brs, 1H, NH or OH), 7.55 (d, 2H, *J* = 8.9 Hz, C15 and C16 AB), 7.44 (d, 2H, *J* = 8.9 Hz, C15 and C16 CD), 7.34 (t, 2H, *J* = 7.9 Hz, C23 and C24), 7.11 (t, 1H, *J* = 7.4 Hz, C25), 7.05-7.00 (m, 4H, C17, C18, C21 and C22), 4.69 (s, 1H, C8), 3.95 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.88 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.49 (d, 1H, *J* = 8.3 Hz, C7), 1.65 (s, 3H, C6 AB), 1.58 (s, 3H, C6 CD), 1.06 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 187.7 (C4), 175.4 (C2), 163.9 (C13), 157.2 (quart C), 154.2 (quart C), 131.9 (quart C), 129.8 (tert C), 123.3 (C25), 121.9 (tert C), 119.5 (tert C), 118.7 (tert C), 98.3 (C3), 97.2 (C8), 72.3 (C7), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 421.19 (M-H); **HRMS** (M-H); calcd for $C_{24}H_{25}N_2O_5$; 421.1769; found; 421.1764.

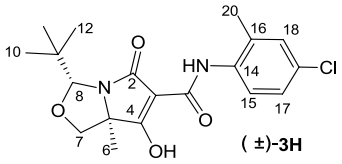
3.2.16. Synthesis of (±)-**3G**



(±)-3G

Yield; 51 %; M.P.; 184 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.98 (brs, 1H, NH or OH), 9.10 (brs, 1H, NH or OH), 8.34 (d, 1H, *J* = 8.9 Hz, C15), 7.43 (d, 1H, *J* = 2.4 Hz, C19), 7.26 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.4 Hz, C16), 4.72 (s, 1H, C8), 3.95 (d, 1H, *J* = 8.3 Hz, C7), 3.49 (d, 1H, *J* = 8.3 Hz, C7), 1.65 (s, 3H, C6), 1.05 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$); 187.6 (C4), 174.9 (C2), 164.2 (C13), 132.7 (quart Ar-C), 129.77 (quart Ar-C), 129.2 (C19), 127.7 (C15), 124.41 (quart Ar-C), 122.6 (C16), 98.9 (C3), 97.2 (C8), 72.3 (C7), 69.2 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 397.09 (M-H), **HRMS** (M-H); calcd for $C_{18}H_{19}Cl_2N_2O_4$; 397.0727; found; 397.0731.

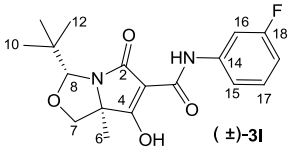
3.2.17. Synthesis of (±)-**3H**



(±)-3H

Yield; 56 %; M.P.; 149 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, DMSO-*d*6): 10.08 (brs, 1H, NH or OH), 8.12 (d, 1H, *J* = 8.6 Hz, C15), 7.32 (s, 1H, C18), 7.24 (d, 1H, *J* = 8.6 Hz, C17), 4.60 (s, 1H, C8), 3.92 (d, 1H, *J* = 8.1 Hz, C7), 3.49 (d, 1H, *J* = 8.1 Hz, C7), 2.27 (s, 3H, C20), 1.49 (s, 3H, C6), 0.97 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, DMSO-*d*6): 185.4 (C4), 176.9 (C2), 160.9 (C13), 135.1 (quart Ar-C), 129.8 (C18), 129.7 (quart Ar-C), 127.3 (quart Ar-C), 126.1 (C17), 121.9 (C15), 97.7 (C3), 96.5 (C8), 71.7 (C7), 68.7 (C5), 34.4 (C9), 25.5 (C10-C12), 20.8 (C6), 17.3 (C20). **MS** (ES^-); 377.14 (M-H), **HRMS** (M-H); calcd for $C_{19}H_{22}Cl_1N_2O_4$; 377.1274; found; 377.1267.

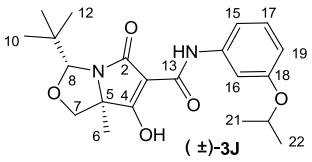
3.2.18. Synthesis of (±)-**3I**



(±)-3I

Yield; 52 %; M.P.; 161 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.57 (d, 1H, *J* = 10.0 Hz, C15), 7.31-7.19 (m, 2H, C16 and C18), 7 6.84 (t, 1H, *J* = 7.7 Hz, C17), 4.68 (s, 1H, C8), 3.94 (d, 1H, *J* = 8.2 Hz, C7), 3.47 (d, 1H, *J* = 8.2 Hz, C7), 1.63 (s, 3H, C6), 1.05 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 187.6 (C4), 175.3 (C2), 164.1 (C13), 162.9 (d, $J_{C\text{-}F}$ = 244 Hz, C18), 138.1 (d, $J_{C\text{-}F}$ = 10.4 Hz, C14), 130.2 (d, $J_{C\text{-}F}$ = 8.5 Hz, C17), 115.5 (C15), 111.7 (d, $J_{C\text{-}F}$ = 21.8 Hz, C16 or C19), 107.9 (d, $J_{C\text{-}F}$ = 26.7 Hz, , C16 or C19), 98.4 (C3), 97.3 (C8), 72.3 (C7), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 347.15 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{20}F_1N_2O_4$; 347.1413; found; 347.1414.

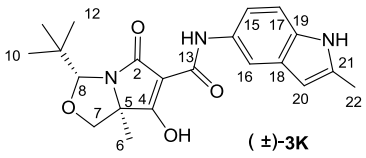
3.2.19. Synthesis of (±)-**3J**



(±)-3J

Yield;58 % (oil); Form AB: CD = 90: 10; **^{1}H NMR** (400 MHz, $CDCl_3$); 9.38 (brs, 1H, NH or OH), 9.19 (brs, 1H, NH or OH), 7.31-7.16 (m, 2H, C16 and C17), 7.08 (d, 1H, *J* = 7.6 Hz, C15 AB), 7.00 (d, 1H, *J* = 7.6 Hz, C15 CD), 6.73 (dd, 2H, J_1 = 8.4 Hz, J_2 = 2.1 Hz, C19 CD), 6.68 (dd, 2H, J_1 = 8.4 Hz, J_2 = 2.1 Hz, C19 AB), 4.68 (s, 1H, C8), 4.59-4.50 (m, 1H, C20), 3.94 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.87 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.48 (d, 1H, *J* = 8.3 Hz, C7), 1.63 (s, 3H, C6 AB), 1.57 (s, 3H, C6 CD), 1.34 (d, 6H, *J* = 6.1 Hz, C21 and C22), 1.05 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 187.8 (C4), 175.4 (C2), 164.1 (C13), 158.5 (C18), 137.7 (C14), 129.8 (C17), 112.8 (Ar-C), 112.4 (Ar-C), 107.8 (Ar-C), 98.4 (C3), 97.2 (C8), 72.3 (C7), 70.0 (C20), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 22.0 (C21 and C22), 20.6 (C6). **MS** (ES^-); 387.21 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{27}N_2O_5$; 387.1925; found; 387.1921.

3.2.20. Synthesis of (±)-**3K**

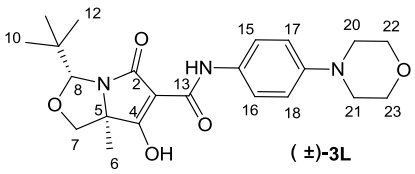


(±)-3K

Yield; 42 %; M.P.; 141 ℃; Form AB: CD = 90: 10**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.31 (brs, 1H, NH or OH), 7.92-7.86 (m, 1H, Ar-H AB), 7.73-7.70 (m, 1H, Ar-H CD), 7.48 (brs, 1H, C16), 6.98-6.90 (m, 2H, Ar-H), 4.70 (s, 1H, C8 AB),

4.69 (s, 1H, C8 CD), 3.95 (d, 2H, *J* = 8.3 Hz, C7 AB), 3.88 (d, 2H, *J* = 8.3 Hz, C7 CD), 3.50 (d, 1H, *J* = 8.3 Hz, C7), 2.37 (s, 3H, C22 CD), 2.36 (s, 3H, C22 AB), 1.65 (s, 3H, C6 AB), 1.59 (s, 3H, C6 CD), 1.06 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 187.7 (C4), 175.4 (C2), 164.2 (C13), 131.8 (quart C), 130.6 (quart C), 124.0 (quart C), 123.9 (quart C), 117.3 (tert C), 117.1 (tert C), 113.3 (tert C), 113.1 (tert C), 98.5 (C3), 97.2 (C8), 72.3 (C7), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 20.5 (C6), 17.9 (C22). **MS** (ES^-); 382.19 (M-H), **HRMS** (M-H); calcd for $C_{21}H_{24}N_3O_4$; 382.1772; found; 382.1777.

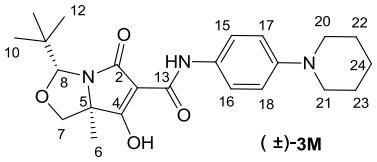
3.2.21. Synthesis of (±)-**3L**



(±)-3L

Yield; 21 %; M.P.; 119 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (500 MHz, $CDCl_3$); 9.49 (brs, 1H, NH or OH), 7.64 (2H, d, *J* = 8.2 Hz, C15 and C16), 7.48 (brs, 2H, C17 and C18), 4.66 (s, 1H, C8), 4.14 (brs, 4H, C22 and C23), 3.93 (d, 1H, *J* = 8.2 Hz, C7), 3.46 (d, 1H, *J* = 8.2 Hz, C7), 3.36 (brs, 4H, C20 and C21), 1.62 (s, 3H, C6), 1.03 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 187.8 (C4), 175.3 (C2), 164.0 (C13), 121.6 (C15 and C16), 119.9 (C17 and C18), 98.3 (C3), 97.2 (C8), 72.3 (C7), 69.3 (C5), 64.9 (C22 and C23), 53.0 (C20 and C21), 34.7 (C9), 25.4 (C10-C12), 20.6 (C6). **MS** (ES^-); 414.21 (M-H), **HRMS** (M-H); calcd for $C_{22}H_{28}N_3O_5$; 414.2034; found; 414.2033.

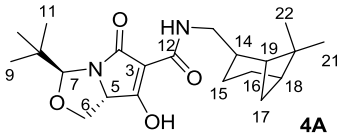
3.2.22. Synthesis of (±)-**3M**



(±)-3M

Yield; 33 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.62 (br s, 1H, NH or OH), 7.89-7.77 (m, 2H, C15 and C16), 7.69 (d, 2H, *J* = 8.5 Hz, C7 and C18), 4.66 (s, 1H, C8), 3.93 (d, 1H, *J* = 8.2 Hz, C7), 3.47-3.41 (m, 5H, C7, C20 and C21), 2.31-1.23 (m, 9H, C6 and C22-C24), 1.03 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 187.9 (C4), 175.3 (C2), 164.2 (C13), 139.1 (quart Ar-C), 137.9 (quart Ar-C), 122.2 (C15 and C16), 121.3 (C17 and C18), 98.3 (C3), 97.3 (C8), 72.2 (C7), 69.3 (C5), 57.3 (C20 and C21), 34.7 (C9), 25.4 (C10-C12), 23.1 (C22 and C23), 21.8 (C24), 20.6 (C6). **MS** (ES^-); 412.23 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{30}N_3O_4$; 412.2242; found; 412.2247.

3.2.23. Synthesis of **4A**

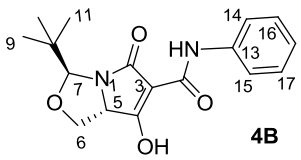


4A

Yield; 43 %; M.P.; 144 ℃; Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, $CDCl_3$); 11.56 (brs, 1H, NH or OH), 7.93 (brs, 1H, NH or OH CD), 7.53 (brs, 2H, NH or OH AB), 4.83 (s, 1H, C7 CD), 4.79 (s, 1H, C7 AB), 4.37 (dd, 1H, J_1 = 9.2 Hz, J_2 = 7.0 Hz, C5 AB), 4.28 (dd, 1H, J_1 = 7.0 Hz, J_2 = 6.8 Hz, C6 AB), 4.23 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz, C5 CD), 4.11 (dd, 1H, J_1 = 7.0 Hz, J_2 = 6.8 Hz, C6 CD), 3.47-3.33 (m, 3H, C6 and C13), 2.39-2.21 (m, 2H), 2.02-1.83 (m, 5H), 1.53-1.45 (m, 1H), 1.19 (s, 3H, C21), 1.03 (s, 3H, C22), 0.96 (s, 9H, C9-C11), 0.93-0.87 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 186.7 (C4), 175.0 (C2), 166.2 (C12), 96.7 (C3), 94.7 (C7), 67.2 (C6), 63.4 (C5), 44.2 (C13), 43.4 (CH), 41.2 (CH), 38.6 (C20), 35.8 (C8), 33.2 (CH_2), 27.9 (C21), 25.8

(CH_2), 24.6 (C9-C11), 23.0 (C22), 19.7 (CH_2). **MS** (ES^-); 375.24 (M-H); MS (ES^+); 377.11 (M+H); **HRMS** (M+H); calcd for $C_{21}H_{31}N_2O_4$; 375.2289; found; 375.2285.

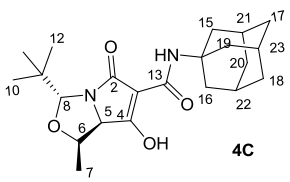
3.2.24. Synthesis of **4B**



4B

Yield; 80 %; M.P.; 156 ℃; Form AB: CD = 90: 10**;** **^{1}H NMR** (400 MHz, $CDCl_3$); 10.53 (brs, 1H, NH or OH), 9.53 (brs, 1H, NH or OH CD), 9.36 (brs, 2H, NH or OH AB), 7.59 (d, 2H, *J* = 8.4 Hz,Ar-H, AB), 7.47 (d, 2H, *J* = 8.4 Hz,Ar-H, CD), 7.41-7.14 (m, 3H, Ar-H), 4.87 (s, 1H, C7 CD), 4.85 (s, 1H, C7 AB), 4.49 (dd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz, C5 AB), 4.36-4.29 (m, 1H, C6 AB and 1H C5 CD), 4.11 (dd, 1H, J_1 = 8.0 Hz, J_2 = 6.8 Hz, C6 CD), 3.52-3.43 (m, 1H, C6), 1.01 (m, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 184.7 (C4), 174.5 (C2), 163.9 (C12), 136.5 (C13), 129.1 (C16 and C17), 125.0 (C18), 120.3 (C14 and C15), 99.5 (C3), 94.8 (C7), 67.4 (C6), 62.7 (C5), 35.8 (C8), 24.6 (C9-C11). **MS** (ES^-); 315.16 (M-H), **HRMS** (M-H); calcd for $C_{17}H_{19}N_2O_4$; 315.1350; found; 315.1352.

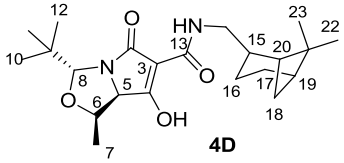
3.2.25. Synthesis of **4C**



4C

Yield; 57 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (500 MHz, $CDCl_3$); 7.37 (brs, 1H, NH or OH), 5.57 (brs, 1H, NH or OH), 4.80 (s, 1H, C8 CD), 4.77 (s, 1H, C8 AB), 3.81 (d, 1H, *J* = 8.8 Hz, C5 AB), 3.67-3.62 (m, 1H, C6), 3.55 (d, 1H, *J* = 9.1 Hz, C5 CD), 2.14 (brs, 3H, C21-C23 CD), 2.11 (brs, 3H, C21-C23 AB), 2.06 (brs, 6H, C15-C16 and C19), 1.70 (brs, 6H, C17, C18 and C20), 1.45 (d, 3H, *J* = 7.3 Hz, C7 AB), 1.454(d, 3H, *J* = 7.3 Hz, C7 CD), 0.97 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 186.7 (C4), 175.1 (C2), 166.0 (C13), 96.7 (C3), 94.7 (C8), 75.7 (C6), 68.8 (C5), 52.8 (C14), 41.6 (CH_2), 36.1 (CH_2), 29.3 (C21-C23), 24.7 (C10-C12), 17.3 (C7). **MS** (ES^-); 387.24 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{31}N_2O_4$; 387.2289; found; 387.2290.

3.2.26. Synthesis of **4D**

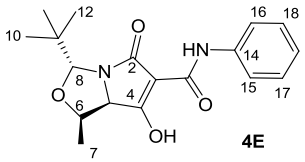


4D

Yield; 39 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (500 MHz, $CDCl_3$); 9.95 (brs, NH or OH), 7.91 (brs, 1H, NH or OH CD), 7.53 (brs, 1H, NH or OH AB), 4.79 (s, 1H, C8 CD), 4.77 (s, 1H, C8 AB), 3.84 (d, 1H, *J* = 8.8 Hz, C5 AB), 3.66-3.61 (m, 1H, C6), 3.55 (d, 1H, *J* = 9.1 Hz, C5 CD), 3.46-3.28 (m, 2H, C14), 2.40-2.33 (m, 1H), 2.27-2.21 (m, 1H), 1.98-1.85 (m, 5H), 1.52-1.42 (m, 4H, C7 and CH_2), 1.19 (s, 3H, C22 CD), 1.18 (s, 3H, C22 AB), 1.03 (s, 3H, C23), 0.96 (s, 9H, C10-C12), 0.88 (d, 1H, *J* = 9.5 Hz). **^{13}C NMR** (125 MHz, $CDCl_3$); 191.0 (C4 CD), 185.4 (C4 AB), 181.0 (C2 CD), 174.8 (C2 AB), 166.8 (C13 CD), 166.0 (C13 AB), 97.2 (C3), 94.7 (C8 CD), 94.5 (C8 AB), 75.6 (C6 AB), 74.8 (C6 CD), 72.4 (C5 CD), 68.6 (C5 AB), 45.2 (C14 CD), 44.2 (C14 AB), 43.4 (C15 AB), 43.2 (C15 CD), 41.2 (C19 and C20 AB), 41.1 (C19 and C20 CD), 38.62 (C21), 35.5 (C9 AB), 35.4 (C9 CD), 33.2 (CH_2 AB), 33.0 (CH_2 CD), 27.9 (C22 AB), 27.8 (C22 CD), 25.9 (CH_2 AB), 25.8

(CH_2 CD), 24.7 (C10-C12 CD), 24.6 (C10-C12 AB), 23.1 (C23 AB), 23.0 (C23 CD), 19.7 (CH_2 AB), 19.5 (CH_2 CD), 17.4 (C7 CD), 17.3 (C7 AB). **MS** (ES^-); 387.26 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{33}N_2O_4$; 389.2446; found; 389.2439.

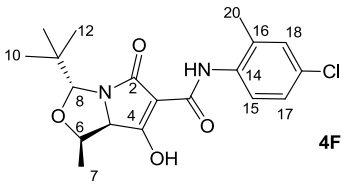
3.2.27. Synthesis of **4E**



4E

Yield; 20 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.37 (brs, 1H, NH or OH), 8.50 (brs, 1H, NH or OH), 7.59 (2H, d, *J* = 7.8. Hz, C15 and C16), 7.35 (t, 2H, *J* = 7.8 Hz, C17 and C18), 7.16 (t, 1H, *J* = 7.8 Hz, C19), 4.84 (s, 1H, C8), 3.97 (d, 1H, *J* = 8.6 Hz, C5), 3.74-3.67 (m, 1H, C6), 1.49 (d, 3H, *J* = 5.8 Hz, C7), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$); 183.9 (C4), 174.4 (C2), 163.9 (C13), 136.5 (C14), 129.1 (C17 and C18), 124.9 (C19), 120.3 (C15 and C16), 99.6 (C3), 94.8 (C8), 75.9 (C6), 68.1 (C5), 35.6 (C9), 24.7 (C10-C12), 17.2 (C7). **MS** (ES^-); 329.15 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{21}N_2O_4$; 329.1507; found; 329.1509.

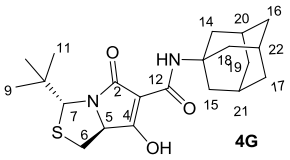
3.2.28. Synthesis of **4F**



4F

Yield; 48 %; M.P.; 119 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.38 (brs, 1H, NH or OH), 8.01 (d, 1H, *J* = 9.2 Hz, C15), 7.25-7.14 (m, 2H, C17 and C18), 4.85 (s, 1H, C8), 3.98 (d, 1H, *J* = 8.6 Hz, C5), 3.74-3.68 (m, 1H, C6), 2.35 (s, 3H, C20), 1.50 (d, 3H, *J* = 6.1 Hz, C7), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 183.7 (C4), 174.4 (C2), 163.9 (C13), 133.4 (quart Ar-C), 130.4 (C18), 130.2 (quart Ar-C), 130.1 (quart Ar-C), 126.6 (C17), 122.8 (C15), 99.9 (C3), 94.7 (C8), 75.9 (C6), 68.1 (C5), 35.6 (C9), 24.7 (C10-C12), 17.7 (CH_3), 17.3 (CH_3). **MS** (ES^-); 377.14 (M-H), **HRMS** (M-H); calcd for $C_{19}H_{22}Cl_1N_2O_4$; 377.1274; found; 377.1267.

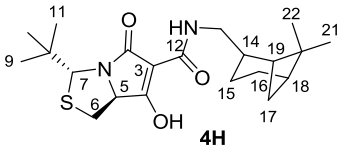
3.2.29. Synthesis of **4G**



4G

Yield; 31 %; M.P.; 97 ℃; Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.84 (brs, 1H, NH or OH CD), 7.41 (brs, 1H, NH or OH AB), 5.00 (s, 1H, C7 CD), 4.95 (s, 1H, C7 AB), 4.49 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6.8 Hz, C5 AB), 4.25 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6.8 Hz, C5 CD), 3.15 (dd, 1H, J_1 = 10.7 Hz, J_2 = 6.8 Hz, C6), 2.78-2.72 (m, 1H, C6), 2.10 (brs, 3H, C20-C22), 2.05 (brs, 6H, C14, C15 and C18), 1.69 (brs, 6H, C16, C17 and C19), 1.00 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 187.4 (C4), 172.1 (C2), 166.0 (C12), 94.4 (C3), 69.6 (C7), 67.7 (C5), 52.9 (C13), 41.6 (C14, C15 and C18), 37.4 (C8), 36.1 (C16, C17 and C19), 31.8 (C6), 29.3 (C20-C22), 26.2 (C9-C11). **MS** (ES^-); 389.17 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{29}N_2O_3S_1$; 389.1904; found; 389.1893.

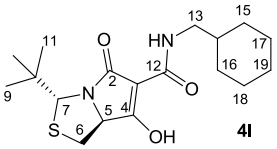
3.2.30. Synthesis of **4H**



4H

Yield; 41 %; M.P.; 143 ℃; Form AB: CD = 80: 20; **^{1}H NMR** (500 MHz, $CDCl_3$); 7.69 (brs, 1H, NH or OH), 7.55 (brs, 1H, NH or OH), 5.02 (s, 1H, C7 CD), 4.97 (s, 1H, C7 AB), 4.55 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6.8 Hz, C5 AB), 4.28 (dd, J_1 = 9.8 Hz, J_2 = 6.8 Hz, C5 CD), 3.44-3.29 (m, 2H, C13), 3.17 (dd, J_1 = 10.7 Hz, J_2 = 6.6 Hz, C6), 2.80-2.73 (m, 1H, C6), 2.40-2.35 (m, 1H), 2.31-2.22 (m, 1H), 2.02-1.84 (m, 5H), 1.54-1.45 (m, 1H), 1.21 (s, 3H, C21 CD), 1.20 (s, 3H, C21 AB), 1.04 (s, 3H, C22), 1.02 (s, 9H, C9-C11), 0.92-0.88 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$); 191.3 (C4 CD), 186.2 (C4 AB), 177.7 (C2 CD), 171.8 (C2 AB), 166.6 (C12 CD), 166.2 (C12 AB), 95.0 (C3 AB), 84.1 (C3 CD), 71.5 (C7 CD), 70.4 (C5 CD), 69.5 (C7 AB), 67.5 (C5 AB), 45.3 (C13 CD), 44.3 (C13 AB), 43.5 (C14 AB), 43.2 (C14 CD), 41.2 (C18 and C19 AB), 41.1 (C18 and C19 CD), 38.7 (C20), 37.4 (C8 AB), 37.4 (C8 CD), 33.2 (CH_2 AB), 33.1 (CH_2 CD), 32.1 (C6 AB), 31.8 (C6 CD), 27.9 (C21 AB), 27.9 (C21 CD), 26.2 (C9-C11), 25.9 (CH_2 AB), 25.8 (CH_2 CD), 23.1 (C22 AB), 23.0 (C22 CD), 19.7 (CH_2 AB), 19.5 (CH_2 CD). **MS** (ES^-); 391.21 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{31}N_2O_3S_1$; 391.2061; found; 391.2063.

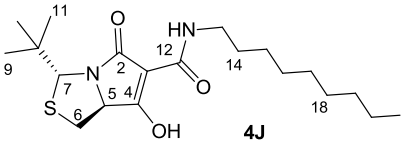
3.2.31. Synthesis of **4I**



4I

Yield; 38% (oil); Form AB: CD = 80: 20; **^{1}H NMR** (400 MHz, $CDCl_3$); 10.87 (brs, 1H, NH or OH), 7.92 (brs, 1H, NH or OH CD), 7.58 (brs, 1H, NH or OH AB), 5.00 (s, 1H, C7 CD), 4.95 (s, 1H, C7 AB), 4.54 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6.8 Hz, C5 AB), 4.26 (dd, J_1 = 9.8 Hz, J_2 = 6.8 Hz, C5 CD), 3.25-3.11 (m, 3H, C6 and C13), 2.75 (dd, 1H, J_1 = 10.4 Hz, J_2 = 10.0 Hz, C6), 1.75-1.67 (m, 6H, CH_2), 1.58-1.47 (m, 1H, C14), 1.24-1.09 (m, 4H, CH_2), 1.00 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 185.9 (C4), 171.8 (C2), 166.1 (C12), 95.6 (C3), 69.6 (C7), 67.2 (C5), 44.9 (C13), 37.8 (C14), 37.4 (C8), 31.8 (C6), 30.7 (CH_2), 26.2 (C9-C11), 25.7 (CH_2). **MS** (ES^-); 351.18 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{27}N_2O_3S_1$; 351.1748; found; 351.1742.

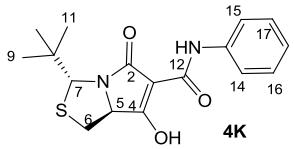
3.2.32. Synthesis of **4J**



4J

Yield; 42 %; M.P.; 121 ℃; Form AB: CD = 80: 20; **^{1}H NMR** (400 MHz, $CDCl_3$); 10.13 (brs, 1H, NH or OH), 7.86 (brs, 1H, NH or OH), 7.53 (brs, 1H, NH or OH), 5.01 (s, 1H, C7 CD), 4.96 (s, 1H, C7 AB), 4.55 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6.8 Hz, C5 AB), 4.28 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6.9 Hz, C5 CD), 3.42-3.31 (m, 2H, C13), 3.16 (dd, J_1 = 10.7 Hz, J_2 = 6.6 Hz, C6), 2.75 (dd, 1H, J_1 = 10.4 Hz, J_2 = 10.0 Hz, C6), 1.61-1.53 (m, 2H, C14), 1.31-1.26 (m, 12H, C15-C20), 1.00 (s, 9H, C9-C11), 0.88 (t, 3H, J = 6.4 Hz, C21). **^{13}C NMR** (100 MHz, $CDCl_3$); 191.3 (C4 CD), 185.8 (C4 AB), 177.7 (C2 CD), 171.8 (C2 AB), 166.6 (C12 CD), 166.0 (C12 AB), 95.2 (C3 AB), 84.1 (C3 CD), 71.5 (C7 CD), 70.4 (C5 CD), 69.4 (C7 AB), 67.4 (C5 AB), 40.0 (C13 CD), 38.8 (C13 AB), 37.4 (C8 AB), 37.3 (C8 CD), 32.1 (C6 CD), 31.8 (C6 AB), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2 AB), 29.1 (CH_2 CD), 26.8 (CH_2 AB), 26.6 (CH_2 CD), 26.2 (C9-C11), 22.6 (CH_2), 14.1 (C21). **MS** (ES^-); 381.22 (M-H); **HRMS** (M-H); calcd for $C_{20}H_{33}N_2O_3S_1$; 381.2217; found; 381.2221.

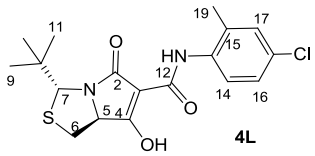
3.2.33. Synthesis of **4K**



4K

Yield; 47 %; M.P.; 109 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.40 (brs, 1H, NH or OH), 7.58 (d, 2H, *J* = 7.6 Hz, C14 and C15), 7.36 (t, 2H, *J* = 9.9 Hz, C16 and C17), 7.16 (t, 1H, *J* = 7.3 Hz, C18), 5.01 (s, 1H, C7), 4.66 (brs, 1H, C5), 3.21 (dd, 1H, J_1 = 10.4 Hz, J_2 = 6.8 Hz, C6), 2.79 (dd, 1H, J_1 = 10.4 Hz, J_2 = 10.4 Hz, C6), 1.05 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 183.9 (C4), 171.3 (C2), 163.9 (C12), 136.5 (C13), 129.1 (C17 and C18), 124.9 (C18), 120.3 (C14 and C15), 97.9 (C3), 69.3 (C7), 66.8 (C5), 37.4 (C8), 31.7 (C6), 26.2 (C9-C11). **MS** (ES^-); 331.12 (M-H); **HRMS** (M-H); calcd for $C_{17}H_{19}N_2O_3S_1$; 331.1122; found; 331.1121.

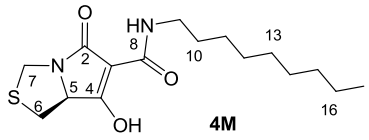
3.2.34. Synthesis of **4L**



4L

Yield; 52 %; M.P.; 118 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 10.07 (brs, 1H, NH or OH), 9.43 (brs, 1H, NH or OH), 8.00 (d, 1H, *J* = 8.3 Hz, C14), 7.25-7.15 (m, 2H, C16 and C17), 5.01 (s, 1H, C7), 4.67 (dd, 1H, J_1 = 9.2 Hz, J_2 = 6.8 Hz, C5), 3.21 (dd, 1H, J_1 = 10.6 Hz, J_2 = 6.8 Hz, C6), 2.80 (dd, 1H, J_1 = 10.6 Hz, J_2 = 9.2 Hz, C6), 2.34 (s, 3H, C19), 1.04 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 183.7 (C4), 171.4 (C2), 163.8 (C12), 133.5 (quart Ar-C), 130.3 (C17), 130.1 (quart Ar-C), 129.9 (quart Ar-C), 126.6 (C16), 122.7 (C14), 98.2 (C3), 68.3 (C7), 66.8 (C5), 37.4 (C8), 31.6 (C6), 26.2 (C9-C11), 17.7 (C19). **MS** (ES^-); 379.10 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{20}Cl_1N_2O_5S_1$; 379.0889; found; 379.0882.

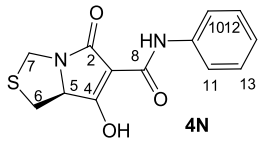
3.2.35. Synthesis of **4M**



4M

Yield; 43 % (oil); Form AB: CD = 20: 80**; ^{1}H NMR** (500 MHz, $CDCl_3$); 7.49 (brs, 1H, NH or OH), 4.88 (d, 1H, *J* = 9.1 Hz, C7), 4.46 (t, 1H, *J* = 7.9 Hz, C5), 4.10 (d, 1H, *J* = 9.1 Hz, C7), 3.41-3.29 (m, 2H, C9), 3.21 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.9 Hz, C6), 2.90 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.9 Hz, C6), 1.58-1.55 (m, 2H, C10), 1.34-1.24 (m, 12 H, C11-C16), 0.87 (t, 3H, *J* = 6.8 Hz, C17). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 187.4 (C4), 172.9 (C2), 165.9 (C8), 95.7 (C3), 66.3 (C5), 45.3 (C7), 38.9 (C9), 31.8 (CH_2), 31.1 (C6), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 14.1 (C17). **MS** (ES^-); 325.16 (M-H); **HRMS** (M-H); calcd for $C_{16}H_{25}N_2O_3S_1$; 325.1591; found; 325.1597.

3.2.36. Synthesis of **4N**

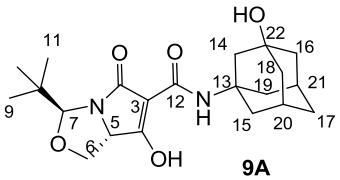


4N

Yield; 23 %; M.P.; 94 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.32 (brs, 1H, NH or OH), 7.58 (d, 2H, *J* = 7.8 Hz, C10 and C11), 7.37 (t, 2H, *J* = 7.8 Hz, C12 and C13), 7.17 (t, 1H, *J* = 7.8 Hz, C14), 6.64 (brs, 1H, NH or OH), 4.92 (d, 1H, *J* = 9.1 Hz, C7), 4.60 (t, 1H, *J* = 7.6 Hz, C5), 4.17 (d, 2H, *J* = 9.1 Hz, C7), 3.27 (dd, 1H, J_1 = 11.1 Hz, J_2 = 7.6 Hz, C6), 2.95 (dd, 1H, J_1 = 11.1 Hz, J_2 = 7.6 Hz, C6). **^{13}C NMR** (100 MHz, $CDCl_3$); 184.9 (C4), 172.3 (C2), 163.8 (C8),

136.4 (C9), 129.1 (C12 and C13), 125.1 (C14), 120.4 (C10 and C11), 98.8 (C3), 65.6 (C5), 45.1 (C7), 30.9 (C6). **MS** (ES^-); 275.05 (M-H); **HRMS** (M-H); calcd for $C_{13}H_{11}N_2O_3S_1$; 275.0496; found; 275.0494.

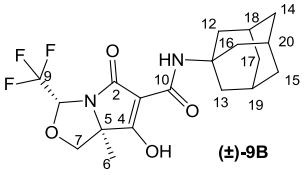
3.2.37. Synthesis of **9A**



9A

Yield; 26 %; M.P.; 106 ℃; Form AB: CD = 85: 15**; ^{1}H NMR** (500 MHz, $CDCl_3$); 7.92 (brs, 1H, NH or OH CD), 7.43 (brs, 1H, NH or OH AB), 6.33 (brs, 2H, NH or OH), 4.82 (s, 1H, C7 CD), 4.78 (s, 1H, C7 AB), 4.35 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz, C5 AB), 4.27 (dd, 1H, J_1 = 7.5 Hz, J_2 = 7.0 Hz, C6), 4.23 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz, C5 CD), 3.40 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz, C6), 2.33-2.30 (m, 2H, C20 and C21), 2.06-1.91 (m, 6H, CH_2), 1.71 (brs, 4H, CH_2), 1.60-1.53 (m, 2H, CH_2), 0.96 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 191.37 (C4 CD), 186.75 (C4 AB), 181.47 (C2 CD), 175.07 (C2 AB), 166.95 (C12 CD), 165.89 (C12 AB), 97.23 (C3 AB), 94.74 (C3 CD), 95.09 (C7 AB), 86.14 (C7 CD), 69.02 (C22 AB), 68.94 (C22 CD), 67.22 (C6 AB), 66.80 (C6 CD), 63.20 (C5 AB), 60.38 (C5 CD), 56.28 (C13 CD), 54.88 (C13 AB), 48.94 (CH_2), 43.87 (CH_2), 43.71 (CH_2 CD), 40.35 (CH_2 CD), 40.29 (CH_2), 35.77 (C8), 34.65 (CH_2), 34.40 (CH_2 CD), 30.48 (C20 and C21), 24.61 (C9-C11). **MS** (ES^+); 413.29 (M+Na); **HRMS** (M-H); calcd for $C_{21}H_{29}N_2O_5$; 389.2082; found; 389.2076.

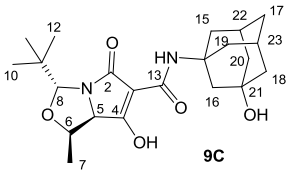
3.2.38. Synthesis of (±)-**9B**



(±)-9B

Yield; 46 % (oil); Form AB: CD = 70: 30; **^{1}H NMR** (400 MHz, $CDCl_3$); 8.08 (brs, 1H, NH or OH CD), 7.44 (brs, 1H, NH or OH AB), 5.42-5.34 (m, 1H, C8), 3.99 (d, 1H, J = 8.3 Hz, C7 AB), 3.94 (d, 1H, J = 8.3 Hz, C7 CD), 3.78 (d, 1H, J = 8.3 Hz, C7), 2.13 (brs, 3H, C18-C20), 2.06 (brs, 6H, C12, C13 and C16), 1.70 (brs, 6H, C14, C15 and C17), 1.60 (s, 3H, C6 AB), 1.55 (s, 3H, C6 CD). **^{13}C NMR** (125 MHz, $CDCl_3$); 194.5 (C4 AB), 194.1 (C4 CD), 180.8 (C2 CD), 175.1 (C2 AB), 166.7 (C10 CD), 166.4 (C10 AB), 121.8 (q, $J_{C\text{-}F}$ = 280 Hz, C9), 91.1 (C3), 84.6 (q, $J_{C\text{-}F}$ = 36.5 Hz,C8 CD), 84.5 (q, $J_{C\text{-}F}$ = 36.5 Hz,C8 AB), 72.9 (C7 CD), 72.8 (C7 AB), 72.4 (C5 CD), 70.3 (C5 AB), 54.9 (C11 CD), 53.9 (C11 AB), 41.5 (C12, C13 and C16), 36.9 (C14, C15 and C17 AB), 35.8 (C14, C15 and C17 CD), 29.3 (C18-C20), 20.3 (C6 CD), 20.2 (C6 AB). **MS** (ES^-); 399.16 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{22}F_3N_2O_4$; 399.1537; found; 399.1541.

3.2.39. Synthesis of **9C**

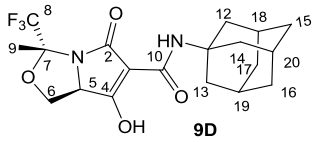


9C

Yield; 29 %; M.P.; 143 ℃; Form AB: CD = 90: 10; **^{1}H NMR** (400 MHz, $CDCl_3$); 7.89 (brs, 1H, NH or OH CD), 7.40 (brs, 1H, NH or OH AB), 4.77 (s, 1H, C8 CD), 4.75 (s, 1H, C8 AB), 3.82 (d, 1H, J = 8.6 Hz, C5 AB), 3.66-3.59 (m, 1H, C6), 3.24 (d, 1H, J = 8.6 Hz, C5 CD), 2.28 (brs, 2H, C22 and C23), 2.04-1.89 (m, 6H, CH_2), 1.69 (brs, 4H, CH_2), 1.56 (brs, 2H, CH_2), 1.42 (d, 3H, J = 6.7 Hz, C7), 0.95 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 185.6 (C4), 174.9 (C2), 165.8 (C13), 97.7 (C3), 94.7 (C8), 75.7 (C6), 69.1 (C21), 68.5

(C5), 54.8 (C14), 48.9 (CH_2), 43.8 (CH_2), 40.3 (CH_2), 35.5 (C9), 34.7 (CH_2), 30.5 (C22 and C23), 24.7 (C10-C12), 17.3 (C7). **MS** (ES^-); 403.23 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{31}N_2O_5$; 403.2238; found; 403.2239.

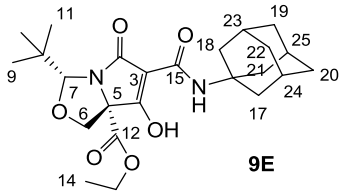
3.2.40. Synthesis of **9D**



9D

Yield; 39 % (oil); Form AB: CD = 70: 30; **^{1}H NMR** (400 MHz, $CDCl_3$); 8.04 (brs, 1H, NH or OH CD), 7.49 (brs, 1H, NH or OH AB), 4.61 (t, 1H, *J* = 8.2 Hz, C5 AB), 4.41 (t, 1H, *J* = 8.2 Hz, C5 CD), 4.35-4.29 (m, 1H, C6), 3.78-3.73 (m, 1H, C6), 2.13 (brs, 3H, C18-C20), 2.06 (brs, 6H, C12-C14), 1.81 (s, C9), 1.70 (brs, 6H, 15-C17). **^{13}C NMR** (125 MHz, $CDCl_3$); 190.5 (C4 CD), 189.1 (C4 AB), 178.4 (C2 CD), 171.8 (C2 AB), 166.8 (C10 CD), 166.2 (C10 AB), 123.3 (q, $J_{C\text{-}F}$ = 284 Hz, C8), 94.9 (C3 AB), 92.2-91.1 (m, C7), 86.7 (C3 CD), 67.5 (C5 CD), 66.3 (C6 CD), 66.2 (C6 AB), 64.6 (C5 AB), 54.7 (C11 CD), 53.5 (C11 AB), 41.6 (C12-C14 CD), 41.5 (C12-C14 AB), 36.0 (C15-C17 AB), 35.8 (C15-C17 CD), 29.3 (C18-C20 AB), 29.3 (C18-C20 CD), 16.5 (C9 CD), 16.4 (C9 AB). **MS** (ES^-); 399.16 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{22}F_3N_2O_4$; 399.1537; found; 399.1539.

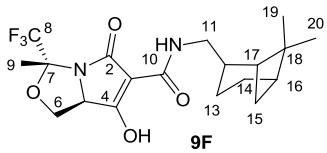
3.2.41. Synthesis of **9E**



9E

Yield; 50 %; M.P. 75 ℃; AB: CD = 50: 50**; ^{1}H NMR** (500 MHz, $CDCl_3$); 10.87 (brs, 1H, NH or OH), 7.80 (brs, 1H, NH or OH a), 7.65 (brs, 1H, NH or OH c), 4.82 (d, 1H, *J* = 8.5 Hz, C6 a), 4.79 (d, 1H, *J* = 8.5 Hz, C6 c), 4.73 (s, 1H, C7 a), 4.72 (s, 1H, C7 c), 4.30-4.20 (m, 2H, C13), 3.49 (d, 1H, *J* = 8.5 Hz, C6 a), 3.48 (d, 1H, *J* = 8.5 Hz, C6 c), 2.13 (brs, 3H, C23-C25), 2.06-2.05 (m, 6H, adamantyl CH_2), 1.70 (brs, 6H, adamantyl CH_2), 1.30 (t, 3H, *J* = 7.5 Hz, C14), 0.93 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 189.6 (C4), 187.8 (C4), 182.6 (C2), 176.8 (C2), 167.7 (C13), 167.3 (C13), 166.9 (C15), 166.6 (C15), 97.5 (C7), 97.3 (C7), 90.9 (C3), 84.9 (C3), 78.4 (C5), 76.5 (C5), 68.6 (C6), 68.4 (C6), 62.6 (C13), 62.4 (C13), 54.7 (C16), 54.1 (C16), 41.5 (C17, C18 and C21), 41.4 (C17, C18 and C21), 35.9 (C19, C20 and C22), 35.8 (C19, C20 and C22), 35.1 (C8), 35.0 (C8), 29.2 (C23-C25), 24.7 (C9-C11), 24.6 (C9-C11), 14.1 (C14), 14.0 (C14). **MS** (ES^-); 445.23 (M-H); **HRMS** (M-H); calcd for $C_{24}H_{33}N_2O_6$; 445.2344; found; 445.2349.

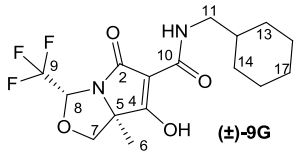
3.2.42. Synthesis of **9F**



9F

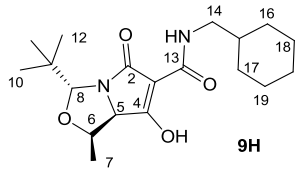
Yield; 48 % (oil); Form AB: CD = 99: 1; **^{1}H NMR** (400 MHz, $CDCl_3$); 10.41 (brs, 1H, OH), 7.61 (brs, 1H, NH), 4.65 (brs, 1H, C5), 4.34 (t, 1H, *J* = 7.9 Hz, C6), 3.76 (t, 1H, *J* = 8.5 Hz, C6), 3.47-3.31 (m, 2H, C11), 2.41-2.36 (m, 1H), 2.29-2.21 (m, 1H), 2.03-1.88 (m, 5H), 1.81 (s, 3H, C9), 1.54-1.45 (m, 1H), 1.20 (s, 3H, C19), 1.04 (s, 3H, C20), 0.91 (d, 1H, *J* = 9.9 Hz). **^{13}C NMR** (125 MHz, $CDCl_3$); 187.9 (C4), 171.6 (C2), 166.3 (C10), 123.3 (q, $J_{C\text{-}F}$ = 284 Hz, C8), 95.5 (C3), 91.5 (q, $J_{C\text{-}F}$ = 34.1 Hz,C7), 66.2 (C6), 64.5 (C5), 44.5 (C11), 43.3 (C12), 41.1 (C16 and C17), 38.6 (C18), 33.1 (CH_2), 27.8 (C19), 25.8 (CH_2), 23.0 (C20), 19.6 (CH_2), 16.4 (C9). **MS** (ES^-); 401.18 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{24}F_3N_2O_4$; 401.1694; found; 401.1695.

3.2.43. Synthesis of (±)-**9G**



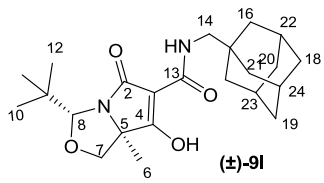
Yield; 32% (oil); Form AB: CD = 70: 30; **^{1}H NMR** (400 MHz, $CDCl_3$); 8.14 (brs, 1H, NH or OH), 7.70 (brs, 1H, NH or OH), 7.06 (brs, NH or OH), 5.28-5.14 (m, 1H, C8), 3.87 (d, 1H, *J* = 8.0 Hz, C7 AB), 3.81 (d, 1H, *J* = 8.0 Hz, C7 CD), 3.76 (d, 1H, *J* = 8.3 Hz, C7), 3.32-3.25 (m, 1H, C11), 3.18-3.08 (m, 2H, C11 and C12), 1.75-1.62 (m, 5H, CH_2), 1.58 (s, 3H, C6 AB), 1.52 (s, 3H, C6 CD), 1.25-0.88 (m, 5H, CH_2). **^{13}C NMR** (125 MHz, $CDCl_3$); 192.2 (C4 CD), 189.8 (C4 AB), 175.6 (C2 CD), 169.5 (C2 AB), 167.6 (C10 CD), 166.6 (C10 AB), 121.7 (q, $J_{C\text{-}F}$ = 280 Hz, C9), 94.1 (C3 AB), 85.5 (C3 CD), 84.2 (q, $J_{C\text{-}F}$ = 36.0 Hz,C8 CD), 84.0 (q, $J_{C\text{-}F}$ = 36.0 Hz,C8 AB), 73.8 (C5 CD), 71.1 (C5 AB), 70.7 (C7 AB), 70.6 (C7 CD), 45.8 (C11 CD), 45.3 (C11 AB), 37.7 (C12 CD), 37.6 (C12 AB), 30.7 (CH_2 CD), 30.6 (CH_2 AB), 26.3 (CH_2 CD), 26.1 (CH_2 AB), 25.7 (CH_2 CD), 25.5 (CH_2 AB), 20.4 (C6). **MS** (ES^-); 361.13 (M-H); **HRMS** (M-H); calcd for $C_{16}H_{20}F_3N_2O_4$; 361.1381; found; 361.1381.

3.2.44. Synthesis of **9H**



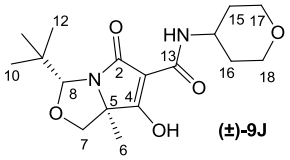
Yield; 42 % (oil); Form AB: CD = 85: 15**; ^{1}H NMR** (500 MHz, $CDCl_3$); 7.98 (brs, 1H, NH or OH CD), 7.57 (brs, 1H, NH or OH AB), 4.79 (s, 1H, C8 CD), 4.78 (s, 1H, C8 AB), 3.85 (d, 1H, *J* = 8.8 Hz, C5 AB), 3.67-3.62 (m, 1H, C6), 3.56 (d, 1H, *J* = 8.8 Hz, C5 CD), 3.26-3.13 (m, 2H, C14), 1.75-1.65 (m, 5H, CH_2), 1.58-1.47 (m, 1H, C15), 1.44 (d, 3H, *J* = 6.0 Hz, C7 AB), 1.42 (d, 3H, *J* = 6.0 Hz, C7 CD), 1.30-1.13 (m, 5H, CH_2), 0.96 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 191.0 (C4 CD), 185.3 (C4 AB), 181.1 (C2 CD), 174.8 (C2 AB), 166.9 (C13 CD), 166.1 (C13 AB), 97.4 (C3), 94.8 (C8 CD), 94.6 (C8 AB), 75.7 (C6 AB), 74.9 (C6 CD), 72.4 (C5 CD), 68.6 (C5 AB), 46.0 (C14 CD), 44.8 (C14 AB), 37.8 (C15), 35.5 (C9 AB), 35.4 (C9 CD), 30.7 (CH_2 AB), 30.5 (CH_2 CD), 26.2 (CH_2 AB), 26.1 (CH_2 CD), 25.7 (CH_2 AB), 25.6 (CH_2 CD), 24.7 (C10-C12 AB), 24.6 (C10-C12 AB), 17.4 (C7 CD), 17.3 (C7 AB). **MS** (ES^-); 349.21 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{29}N_2O_4$; 349.2133; found; 349.2134.

3.2.45. Synthesis of (±)-**9I**



Yield; 36 % (oil); Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, $CDCl_3$); 8.06 (brs, 1H, NH or OH CD), 7.64 (brs, 1H, NH or OH AB), 4.67 (s, 1H, C8), 3.89 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.82 (d, 1H, *J* = 8.1 Hz, C7 CD), 3.45 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.43 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.13-2.97 (m, 2H, C14), 1.99 (brs, 3H, C22-C24), 1.73-1.63 (m, 6H, C16, C17 and C21), 1.59 (s, 3H, C6), 1.53 (brs, 6H, C18, C19 and C20), 1.03 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 189.4 (C4), 175.8 (C2), 166.6 (C13), 97.5 (C3), 97.1 (C8), 72.2 (C7), 69.7 (C5), 50.3 (C14), 40.1 (C16, C17 and C21), 36.8 (C18, C19 and C20), 34.7 (C9), 33.8 (C15), 28.1 (C22-C24), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 401.26 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{33}N_2O_4$; 401.2446; found; 401.2447.

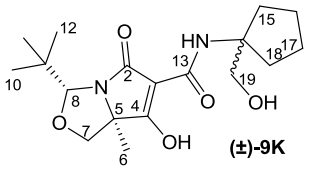
3.2.46. Synthesis of (±)-**9J**



(±)-9J

Yield; 35 %; M.P.; 164 ℃; Form AB: CD = 90: 10**; ^{1}H NMR** (500 MHz, $CDCl_3$); 8.45 (brs, 1H, NH or OH), 7.49 (brs, 1H, NH or OH), 4.65 (s, 1H, C8 CD), 4.64 (s, 1H, C8 AB), 4.11-4.03 (m,1H, C14), 3.97 (dt, 2H J_1 = 11.7 Hz, J_2 = 3.4 Hz, C17 and C18), 3.90 (d, 1H, J = 8.4 Hz, C7 AB), 3.82 (d, 1H, J = 8.4 Hz, C7 CD), 3.49 (dt, 2H J_1 = 11.7 Hz, J_2 = 3.4 Hz, C17 and C18), 3.44 (d, 1H, J = 8.4 Hz, C7 AB), 3.42 (d, 1H, J = 8.4 Hz, C7 CD), 1.97-1.890 (m, 2H, C15 and C16), 1.64-1.51 (m, 5H, C6, C15 and C16), 1.02 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 194.2 (C4 CD), 188.6 (C4 AB), 182.1 (C2 CD), 175.6 (C2 AB), 166.6 (C13 CD), 165.5 (C13 AB), 97.5 (C8 CD), 97.2 (C8 AB), 97.0 (C3), 73.5 (C7 CD), 72.2 (C7 AB), 71.6 (C5 CD), 69.4 (C5 AB), 66.2 (C17 and C18 CD), 66.5 (C17 and C18 AB), 46.6 (C14 CD), 45.2 (C14 AB), 34.7 (C9 AB), 34.6 (C9 CD), 32.8 (CH_2), 32.7 (CH_2), 25.5 (C10-C12), 20.7 (C6 CD), 20.5 (C6 AB). **MS** (ES^-); 337.19 (M-H); **HRMS** (M-H); calcd for $C_{17}H_{25}N_2O_5$; 337.1769; found; 337.1768.

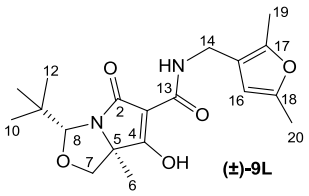
3.2.47. Synthesis of (±)-**9K**



(±)-9K

Yield; 51% (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.62 (s, 1H, C8), 3.89 (d, 1H, J = 8.3 Hz, C7), 3.68 (s, 2H, C19), 3.43 (d, 1H, J = 8.3 Hz, C7), 1.94-1.65 (m, 8H, C15-C18), 1.57 (s, 3H, C6), 1.00 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 166.3 (C13), 97.2 (C8), 72.2 (C7), 68.4 (C5), 67.0 (C14), 66.9 (C19), 35.7 (C15 and C18), 34.6 (C9), 25.5 (C10-C12), 23.9 (C16 and C17), 20.6 (C6). **MS** (ES^-); 351.19 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{27}N_2O_5$; 351.1925; found; 351.1912.

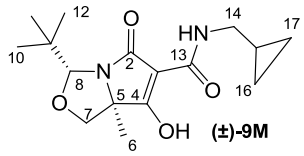
3.2.48. Synthesis of (±)-**9L**



(±)-9L

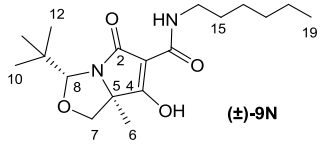
Yield; 38 % (oil); Form AB: CD = 80: 20**; ^{1}H NMR** (500 MHz, $CDCl_3$); 7.57 (brs, 1H, NH or OH CD), 7.57 (brs, 1H, NH or OH AB), 5.87 (s, 1H, C16 AB), 5.85 (s, 1H, C16 CD), 4.65 (s, 1H, C8 CD), 4.62 (s, 1H, C8 AB), 4.22 (d, 2H, J = 5.7 Hz, C14 AB), 4.13 (d, 2H, J = 5.7 Hz, C14 CD), 3.89 (d, 1H, J = 8.2 Hz, C7 AB), 3.89 (d, 1H, J = 8.2 Hz, C7 CD), 3.43 (d, 1H, J = 8.2 Hz, C7 AB), 3.41 (d, 1H, J = 8.2 Hz, C7 CD), 2.24 (s, 3H, CH_3 CD), 2.23 (s, 3H, CH_3 AB), 2.22 (s, 3H, CH_3 CD), 2.21 (s, 3H, CH_3 AB), 1.58 (s, 3H, C6 AB), 1.49 (s, 3H, C6 CD), 1.02 (s, 9H, C10-C12 CD), 1.01 (s, 9H, C10-C12 AB). **^{13}C NMR** (125 MHz, $CDCl_3$); 194.1 (C4 CD), 188.6 (C4 AB), 182.2 (C2 CD), 175.5 (C2 AB), 166.8 (C13 CD), 165.8 (C13 AB), 150.5 (C18 CD), 150.2 (C18 AB), 147.6 (C17 CD), 147.3 (C17 AB), 115.3 (C15 AB), 114.4 (C15 CD), 106.7 (C16 AB), 106.5 (C16 CD), 97.5 (C8 CD), 97.1 (C8 AB), 96.9 (C3 AB), 96.8 (C3 CD), 73.4 (C7 CD), 72.2 (C7 AB), 71.6 (C5 CD), 69.4 (C5 AB), 35.0 (C9 CD), 34.6 (C9 AB), 34.5 (C14 CD), 33.8 (C14 AB), 25.4 (C10-C12), 20.7 (C6 CD), 20.6 (C6 AB), 13.4 (C20), 11.4 (C19). **MS** (ES^-); 361.19 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{25}N_2O_5$; 361.1769; found; 361.1749.

3.2.49. Synthesis of (±)-**9M**



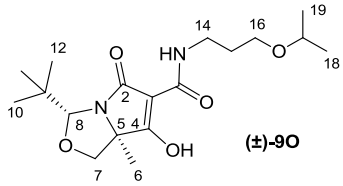
Yield; 41% (oil); Form AB: CD = 99: 1; **^{1}H NMR** (500 MHz, $CDCl_3$); 9.62 (brs, 1H, NH or OH), 7.78 (brs, 1H, NH or OH), 4.63 (s, 1H, C8), 3.87 (d, 1H, *J* = 8.4 Hz, C7), 3.41 (d, 1H, *J* = 8.4 Hz, C7), 3.19 (brs, 2H, C14), 1.55 (s, 3H, C6), 1.01 (brs, 10H, C10-C12 and C15), 0.53 (brs, 2H, C16 and C17), 0.22 (brs, 2H, C16 and C17). **^{13}C NMR** (100 MHz, $CDCl_3$); 188.6 (C4), 175.9 (C2), 165.7 (C13), 97.2 (C8), 96.4 (C3), 72.3 (C7), 69.5 (C5), 43.6 (C14), 34.6 (C9), 25.5 (C10-C12), 20.7 (C6), 10.5 (C15), 3.57 (C16 and C17). **MS** (ES^-); 307.19 (M-H); **HRMS** (M-H); calcd for $C_{16}H_{23}N_2O_4$; 307.1663; found; 307.1667.

3.2.50. Synthesis of (±)-**9N**



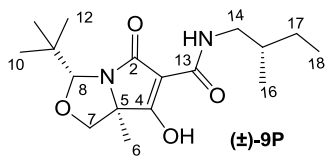
Yield; 39 % (oil); Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.55 (brs, 1H, NH or OH), 4.66 (s, 1H, C8 CD), 4.64 (s, 1H, C8 AB), 3.89 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.81 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.43 (d, 1H, *J* = 8.3 Hz, C7), 3.54 (q, 2H, *J* = 7.6 Hz, C14), 1.63-1.51 (m, 5H, C6 and C15), 1.38-1.26 (m, 6H, C16-C18), 1.02 (s, 9H, C10-C12), 0.93-0.84 (m, 3H, C19). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 189.2 (C4), 175.7 (C2), 166.3 (C13), 97.5 (C3), 97.1 (C8), 72.2 (C7), 69.6 (C5), 38.8 (C14), 34.7 (C9), 31.4 (CH_2), 29.4 (CH_2), 26.5 (CH_2), 25.5 (C10-C12), 22.5 (CH_2), 20.6 (C6), 13.9 (C19). **MS** (ES^-); 337.21 (M-H), **HRMS** (M-H); calcd for $C_{18}H_{29}N_2O_4$; 337.2133; found; 337.2135.

3.2.51. Synthesis of (±)-**9O**



Yield; 33 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (400 MHz, $CDCl_3$); 8.63 (brs, 1H, NH or OH), 8.14 (brs, 1H, NH or OH CD), 7.78 (brs, 1H, NH or OH AB), 4.65 (s, 1H, C8 CD), 4.63 (s, 1H, C8 AB), 3.88 (d, 1H, *J* = 8.1 Hz, C7 AB), 3.81 (d, 1H, *J* 8.3 Hz, C7 CD), 3.61-3.36 (m, 6H, C7, C14, C16 and C17), 1.89-1.77 (m, 2H, C15), 1.57 (s, 3H, C6 AB), 1.50 (s, 3H, C6 CD), 1.17 (d, 3H, *J* = 6.4 Hz, C18), 1.16 (d, 3H, *J* = 6.4 Hz, C19), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 189.2 (C4), 175.5 (C2), 166.2 (C13), 97.5 (C3), 97.1 (C8), 72.2 (C7), 71.8 (C17), 69.5 (C5), 65.8 (C16), 36.7 (C14), 34.6 (C9), 29.6 (C15), 25.5 (C10-C12), 21.9 (C18 and C19), 20.6 (C6). **MS** (ES^-); 353.22 (M-H), **HRMS** (M-H); calcd for $C_{18}H_{29}N_2O_5$; 353.2082; found; 353.2076.

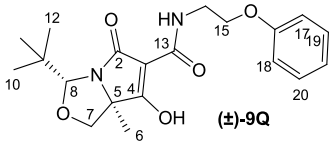
3.2.52. Synthesis of (±)-**9P**



Yield; 44 %; M.P.; 87 °C; Form AB: CD = 80: 20**; ^{1}H NMR** (500 MHz, $CDCl_3$); 9.04 (br s, 1H, NH or OH), 7.60 (br s, 1H, NH or OH), 4.66 (s, 1H, C8 CD), 4.64 (s, 1H, C8 AB), 3.89 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.81 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.44 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.42 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.37-3.13 (m,

2H, C14), 1.71-1.61 (m, 1H, C15), 1.58 (s, 3H, C6 AB), 1.53 (s, 3H, C6 CD), 1.47-1.40 (m, 1H, C17), 1.24-1.15 (m, 1H, C17), 1.02 (s, 9H, C10-C12), 0.98-0.88 (m, 6H, C16 and C18). **^{13}C NMR** (125 MHz, $CDCl_3$); 194.3 (C4 CD), 189.2 (C4 AB), 181.8 (C2 CD), 175.8 (C2 AB), 167.3 (C13 CD), 166.4 (C13 AB), 97.5 (C8 CD), 97.1 (C8 AB), 96.2 (C3), 73.3 (C7 CD), 72.2 (C7 AB), 71.1 (C5 CD), 69.6 (C5 AB), 45.4 (C14 CD), 44.3 (C4 AB), 34.84 and 34.84 (C15 AB), 34.80 and 34.77 (C15 CD), 34.7 (C9 AB), 34.6 (C9 CD), 26.88 and 26.84 (C17 AB), 26.70 and 26.65 (C17 CD), 25.5 (C10-C12), 20.8 (C6 CD), 20.6 (C6 AB), 17.1 (C16 AB), 16.9 (C16 CD), 11.22 and 11.20 (C18 AB), 11.14 and 11.10 (C18 CD). **MS** (ES^-); 323.20 (M-H), **HRMS** (M-H); calcd for $C_{17}H_{27}N_2O_4$; 323.1976; found; 323.1969.

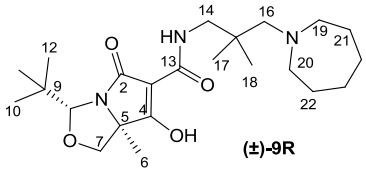
3.2.53. Synthesis of (±)-**9Q**



(±)-9Q

Yield; 39 % (oil); Form AB: CD = 80: 20; **^{1}H NMR** (400 MHz, $CDCl_3$); 8.85 (brs, 1H, NH or OH), 8.13 (brs, 1H, NH or OH CD), 7.89 (brs, 1H, NH or OH AB), 7.34-7.27 (m, 2H, C19 and C20), 6.97 (t, 1H, *J* = 7.6 Hz, C21), 6.91 (d, 2H, *J* = 7.6 Hz, C17 and C18), 4.66 (s, 1H, C8 CD), 4.64 (s, 1H, C8 AB), 4.13 (t, 2H, *J* = 5.3 Hz, C15 CD), 4.09 (t, 2H, *J* = 5.3 Hz, C15 AB), 3.90 (d, 1H, *J* = 8.3 Hz, C7), 3.83-3.81 (m, 2H, C14 CD), 3.76 (q, 2H, *J* = 5.6 Hz, C14), 3.44 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.44 (d, 1H, *J* = 8.3 Hz, C7 CD), 1.59 (s, 3H, C6 AB), 1.52 (s, 3H, C6 CD), 1.02 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 188.1 (C4), 175.3 (C2), 166.4 (C13), 158.4 (C16), 129.5 (C19 and C20), 121.2 (C21), 114.6 (C17 and C18), 97.2 (C3), 97.1 (C8), 72.3 (C7), 69.3 (C5), 66.1 (C15), 38.2 (C14), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6). **MS** (ES^-); 373.19 (M-H), **HRMS** (M-H); calcd for $C_{20}H_{25}N_2O_5$; 373.1769; found; 373.1767.

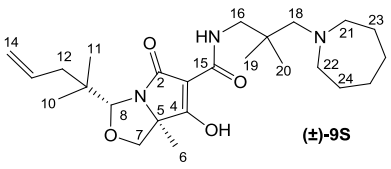
3.2.54. Synthesis of (±)-**9R**



(±)-9R

Yield; 21 % (oil); Form AB: CD = 99: 1; **^{1}H NMR** (400 MHz, $CDCl_3$); 7.78 (brs, 1H, NH or OH), 4.62 (s, 1H, C8), 3.89 (d, 1H, *J* = 8.3 Hz, C7), 3.79 (brs, 2H, C19 and C20), 3.84-3.40 (m, 3H, C7 and C14), 3.07 (brs, 2H, C19 and C20), 2.90 (s, 2H, C16), 2.14-2.06 (m, 2H, CH_2), 1.88-1.57 (m, 6H, CH_2), 1.58 (s, 3H, C6), 1.30 (s, 6H, C17 and C18), 1.00 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 166.7 (C13), 97.2 (C8), 72.1 (C7), 66.2 (C16), 58.5 (CH_2), 47.1 (CH_2), 36.5 (C15), 34.6 (C9), 27.9 (CH_2), 25.4 (C10-C12), 24.1 (C17 and C18), 22.4 (CH_2), 20.6 (C6). **MS** (ES^+); 444.29 (M+Na); **HRMS** (M+Na); calcd for $C_{23}H_{39}N_3Na_1O_4$; 444.2833; found; 444.2814.

3.2.55. Synthesis of (±)-**9S**

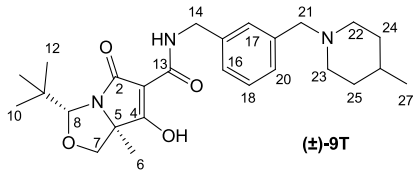


(±)-9S

Yield; 23 %; M.P.; 139 ℃ Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.79 (brs, NH or OH), 7.49 (brs, NH or OH), 5.91-5.80 (m, 1H, C13), 5.07-5.03 (m, 2H, C14), 4.67 (s, 1H, C8), 3.89 (d, 1H, *J* = 8.3 Hz, C7), 3.79-3.69 (m, 2H, C21 and C22), 3.51-3.36 (m, 3H, C7 and C16), 3.07 (brs, 2H, C21

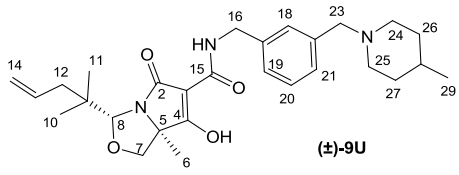
and C22), 2.90 (s, 2H, C18), 2.18-2.02 (m, 4H, C12 and CH_2), 1.82-1.64 (m, 6H, CH_2), 1.58 (s, 3H, C6), 1.29 (s, 6H, C19 and C20), 0.98 (s, 3H, C10), 0.95 (s, 3H, C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 166.7 (C15), 134.4 (C13), 117.7 (C14), 96.6 (C8), 72.2 (C7), 66.2 (C20), 58.5 (C21 and C22), 47.1 (C16), 42.5 (C12), 37.5 (C9), 36.6 (C17), 27.9 (C19 and C20), 24.1 (CH_2), 22.5 (C10), 22.2 (CH_2), 22.1 (C11), 20.6 (C6). **MS** (ES^-); 446.30 (M-H); **HRMS** (M-H); calcd for $C_{25}H_{40}N_3O_4$; 446.3024; found; 446.3027.

3.2.56. Synthesis of (±)-**9T**



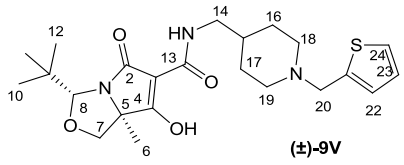
Yield; 42 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.90 (d, 1H, *J* = 7.6 Hz, NH), 7.61 (d, 1H, *J* = 6.8 Hz, C18), 7.47 (s, 1H, C17), 7.42-7.31 (m, 2H, C16 and C20), 4.58 (s, 1H, C8), 4.52 (d, 2H, *J* = 5.8 Hz, C14), 4.12 (s, 2H, C21), 3.86 (d, 1H, *J* = 8.1 Hz, C7), 3.47-3.34 (m, 3H, C7, C22 and C23), 2.62 (t, 2H, *J* = 12.0 Hz, C22-C23), 1.99-1.86 (m, 2H, C24 and C25), 1.79-1.66 (m, 3H, C24-C26), 1.55 (s, 3H, C6), 0.96-0.93 (m, 12H, C10-C12 and C27). **^{13}C NMR** (125 MHz, $CDCl_3$); 187.9 (C4), 175.3 (C2), 165.9 (C13), 138.4 (quart C), 130.9 (quart C), 130.7 (tert C), 129.7 (tert C), 129.2 (tert C), 97.5 (C3), 97.0 (C8), 72.1 (C7), 69.3 (C5), 60.4 (C21), 52.4 (C22 and C23), 42.1 (C14), 34.6 (C9), 30.7 (C24 and C25), 29.1 (C26), 25.4 (C10-C12), 20.9 (CH_3), 20.5 (CH_3). **MS** (ES^+); 478.28 (M+Na); **HRMS** (M+Na); calcd for $C_{26}H_{37}N_3Na_1O_4$; 478.2676; found; 478.2667.

3.2.57. Synthesis of (±)-**9U**



Yield; 27 %; M.P.; 129 °C; Form AB: CD = not determined**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.89-7.35 m, 4H, C18-C21), 5.87-5.77 (m, 1H, C13), 5.04-5.00 (m, 2H, C14), 4.64 (s, 1H, C8), 4.53 (brs, 2H, C16), 4.12 (brs, 2H, C23), 3.88 (d, 1H, *J* = 7.8 Hz, C7), 3.49-3.30 (m, 3H, C7, C24 and C25), 2.60 (brs, 2H, C24-C25), 2.15-1.95 (m, 5H, C12 and C26-C28), 1.76-1.72 (m, 2H, C26 and C27), 1.57 (brs, 3H, C6), 0.97-0.92 (m, 9H, C10-C11, C29). **^{13}C NMR** (125 MHz, $CDCl_3$); 188.0 (C4), 175.4 (C2), 165.9 (C15), 138.5 (C22), 134.4 (C13), 130.9 (tert C), 130.8 (tert C), 129.8 (tert C), 129.3 (tert C), 128.8 (C17), 117.7 (C14), 97.5 (C3), 96.5 (C8), 72.2 (C7), 69.3 (C5), 60.6 (C23), 52.5 (C24 and C25), 42.5 (C12), 42.1 (C16), 37.5 (C9), 30.7 (C26 and C27), 29.2 (C28), 22.5 (C10), 22.2 (C11), 20.9 (CH_3), 20.6 (CH_3). **MS** (ES^+); 481.30 (M+H), 504.28 (M+Na); **HRMS** (M+Na); calcd for $C_{28}H_{39}N_3Na_1O_4$; 504.2833; found; 504.2837.

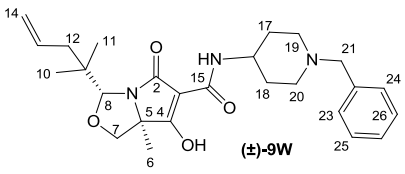
3.2.58. Synthesis of (±)-**9V**



Yield; 39 %; M.P.; 161 °C; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, CD_3OD); 7.46 (d, 1H, *J* = 5.1 Hz, C24), 7.39 (d, 1H, *J* = 3.4 Hz, C22), 7.16 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.4 Hz, C23), 4.61 (s, 1H, C8), 4.58 (s, 2H, C20), 3.92 (d, 1H, *J* = 8.4 Hz, C7), 3.63-3.53 (m, 2H, C18 and 19), 3.45 (d, 1H, *J* = 8.4 Hz, C7), 3.31 (m, 1H, C15), 3.11-2.96 (m, 2H, C18 and 19), 2.01-1.98 (m, 2H, C16 and C17), 1.61-

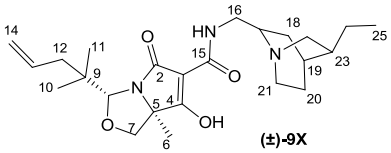
1.51 (m, 5H, C6, C16 and 17), 1.00 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, CD_3OD); 190.0 (C4), 178.2 (C2), 167.3 (C13), 133.9 (tert C), 130.9 (C21), 130.5 (tert C), 128.9 (tert C), 99.0 (C3), 98.6 (C8), 73.3 (C7), 71.1 (C5), 55.1 (CH_2), 53.0 (CH_2), 43.9 (C14), 35.6 (C9), 35.4 (C15), 28.3 (C16 and C17), 26.1 (C10-C12), 21.4 (C6). **MS** (ES^-); 446.21 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{32}N_3O_4S_1$; 446.2119; found; 446.2123.

3.2.59. Synthesis of (±)-**9W**



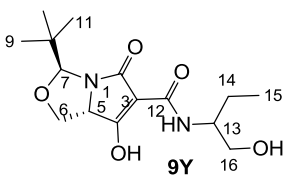
Yield; 51 %; M.P.; 179 ℃; Form AB: CD = 80: 20**; ^{1}H NMR** (400 MHz, CD_3OD): 7.56-7.52 (m, 5H, C23-C27), 5.92 (brs, 1H, C13), 5.06 (brs, 2H, C14), 4.70 (s, 1H, C8 CD), 4.66 (s, 1H, C8 AB), 4.43 (s, 2H, C21 CD), 4.35 (s, 2H, C21 AB), 4.26 (brs, 1H, C16 CD), 4.11 (brs, 1H, C16 AB), 3.94 (d, 1H, *J* = 6.0 Hz, C7), 3.57-3.55 (m, 2H, C19-C20), 3.44 (d, 1H, *J* = 6.0 Hz, C7), 3.20-3.14 (m, 2H, C19-C20), 2.24-2.16 (m, 4H, C12, C17 and C18), 1.88-1.85 (m, 2H, C17 and C18), 1.57 (s, 3H, C6), 0.98 (s, 3H, C10), 0.96 (s, 3H, C11). **^{13}C NMR** (125 MHz, CD_3OD and $CDCl_3$, Tautomer AB only): 189.2 (C4), 178.1 (C2), 166.3 (C13), 135.9 (C13), 132.4 (tert C), 131.4 (tert C), 130.5 (tert C), 130.3 (C22), 118.0 (C14), 98.0 (C8), 97.6 (C3), 73.3 (C7), 70.9 (C5), 61.7 (C21), 52.6 (C19 and C20), 45.1 (C16), 43.9 (C12), 38.5 (C9), 30.2 (C17 and C18), 23.2 (C10), 22.9 (C11), 21.4 (C6). **MS** (ES^-); 452.27 (M-H), **HRMS** (M-H); calcd for $C_{26}H_{34}N_3O_4$; 452.2555; found; 452.2553.

3.2.60. Synthesis of (±)-**9X**



Yield; 23 % (oil); Form AB: CD = 99: 1; **^{1}H NMR** (500 MHz, $CDCl_3$); 8.04 (brs, 1H, NH or OH), 5.89-5.81 (m, 1H, C13), 5.06-5.03 (m, 2H, C14), 4.67 (s, 1H, C8), 4.02-3.80 (m, 2H, C7 and CH_2), 3.70-3.61 (m, 2H), 3.53-3.44 (m, 3H, C7 and CH_2), 3.28-3.26 (m, 1H), 3.01-2.92 (m, 1H), 2.16-2.07 (m, 2H, C12), 1.99-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.57 (s, 3H, C6), 1.52-1.42 (m, 2H, C24), 1.35-1.26 (m, 1H), 0.96-0.91 (m, 9H, C10, C11 and C25). **^{13}C NMR** (125 MHz, $CDCl_3$, two set of signals in some case caused by two diastereomers); 166.9 (C15), 134.6 (C13), 117.7 (C14), 96.6 (C8), 72.1 (C7), 57.3 and 57.0 (C17), 48.5 and 48.4 (CH_2), 48.1 and 48.0 (CH_2), 42.5 (CH_2), 38.9 and 38.7 (CH_2), 37.5 (C9), 35.2 (C23), 24.9 (CH_2), 24.7 (C19), 23.9 and 23.8 (CH_2), 22.5 (C10), 22.2 (C11), 20.6 and 20.5 (C6), 11.5 (C25). **MS** (ES^+); 432.30 (M+H), 454.28 (M+Na); **HRMS** (M+Na); calcd for $C_{24}H_{37}N_3Na_1O_4$; 454.2676; found; 454.2674.

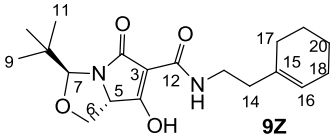
3.2.61. Synthesis of **9Y**



Yield; 43 % (oil); Form AB: CD = 85: 15**; ^{1}H NMR** (500 MHz, $CDCl_3$); 7.89 (brs, 1H, NH or OH CD), 7.58 (brs, 1H, NH or OH AB), 6.72 (brs, 1H, NH or OH CD), 6.59 (brs, 1H, NH or OH AB), 4.80 (s, 1H, C7 AB), 4.79 (s, 1H, C7 CD), 4.40 (t, 1H, *J* = 8.0 Hz, C5), 4.31-4.28 (m, 1H, C6), 3.97-3.92 (m, 1H, C13), 3.74-3.61 (m, 2H, C16), 3.44-4.41 (m, 1H, C6), 1.71-1.53 (m, 2H, C14), 1.00-0.96 (m, 12H, C9-C11 and C15). **^{13}C NMR** (125 MHz,

$CDCl_3$, tautomer AB only); 186.77 and 185.60 (C4), 174.85 and 174.79 (C2), 166.53 and 166.48 (C12), 97.78 and 97.65 (C3), 94.77 and 94.72 (C7), 67.24 and 67.21 (C6), 64.93 and 64.80 (C16), 63.02 (C5), 53.16 and 53.02 (C13), 35.76 (C8), 24.59 (C9-C11), 24.13 (C14), 10.44 (C15). **MS** (ES^-); 311.16 (M-H); **HRMS** (M-H); calcd for $C_{15}H_{23}N_2O_5$; 311.1612; found; 311.1607.

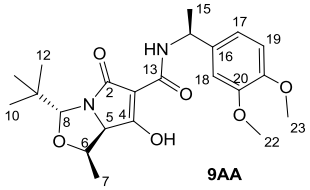
3.2.62. Synthesis of **9Z**



9Z

Yield; 41 %; M.P. 127 ℃; AB: CD = 75: 25; **^{1}H NMR** (400 MHz, $CDCl_3$); 10.37 (s, 1H, NH or OH), 7.90 (brs, 1H, NH or OH CD), 7.48 (s, 1H, NH or OH AB), 5.51 (brs, 1H, C16), 4.83 (s, 1H, C7 CD), 4.80 (s, 1H, C7 AB), 4.37 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.2 Hz, C5 AB), 4.28 (dd, 1H, J_1 = 7.6 Hz, J_2 = 7.2 Hz, C6), 4.11 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.2 Hz, C5 CD), 3.45-3.38 (m, 3H, C6 and C13), 2.19 (t, 2H, J = 6.8 Hz, C14), 2.00 (brs, 2H, C18), 1.93 (brs, 2H, C17), 1.66-1.52 (m, 4H, C19 and C29), 0.96 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer AB only); 186.5 (C4), 174.8 (C2), 166.1 (C12), 133.7 (C15), 124.0 (C16), 97.0 (C3), 94.7 (C7), 67.3 (C6), 63.2 (C5), 37.4 (C14), 37.1 (C13), 35.8 (C8), 28.0 (C17), 25.2 (C18), 24.6 (C9-C11), 22.7 (CH_2), 22.2 (CH_2). **MS** (ES^-); 347.19 (M-H); MS (ES^+); 349.22 (M+H), 371.19 (M+Na); **HRMS** (M-H); calcd for $C_{19}H_{27}N_2O_4$; 347.1976; found; 347.1981.

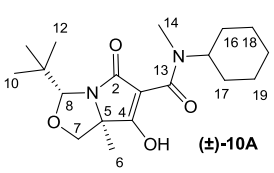
3.2.63. Synthesis of **9AA**



9AA

Yield; 31 % (oil); Form AB: CD = 90: 10**; ^{1}H NMR** (400 MHz, $CDCl_3$); 8.04 (d, 1H, J = 8.2 Hz, NH CD), 7.55 (d, 1H, J = 8.2 Hz, NH AB), 6.90-6.81 (m, 3H, C17-C19), 5.15-5.06 (m, 1H, C14), 4.79 (s, 1H, C8 CD), 4.75 (s, 1H, C8 AB), 3.87-3.84 (m, 5H, C5, C22 and C23), 3.66-3.58 (m, 1H, C6), 1.59 (d, 3H, J = 6.9 Hz, C7 CD), 1.52 (d, 3H, J = 6.9 Hz, C7 AB), 1.42 (d, 3H, J = 6.0 Hz, C15), 0.95 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 184.7 (C4), 174.6 (C2), 165.0 (C13), 149.1 (C20), 148.5 (C21), 135.0 (C16), 118.0 (tert C), 111.3 (tert C), 109.6 (tert C), 98.2 (C3), 94.6 (C8), 75.8 (C6), 68.4 (C5), 55.93 (CH_3), 55.90 (CH_3), 48.2 (C14), 35.5 (C9), 24.6 (C10-C12), 22.3 (C15), 17.2 (C7). **MS** (ES^-); 417.21 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{29}N_2O_6$; 417.2031; found; 417.2033.

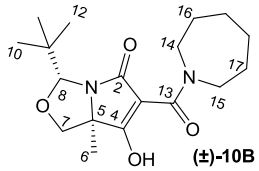
3.2.64. Synthesis of (±)-**10A**



(±)-10A

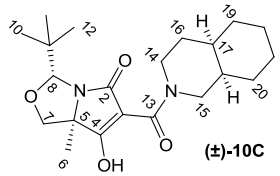
Yield; 39 %; M.P.; 123 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (500 MHz, $CDCl_3$); 4.72 (s, 1H, C8), 4.27 (brs, 1H, C15), 3.84 (d, 1H, J = 8.8 Hz, C7), 3.42 (d, 1H, J = 8.8 Hz, C7), 3.11 (brs, 3H, C14), 1.89-1.73 (m, 4H, CH_2), 1.53 (s, 3H, C6), 1.50-1.34 (m, 4H, CH_2), 1.16-1.06 (m, 2H, CH_2), 1.02 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 167.1 (C13), 97.8 (C8), 72.3 (C7), 34.7 (C9), 29.7 (CH_2), 25.6 (CH_2), 25.4 (C10-C12), 21.4 (C6). **MS** (ES^-); 349.21 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{29}N_2O_4$; 349.2133; found; 349.2134.

3.2.65. Synthesis of (±)-**10B**



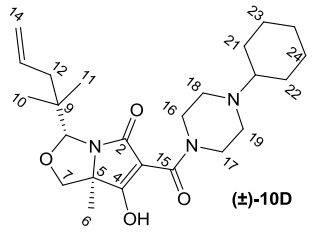
Yield; 39 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (500 MHz, $CDCl_3$); 4.71 (s, 1H, C8), 4.03 (brs, 2H, C14 and C15), 3.83 (d, 1H, *J* = 8.5 Hz, C7), 3.62 (brs, 2H, C14 and C15), 3.41 (d, 1H, *J* = 8.5 Hz, C7), 1.80 (brs, 4H, CH_2), 1.59 (brs, 4H, CH_2), 1.52 (s, 3H, C6), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 167.6 (C13), 97.9 (C8), 72.3 (C7), 70.3 (C5), 34.7 (C9), 25.6 (C10-C12), 21.4 (C6). **MS** (ES^-); 335.21 (M-H); **HRMS** (M-H); calcd for $C_{18}H_{27}N_2O_4$; 335.1976; found; 335.1967.

3.2.66. Synthesis of (±)-**10C**



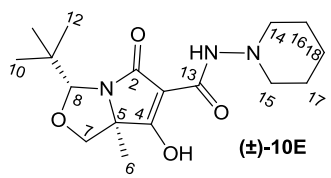
Yield; 72 % (oil); Form AB: CD = not determined**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.70 (s, 2H, C8 and CH_2), 4.49 (brs, 1H, CH_2), 3.83 (d, 1H, *J* = 8.3 Hz, C7), 3.41 (d, 1H, *J* = 8.3 Hz, C7), 2.92 (t, 1H, *J* = 12.1 Hz, CH_2), 2.52 (d, 1H, *J* = 10.6 Hz, CH_2), 1.83-1.61 (m, 6H), 1.52 (s, 3H, C6), 1.41-1.12 (m, 6H), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, two set of signals in some case are caused by two diastereomers); 193.76 and 193.58 (C4), 179.8 (C2), 165.88 and 165.33 (C13), 87.87 (C3), 97.80 and 97.77 (C8), 72.2 (C7), 70.38 and 70.26 (C5), 42.50 and 42.30 (CH_2), 41.80 and 41.78 (C17 and C18), 34.7 (C9), 33.1 (CH_2), 32.5 (CH_2), 29.8 (CH_2), 26.1 (C21), 26.06 and 26.03 (CH_2), 25.66 and 25.63 (CH_2), 25.5 (C10-C12), 21.38 and 21.34 (C6). **MS** (ES^-); 375.24 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{31}N_2O_4$; 375.2289; found; 375.2280.

3.2.67. Synthesis of (±)-**10D**



Yield; 33 % (oil); Form AB: CD = 99: 1; **^{1}H NMR** (400 MHz, CD_3OD); 5.97-5.87 (m, 1H, C13), 5.08-5.03 (m, 2H, C14), 4.70 (s, 1H, C8), 3.93 (d, 1H, *J* = 8.2 Hz, C7), 3.72-3.58 (m, 4H, CH_2), 3.48 (d, 1H, *J* = 8.2 Hz, C7), 3.31-3.13 (m, 5H, C20 and CH_2), 2.20-2.11 (m, 4H, C12 and CH_2), 1.98-1.95 (m, 2H, CH_2), 1.76-1.72 (m, 1H, CH_2), 1.58 (s, 3H, C6), 1.56-1.22 (m, 5H, CH_2), 0.99 (s, 3H, C10), 0.98 (s, 3H, C11). **^{13}C NMR** (125 MHz, CD_3OD); 178.5 (C2), 164.5 (C15), 136.1 (C13), 117.9 (C14), 99.5 (C3), 98.3 (C8), 73.4 (C7), 71.0 (C5), 67.4 (C20), 46.6 (CH_2), 44.1 (CH_2), 42.3 (C12), 38.6 (C9), 28.1 (CH_2), 26.1 (CH_2), 23.2 (C10), 23.0 (C11), 21.8 (C6). **MS** (ES^+); 432.29 (M+H), 454.27 (M+Na); **HRMS** (M+Na); calcd for $C_{24}H_{37}N_3Na_1O_4$; 454.2676; found; 454.2674.

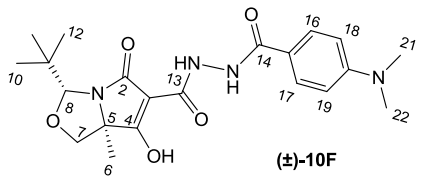
3.2.68. Synthesis of (±)-**10E**



Yield; 52 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.64 (s, 1H, C8), 3.89 (d, 1H, *J* = 8.4 Hz, C7), 3.45 (d, 1H, *J* = 8.4 Hz, C7), 2.81 (brs, 4H, C14 and C15), 1.80-1.69 (m, 4H, C16-C17), 1.58 (s, 3H, C6), 1.50-1.40 (m, 2H, C18), 1.02 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 97.2 (C8), 72.2 (C7), 57.1 (C14 and C15), 34.7 (C9), 25.5 (C16 and C17), 24.9 (C10-C12), 23.0 (C18), 20.6 (C6). **MS** (ES^-); 336.20

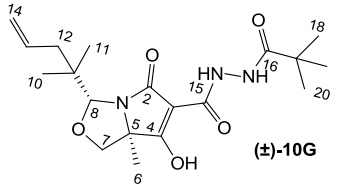
(M-H); **HRMS** (M-H); calcd for $C_{17}H_{26}N_3O_4$; 336.1929; found; 336.1928.

3.2.69. Synthesis of (±)-**10F**



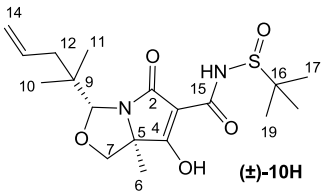
Yield; 27 %; M.P.; 169 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 8.53 (brs, 1H, NH or OH), 7.75 (d, 2H, *J* = 8.3 Hz, C16 and C17), 6.66 (d, 2H, *J* = 8.3 Hz, C18 and C19), 4.63 (s, 1H, C8), 3.88 (d, 1H, *J* = 8.1 Hz, C7), 3.44 (d, 1H, *J*= 8.1 Hz, C7), 3.02 (s, 6H, C21 and C22), 1.59 (s, 3H, C6), 1.02 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 186.7 (C4), 174.4 (C2), 165.3 (C13), 163.6 (C14), 152.9 (C20), 128.9 (C16 and C17), 117.8 (C15), 111.1 (C18 and C19), 98.1 (C3), 97.2 (C8), 72.2 (C7), 69.5 (C5), 40.1 (C21 and C22), 34.7 (C9), 25.4 (C10-C12), 20.6 (C6). **MS** (ES^-); 415.21 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{27}N_4O_5$; 415.1987; found; 415.1985.

3.2.70. Synthesis of (±)-**10G**



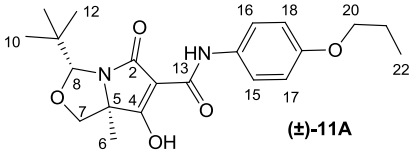
Yield; 23 %; M.P.; 151 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.58 (brs, 1H, NH or OH), 5.93-5.82 (m, 1H, C13), 5.09-5.05 (m, 2H, C14), 4.70 (s, 1H, C8), 3.91 (d, 1H, *J* = 8.3 Hz, C7), 3.46 (d, 1H, *J* = 8.3 Hz, C7), 2.14 (d, 2H, *J* = 7.3 Hz, C12), 1.61 (s, 3H, C6), 1.28 (s, 9H, C18-C20), 0.99 (s, 3H, C10), 0.97 (s, 3H, C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 186.8 (C4), 176.0 (C16), 174.4 (C2), 163.4 (C15), 134.5 (C13), 117.7 (C14), 97.9 (C3), 96.6 (C8), 72.2 (C7), 69.4 (C5), 42.5 (C12), 38.3 (C17), 37.5 (C9), 27.2 (C18-C20), 22.5 (C10), 22.2 (C11), 20.6 (C6). **MS** (ES^-); 378.19 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{28}N_3O_5$; 378.2034; found; 378.2037.

3.2.71. Synthesis of (±)-**10H**



Yield; 31 %; M.P.; 151 ℃; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, CD_3OD); 5.97-5.87 (m, 1H, C13), 5.08-5.03 (m, 2H, C14), 4.71 (s, 1H, C8), 3.96 (d, 1H, *J* = 8.3 Hz, C7), 3.50 (d, 1H, *J* = 8.3 Hz, C7), 2.17 (dd, 2H, J_1 = 7.2 Hz, J_2 = 4.7 Hz, C12), 1.60 (s, 3H, C6), 1.27 (s, 9H, C17-C19), 1.00 (s, 3H, C10), 0.98 (s, 3H, C11). **^{13}C NMR** (125 MHz, CD_3OD); 134.9 (C13), 116.9 (C14), 97.1 (C8), 72.3 (C7), 69.8 (C5), 63.59 (C16), 42.9 (C12), 37.5 (C9), 26.5 (C17-C19), 22.2 (C10), 21.9 (C11), 20.4 (C6). **MS** (ES^+); 385.19 (M+H); **HRMS** (M+H); calcd for $C_{18}H_{29}N_2O_5S_1$; 385.1792; found; 385.1789.

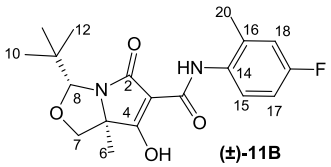
3.2.72. Synthesis of (±)-**11A**



Yield; 46 % (oil); Form AB: CD = 90: 10; **^{1}H NMR** (500 MHz, $CDCl_3$); 9.44 (brs, 1H, NH or OH CD), 9.29 (brs, 1H, NH or OH AB), 7.47 (d, 2H, *J* = 8.8 Hz, C15 and C16 AB), 7.36 (d, 2H, *J* = 8.8 Hz, C15 and C16 CD), 6.88 (d, 1H, *J* = 8.8 Hz, C17 and C18), 4.68 (s, 1H, C8), 3.97-3.87 (m,

3H, C7 and C20), 3.48 (d, 1H, *J* = 8.5 Hz, C7), 1.84-1.77 (m, 2H, C21), 1.63 (s, 3H, C6 AB), 1.57 (s, 3H, C6 CD), 1.08-1.02 (m, 12H, C10-C12, C22). **^{13}C NMR** (125 MHz, $CDCl_3$); 187.8 (C4), 175.5 (C2), 163.8 (C13), 156.5 (C19), 129.3 (C14), 121.9 (C15 and C16), 114.9 (C17 and C18), 98.1 (C3), 97.2 (C8), 72.3 (C7), 69.7 (C20), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 22.5 (C21), 20.6 (C6), 10.5 (C22). **MS** (ES^-); 387.21 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{27}N_2O_5$; 387.1925; found; 387.1921.

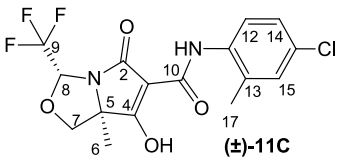
3.2.73. Synthesis of (±)-**11B**



(±)-11B

Yield; 53 %; M.P.; 142 °C; Form AB: CD = 95: 5; **^{1}H NMR** (400 MHz, $CDCl_3$); 9.40 (brs, 1H, NH or OH CD), 9.31 (brs, 1H, NH or OH AB), 7.89 (dd, 1H, J_1 = 8.5 Hz, J_2 = 5.4 Hz, C17 AB), 7.71 (dd, 1H, J_1 = 8.5 Hz, J_2 = 5.4 Hz, C17 CD), 6.98-6.89 (m, 2H, C15 and C18), 4.70 (s, 1H, C8), 3.95 (d, 1H, *J* = 8.3 Hz, C7 AB), 3.88 (d, 1H, *J* = 8.3 Hz, C7 CD), 3.50 (d, 1H, *J* = 8.3 Hz, C7), 2.36 (s, 3H, C20), 1.65 (s, 3H, C6 AB), 1.59 (s, 3H, C6 CD), 1.06 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$, Tautomer AB only); 187.6 (C4), 175.4 (C2), 164.2 (C13), 159.9 (d, $J_{C\text{-}F}$ = 244 Hz, C19), 131.7 (d, $J_{C\text{-}F}$ = 27.6 Hz, C16), 130.5 (d, $J_{C\text{-}F}$ = 2.88 Hz, C14), 124.0 (d, $J_{C\text{-}F}$ = 8.63 Hz, C15), 117.2 (d, $J_{C\text{-}F}$ = 21.8 Hz, C18), 113.1 (d, $J_{C\text{-}F}$ = 21.8 Hz, C17), 98.5 (C3), 97.1 (C8), 72.3 (C7), 69.3 (C5), 34.7 (C9), 25.5 (C10-C12), 20.6 (C6), 17.9 (C20). **MS** (ES^-); 361.16 (M-H), **HRMS** (M-H); calcd for $C_{19}H_{22}F_1N_2O_4$; 361.1569; found; 361.1564.

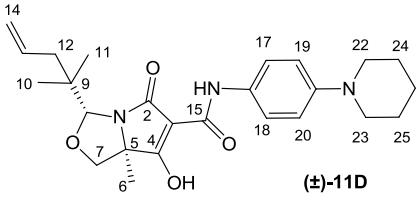
3.2.74. Synthesis of (±)-**11C**



(±)-11C

Yield; 46 %; M.P.; 172 °C; Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 11.37 (s, 1H, NH or OH), 9.21 (brs, 1H, NH or OH), 7.98 (d, 1H, *J* = 9.4 Hz, C12), 7.25-7.14 (m, 2H, C14 and C15), 5,42 (q, 1H, *J* = 5.2 Hz, C8), 4.10 (d, 1H, *J* = 8.6 Hz, C7), 3.87 (d, 1H, *J* = 8.6 Hz, C7), 2.34 (s, 3H, C17), 1.72 (s, 3H, C6). **^{13}C NMR** (125 MHz, $CDCl_3$); 189.6 (C4), 174.5 (C2), 163.5 (C10), 133.0 (quart C), 130.5 (quart C), 130.4 (tert C), 130.2 (quart C), 126.8 (tert C), 122.8 (tert C), 121.8 (q, $J_{C\text{-}F}$ = 280 Hz, C9), 97.0 (C3), 84.3 (q, $J_{C\text{-}F}$ = 37.0 Hz,C8), 72.7 (C7), 69.4 (C5), 20.2 (C6), 17.5 (C17). **MS** (ES^-); 389.06 (M-H); **HRMS** (M-H); calcd for $C_{16}H_{13}Cl_1F_3N_2O_4$; 389.0521; found; 389.0522.

3.2.75. Synthesis of (±)-**11D**

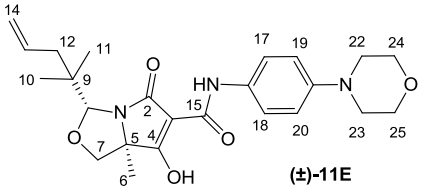


(±)-11D

Yield; 31 % (oil); Form AB: CD = not determined; **^{1}H NMR** (400 MHz, $CDCl_3$); 9.62 (brs, 1H, NH or OH), 7.77 (d, 2H, *J* = 8.6 Hz, C17 and C18), 7.70 (d, 2H, *J* = 8.6 Hz, C19 and C20), 5.94-5.83 (m, 1H, C13), 5.10-5.06 (m, 2H, C14), 4.73 (s, 1H, C8), 3.95 (d, 1H, *J* = 8.3 Hz, C7), 3.48 (d, 1H, *J* = 8.3 Hz, C7), 3.44 (brs, 4H, C22 and C23), 2.25 (brs, 4H, C24 and C25), 2.20-2.12 (m, 2H, C12), 1.75 (brs, 2H, C26), 1.64 (s, 3H, C6), 1.02 (s, 3H, C10), 0.99 (s, 3H, C11). **^{13}C NMR** (125 MHz, CDCl3); 164.2 (C15), 139.2 (quart C), 137.7 (quart C), 134.3 (C13), 122.0 (tert C), 121.4 (tert C), 117.9 (C14), 99.4 (C3),

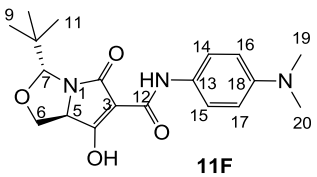
96.7 (C8), 72.2 (C7), 64.9 (C5), 57.3 (C22 and C23), 42.5 (C12), 37.5 (C9), 23.2 (C24 and C25), 22.6 (C10), 22.2 (C11), 21.8 (C26), 20.6 (C6). **MS** (ES^-); 438.25 (M-H); **HRMS** (M-H); calcd for $C_{25}H_{32}N_3O_4$; 438.2398; found; 438.2391.

3.2.76. Synthesis of (±)-**11E**



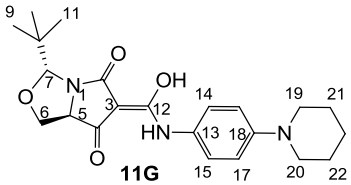
Yield; 38 %; M.P.; 173 ℃; Form AB: CD = 99: 1; **^{1}H NMR** (400 MHz, $CDCl_3$); 9.41 (brs, 1H, NH or OH), 7.64 (d, 2H, *J* = 8.1 Hz, C17 and C18), 7.48 (brs, 2H, C19 and C20), 5.92-5.82 (m, 1H, C13), 5.09-5.05 (m, 2H, C14), 4.72 (s, 1H, C8), 4.04 (brs, 4H, C24 and C25), 3.94 (d, 1H, *J* = 8.3 Hz, C7), 3.46 (d, 1H, *J* = 8.3 Hz, C7), 3.27 (brs, 4H, C22 and C23), 2.21-2.10 (m, 2H, C12), 1.63 (s, 3H, C6), 1.01 (s, 3H, C10), 0.98 (s, 3H, C11). **^{13}C NMR** (125 MHz, CDCl3); 187.8 (C4), 175.3 (C2), 163.8 (C15), 134.4 (C13), 128.9 (Ar-C), 128.1 (Ar-C), 125.2 (Ar-C), 121.5 (Ar-C), 117.8 (C14), 98.1 (C3), 96.6 (C8), 72.2 (C7), 69.3 (C5), 65.6 (C24 and C25), 51.4 (C22 and C23), 42.5 (C12), 37.5 (C9), 22.5 (C10), 22.1 (C11), 20.5 (C6). **MS** (ES^-); 440.22 (M-H); **HRMS** (M-H); calcd for $C_{24}H_{30}N_3O_5$; 440.2191; found; 440.2190.

3.2.77. Synthesis of **11F**



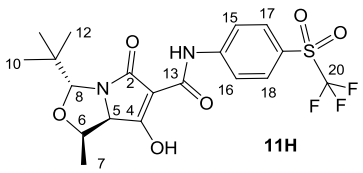
Yield; 55 %; M.P.; 111 ℃; Form AB: CD = 99:1**;** **^{1}H NMR** (500 MHz, $CDCl_3$); 7.41 (d, 2H, *J* = 7.0 Hz, C14 and C15), 6.72 (d, 2H, *J* = 7.0 Hz, C16 and C17), 4.85 (s, 1H, C7), 4.43 (brs, 1H, C5), 4.33 (t, 1H, *J* = 7.5 Hz, C6), 3.46 (t, 1H, *J* = 9.0 Hz, C6), 2.95 (s, 6H, C19 and C20), 1.00 (m, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 122.00 (C14 and C15), 112.88 (C16 and C17), 94.84 (C7), 67.34 (C6), 40.78 (C19 and C20), 35.81 (C8), 24.64 (C9-C11). **MS** (ES^-); 358.21 (M-H), **HRMS** (M-H); calcd for $C_{19}H_{24}N_3O_4$; 358.1772; found; 358.1776.

3.2.78. Synthesis of **11G**



Yield; 68 %; M.P.; 249 ℃(decomposed); Form AB: CD = 99: 1**;** **^{1}H NMR** (500 MHz, $CDCl_3$); 9.65 (brs, 1H, NH), 7.82 (d, 2H, *J* = 9.0 Hz, C16 and C17), 7.67 (d, 2H, *J* = 9.0 Hz, C14 and C15), 4.81 (s, 1H, C7), 4.43 (brs, 1H, C5), 4.32 (t, 1H, *J* = 7.5 Hz, C6), 3.44-3.41 (m, 5H, C6, C19 and C20), 2.24 (brs, 4H, CH_2), 1.74 (brs, 2H, CH_2), 0.96 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 184.10 (C4), 174.97 (C2), 163.92 (C12), 138.82 (quart C), 138.06 (quart C), 122.16 (C14 and C15), 121.13 (C16 and C17), 98.84 (C3), 94.84 (C7), 67.31 (C6), 62.88 (C5), 57.29 (C19 and C20), 35.72 (C8), 24.53 (C9-C11), 23.03 (C21 and C22), 21.61 (C23). **MS** (ES^-); 398.21 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{28}N_3O_4$; 398.2085; found; 398.2081.

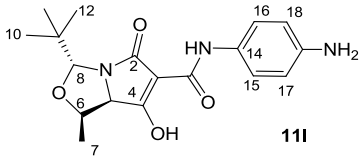
3.2.79. Synthesis of **11H**



Yield; 40 %; M.P.; 196 ℃; Form AB: CD = 99: 1; **^{1}H NMR** (400 MHz, $CDCl_3$);

9.89 (brs, 1H, NH or OH), 8.01 (d, 2H, *J* = 8.8 Hz, C15 and C16), 7.92 (d, 2H, *J* = 8.8 Hz, C17 and C18), 4.84 (s, 1H, C8), 4.02 (d, 1H, *J* = 8.6 Hz, C5), 3.77-3.69 (m, 1H, C6), 1.51 (d, 3H, *J* = 6.1 Hz, C7), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$); 184.1 (C4), 173.9 (C2), 164.3 (C13), 144.3 (C14), 132.4 (C17-C18), 125.7 (C19), 120.2 (C15-C16), 99.9 (C3), 94.9 (C8), 75.9 (C6), 68.1 (C5), 35.6 (C9), 24.6 (C10-C12), 17.2 (C7). **MS** (ES^-); 461.10 (M-H), **HRMS** (M-H); calcd for $C_{19}H_{20}F_3N_2O_6S_1$; 461.1000; found; 461.1003.

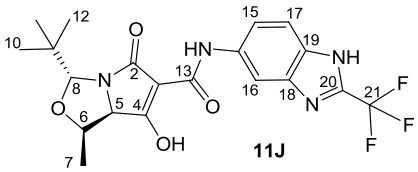
3.2.80. Synthesis of **11I**



11I

Yield; 32 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.89 (brs, 1H, NH or OH), 8.01 (d, 2H, *J* = 8.8 Hz, C15 and C16), 7.92 (d, 2H, *J* = 8.8 Hz, C17 and C18), 4.84 (s, 1H, C8), 4.02 (d, 1H, *J* = 8.6 Hz, C5), 3.75-3.69 (m, 1H, C6), 1.51 (d, 3H, *J*= 6.1 Hz, C7), 1.01 (s, 9H, C10-C12). **^{13}C NMR** (100 MHz, $CDCl_3$); 184.1 (C4), 173.9 (C2), 164.4 (C13), 144.3 (C19), 132.4 (C15 and C16), 125.8 (C14), 120.2 (C17 and C18), 99.3 (C3), 94.9 (C8), 76.0 (C6), 68.1 (C5), 35.6 (C9), 24.6 (C10-C12), 17.2 (C7). **MS** (ES^-); 344.17 (M-H), **HRMS** (M-H); calcd for $C_{18}H_{22}N_3O_4$; 344.1616; found; 344.1609.

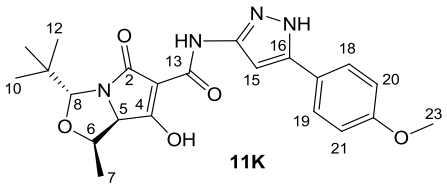
3.2.81. Synthesis of **11J**



11J

Yield; 38 %; M.P.; 135 ℃; Form AB: CD = 99: 1; **^{1}H NMR** (400 MHz, $CDCl_3$); 9.58 (brs, 1H, NH or OH), 8.13 (s, 1H, C16), 7.66 (d, 1H, *J* = 9.2 Hz, C15), 7.34 (dd, 1H, J_1 = 9.2 Hz, J_2 = 1.6 Hz, C17), 4.84 (s, 1H, C8), 3.98 (d, 1H, *J* = 8.8 Hz, C5), 3.75-3.68 (m, 1H, C6), 1.49 (d, 3H, *J* = 6.4 Hz, C7), 1.00 (s, 9H, C10-C12). **^{13}C NMR** (125 MHz, $CDCl_3$,); 183.7 (C4), 174.3 (C2), 164.0 (C13), 141.3 (q, $J_{C\text{-}F}$ = 39.8 Hz, C20), 133.7 (Ar-tert C), 118.6 (q, $J_{C\text{-}F}$ = 270 Hz, C21), 118.3 (Ar-tert C), 99.6 (C3), 94.8 (C8), 76.0 (C6), 68.1 (C5), 35.6 (C9), 24.6 (C10-C12), 17.2 (C7). **MS** (ES^+); 439.17 (M+H), 461.14 (M+Na); **HRMS** (M+H); calcd for $C_{20}H_{21}F_3N_4Na_1O_4$; 461.1407; found; 461.1409.

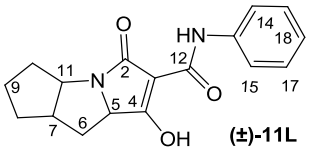
3.2.82. Synthesis of **11K**



11K

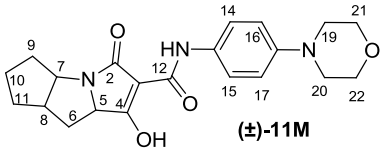
Yield; 34 % (oil); Form AB: CD = 70: 30**; ^{1}H NMR** (400 MHz, $CDCl_3$); 11.67 (s, 1H, NH AB), 11.44 (s, 1H, NH CD), 7.82 (d, 2H, *J* = 8.3 Hz, C18 and C19 CD), 7.73 (d, 2H, *J* = 8.3 Hz, C18 and C19 AB), 6.98-6.79 (m, 2H, C20 and C21), 6.05 (s, 1H, C15), 4.85 (s, 1H, C8 CD), 4.83 (s, 1H, C8 AB), 3.85 (s, 3H, C23 CD), 3.82 (s, 3H, C23 AB), 3.71-3.61 (m, 1H, C6), 3.54 (d, 1H, *J* = 8.8 Hz, C5 AB), 3.49 (d, 1H, *J* = 8.8 Hz, C5 CD), 1.46 (d, 3H, *J* = 5.8 Hz, C7), 1.03 (s, 9H, C10-C12 AB), 1.00 (s, 9H, C10-C12 CD). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer AB only); 193.6 (C4), 179.2 (C2), 163.5 (C13), 161.5 (C22), 145.2 (C16), 142.5 (C14), 128.0 (C18 and C19), 118.6 (C17), 114.4 (C20 and C21), 95.1 (C8), 92.3 (C3), 89.1 (C15), 75.3 (C6), 70.9 (C5), 52.3 (C23), 35.8 (C9), 25.1 (C10-C12), 17.8 (C7). **MS** (ES^-); 425.19 (M-H), **HRMS** (M-H); calcd for $C_{22}H_{25}N_4O_5$; 425.1830; found; 425.1824.

3.2.83. Synthesis of (±)-**11L**



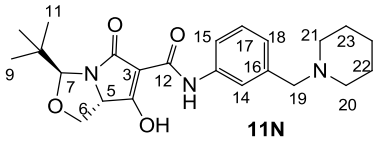
Yield; 23 % (oil); Form AB: CD = 99: 1**; ^{1}H NMR** (400 MHz, $CDCl_3$); 9.55 (brs, 1H, NH or OH), 7.58 (d, 2H, *J* = 7.6 Hz, C14 and C15), 7.34 (t, 2H, *J* = 7.6 Hz, C16-C17), 7.15 (t, 1H, *J* = 7.6 Hz, C18), 4.45-4.24 (m, 2H, C5 and C11), 3.13-3.05 (m, 1H, C7), 2.09-2.04 (m, 1H, CH_2), 1.96-1.79 (m, 3H, CH_2), 1.74-1.65 (m, 3H, CH_2), 1.56-1.48 (m, 1H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$); 185.9 (C4), 172.1 (C2), 164.4 (C12), 136.9 (C13), 129.1 (C16 and C17), 124.6 (C18), 120.2 (C14 and C15), 98.9 (C3), 63.6 (C11), 59.7 (C5), 47.7 (C7), 35.1 (CH_2), 34.1 (CH_2), 30.9 (CH_2), 26.4 (CH_2). **MS** (ES^-); 297.13 (M-H); **HRMS** (M-H); calcd for $C_{17}H_{17}N_2O_3$; 297.1245; found; 297.1247.

3.2.84. Synthesis of (±)-**11M**



Yield; 23 % (oil); Form AB: CD = 99: 1; **^{1}H NMR** (500 MHz, $CDCl_3$); 9.48 (brs, 1H, NH or OH), 7.54 (d, 2H, *J* = 8.8 Hz, C14 and C15), 7.07 (d, 2H, *J* = 8.8 Hz, C16 and 17), 6.16 (brs, 1H, NH or OH), 4.38-4.31 (m, 2H, C5 and C7), 3.96 (brs, 4H, C21 and C22), 3.21 (brs, 4H, C19 and C20), 3.11-3.04 (m, 1H, C8), 2.08-2.04 (m, 1H, CH_2), 1.94-1.87 (m, 2H, CH_2), 1.83-1.80 (m, 1H, CH_2), 1.73-1.65 (m, 3H, CH_2), 1.55-1.49 (m, 1H, CH_2). **^{13}C NMR** (125 MHz, $CDCl_3$); 186.0 (C4), 172.0 (C2), 164.3 (C12), 142.2 (C18), 134.7 (C13), 121.5 (C14 and C15), 119.5 (C16 and C17), 98.8 (C3), 65.2 (C21 and C22), 63.7 (C7), 59.7 (C5), 52.8 (C19 and C20), 47.7 (C8), 35.1 (CH_2), 34.1 (CH_2), 32.4 (CH_2), 26.4 (CH_2). **MS** (ES^-); 382.19 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{24}N_3O_4$; 382.1772; found; 382.1776

3.2.85. Synthesis of **11N**

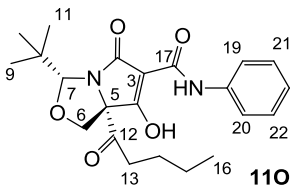


Yield; 60 %; M.P. 242 ℃; AB: CD = Not determined; **^{1}H NMR** (500 MHz, $CDCl_3$); 8.77 (s, 1H, C14), 7.31 (t, 1H, *J* = 8.0 Hz, C17), 7.05 (d, 1H, *J* = 8.0 Hz, C15), 6.90 (d, 1H, *J* = 8.0 Hz, C18), 4.90 (s, 1H, C7), 4.43 (s, 2H, C19), 4.27 (t, 1H, *J* = 7.5 Hz, C6), 4.04 (brs, 1H, C5), 3.68 (brs, 2H, CH_2), 3.46 (t, 1H, *J* = 9.0 Hz, C6), 2.62 (brs, 2H, CH_2), 1.91 (brs, 2H, CH_2), 1.76-1.70 (m, 3H, CH_2), 1.15-1.10 (m, 1H, CH_2), 0.99 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$); 193.0 (C4), 181.7 (C2), 165.0 (C12), 141.2 (C13), 129.1 (C17), 127.7 (C18), 124.5 (Ar-C), 123.2 (Ar-C), 120.0 (Ar-C), 95.4 (C3), 92.5 (C7), 68.0 (C6), 66.0 (C19), 60.9 (C5), 51.7 (C20 and C21), 36.0 (C8), 24.9 (C9-C11), 23.4 (C22 and C23), 21.5 (C24). **MS** (ES^-); 412.23 (M-H); MS (ES^+); 414.25 (M+H), 436.23 (M+Na); **HRMS** (M-H); calcd for $C_{23}H_{31}N_3Na_1O_4$; 436.2207; found; 436.2208.

3.3. Synthesis of 11O with phenyl isocyanate

To the solution of tetramic acid **16G** (150 mg, 0.53 mmol) and DMAP (80 mg, 0.64 mmol) in dichloromethane (30 ml) was added phenyl isocyanate (70 mg, 0.59 mmol) under nitrogen atmosphere. After strring the solution overnight, concentration in vacuo followed by flash column chromatography gave metal-chelated 3-

carboxamide tetramic acid. The compound was dissolved in dichloromethane (50 mL) and washed with aqueous HCl (3< pH <5, 50 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give free form of 3-carboxamide tetramic acid **11O** (100 mg, 0.26 mmol, 46 % yield, M.P. 91 ℃; AB: CD = 80: 20).



11O

^{1}H NMR (500 MHz, $CDCl_3$); 10.73 (brs, 1H, NH or OH), 9.53 (brs, 1H, NH or OH CD), 9.38 (brs, 1H, NH or OH AB), 7.59 (d, 2H, *J* = 8.0 Hz, C19 and C20 AB), 7.47 (d, 2H, *J* = 8.0 Hz, C19 and C20 CD), 7.43-7.37 (m, 2H, C21 and C22), 7.28-7.19 (m, 1H, C23), 5.00 (d, 1H, *J* = 8.5 Hz, C6 AB), 4.94 (d, 1H, *J* = 8.5 Hz, C6 CD), 4.78 (s, 1H, C7 CD), 4.75 (s, 1H, C7 AB), 3.50 (d, 1H, *J* = 8.5 Hz, C6 CD), 3.48 (d, 1H, *J* = 8.5 Hz, C6 AB), 2.89-2.82 (m, 1H, C13), 2.47-2.39 (m, 1H, C13), 1.70-1.61 (m, 1H, C14), 1.57-1.48 (m, 1H, C14), 1.36-1.29 (m, 2H, C15), 0.94 (s, 9H, C9-C11), 0.91 (t, 3H, *J* = 7.5 Hz, C16). **^{13}C NMR** (125 MHz, $CDCl_3$); 201.6 (C12 CD), 200.7 (C12 AB), 188.7 (C4 CD), 184.8 (C4 AB), 183.9 (C2 CD), 176.7 (C2 AB), 165.7 (C17 CD), 163.7 (C17 AB), 135.9 (C18 AB), 134.5 (C18 CD), 129.5 (C21 and C22 CD), 129.2 (C21 and C22 AB), 126.6 (C23 CD), 125.5 (C23 AB), 121.5 (C19 and C20 CD), 120.5 (C19 and C20 AB), 98.7 (C3 AB), 98.0 (C7 CD), 97.5 (C7 AB), 86.9 (C3 CD), 84.0 (C5 CD), 79.5 (C5 AB), 66.9 (C6 AB), 66.5 (C6 CD), 37.0 (C13 CD), 36.2 (C13 AB), 35.1 (C8 AB), 35.0 (C8 CD), 25.3 (C14 AB), 25.2 (C14 CD), 25.0 (C9-C11), 22.1 (C15 CD), 22.0 (C15 AB), 13.8 (C16 CD), 13.7 (C16 AB). **MS** (ES^-); 399.19 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{27}N_2O_5$; 399.1925; found; 399.1924.

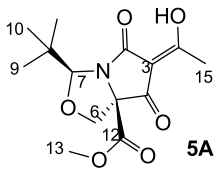
4. Synthesis of 3-acyltetramic acids

4.1. Synthesis of 3-acyltetramic acids via direct 3-acyllation

(a) carboxylic acid (1.1 eq), DCC (1.1 eq), DMAP (1.2 eq), CH_2Cl_2, r.t..

General procedure: To a solution of carboxilic acid (1.0 eq) in dichloromethane were added DCC (1.1 eq), tetramic acid (1.0 eq) and DMAP (1.2 eq), and the mixture was stirred overnight at room temperature. The crude reaction mixture was filtered with dichloromethane. Concentration in vacuo followed by flash column chromatography gave metal-chelated tetramic acid. The compound was dissolved in dichloromethane and washed with aqueous HCl (3< pH <5). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give free form of 3-acyltetramic acid.

4.1.1. Synthesis of **5A**

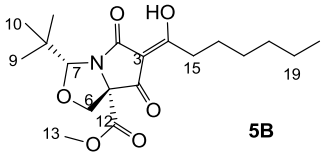


5A

Yield; 79 % (oil); Form AB: CD= 20: 80**; ^{1}H NMR** (500 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.83-4.82 (m, 1H, C6), 3.80 (s, 3H, C13 AB), 3.79 (s, 3H, C13 CD),

3.50 (d, 1H, *J* = 9.0 Hz, C6), 2.56 (s, 3H, C15 AB), 2.49 (s, 3H, C15 CD), 0.93 (s, 9H, C9-11 CD), 0.92 (s, 9H, C9-11 AB). **^{13}C NMR** (125 MHz, $CDCl_3$); 195.5 (C4 AB), 190.1 (C14 AB), 188.4 (C14 CD), 188.0 (C4 CD), 179.8 (C2 CD), 172.3 (C2 AB), 167.4 (C12 CD), 166.3 (C12 AB), 104.4 (C3 AB), 101.7 (C3 CD), 98.3 (C7 AB), 98.2 (C7 CD), 78.4 (C5 CD), 76.5 (C5 AB), 68.1 (C6 CD), 68.1 (C6 AB), 53.4 (C13 AB), 53.3 (C13 CD), 35.3 (C8 AB), 35.1 (C8 CD), 24.7 (C9-11 AB), 24.6 (C9-11 CD), 19.9 (C15 CD), 19.8 (C15 AB). **MS** (ES^-); 296.10 (M-H); **HRMS** (M-H); calcd for $C_{14}H_{18}N_1O_6$; 296.1140; found; 296.1138.

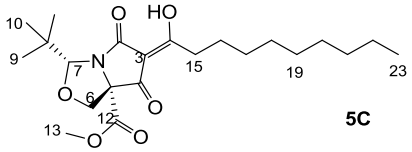
4.1.2. Synthesis of **5B**



5B

Yield; 78 % (oil); form AB: CD= 20: 80**; ^{1}H NMR** (500 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.82 (d, 1H, *J* = 9.5 Hz, C6), 3.80 (s, 3H, C13 AB), 3.78 (s, 3H, C13 CD), 3.49 (d, 1H, *J* = 9.5 Hz, C6), 3.01-2.79 (m, 2H, C15), 1.72-1.63 (m, 2H, C16), 1.40-1.25 (m, 6H, C17-C19), 0.93 (s, 9H, C9-11), 0.88 (t, 3H, *J* = 7.0 HZ, C20). **^{13}C NMR** (125 MHz, $CDCl_3$); 195.7 (C4 AB), 194.0 (C14 AB), 192.5 (C14 CD), 187.7 (C4 CD), 180.3 (C2 CD), 172.3 (C2 AB), 167.5 (C12 CD), 167.4 (C12 AB), 103.7 (C3 AB), 101.0 (C3 CD), 98.3 (C7 AB), 98.2 (C7 CD), 78.3 (C5 CD), 76.4 (C5 AB), 68.2 (C6 CD), 68.2 (C6 AB), 53.4 (C13 AB), 53.2 (C13 CD), 35.3 (C8 AB), 35.1 (C8 CD), 33.8 (C15 AB), 33.0 (C15 CD), 31.3 (CH_2 AB), 31.3 (CH_2 CD), 29.0 (CH_2 AB), 28.8 (CH_2 CD),25.8 (CH_2 CD), 25.7 (CH_2 AB), 24.9 (CH_2 AB), 24.7 (C9-11 AB), 24.6 (C9-11 CD), 22.4 (CH_2 CD), 15.2 (C20 AB), 13.9 (C20 CD). **MS** (ES^-); 366.18 (M-H); MS (ES^+); 390.20 (M+Na); **HRMS** (M+Na); calcd for $C_{19}H_{29}N_1Na_1O_6$; 390.1887; found; 390.1883.

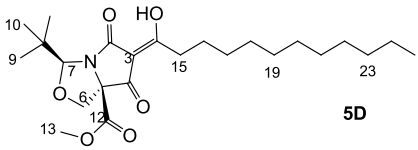
4.1.3. Synthesis of **5C**



5C

Yield; 45 % (oil); form AB: CD= 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.82 (d, 1H, *J* = 8.8 Hz, C6), 3.78 (s, 3H, C13), 3.49 (d, 1H, *J* = 8.8 Hz, C6), 3.01-2.78 (m, 2H, C15), 1.70-1.61 (m, 2H, C16), 1.37-1.25 (m, 12H, C17-C22), 0.92 (s, 9H, C9-11), 0.87 (t, 3H, *J* = 6.8 HZ, C23). **^{13}C NMR** (100 MHz, $CDCl_3$, taumer CD only); 192.5 (C14), 187.7 (C4), 180.3 (C2), 167.5 (C12), 101.0 (C3), 98.2 (C7), 78.3 (C5), 68.2 (C6), 53.2 (C13), 35.1 (C8), 33.0 (C15), 31.8 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.9 (CH_2), 24.6 (C9-11), 22.6 (CH_2), 14.0 (C23). **MS** (ES^-); 408.2 (M-H); **HRMS** (M+Na); calcd for $C_{22}H_{35}N_1Na_1O_6$; 432.2357; found; 432.2350.

4.1.4. Synthesis of **5D**

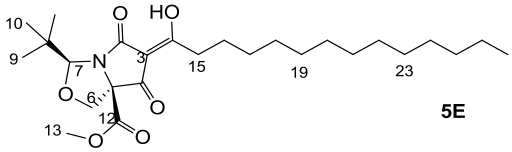


5D

Yield; 58 % (oil); form AB: CD= 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.82 (d, 1H, *J* = 8.8 Hz, C6), 3.78 (s, 3H, C13), 3.49 (d, 1H, *J* = 8.8 Hz, C6), 3.01-2.78 (m, 2H, C15), 1.70-1.61 (m, 2H, C16), 1.38-1.25 (m, 16H, C17-24), 0.93 (s, 9H, C9-11), 0.87 (t, 3H, *J* = 7.2 Hz, C27). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 192.5 (C14), 187.7 (C4), 180.3 (C2), 167.5 (C12), 101.0 (C3), 98.2 (C7),

78.3 (C5), 68.2 (C6), 53.2 (C13), 35.1 (C8), 33.0 (C15), 31.9 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.9 (CH_2), 24.6 (C9-11), 22.6 (CH_2), 14.1 (C27). **MS** (ES^-); 436.3 (M-H); **HRMS** (M-H); calcd for $C_{24}H_{38}NO_6$; 436.2705; found; 436.2696.

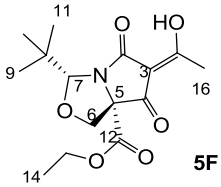
4.1.5. Synthesis of **5E**



5E

Yield; 49 % (oil); form AB: CD= 20: 80**;** **^{1}H NMR** (400 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.83-4.81 (m, 1H, C6), 3.80 (s, 3H, C13 AB), 3.79 (s, 3H, C13 CD), 3.50 (d, 1H, *J* = 8.8 Hz, C6 AB), 3.49 (d, 1H, *J* = 8.8 Hz, C6 CD), 3.02-2.78 (m, 2H, C15), 1.74-1.63 (m, 2H, C16), 1.38-1.25 (m, 20H, C17-26), 0.93 (s, 9H, C9-11 CD), 0.92 (s, 9H, C9-11 AB), 0.88 (t, 3H, *J* = 7.2 Hz, C27). **^{13}C NMR** (100 MHz, $CDCl_3$); 195.7 (C4 AB), 190.0 (C14 AB), 192.5 (C14 CD), 187.7 (C4 CD), 180.3 (C2 CD), 172.3 (C2 AB), 167.5 (C12 CD), 167.3 (C12 AB), 103.7 (C3 AB), 101.0 (C3 CD), 98.3 (C7 AB), 98.2 (C7 CD), 78.3 (C5 CD), 76.4 (C5 AB), 68.2 (C6 CD), 68.2 (C6 AB), 53.4 (C13 AB), 53.2 (C13 CD), 35.3 (C8 AB), 35.1 (C8 CD), 33.0 (C15 CD), 33.0 (C15 AB), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 24.7 (C9-11 AB), 24.6 (C9-11 CD), 22.6 (CH_2), 14.1 (C27). **MS** (ES^-); 364.3 (M-H); **HRMS** (M-H); calcd for $C_{26}H_{42}NO_6$; 464.3018; found; 464.3007.

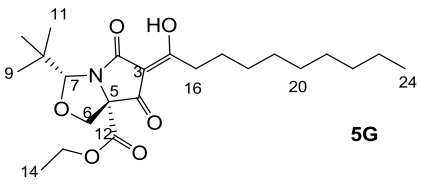
4.1.6. Synthesis of **5F**



5F

Yield; 63 % (oil); Form AB: CD= 20: 80**;** **^{1}H NMR** (500 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.83-4.82 (m, 1H, C6), 4.28-4.23 (m, 2H, C13), 3.50 (d, 1H, *J* = 8.5 Hz, C6), 2.57 (s, 3H, C16 AB), 2.49 (s, 3H, C16 CD), 1.29 (t, 3H, *J* = 7.0 Hz, C14), 0.94 (s, 9H, C9-11 CD), 0.93 (s, 9H, C9-11 AB). **^{13}C NMR** (125 MHz, $CDCl_3$); 195.7 (C4 AB), 190.0 (C15 AB), 188.2 (C15 CD), 188.2 (C4 CD), 180.0 (C2 CD), 172.4 (C2 AB), 166.9 (C12 CD), 166.8 (C12 AB), 104.4 (C3 AB), 101.7 (C3 CD), 98.3 (C7 AB), 98.2 (C7 CD), 78.5 (C5 CD), 76.5 (C5 AB), 68.2 (C6 CD), 68.1 (C6 AB), 62.9 (C13 AB), 62.7 (C13 CD), 35.3 (C8 AB), 35.1 (C8 CD), 24.8 (C9-11 AB), 24.7 (C9-11 CD), 19.9 (C16 CD), 19.8 (C16 AB), 14.0 (C14). **MS** (ES^-); 310.11 (M-H); **HRMS** (M-H); calcd for $C_{15}H_{20}N_1O_6$; 310.1296; found; 310.1297.

4.1.7. Synthesis of **5G**

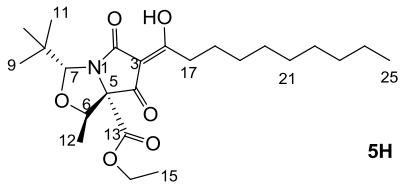


5G

Yield; 65 % (oil); Form AB: CD= 20: 80**;** **^{1}H NMR** (400 MHz, $CDCl_3$); 4.87 (s, 1H, C7 AB), 4.84 (s, 1H, C7 CD), 4.81 (d, 1H, *J* = 8.8 Hz, C6), 4.30-4.18 (m, 2H, C13), 3.48 (d, 1H, *J* = 8.8 Hz, C6), 3.02-2.77 (m, 2H, C16), 1.72-1.62 (m, 2H, C17), 1.37-1.24 (m, 15H, C14 and C18-C23), 0.93 (s, 9H, C9-11), 0.86 (t, 3H, *J* = 7.2 Hz, C24). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 192.3 (C15), 187.9 (C4), 180.3 (C2), 166.9 (C12), 101.0 (C3), 98.2 (C7), 78.3 (C5), 68.2 (C6), 62.6 (C13), 35.1 (C8), 33.0 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 25.9 (CH_2), 24.7 (C9-11), 22.6 (CH_2), 14.0

(CH_3), 13.9 (CH_3). **MS** (ES^-); 422.28 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{36}N_1O_6$; 422.2548; found; 422.2542.

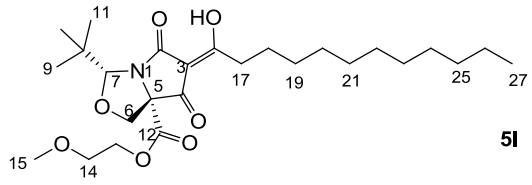
4.1.8. Synthesis of **5H**



5H

Yield: 47 % (oil); Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.8 Hz, C6), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.31-4.18 (m, 2H, C14), 2.92-2.78 (m, 2H, C17), 1.74-1.63 (m, 2H, C18), 1.40-1.26 (m, 15H, C15 and C19-C24), 1.05 (d, 3H, *J* = 6.8 Hz, C12), 0.94 (s, 9H, C9-C11), 0.88 (t, 3H, *J* = 6.8 Hz, C25). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 191.2 (C16), 188.4 (C4), 179.8 (C2), 167.4 (C13), 102.7 (C3), 95.7 (C7), 81.3 (C5), 74.8 (C6), 62.6 (C14), 35.2 (C8), 33.9 (CH_2), 32.8 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.1 (CH_2), 24.8 (C9-C11), 22.6 (CH_2), 14.5 (CH_3), 14.1 (CH_3), 13.9 (CH_3). **MS** (ES^-): 436.29 (M-H); **HRMS** (M-H): calcd for $C_{24}H_{38}NO_6$ 436.2705, found 436.2708.

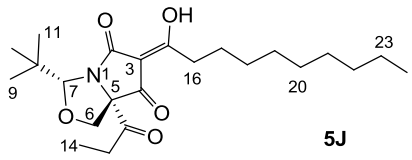
4.1.9. Synthesis of **5I**



5I

Yield; 43 %; M.P.; 118 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 4.89 (s, 1H, C7 AB), 4.86 (s, 1H, C7 CD), 4.84 (d, 1H, *J* = 8.8 Hz, C6), 4.34 (t, 2H, *J* = 4.7 Hz, C13), 3.60-3.57 (m, 2H, C14), 3.52 (d, 1H, *J* = 8.8 Hz, C6 AB), 3.51 (d, 1H, *J* = 8.8 Hz, C6 CD), 3.38 (s, 3H, C15 AB), 3.34 (s, 3H, C15 CD), 3.03-2.78 (m, 2H, C17), 1.73-1.63 (m, 2H, C18), 1.37-1.26 (m, 16H, C19-C26), 0.95 (s, 9H, C9-C11), 0.88 (t, 3H, *J* = 6.8 Hz, C27). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 192.5 (C16), 187.7 (C4), 180.4 (C2), 167.0 (C12), 101.0 (C3), 98.3 (C7), 78.4 (C5), 69.9 (C14), 68.2 (C6), 65.5 (C13), 58.9 (C15), 35.2 (C8), 33.1 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.9 (CH_2), 24.7 (C9-C11), 22.7 (CH_2), 14.1 (C25). **MS** (ES^-); 480.32 (M-H); **HRMS** (M-H); calculated for $C_{26}H_{42}NO_7$; 480.2967; found; 480.2968.

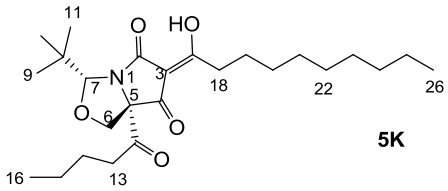
4.1.10. Synthesis of **5J**



5J

Yield; 55 % (oil); form AB: CD= not determined, major: CD. **^{1}H NMR** (400 MHz, $CDCl_3$); 4.91-4.84 (m, 2H,C6 and C7), 3.47-3.42 (m, 1H, C6), 2.99-2.78 (m, 3H, C13 and C16), 2.35-2.26 (m, 1H, C13), 1.70-1.58 (m, 2H, C17), 1.36-1.25 (m, 12H, C18-C23), 1.06 (t, 3H, *J* = 7.2 Hz, C14), 0.89-0.85 (m, 12H, C9-C11 and C24). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer CD only); 201.8 (C12), 192.9 (C15), 188.9 (C4), 181.4 (C2), 101.4 (C3), 98.6 (C7), 83.5 (C5), 66.7 (C6), 35.1 (C8), 33.9 (CH_2), 33.1 (CH_2), 31.8 (CH_2), 30.9 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 25.0 (C9-C11), 22.6 (CH_2), 14.0 (C24), 7.3 (C14). **MS** (ES^-); 406.26 (M-H); MS (ES^+); 430.29 (M+Na); **HRMS** (M+Na); calcd for $C_{23}H_{37}N_1Na_1O_5$; 430.2564; found; 430.2558.

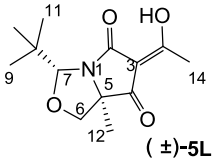
4.1.11. Synthesis of **5K**



5K

Yield; 43 % (oil); form AB: CD= 20: 80. **^{1}H NMR** (500 MHz, $CDCl_3$); 4.93 (d, 1H, *J* = 10.0 Hz, C6 AB), 4.93 (d, 1H, *J* = 10.0 Hz, C6 CD), 4.87 (s, 1H, C7 AB), 4.85 (s, 1H, C7 AB), 3.46 (d, 1H, *J* = 10.0 Hz, C6 AB), 3.44 (d, 1H, *J* = 10.0 Hz, C6 CD), 3.04-2.76 (m, 3H, C13 and C18), 2.37-2.29 (m, 1H, C13), 1.76-1.47 (m, 4H, C14 and C19), 1.41-1.26 (m, 14H, C15 and C20-C25), 0.91-0.86 (m, 15H, C9-C11, C16 and C26). **^{13}C NMR** (125 MHz, $CDCl_3$); 201.3 (C12 CD), 201.2 (C12 AB), 196.4 (C4 AB), 195.1 (C17 AB), 192.9 (C17 CD), 188.9 (C4 CD), 181.5 (C2 CD), 173.5 (C2 AB), 104.3 (C3 AB), 101.5 (C3 CD), 98.7 (C7 AB), 98.7 (C7 CD), 83.7 (C5 CD), 81.5 (C5 AB), 66.7 (C6 CD), 66.7 (C6 AB), 37.5 (CH_2 CD), 37.2 (CH_2 AB), 35.3 (C8 AB), 35.1 (C8 CD), 33.5 (CH_2 AB), 33.1 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 25.6 (CH_2 AB), 25.3 (CH_2), 25.1 (C9-C11 AB), 25.0 (C9-C11 CD), 22.6 (CH_2), 22.3 (CH_2 AB), 22.1 (CH_2), 22.1 (CH_2 AB), 14.1 (C26), 13.8 (C16). **MS** (ES^-); 434.32 (M-H); **HRMS** (M-H); calcd for $C_{25}H_{40}N_1O_5$; 434.2912; found; 434.2911.

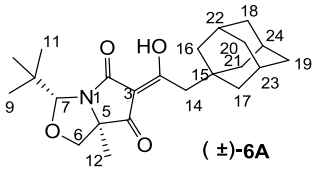
4.1.12. Synthesis of (±)-**5L**



(±)-5L

Yield; 44 %; M.P.; 131 ℃; Form AB: CD = 25: 75; **^{1}HNMR** (400 MHz, $CDCl_3$): 4.75 (s, 1H, C7), 3.81 (d, 1H, *J* = 8.3 Hz, C6), 3.41 (d, 1H, *J* = 8.3 Hz, C6), 2.51 (s, 3H, C14 AB), 2.47 (s, 3H, C14 CD), 1.54 (s, 3H, C12 AB), 1.50 (s, 3H, C12 CD), 1.01 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 194.9 (C13), 187.3 (C4), 179.7 (C2), 102.5 (C3), 98.2 (C7), 73.2 (C5), 71.4 (C6), 34.6 (C8), 25.5 (C9-C11), 21.3 (C12), 19.7 (C14). **MS** (ES^-); 252.13 (M-H); **HRMS** (M-H); calculated for $C_{13}H_{18}NO_4$; 252.1241 found; 252.1234.

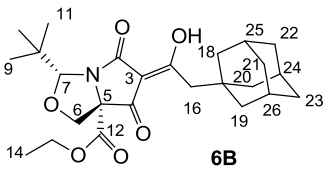
4.1.13. Synthesis of (±)-**6A**



(±)-6A

Yield; 61 % (oil); Form AB: CD = 20: 80**;** **^{1}HNMR** (400 MHz, $CDCl_3$): 4.79 (s, 1H, C7 AB), 4.78 (s, 1H, C7 CD), 3.85 (d, 1H, *J* = 8.4 Hz, C6 AB), 3.82 (d, 1H, *J* = 8.4 Hz, C6 CD), 3.43 (d, 1H, *J* = 8.4 Hz, C6 AB), 3.40 (d, 1H, *J* = 8.4 Hz, C6 CD), 2.77-2.58 (m, 2H, C14), 1.96 (brs, 3H, C22-C24), 1.70-1.62 (m, 12H, C16-C21), 1.56 (s, 3H, C12 AB), 1.51 (s, 3H, C12 CD), 1.03 (s, 9H, C9-C11 CD), 1.02 (s, 9H, C9-C11 AB). **^{13}C NMR** (100 MHz, $CDCl_3$): 201.7 (C4 AB), 194.8 (C13 CD), 192.3 (C13 AB), 189.3 (C4 CD), 180.1 (C2 CD), 172.6 (C2 AB), 106.0 (C3 AB), 103.5 (C3 CD), 98.4 (C7 AB), 98.4 (C7 CD), 73.0 (C5 CD), 71.6 (C6 CD), 71.5 (C6 AB), 70.2 (C5 AB), 46.1 (CH_2 AB), 46.0 (CH_2 CD), 42.6 (CH_2 AB), 42.5 (CH_2 CD), 36.6 (CH_2), 36.2 (C15 CD), 35.9 (C15 AB), 34.8 (C8 AB), 34.6 (C8 CD), 28.8 (C22-C24), 25.7 (C9-C11 AB), 25.6 (C9-C11 CD), 21.3 (C12 CD), 21.2 (C12 AB). **MS** (ES^-); 386.24 (M-H); **HRMS** (M-H); calculated for $C_{23}H_{32}NO_4$; 386.2337; found; 386.2327.

4.1.14. Synthesis of **6B**

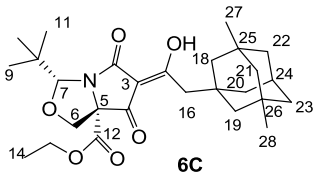


6B

Yield; 45 %; M.P.; 122 ℃; form AB: CD= 15: 85; **^{1}H NMR** (400 MHz, $CDCl_3$);

4.90 (s, 1H, C7 AB), 4.87 (s, 1H, C7 CD), 4.84 (d, 1H, *J* = 8.8 Hz, C6 AB), 4.82 (d, 1H, *J* = 8.8 Hz, C6 CD), 4.33-4.14 (m, 2H, C13), 3.51 (d, 1H, *J* = 8.4 Hz, C6 AB), 3.48 (d, 1H, *J* = 8.4 Hz, C6 CD), 2.81 (d, 1H, *J* = 11.6, C16), 2.51 (d, 1H, *J* = 11.6, C16), 1.96 (brs, 3H, C24-C26), 1.70-1.62 (m, 12H, C18-23), 1.29 (t, 3H, *J* = 7.2 Hz, C14 AB), 1.26 (t, 3H, *J* = 7.2 Hz, C14 CD), 0.94 (s, 9H, C9-11 CD), 0.93 (s, 9H, C9-11 AB). **^{13}C NMR** (100 MHz, $CDCl_3$,Only CD form); 190.2 (C15), 188.3 (C4), 180.3 (C2), 167.0 (C12), 102.9 (C3), 98.2 (C7), 78.3 (C5), 68.1 (C6), 62.5 (C13), 46.3 (C16), 42.4 ($\underline{C}H_2$), 36.7 (quart C), 36.5 ($\underline{C}H_2$), 35.2 (quart C), 28.8 (C24-C26), 24.7 (C9-11), 13.9 (C14). **MS** (ES^-); 444.24 (M-H); **HRMS** (M-H); calcd for $C_{25}H_{34}N_1O_6$; 444.2392; found; 444.2397.

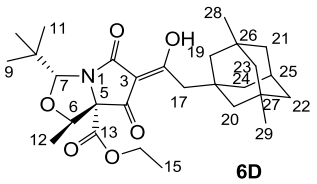
4.1.15. Synthesis of **6C**



6C

Yield; 39 %; M.P.; 115 ℃; Form AB: CD= 15: 85; **^{1}H NMR** (400 MHz, $CDCl_3$); 4.90 (s, 1H, C7 AB), 4.87 (s, 1H, C7 CD), 4.84 (d, 1H, *J* = 8.4 Hz, C6 AB), 4.83 (d, 1H, *J* = 8.4 Hz, C6 CD), 4.31-4.16 (m, 2H, C13), 3.50 (d, 1H, *J* = 8.4 Hz, C6 AB), 3.47 (d, 1H, *J* = 8.4 Hz, C6 CD), 2.86 (d, 1H, *J* = 11.6, C16), 2.51 (d, 1H, *J* = 11.6, C16), 2.07-2.02 (m, 1H, C24), 1.48-1.09 (m, 15H, C14, C18-23), 0.94 (s, 9H, C9-11 CD), 0.93 (s, 9H, C9-11 AB), 0.81-0.79 (m, 6H, C27 and C28). **^{13}C NMR** (100 MHz, $CDCl_3$,Only CD form); 190.1 (C15), 188.3 (C4), 180.3 (C2), 166.9 (C12), 102.8 (C3), 98.2 (C7), 78.3 (C5), 68.1 (C6), 62.6 (C13), 50.7 ($\underline{C}H_2$), 48.7 ($\underline{C}H_2$), 48.7 ($\underline{C}H_2$), 45.6 (C16), 42.8 ($\underline{C}H_2$), 40.9 ($\underline{C}H_2$), 38.0 (quart C), 35.2 (C8), 31.5 (quart C), 30.4 (C27 and C28), 29.8 (C24), 24.7 (C9-11), 14.0 (C14). **MS** (ES^-); 472.20 (M-H); MS (ES^+); 496.35 (M+Na); **HRMS** (M+Na); calcd for $C_{27}H_{39}N_1Na_1O_6$; 496.2670; found; 496.2667.

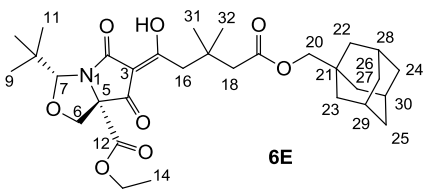
4.1.16. Synthesis of **6D**



6D

Yield; 38 % (oil); Form AB: CD = 15: 85; **^{1}HNMR** (400 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.4 Hz, C6), 4.99 (s, 1H, C7 AB), 4.97 (s, 1H, C7 CD), 4.28-4.15 (m, 2H, C14), 2.71 (d, 1H, *J* = 11.6 Hz, C17), 2.66 (d, 1H, *J* = 11.6 Hz, C17), 2.05-2.03 (m, 1H, C25), 1.34-1.19 (m, 15H, C19-C24 and C15), 1.05 (d, 3H, *J* = 6.8 Hz, C12), 0.94 (s, 9H, C9-C11 CD), 0.93 (s, 9H, C9-C11 AB), 0.80 (s, 6H, C28 and C29 AB), 0.78 (s, 6H, C28 and C29 CD). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 189.1 (C16), 188.7 (C4), 179.8 (C2), 167.3 (C13), 104.4 (C3), 95.7 (C7), 81.3 (C5), 74.9 (C6), 62.5 (C14), 50.7 (CH_2), 48.8 (CH_2), 48.6 (CH_2), 45.4 (C17), 42.8 (CH_2), 41.1 (CH_2), 38.2 (quart C), 35.2 (C8), 31.5 (quart C), 30.4 (C28 and C29), 29.8 (C25), 24.8 (C9-C11), 14.6 (CH_3), 14.0 (CH_3). **MS** (ES^-); 486.27 (M-H); **HRMS** (M-H); calculated for $C_{28}H_{40}NO_6$; 486.2861; found; 486.2864.

4.1.17. Synthesis of **6E**

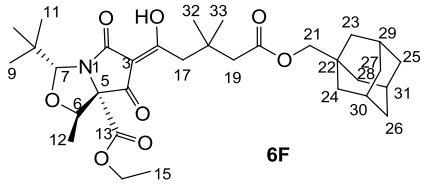


6E

Yield; 35 % (oil); Form AB: CD= 15: 85; **^{1}HNMR** (400 MHz, $CDCl_3$): 4.88 (s, 1H, C7 AB), 4.86 (s, 1H, C7 CD), 4.82 (d, 1H, *J* = 8.8 Hz, C6), 4.32-4.14 (m, 2H, C13), 3.676(s, 2H, C20), 3.48 (d, 1H, *J* = 8.8 Hz, C6), 3.10

(d, 1H, *J* = 12.4 Hz, C16), 2.91 (d, 1H, *J* = 12.4 Hz, C16), 2.46 (s, 2H, C18 AB), 2.41 (s, 2H, C18 CD), 1.98 (brs, 3H, C28-C30), 1.74-1.52 (m, 12H, C22-C27), 1,25 (t, 3H, *J* = 7.2 Hz, C14), 1.17 (s, 6H, C32 and C33 AB), 1.14 (s, 3H, CH_3 CD), 1.13 (s, 3H, CH_3 CD), 0.94 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 189.8 (C15), 188.2 (C4), 180.1 (C2), 171.7 (C19), 166.3 (C12), 103.0 (C3), 98.2 (C7), 78.3 (C5), 74.1 (C20), 68.0 (C6), 62.6 (C13), 46.2 (CH_2), 42.9 (CH_2), 39.3 (CH_2), 36.9 (CH_2), 35.5 (C8), 35.1 (C21), 32.9 (C17), 28.0 (C31 and C32), 27.4 and 27.3 (C28-C30), 24.7 (C9-C11), 13.9 (C14). **MS** (ES^-); 558.25 (M-H); MS (ES^+); 582.30 (M+Na); **HRMS** (M-H); calcd for $C_{31}H_{44}N_1O_8$; 558.3072; found; 558.3078.

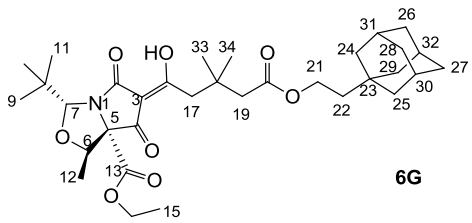
4.1.18. Synthesis of **6F**



6F

Yield; 39 % (oil); Form AB: CD = 20: 80**; ^{1}HNMR** (500 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.7 Hz, C6), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.30-4.14 (m, 2H, C14), 3.67 (s, 2H, C21), 3.18-2.97 (m, 2H, C17), 2.46 (s, 2H, C19 AB), 2.41 (s, 2H, C19 CD), 1.98 (brs, 3H, C29-C31), 1.74-1.53 (m, 12H, C23-C28), 1,25 (t, 3H, *J* = 7.1 Hz, C15), 1.17 (s, 6H, C32 and C33 AB), 1.13 (s, 6H, C32 and C33 CD), 1.04 (d, 3H, *J* = 6.7 Hz, C12), 0.93 (s, 9H, C9-C11 CD), 0.92 (s, 9H, C9-C11 AB). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 188.6 (C16), 188.6 (C4), 177.6 (C2), 171.7 (C20), 167.2 (C13), 104.6 (C3), 95.7 (C7), 81.3 (C5), 74.8 (C6), 62.6 (C14 and C21), 46.3 (CH_2), 42.9 (CH_2), 39.3 (CH_2), 36.9 (CH_2), 35.7 (C8), 35.2 (C22), 33.0 (C18), 28.0 (C32 and C33), 27.3 (C29-C31), 24.7 (C9-C11), 14.6 (CH_3), 13.9 (CH_3). **MS** (ES^-); 572.34 (M-H); **HRMS** (M-H); calculated for $C_{32}H_{46}NO_8$; 572.3229; found; 572.3232.

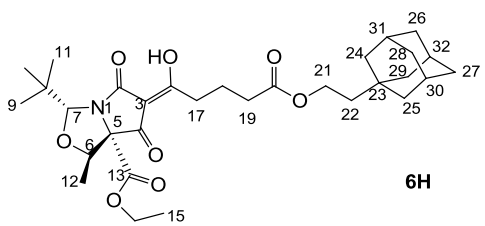
4.1.19. Synthesis of **6G**



6G

Yield; 40 % (oil); Form AB: CD = not determined; **^{1}HNMR** (400 MHz, $CDCl_3$): 5.10 (q, 1H, *J* = 6.8 Hz, C6), 4.92 (s, 1H, C7), 4.22-4.06 (m, 4H, C14 and C21), 3.71 (d, 1H, *J* = 12.4 Hz, C17), 2.59 (d, 1H, *J* = 12.4 Hz, C17), 1.98-1.87 (m, 5H, C19, C30-C32), 1.74-1.51 (m, 12H, C24-C29), 1.40 (t, 2H, *J* = 7.3 Hz, C22), 1.27 (t, 2H, *J* = 7.3 Hz, C15), 1.05 (s, 3H, C33), 1.00 (d, 3H, *J* = 6.8 Hz, C12), 0.89 (s, 3H, C34), 0.84 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 195.8 (C16), 189.6 (C4), 182.3 (C2), 175.3 (C20), 168.5 (C13), 103.9 (C3), 95.2 (C7), 80.3 (C5), 74.8 (C6), 61.9 (CH_2), 61.3 (CH_2), 44.9 (CH_2), 43.3 (CH_2), 42.5 (CH_2), 42.3 (CH_2), 36.9 (CH_2), 35.2 (C8 and C23), 31.8 (C18), 30.0 (C33 and C34), 28.5 (C30-C32), 25.0 (C9-C11), 14.4 (CH_3), 14.2 (CH_3). **MS** (ES^-); 585.35 ((M-H); **HRMS** (M-H); calculated for $C_{33}H_{48}NO_8$; 586.3385; found; 586.3386.

4.1.20. Synthesis of **6H**

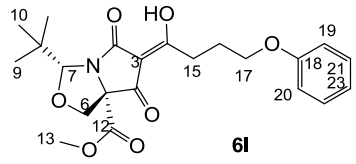


6H

Yield; 41 % (oil); Form AB: CD = not determined**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.13 (q, 1H, *J* = 6.8 Hz, C6), 4.95 (s, 1H, C7), 4.28-4.19 (m, 2H, C14), 4.13 (t, 2H, *J* = 7.5 Hz, C21), 3.11-2.89 (m, 2H,

C17), 2.43-2.35 (m, 2H, C19), 2.05-1.91 (m, 5H, C18, C30-C32), 1.74-1.51 (m, 12H, C24-C29), 1.43-1.39 (m, 2H, C22), 1.30-1.26 (m, 3H, C15), 1.04 (d, 3H, *J* = 6.8 Hz, C12), 0.93 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 189.4 (C16), 188.4 (C4), 179.5 (C2), 172.6 (C20), 167.2 (C13), 102.9 (C3), 95.6 (C7), 81.3 (C5), 74.8 (C6), 62.6 (CH_2), 61.1 (CH_2), 42.4 (CH_2), 42.3 (CH_2), 36.9 (CH_2), 35.2 (C8), 33.3 (CH_2), 33.2 (CH_2), 31.9 (CH_2), 31.7 (C23), 28.5 (C30-C32), 25.4 (CH_2), 24.7 (C9-C11), 21.0 (CH_2), 14.5 (CH_3), 13.9 (CH_3). **MS** (ES^+); 560.34 ((M+H); **HRMS** (M+Na); calculated for $C_{31}H_{45}NNaO_8$; 582.3037; found; 582.3042.

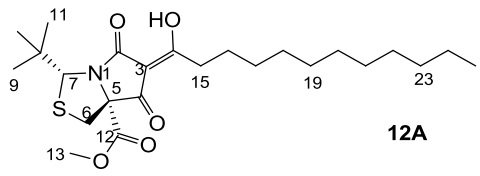
4.1.21. Synthesis of **6I**



6I

Yield; 61 % (oil); form AB: CD= 20: 80. **^{1}H NMR** (400 MHz, $CDCl_3$); 7.27 (dd, 2H, J_1 = 8.4 Hz, J_2 = 8.2 Hz, C21 and C22), 6.96-6.82 (m, 3H, C19, C20 and C23), 4.82-4.80 (m, 1H, C7 and 1H C6 AB), 4.71 (d, 1H, J = 9.2 Hz, C6 CD), 4.03 (t, 2H, *J* = 6.0 Hz, C17), 3.79 (s, 3H, C13 AB), 3.74 (s, 3H, C13 CD), 3.41-2.96 (m, 3H, C6 and C15), 2.29-2.12 (m, 2H, C16), 0.93 (s, 9H, C9-11 CD), 0.92 (s, 9H, C9-11 AB). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 191.5 (C14), 187.8 (C4), 180.1 (C2), 167.4 (C12), 158.3 (C18), 129.4 (C21 and C22), 120.9 (C23), 114.3 (C19 and C20), 101.3 (C3), 98.1 (C7), 78.2 (C5), 68.0 (C6), 66.5 (C17), 53.2 (C13), 35.1 (C8), 30.1 (C15), 25.6 (C16), 24.6 (C9-C11). **MS** (ES^-); 416.18 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{26}N_1O_7$; 416.1715; found; 416.1724.

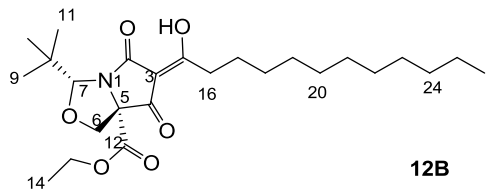
4.1.22. Synthesis of **12A**



12A

Yield; 37 %; M.P.; 107 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.18 (s, 1H, C7 AB), 5.11 (s, 1H, C7 CD), 3.80-3.76 (m, 4H, C6 and C13), 2.87-2.82 (m, 3H, C6 and C15), 1.71-1.63 (m, 2H, C16), 1.39-1.26 (m, 16H, C17-C24), 0.98 (s, 9H, C9-C11 CD), 0.97 (s, 9H, C9-C11 AB), 0.88 (t, 3H, *J* = 7.2 Hz, C25). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 191.61 (C14), 188.51 (C4), 177.70 (C2), 167.54 (C12), 99.51 (C3), 82.85 (C5), 73.51 (C7), 53.31 (C13), 36.68 (C8), 33.66 (C6), 33.30 (CH_2), 32.98 (CH_2), 31.87 (CH_2), 29.56 (CH_2), 29.54 (CH_2), 29.39 (CH_2), 29.29 (CH_2), 29.18 (CH_2), 29.15 (CH_2), 26.43 (C9-C11), 25.91 (CH_2), 25.48 (CH_2), 24.83 (CH_2), 22.65 (CH_2), 14.09 (C25). **MS** (ES^-); 452.26 (M-H); **HRMS** (M+Na); calculated for $C_{24}H_{39}NNaO_5S$; 476.2441; found; 476.2448.

4.1.23. Synthesis of **12B**

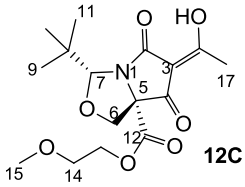


12B

Yield; 52 % (oil); Form AB: CD= 20: 80; **^{1}H NMR** (500 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.82 (d, 1H, *J* = 8.5 Hz, C6), 4.30-4.20 (m, 2H, C13), 3.50 (d, 1H, *J* = 8.5 Hz, C6 AB), 3.49 (d, 1H, *J* = 8.5 Hz, C6 CD), 3.02-2.96 (m, 2H, C16 AB), 2.92-2.79 (m, 2H, C16 CD), 1.74-1.63 (m, 2H, C17), 1.42-1.25 (m, 19H, C14 and C18-C25), 0.94 (s, 9H, C9-11), 0.88 (t, 3H, *J* = 7.5 Hz, C24). **^{13}C NMR** (125 MHz, $CDCl_3$); 195.9 (C4 AB), 194.0 (C15 AB), 192.3 (C15 CD), 188.0 (C4

CD), 180.4 (C2 CD), 172.4 (C2 AB), 166.8 (C12 AB), 167.0 (C12 CD), 103.8 (C3 AB), 101.1 (C3 CD), 98.3 (C7 AB), 98.2 (C7 CD), 78.4 (C5 CD), 76.5 (C5 AB), 68.2 (C6), 62.8 (C13 AB), 62.6 (C13 CD), 35.3 (C8 AB), 35.1 (C8 CD), 33.0 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 25.9 (CH_2 CD), 25.7 (CH_2 AB), 24.8 (C9-11 AB), 24.7 (C9-11 CD), 22.6 (CH_2), 14.1 (CH_3), 14.0 (CH_3). **MS** (ES^-); 450.30 (M-H); **HRMS** (M-H); calcd for $C_{25}H_{40}N_1O_6$; 450.2861; found; 450.2857.

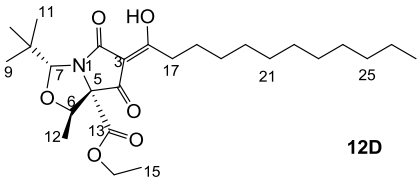
4.1.24. Synthesis of **12C**



12C

Yield; 49 % (oil); form AB: CD = 20: 80; **^{1}HNMR** (400 MHz, $CDCl_3$): 4.88 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.83 (d, 1H, *J* = 9.2 Hz, C6), 4.37-4.30 (m, 2H, C13), 3.59 (t, 2H, *J* = 5.2 Hz, C14), 3.51 (d, 1H, *J* = 9.2 Hz, C6), 3.34 (s, 3H, C15), 2.56 (s, 3H, C17 AB), 2.48 (s, 3H, C17 AB), 0.94 (s, 9H, C9-C11 CD), 0.90 (s, 9H, C9-C11 AB). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 188.32 (C16), 187.93 (C4), 179.96 (C2), 166.98 (C12), 101.67 (C3), 98.29 (C7), 78.45 (C5), 69.83 (C14), 68.16 (C6), 65.51 (C13), 58.86 (C15), 35.12 (C8), 24.63 (C9-C11), 19.90 (C17). **MS** (ES^-); 340.15 (M-H); **HRMS** (M-H); calculated for $C_{16}H_{22}NO_7$; 340.1402; found 340.1402.

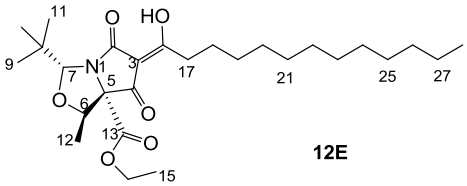
4.1.25. Synthesis of **12D**



12D

Yield: 42 %; M.P.; 121 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.8 Hz, C6), 4.97 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.31-4.17 (m, 2H, C14), 2.92-2.78 (m, 2H, C17), 1.73-1.62 (m, 2H, C18), 1.37-1.25 (m, 19H, C15 and C19-C26), 1.04 (d, 3H, *J* = 6.8 Hz, C12), 0.93 (s, 9H, C9-C11), 0.88 (t, 3H, *J* = 6.8 Hz, C27). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 191.1 (C16), 188.4 (C4), 179.8 (C2), 167.3 (C13), 102.7 (C3), 95.7 (C7), 81.3 (C5), 74.8 (C6), 62.6 (C14), 35.2 (C8), 33.9 (CH_2), 32.8 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 24.9 (CH_2), 24.8 (C9-C11), 22.7 (CH_2), 14.5 (CH_3), 14.1 (CH_3), 13.9 (CH_3). **MS** (ES^-): 464.33 (M-H); **HRMS** (M-H): calcd for $C_{24}H_{38}NO_6$; 464.3018; found; 464.3019.

4.1.26. Synthesis of **12E**

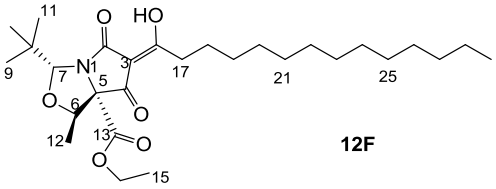


12E

Yield: 38 %; M.P.; 117 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (500 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.5 Hz, C6), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.30-4.18 (m, 2H, C14), 2.91-2.79 (m, 2H, C17), 1.74-1.65 (m, 2H, C18), 1.41-1.25 (m, 21H, C15 and C19-C27), 1.05 (d, 3H, *J* = 6.5 Hz, C12), 0.94 (s, 9H, C9-C11 CD), 0.93 (s, 9H, C9-C11 AB), 0.88 (t, 3H, *J* = 6.5 Hz, C28). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 191.2 (C16), 188.4 (C4), 179.8 (C2), 167.4 (C13), 102.7 (C3), 95.7 (C7), 81.3 (C5), 74.8 (C6), 62.6 (C14), 35.2 (C8), 33.6 (CH_2), 32.8 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.1 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 24.8 (C9-C11), 22.7 (CH_2), 14.5 (CH_3), 14.1 (CH_3), 14.0 (CH_3). **MS** (ES^-) 478.33 (M-H); **HRMS** (M-H): calcd for

$C_{27}H_{44}NO_6$; 478.3174; found 478.3177.

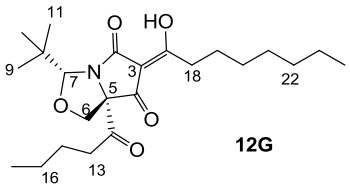
4.1.27. Synthesis of **12F**



12F

Yield: 35 %; M.P.; 108 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.8 Hz, C6), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.31-4.19 (m, 2H, C14), 2.92-2.78 (m, 2H, C17), 1.72-1.63 (m, 2H, C18), 1.40-1.26 (m, 23H, C15 and C19-C28), 1.05 (d, 3H, *J* = 6.8 Hz, C12), 0.94 (s, 9H, C9-C11), 0.89 (t, 3H, *J* = 7.2 Hz, C29). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 191.2 (C16), 188.4 (C4), 179.8 (C2), 167.4 (C13), 102.7 (C3), 95.7 (C7), 81.3 (C5), 74.8 (C6), 62.6 (C14), 35.2 (C8), 33.6 (CH_2), 32.9 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.1 (CH_2), 24.8 (CH_2), 24.8 (C9-C11), 22.7 (CH_2), 14.5 (CH_3), 14.1 (CH_3), 14.0 (CH_3). **MS** (ES^-): 492.36 (M-H); **HRMS** (M-H): calcd for $C_{28}H_{46}NO_6$ 492.3331; found 492.3329.

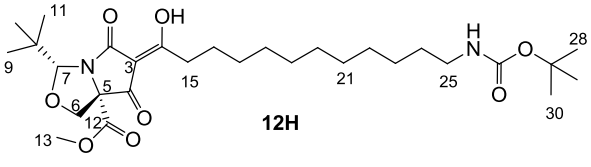
4.1.28. Synthesis of **12G**



12G

Yield; 43 % (oil); form AB: CD= 20: 80; **^{1}H NMR** (500 MHz, $CDCl_3$); 4.93-4.84 (m, 2H, C6 and C7), 3.46 (d, 1H, *J* = 10.5 Hz, C6 AB), 3.44 (d, 1H, *J* = 8.5 Hz, C6 CD), 3.03-2.30 (m, 4H, C13 and C18), 1.74-1.58 (m, 4H, C14 and C19), 1.39-1.27 (m, 10H, C15 and C20-C23), 0.91-0.86 (m, 15H, C9-C11, C16 and C24). **^{13}C NMR** (125 MHz, $CDCl_3$); 201.3 (C12 CD), 201.2 (C12 AB), 196.3 (C4 AB), 195.2 (C17 AB), 193.0 (C17 CD), 188.9 (C4 CD), 181.5 (C2 CD), 173.6 (C2 AB), 104.3 (C3 AB), 101.5 (C3 CD), 98.7 (C7 AB), 98.7 (C7 CD), 83.7 (C5 CD), 81.5 (C5 AB), 66.7 (C6 CD), 66.7 (C6 AB), 37.4 (CH_2 CD), 37.2 (CH_2 AB), 35.3 (C8 AB), 35.1 (C8 CD), 34.0 (CH_2), 33.5 (CH_2 AB), 33.5 (CH_2 AB), 33.1 (CH_2), 31.6 (CH_2), 31.6 (CH_2), 29.2 (CH_2 AB), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 26.0 (CH_2), 25.6 (CH_2 AB), 25.4 (CH_2 AB), 25.4 (CH_2), 25.1 (C9-C11 AB), 25.0 (C9-C11 CD), 24.7 (CH_2 AB), 24.7 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 22.1 (CH_2), 22.0 (CH_2 AB), 14.0 (C24), 13.8 (C16). **MS** (ES^-); 406.21 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{36}N_1O_5$; 406.2599; found; 406.2592.

4.1.29. Synthesis of **12H**

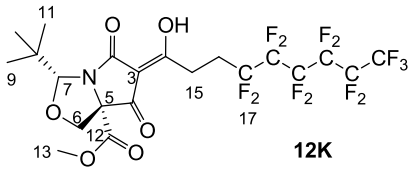


12H

Yield; 46 % (oil); Form AB: CD= 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.86 (s, 1H, C7 AB), 4.82 (s, 1H, C7 CD), 4.80 (d, 1H, *J* = 9.2 Hz, C6), 4.57 (brs, 1H, NH), 3.77 (s, 3H, C13 AB), 3.76 (s, 3H, C13 CD), 3.47 (d, 1H, *J* = 9.2 Hz, C6), 3.07 (brs, 2H, C25), 2.97-2.86 (m, 2H, C15 AB), 2.84-2.80 (m, 2H, C15 CD), 1.70-1.60 (m, 2H, C16), 1.41 (s, 9H, C28-C30), 1.36-1.24 (m, 16H, C17-C24), 0.90 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 192.39 (C14), 187.66 (C4), 180.19 (C2), 167.41 (C12), 155.91 (C26), 100.94 (C3), 98.14

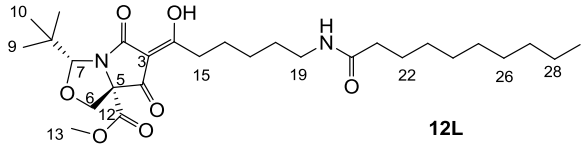
(C7), 79.85 (C27), 78.23 (C5), 68.14 (C6), 53.18 (C13), 40.53 (C25), 35.08 (C8), 32.95 (C15), 29.97 (CH_2), 29.39 (CH_2), 29.35 (CH_2), 29.24 (CH_2), 29.16 (CH_2), 29.08 (CH_2), 29.03 (CH_2), 28.34 (C28-C30), 26.69 (CH_2), 25.79 (CH_2), 24.55 (C9-11). **MS** (ES^-); 551.30 (M-H); **HRMS** (M-H); calcd for $C_{29}H_{47}N_2O_8$; 551.3338; found; 551.3346.

4.1.30. Synthesis of **12K**



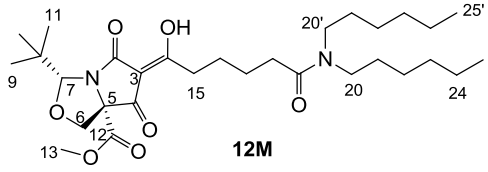
Yield; 66 % (oil); Form AB: CD= 20: 80. **^{1}H NMR** (400 MHz, $CDCl_3$); 4.88-4.84 (m, 2H, C6 and C7), 3.82 (s, 3H, C13 AB), 3.80 (s, 3H, C13 CD), 3.52 (d, 1H, *J* = 9.2 Hz, C6), 3.44-3.15 (m, 2H, C15), 2.58-2.46 (m, 2H, C16), 0.94 (s, 9H, C9-11). **MS** (ES^-); 628.03 (M-H); **HRMS** (M-H); calcd for $C_{21}H_{19}F_{13}N_1O_6$; 628.1010; found; 628.1001.

4.1.31. Synthesis of **12L**



Yield; 59 % (oil); Form AB: CD= 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$); 5.57 (brs, 1H, NH), 4.86 (s, 1H, C7 AB), 4.84 (s, 1H, C7 CD), 4.81 (d, 1H, *J* = 9.2 Hz, C6), 3.79 (s, 3H, C13 AB), 3.78 (s, 3H, C13 CD), 3.49 (d, 1H, *J* = 9.2 Hz, C6), 3.25-3.20 (m, 2H, C19), 3.01-2.94 (m, 2H, C15 AB), 2.92-2.77 (m, 2H, C15 CD), 2.13 (t, 2H, *J* = 8.0 Hz, C21), 1.75-1.38 (m, 8H, C16, C18, C22 and C28), 1.28-1.24 (m, 12H, C17 and C23-C27), 0.92 (s, 9H, C9-C11), 0.86 (t, 3H, *J* = 7.2 Hz, C29). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 191.88 (C14), 187.79 (C4), 180.10 (C2), 173.11 (C20), 167.44 (C12), 101.11 (C3), 98.18 (C7), 78.27 (C5), 68.14 (C6), 53.26 (C13), 39.01 (C19), 36.80 (C21), 35.10 (C8), 32.74 (C15), 31.79 (CH_2), 29.38 (CH_2), 29.30 (CH_2), 29.26 (CH_2), 29.20 (CH_2), 29.15 (CH_2), 26.31 (CH_2), 25.75 (CH_2), 25.38 (CH_2), 24.56 (C9-11), 22.59 (CH_2), 14.04 (C29). **MS** (ES^-); 521.31 (M-H); **HRMS** (M-H); calcd for $C_{28}H_{45}N_2O_7$; 521.3232; found; 521.3232.

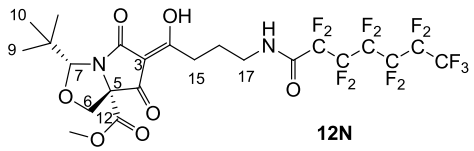
4.1.32. Synthesis of **12M**



Yield; 66 % (oil); Form AB: CD= 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.86 (s, 1H, C7 AB), 4.84 (s, 1H, C7 CD), 4.81 (d, 1H, *J* = 8.8 Hz, C6), 3.79 (s, 3H, C13 AB), 3.78 (s, 3H, C13 CD), 3.49 (d, 1H, *J* = 8.8 Hz, C6), 3.27 (t, 4H, *J* = 8.0 Hz, C20), 3.18 (t, 4H, *J* = 8.0 Hz, C20'), 3.00-2.88 (m, 2H, C15), 2.33-2.30 (m, 2H, C18), 1.74-1.72 (m, 4H, C16 and C17), 1.56-1.45 (m, 4H, C21 and C21'), 1.34-1.23 (m, 12H, C22-24 and C22'-24'), 0.92-0.85 (m, 15H, C9-11, C25 and C25'). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 191.79 (C14), 187.68 (C4), 180.13 (C2), 171.59 (C19), 167.43 (C12), 101.13 (C3), 98.17 (C7), 78.26 (C5), 68.16 (C6), 53.23 (C13), 47.90 (C20'), 45.92 (C20), 35.11 (C8), 32.72 (CH_2), 32.40 (CH_2), 31.56 (CH_2), 31.48 (CH_2), 29.03 (CH_2), 27.69 (CH_2), 26.67 (CH_2), 26.53 (CH_2), 25.41 (CH_2), 24.69 (CH_2), 24.58 (C9-11), 22.54 (CH_2), 13.98 (CH_3), 13.84 (CH_3). **MS** (ES^-); 549.37 (M-H); **HRMS** (M-

H); calcd for $C_{30}H_{49}N_2O_7$; 549.3545; found; 549.3543.

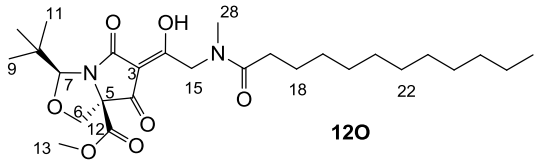
4.1.33. Synthesis of **12N**



12N

Yield; 30 % (oil); Form AB: CD= 20: 80. **^{1}H NMR** (400 MHz, $CDCl_3$); 7.83 (brs, 1H, NH AB), 7.09 (brs, 1H, NH CD), 4.88-4.83 (m, 2H, C6 and C7), 3.82 (s, 3H, C13 AB), 3.80 (s, 3H, C13 CD), 3.55-3.31 (m, 3H, C6 and C17), 3.10-2.82 (m, 2H, C15), 2.04-1.92 (m, 2H, C16), 0.94 (s, 9H, C9-11 CD), 0.92 (s, 9H, C9-11 AB). **MS** (ES^-); 685.03 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{22}F_{13}N_2O_7$; 685.1225; found; 685.1231.

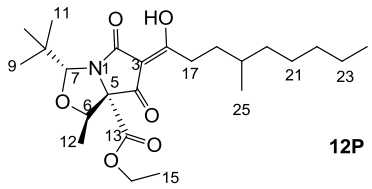
4.1.34. Synthesis of **12O**



12O

Yield; 79 % (oil); form AB: CD= 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$); 4.78-4.61 (m, 4H, C6, C7 and C15), 3.71 (s, 3H, C13), 3.47 (d, 1H, J = 8.8 Hz, C6), 3.03 (s, 3H, C28 CD), 2.91 (s, 3H, C28 AB), 2.32 (t, 2H, *J* = 6.4 Hz, C17 CD), 2.17 (brs, 2H, C17 AB), 1.57 (brs, 2H, C18), 1.19 (brs, 16H, C19-C26), 0.85 (s, 9H, C9-C11), 0.80 (brs, 3H, C27). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 173.87 (C16), 166.92 (C12), 97.91 (C7), 67.93 (C6), 53.12 (C13), 36.75 (C28), 34.92 (C8), 32.72 (C17), 31.67 (C18), 29.38 (CH_2), 29.27 (CH_2), 29.21 (CH_2), 29.10 (CH_2), 24.64 (CH_2), 24.39 (C9-11), 22.44 (CH_2), 13.89 (C27). **MS** (ES^-); 507.26 (M-H); **HRMS** (M+Na); calcd for $C_{27}H_{44}N_2Na_1O_7$; 531.3041; found; 531.3041.

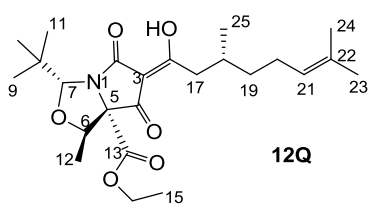
4.1.35. Synthesis of **12P**



12P

Yield; 39 %; M.P.; 109 ℃; Form AB: CD = 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$): 5.13 (q, 1H, *J* = 6.8 Hz, C6), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.31-4.19 (m, 2H, C14), 2.91-2.77 (m, 2H, C17), 1.73-1.62 (m, 1H, C19), 1.54-1.41 (m, 2H, C18), 1.30-1.26 (m, 11H, C15 and C20-C23), 1.05 (d, 3H, *J* = 6.8 Hz, C12), 0.93 (s, 9H, C9-C11), 0.91-0.86 (m, 6H, C24 and C25). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 191.58 (C16), 188.34 (C4), 179.87 (C2), 167.35 (C13), 102.52 (C3), 95.64 (C7), 81.30 (C5), 74.83 (C6), 62.58 (C14), 36.48 (CH_2), 35.19 (C8), 33.65 (CH_2), 32.97 (CH_2), 32.65 (C19), 32.06 (CH_2), 30.72 (CH_2), 26.54 (CH_2), 24.75 (C9-C11), 22.63 (CH_2), 19.22 (C25), 14.50 (CH_3), 14.05 (CH_3), 13.94 (CH_3). **MS** (ES^-); 436.29 ((M-H); **HRMS** (M-H); calcd for $C_{24}H_{38}NO_6$ 436.2705; found 436.2706.

4.1.36. Synthesis of **12Q**

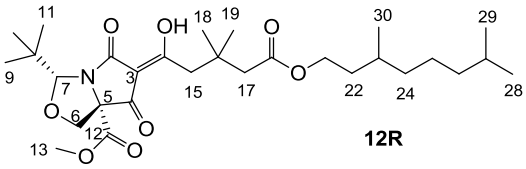


12Q

Yield; 39 %; M.P.; 131 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.15-5.04 (m, 2H, C6 and C21), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.29-4.15 (m, 2H, C14), 2.96-2.71 (m, 2H, C17), 1.04-1.92 (m, 3H, C18 and C19), 1.68 (s, 3H, C23), 1.59 (s, 3H, C24), 1.33-1.24 (m, 5H, C15 and C20),

1.04 (d, 3H, *J* = 6.0 Hz, C12), 0.96 (d, 3H, *J* = 6.4 Hz, C25), 0.93 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 190.43 (C16), 188.54 (C4), 179.68 (C2), 167.31 (C13), 131.72 (C22), 123.91 (C21), 103.55 (C3), 95.64 (C7), 81.26 (C5), 74.78 (C6), 62.54 (C14), 39.62 (CH_2), 36.81 (CH_2), 35.20 (C8), 33.75 (CH_2), 31.88 (C18), 25.66 (C23), 24.73 (C9-C11), 19.15 (C25), 17.63 (C24), 14.49 (CH_3), 13.91 (CH_3). **MS** (ES^+); 436.29 ((M+H); **HRMS** (M+H); calcd for $C_{24}H_{38}NO_6$ 436.2694; found; 436.2692.

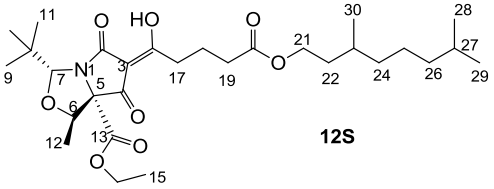
4.1.37. Synthesis of **12R**



12R

Yield; 16 % (oil); form AB: CD= 10: 90. **^{1}H NMR** (400 MHz, $CDCl_3$); 4.88 (s, 1H, C7 AB), 4.86 (s, 1H, C7 CD), 4.82 (d, 1H, *J* = 8.8 Hz, C6), 4.16-4.05 (m, 2H, C21), 3.80 (s, 3H, C13 AB), 3.77 (s, 3H, C13 CD), 3.48 (d, 1H, *J* = 8.8 Hz, C6), 3.12-2.94 (m, 2H, C15), 2,43 (s, 2H, C17 AB), 2.38 (s, 2H, C17 CD), 1.69-1.61 (m, 1H, C23), 1.57-1.49 (m, 2H, C22), 1.46-1.38 (m, 1H, C27), 1.32-1.09 (m, 12H, C18, C19 and C24-C26), 0.93 (s, 9H, C9-C11), 0.89 (d, 3H, *J* = 6.4 Hz, C30), 0.86 (d, 3H, *J* = 6.4 Hz, C28 and C29). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 190.02 (C14), 187.89 (C4), 180.05 (C2), 171.50 (C20), 167.35 (C12), 102.94 (C3), 98.23 (C7), 78.25 (C5), 68.14 (C6), 62.86 (C21), 53.24 (C13), 46.13 (CH_2), 42.89 (CH_2), 39.15 (CH_2), 37.07 (CH_2), 35.53 (CH_2), 35.42 (CH_2), 35.15 (CH_2), 29.80 (C23), 27.90 (C16 and C27), 27.41 (CH_3), 27.33 (CH_3), 24.60 (CH_2), 24.57 (C9-11), 22.65 (CH_3), 22.56 (CH_3), 19.44 (CH_3). **MS** (ES^-); 536.29 (M-H); **HRMS** (M-H); calcd for $C_{29}H_{46}N_1O_8$; 536.3229; found; 536.3223.

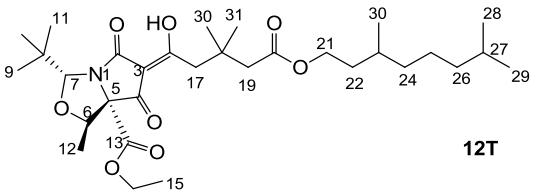
4.1.38. Synthesis of **12S**



12S

Yield; 36 % (oil); Form AB: CD = not determined**; ^{1}H NMR** (400 MHz, $CDCl_3$): 5.13 (q, 1H, *J* = 6.7 Hz, C6), 4.95 (s, 1H, C7), 4.28-4.19 (m, 2H, C14), 4.13-4.06 (m, 2H, C21), 3.11-2.89 (m, 2H, C17), 2.38 (t, 2H, *J* = 7.4 Hz, C19), 2.06-1.96 (m, 2H, C18), 1.70-1.37 (m, 4H, C22, C23 and C27),1.32-1.11(m, 9H, C15 and C24-C26), 1.04 (d, 3H, *J* = 6.7 Hz, C12), 0.93-0.85 (m, 18H, C9-C11 and C28-C30). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 189.40 (C16), 188.37 (C4), 179.53 (C2), 172.57 (C20), 167.19 (C13), 102.96 (C3), 95.65 (C7), 81.33 (C5), 74.80 (C6), 63.20 (CH_2), 62.63 (CH_2), 39.16 (CH_2), 37.08 (CH_2), 35.46 (CH_2), 35.19 (C8), 33.60 (CH_2), 33.16 (CH_2), 31.92 (CH_2), 29.80 (C23), 27.90 (C27), 24.73 (C9-C11), 24.56 (CH_2), 22.65 (CH_3), 22.56 (CH_3), 21.00 (C18), 19.46 (CH_3), 14.50 (CH_3), 13.93 (CH_3). **MS** (ES^-); 536.34 (M-H); **HRMS** (M-H); calculated for $C_{29}H_{46}NO_8$; 536.3229; found; 536.3230.

4.1.39. Synthesis of **12T**

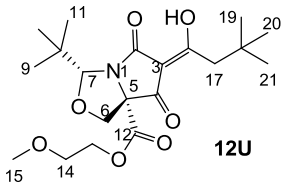


12T

Yield; 39 % (oil); Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.7 Hz, C6), 4.98 (s, 1H, C7 AB), 4.97

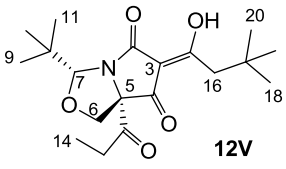
(s, 1H, C7 CD), 4.32-4.06 (m, 4H, C14 and C21), 3.07-2.96 (m, 2H, C17), 2.43 (s, 2H, C19 AB), 2.39 (s, 2H, C19 CD), 1.73-1.40 (m, 4H, C22, C23 and C27),1.31-1.13(m, 15H, C15, C24-C26, C30 and C31), 1.04 (d, 3H, *J* = 6.7 Hz, C12), 0.93-0.85 (m, 18H, C9-C11 and C28-C30). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 188.63 (C16), 188.61 (C4), 179.55 (C2), 171.52 (C20), 167.20 (C13), 104.59 (C3), 95.68 (C7), 81.25 (C5), 74.77 (C6), 62.85 (CH_2), 62.55 (CH_2), 46.19 (CH_2), 42.80 (CH_2), 39.16 (CH_2), 37.07 (CH_2), 35.68 (CH_2), 35.53 (CH_2), 35.21 (C8), 33.74 (C18), 29.80 (C23), 27.90 (C27), 27.26 (CH_3), 27.23 (CH_3), 24.73 (C9-C11), 24.58 (CH_2), 22.66 (CH_3), 22.56 (CH_3), 19.44 (CH_3), 14.55 (CH_3), 13.91 (CH_3). **MS** (ES^-); 564.36 (M-H); **HRMS** (M-H); calculated for $C_{31}H_{50}NO_8$; 564.3542; found; 564.3541.

4.1.40. Synthesis of **12U**



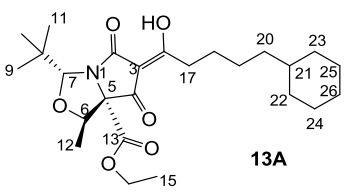
Yield; 41 %; M.P.; 98 ℃; form AB: CD = Not determined**; ^{1}HNMR** (500 MHz, $CDCl_3$): 4.88 (s, 1H, C7), 4.87 (d, 1H, *J* = 9.5 Hz, C6), 4.38-4.27 (m, 2H, C13), 3.61-3.54 (m, 2H, C14), 3.50 (d, 1H, *J* = 9.5 Hz, C6), 3.34 (s, 3H, C15), 2.92 (d, 1H, *J* = 12.0 Hz, C17), 2.64 (d, 1H, *J* = 12.0 Hz, C17), 1.06 (s, 9H, C19-C21), 0.95 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 190.94 (C16), 187.98 (C4), 180.40 (C2), 167.05 (C12), 102.59 (C3), 98.33 (C7), 78.30 (C5), 69.86 (C14), 68.18 (C6), 65.42 (C13), 58.87 (C15), 45.17 (C17), 35.18 (C8), 33.92 (C18), 29.75 (C19-C21), 24.66 (C9-C11). **MS** (ES^-); 396.21 (M-H); **HRMS** (M-H); calculated for $C_{20}H_{30}NO_7$ 396.2028 found 396.2024.

4.1.41. Synthesis of **12V**



Yield; 34 %; M.P.; 79 ℃; form AB: CD= 20: 80. **^{1}H NMR** (400 MHz, $CDCl_3$); 4.93 (d, 1H, *J* = 8.0 Hz, C6 AB), 4.91 (d, 1H, *J* = 8.0 Hz, C6 CD), 4.87 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 3.44 (d, 1H, *J* = 8.0 Hz, C6 AB), 3.40 (d, 1H, *J* = 8.0 Hz, C6 CD), 2.93 (d, 1H, *J* = 12.0 Hz, C16), 2.89-2.80 (m, 1H, C13), 2.63 (d, 1H, *J* = 12.0 Hz, C16), 2.32-2.22 (m, 1H, C13), 1.09-1.03 (m, 12H, C14 and C18-C20), 0.89 (s, 9H, C9-C11 CD), 0.88 (s, 9H, C9-C11 AB). **^{13}C NMR** (100 MHz, $CDCl_3$, Tautomer CD only); 201.71 (C12), 191.44 (C15), 189.03 (C4), 181.52 (C2), 102.91 (C3), 98.60 (C7), 83.45 (C5), 66.67 (C6), 45.21 (C16), 35.08 (C8), 34.15 (C17), 30.77 (C13), 29.72 (C18-C20), 24.96 (C9-C11), 7.37 (C14). **MS** (ES^-); 350.19 (M-H); **HRMS** (M-H); calcd for $C_{19}H_{28}N_1O_5$; 350.1973; found; 350.1971.

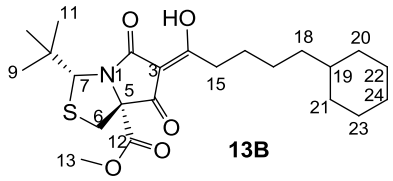
4.1.42. Synthesis of **13A**



Yield; 42 %; M.P.; 152 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 5.14 (q, 1H, *J* = 6.8 Hz, C6), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.29-4.20 (m, 2H, C14), 2.94-2.78 (m, 2H, C17), 1.73-1.59 (m, 8H, C18, C21 and cyclic CH_2), 1.40-1.26 (m, 7H, C15, C19 and C20), 1.19-1.12 (m, 5H, cyclic CH_2), 1.05 (d, 3H, *J* = 6.8 Hz, C12), 0.94 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only):

191.10 (C16), 188.43 (C4), 179.80 (C2), 167.36 (C13), 102.68 (C3), 95.66 (C7), 81.32 (C5), 74.84 (C6), 62.60 (C14), 37.47 (C21), 36.96 (CH_2), 35.21 (C8), 33.87 (CH_2), 33.32 (CH_2), 33.30 (CH_2), 32.86 (CH_2), 26.65 (CH_2), 26.35 (CH_2), 25.57 (CH_2), 24.91 (CH_2), 24.76 (C9-C11), 14.53 (CH_3), 13.95 (CH_3). **MS** (ES^-); 448.29 (M-H); **HRMS** (M-H); calcd for $C_{25}H_{38}NO_6$ 448.2705; found; 448.2702.

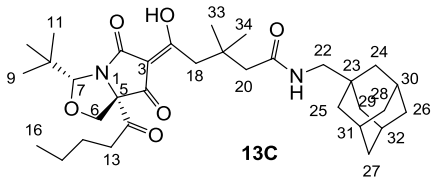
4.1.43. Synthesis of **13B**



13B

Yield; 36 %; M.P.; 129 ℃; Form AB: CD = 20: 80; **^{1}HNMR** (400 MHz, $CDCl_3$): 5.18 (s, 1H, C7 AB), 5.11 (s, 1H, C7 CD), 3.80-3.77 (m, 4H, C6 and C13), 2.87-2.82 (m, 3H, C6 and C15), 1.69-1.60 (m, 8H, CH_2), 1.41-1.34 (m, 2H, CH_2), 1.27-1.14 (m, 7H, CH_2 and CH), 0.99 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 191.61 (C14), 188.50 (C4), 177.70 (C2), 167.54 (C12), 99.52 (C3), 82.86 (C5), 73.52 (C7), 53.32 (C13), 37.48 (C19), 36.93 (CH_2), 36.69 (C8), 33.31 (C6), 32.99 (CH_2), 26.65 (CH_2), 26.47 (CH_2), 26.43 (C9-C11), 26.36 (CH_2), 26.21 (CH_2). **MS** (ES^-); 436.23 (M-H); **HRMS** (M-H); calculated for $C_{23}H_{34}NO_5S$; 436.2163; found; 436.2162.

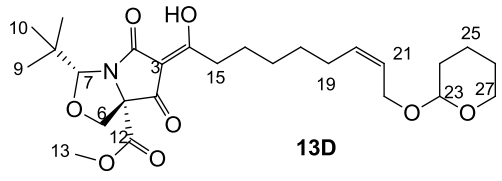
4.1.44. Synthesis of **13C**



13C

Yield; 33 %; M.P.; 111 ℃; form AB: CD= not determined. **^{1}H NMR** (500 MHz, $CDCl_3$); 4.90 (d, 1H, *J* = 9.0 Hz, C6), 4.88 (s, 1H, C7), 3.45-3.40 (m, 1H, C6), 3.27-2.96 (m, 4H, C13, C18 and C20), 2.82-2.76 (m, 1H, C22), 2.39-2.25 (m, 3H, C13, C18 and C22), 1.98 (brs, 3H, C30-C32), 1.73-1.48 (m, 14H, C14 and C24-C29), 1.29-1.25 (m, 2H, C15), 1.18-1.14 (m, 6H, C33 and C34), 0.90 (s, 9H, C9-C11), 0.87 (t, 3H, *J* = 7.5 Hz, C16). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only); 103.74 (C3), 98.78 (C7), 83.47 (C5), 66.76 (C6), 51.29 (CH_2), 48.19 (CH_2), 40.26 (CH_2), 37.44 (CH_2), 36.81 (CH_2), 36.18 (quart C), 35.14 (quart C), 33.58 (quart C), 28.10 (C30-C32), 25.32 (CH_2), 25.19 (C33 and C34), 25.07 (C9-C11), 22.10 (CH_2), 13.76 (C16). **MS** (ES^-); 569.29 (M-H); **HRMS** (M-H); calcd for $C_{22}H_{49}N_2O_6$; 569.3596; found; 569.3595.

4.1.45. Synthesis of **13D**

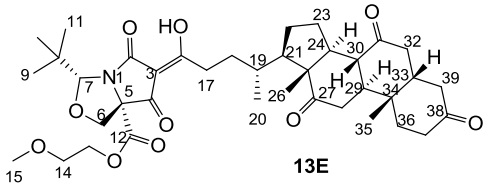


13D

Yield; 21 % (oil); form AB: CD= 20: 80. **^{1}H NMR** (400 MHz, $CDCl_3$); 5.61-5.45 (m, 2H, C20 and C21), 4.86 (s, 1H, C7 AB), 4.83 (s, 1H, C7 CD), 4.80 (d, 1H, *J* = 8.8 Hz, C6), 4.61-4.55 (m, 1H, C23), 4.24-4.02 (m, 2H, C22), 3.88-3.83 (m, 1H, C27), 3.77 (s, 3H, C13), 3.49-3.47 (m, 2H, C6 and C27), 3.00-2.80 (m, 2H, C5), 2.07-1.38 (m, 14H, C16-C19 and C24-C26), 0.91 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 192.2 (C14), 187.7 (C4), 180.2 (C2), 167.4 (C12), 133.1 (C20), 126.1 (C21), 101.0 (C3), 98.1 (C7), 97.8 (C23), 78.2 (C5), 68.1 (C6), 62.6 (CH_2), 62.1 (CH_2), 53.2 (C13), 35.1 (CH_2), 32.9 (CH_2), 30.6 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 27.2 (CH_2), 25.6 (CH_2), 25.4

(CH_2), 24.6 (C9-11), 19.4 (CH_2). **MS** (ES^-); 492.25 (M-H); **HRMS** (M-H); calcd for $C_{26}H_{38}N_1O_8$; 492.2603; found; 492.2617.

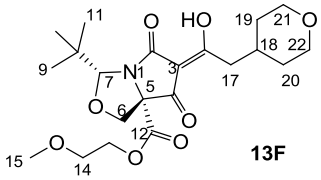
4.1.46. Synthesis of **13E**



13E

Yield; 71 %; M.P.; 138 ℃; Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 4.88 (s, 1H, C7 AB), 4.84 (s, 1H, C7 CD), 4.82 (d, 1H, *J* = 9.2 Hz, C6), 4.33-4.30 (m, 2H, C13), 3.59-3.56 (m, 2H, C14), 3.50 (d, 1H, *J* = 9.2 Hz, C6), 3.33 (s, 3H, C15 CD), 3.32 (s, 3H, C15 AB), 2.93-2.76 (m, 5H), 2.37-2.11 (m, 8H), 2.07-1.93 (m, 5H), 1.87-1.77 (m, 2H), 1.65-1.56 (m, 1H), 1.51-1.41 (m, 1H), 1.39 (s, 3H, C26), 1.36-1.26 (m, 3H), 1.06 (s, 3H, C35), 0.93 (s, 9H, C9-C11), 0.89 (d, 3H, *J* = 6.8 Hz, C20). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 211.71 (C=O), 208.99 (C=O), 208.61 (C=O),192.69 (C16), 187.62 (C4), 180.32 (C2), 166.97 (C12), 100.85 (C3), 98.28 (C7), 78.34 (C5), 69.82 (C14), 68.19 (C6), 65.47 (C13), 58.85 (C15), 56.84 (C25), 51.65 (CH), 48.90 (CH), 46.75 (CH), 45.45 (CH), 45.42 (CH), 44.90 (CH_2), 42.71 (CH_2), 38.54 (CH_2), 36.41 (CH_2), 35.94 (C34), 35.19 (CH_2), 35.10 (C8), 31.63 (CH_2), 30.59 (CH_2), 27.53 (CH_2), 25.06 (CH_2), 24.61 (C9-C11), 21.83 (C20), 18.62 (C26), 11.77 (C35). **MS** (ES^+); 684.39 (M+H); **HRMS** (M+H); calculated for $C_{38}H_{54}NO_{10}$; 684.3742; found; 684.3747.

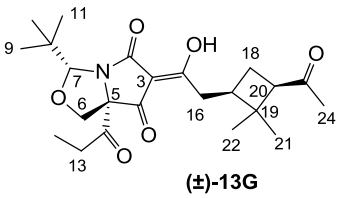
4.1.47. Synthesis of **13F**



13F

Yield; 52 % (oil); form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 4.89 (s, 1H, C7 AB), 4.85 (s, 1H, C7 CD), 4.83 (d, 1H, *J* = 9.2 Hz, C6), 4.38-4.28 (m, 2H, C13), 3.96-3.93 (m, 2H, C21 and C22), 3.59-3.56 (m, 2H, C14), 3.50 (d, 1H, *J* = 9.2 Hz, C6), 3.40-3.37 (m, 2H, C21 and C22), 3.33 (s, 3H, C15), 2.88-2.71 (m, 1H, C17), 2.10-2.00 (m, 1H, C17), 1.66-1.25 (m, 5H, C18-C20), 0.94 (s, 9H, C9-C11 CD), 0.90 (s, 9H, C9-C11 AB). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 190.12 (C16), 187.82 (C4), 180.04 (C2), 166.88 (C12), 101.91 (C3), 98.31 (C7), 78.36 (C5), 69.84 (C14), 68.16 (C6), 67.56 (C21 and C22), 65.47 (C13), 58.83 (C15), 39.57 (C17), 35.12 (C8), 33.61 (C18), 32.64 (C19 and C20), 24.61 (C9-C11). **MS** (ES^-); 424.21 (M-H); **HRMS** (M-H); calculated for $C_{21}H_{30}NO_8$ 424.1977 found 424.1969.

4.1.48. Synthesis of (±)-**13G**

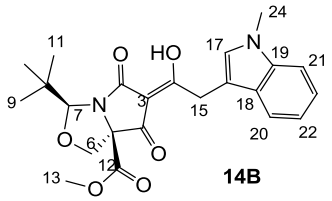


(±)-13G

Yield; 41 % (oil); form AB: CD= 20: 80. **^{1}H NMR** (500 MHz, $CDCl_3$); 12.28 (brs, 1H, OH), 4.85 (d, 1H, *J* = 9.0 Hz, C6), 4.81 (s, 1H, C7 AB), 4.79 (s, 1H, C7 CD), 3.38 (d, 1H, *J* = 9.0 Hz, C6), 2.99-2.74 (m, 4H, C13, C16 and C20), 2.38-2.21 (m, 2H, C13 and C17), 2.08-2.03 (m, 1H, C18), 1.99 (s, 3H, C24), 1.88-1.83 (m, 1H, C18), 1.27 (s, 3H, C21), 1.03-1.00 (m, 3H, C14), 0.90-0.84 (m, 12H, C9-C12 and C22). **^{13}C NMR** (125 MHz, $CDCl_3$, due to two diastereomers, some peakes are splitted); 206.90 (C 23 AB), 206.80 and 206.77 (C23 CD), 201.58 and 201.53 (C12 CD), 201.47 (C12 AB), 195.78 (C4 AB),

193.85 (C15 AB), 191.36 and 191.32 (C15 CD), 188.70 and 188.64 (C4 CD), 181.16 (C2 CD), 173.16 (C2 AB), 104.28 (C3 AB), 101.33 and 101.30 (C3 CD), 98.44 (C7), 83.40 (C5 CD), 81.09 and 81.05 (C5 AB), 66.58 and 66.55 (C6 CD), 66.46 (C6 AB), 54.05 (C20 AB), 53.95 and 53.93 (C20 CD), 43.81 and 43.77 (C19), 39.20 and 39.05 (C17 CD), 38.66 and 38.62 (C17 AB), 35.11 and 35.09 (C8 AB), 34.93 (C8 CD), 33.96 and 33.87 (C16 AB), 33.45 and 33.39 (C16 CD), 30.83 and 30.75 (C13 CD), 30.56 and 30.51 (C13 AB), 29.90 (C24), 29.82 and 29.75 (C21), 24.92 (C9-C11 AB), 24.83 (C9-C11 CD), 23.22 (C18 AB), 23.06 and 23.05 (C18 CD), 17.46 (C22 AB), 17.38 (C22 CD), 7.24 (C14). **MS** (ES^-); 418.21 (M-H); MS (ES^+); 442.23 (M+Na); **HRMS** (M-H); calcd for $C_{23}H_{33}N_1Na_1O_6$; 442.2200; found; 442.2201.

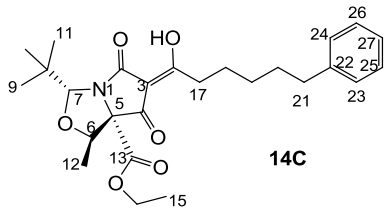
4.1.49. Synthesis of **14B**



14B

Yield; 37 %; M.P.; 85 ℃; form AB: CD= 20: 80; **^{1}H NMR** (400 MHz, $CDCl_3$); 7.76 (d, 1H, *J* = 8.0 Hz, C20 AB), 7.760 (d, 1H, *J* = 8.0 Hz, C20 CD), 7.33-7.14 (m, 4H, C17 and C21-C23), 4.97 (s, 1H, C7 AB), 4.97 (d, 1H, *J* = 8.8 Hz, C6 CD), 4.94 (d, 1H, *J* = 8.8 Hz, C6 AB), 4.82 (s, 1H, C7 CD), 4.49 (d, 1H, *J* = 14.4 Hz, C15 AB), 4.33 (d, 1H, *J* = 14.4 Hz, C15 CD), 4.28 (d, 1H, *J* = 14.4 Hz, C15 AB), 4.22 (d, 1H, *J* = 14.4 Hz, C15 CD), 3.83 (s, 3H, C13 CD), 3.79 (s, 3H, C13 AB), 3.79 (s, 3H, C24 AB), 3.77 (s, 3H, C24 CD), 3.51 (d, 1H, *J* = 8.8 Hz, C6 CD), 3.50 (d, 1H, *J* = 8.8 Hz, C6 AB), 0.99 (s, 9H, C9-11 AB), 0.93 (s, 9H, C9-11 CD). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 192.3 (C14), 187.8 (C4), 180.3 (C2), 167.5 (C12), 136.7 (C19), 128.6 (C17), 127.5 (C18), 121.9 (C23), 119.5 (C22), 119.2 (C20), 109.3 (C21), 105.9 (C16), 100.6 (C3), 98.2 (C7), 78.4 (C5), 68.2 (C6), 53.3 (C13), 35.1 (C8), 32.7 (C24), 29.0, 24.6 (C9-11). **MS** (ES^-); 425.18 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{25}N_2O_6$; 425.1718; found; 425.1712.

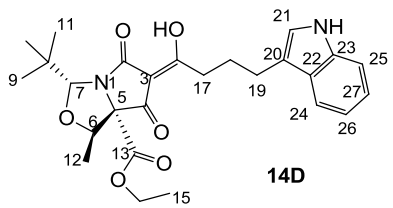
4.1.50. Synthesis of **14C**



14C

Yield; 41 %; M.P.; 126 ℃; Form AB: CD = 20: 80; **^{1}HNMR** (400 MHz, $CDCl_3$): 7.30-7.26 (m, 2H, C25 and C26), 7.20-7.15 (m, 3H, C23, C24 and C27), 5.14 (q, 1H, *J* = 6.8 Hz, C6), 4.98 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.31-4.17 (m, 2H, C14), 3.05-2.79 (m, 2H, C17), 2.64-2.58 (m, 2H, C21), 1.78-1.61 (m, 4H, C18 and C20), 1.50-1.38 (m, 2H, C19), 1.28 (t, 3H, *J* = 7.2 Hz, C15), 1.04 (d, 3H, *J* = 6.8 Hz, C12), 0.94 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 190.86 (C16), 188.42 (C4), 179.78 (C2), 167.32 (C13), 142.26 (C22), 128.33 (Ar-CH), 128.28 (Ar-CH), 125.71 (C27), 102.70 (C3), 95.66 (C7), 81.32 (C5), 74.83 (C6), 62.61 (C14), 35.62 (CH_2), 35.19 (C8), 32.73 (CH_2), 30.95 (CH_2), 28.62 (CH_2), 25.82 (CH_2), 24.75 (C9-C11), 14.51 (CH_3), 13.95 (CH_3). **MS** (ES^-); 456.26 (M-H); **HRMS** (M-H); calculated for $C_{26}H_{34}NO_6$; 456.2392; found; 456.2390.

4.1.51. Synthesis of **14D**

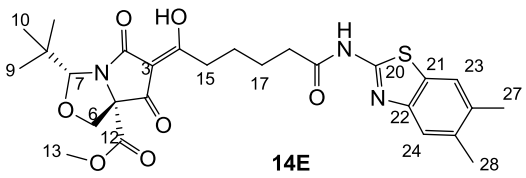


14D

Yield; 44%; M.P.; 129 ℃; Form AB: CD = 20: 80**;** **^{1}HNMR** (400 MHz,

$CDCl_3$): 8.06 (brs, 1H, NH), 7.58 (d, 1H, *J* = 7.8 Hz, C24), 7.36 (d, 1H, *J* = 7.8 Hz, C22), 7.20 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.12 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.02 (d, 1H, *J* = 2.0 Hz, C21), 5.14 (q, 1H, *J* = 6.8 Hz, C6), 4.99 (s, 1H, C7 AB), 4.96 (s, 1H, C7 CD), 4.32-4.19 (m, 2H, C14), 3.08-2.78 (m, 4H, C17 and C19), 2.19-2.06 (m, 2H, C18), 1.28 (t, 3H, *J* = 6.8 Hz, C15), 1.04 (d, 3H, *J* = 6.8 Hz, C12), 0.95 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 190.9 (C16), 188.4 (C4), 179.8 (C2), 167.4 (C13), 136.3 (C23), 127.3 (C22), 122.0 (Ar-CH), 121.6 (Ar-CH), 119.3 (Ar-CH), 118.8 (Ar-CH), 115.2 (C20), 111.1 (C25), 102.7 (C3), 95.7 (C7), 81.4 (C5), 74.9 (C6), 62.7 (C14), 35.2 (C8), 32.8 (CH_2), 26.4 (CH_2), 24.8 (C9-C11), 24.7 (CH_2), 14.5 (CH_3), 14.0 (CH_3). **MS** (ES^-); 467.24 (M-H); **HRMS** (M-H); calculated for $C_{26}H_{31}N_2O_6$; 467.2188; found 467.2189.

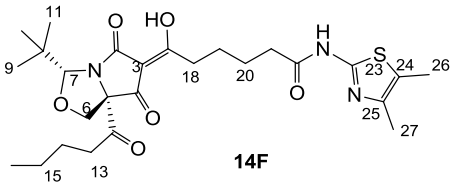
4.1.52. Synthesis of **14E**



14E

Yield; 23 % M.P.; 222 ℃ (decomposed); form AB: CD= 1:99**; ^{1}H NMR** (500 MHz, DMSO); 12.21 (brs, 1H, NH), 7.68 (s, 1H, C24), 7.51 (s, 1H, C23), 4.72 (s, 1H, C7), 4.55 (d, 1H, *J* = 8.5 Hz, C6), 3.65 (s, 3H, C13), 3.49 (d, 1H, *J* = 8.5 Hz, C6), 2.84-2.71 (m, 2H, C15), 2.48-2.46 (m, 2H, C18), 2.31 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.65-1.54 (m, 4H, C16 and C17), 0.81 (s, 9H, C9-11). **^{13}C NMR** (125 MHz, DMSO); 191.03 (C14), 188.14 (C4), 177.50 (C2), 171.83 (C19), 169.01 (C12), 156.94 (C20), 147.08 (C22), 134.67 (quart C), 132.24 (quart C), 128.76 (quart C), 121.40 (tert C), 120.83 (tert C), 100.63 (C3), 97.09 (C7), 76.65 (C5), 67.90 (C6), 52.72 (C13), 34.86 (C8), 33.34 (CH_2), 25.32 (CH_2), 24.82 (CH_2), 24.65 (C9-11), 24.37 (CH_2), 19.70 (CH_3), 19.53 (CH_3). **MS** (ES^-); 542.15 (M-H); **HRMS** (M-H); calcd for $C_{27}H_{32}N_3O_7S_1$; 542.1966; found; 542.1967.

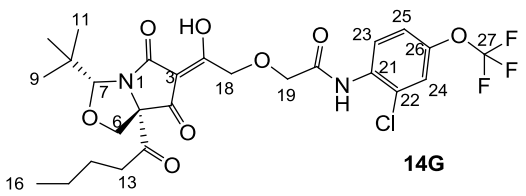
4.1.53. Synthesis of **14F**



14F

Yield; 20 %; M.P.; 111 ℃; form AB: CD= 1: 99. **^{1}H NMR** (500 MHz, $CDCl_3$); 4.85 (d, 1H, *J* = 8.5 Hz, C6), 4.83 (s, 1H, C7), 3.42 (d, 1H, *J* = 8.5 Hz, C6), 2.95-2.80 (m, 3H, C13 and C18), 2.70 (t, 2H, *J* = 7.0 Hz, C21), 2.38-2.32 (m, 1H, C13), 2.34 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.86-1.41 (m, 6H, C14, C19 and C20), 1.30-1.22 (m, 2H, C15), 0.88 (s, 9H, C9-C11), 0.85 (t, 3H, *J* = 7.5 Hz, C16). **^{13}C NMR** (125 MHz, $CDCl_3$); 171.31 (C22), 158.52 (C23), 132.73 (C25), 119.78 (C24), 98.41 (C7), 66.80 (C6), 36.96 (CH_2), 35.94 (CH_2), 35.16 (C8), 25.30 (CH_2), 25.10 (C9-C11), 24.72 (CH_2), 23.84 (CH_2), 22.04 (CH_2), 13.81 (CH_3), 11.74 (CH_3), 10.66 (CH_3). **MS** (ES^-); 518.19 (M-H); **HRMS** (M+H); calcd for $C_{26}H_{38}N_3O_6S_1$; 520.2476; found; 520.2479.

4.1.54. Synthesis of **14G**

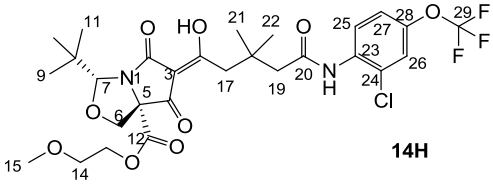


14G

Yield; 16 % (oil); form AB: CD= not determined. **^{1}H NMR** (500 MHz, $CDCl_3$); 9.03 (brs, 1H, NH), 8.47 (d, 1H, *J* = 9.0 Hz, C23), 7.31 (d, 1H, *J* = 2.5 Hz, C24), 7.18 (dd, 1H, J_1= 9.0 Hz, J_2 = 2.5

Hz, C24), 4.99-4.72 (m, 4H, C6, C7 and C19), 4.29 (s, 2H, C18), 3.50-3.48 (m, 1H, C6), 2.83-2.74 (m, 1H, C13), 2.38-2.32 (m, 1H, C13), 1.67-1.46 (m, 2H, C14), 1.32-1.26 (m, 2H, C15), 0.91-0.87 (m, 12H, C9-C11 and C16). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only); 201.28 (C12), 188.14 (C17), 186.52 (C4), 181.46 (C2), 166.68 (C20), 144.92 (*quart*-C), 132.78 (*quart*-C), 123.68 (*quart*-C), 122.11 (*tert*-C), 122.08 (*tert*-C), 120.51 (*tert*-C), 100.86 (C3), 98.85 (C7), 83.75 (C5), 71.33 (OCH_2), 69.08 (OCH_2), 66.77 (C6), 37.72 (C13), 35.09 (C8), 25.22 (CH_2), 24.97 (C9-C11), 22.02 (CH_2), 13.77 (C16). **MS** (ES^-); 589.10 (M-H); **HRMS** (M-H); calcd for $C_{26}H_{29}Cl_1F_3N_2O_8$; 589.1570; found; 589.1558.

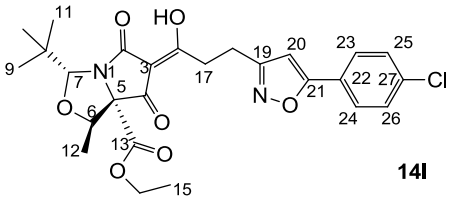
4.1.55. Synthesis of **14H**



14H

Yield; 38 %; M.P.; 129 ℃; Form AB: CD = 1: 99**; ^{1}HNMR** (400 MHz, $CDCl_3$): 8.52 (brs, 1H, NH), 8.35 (d, 1H, *J* = 9.1 Hz, C25), 7.27 (d, 1H, *J* = 2.0 Hz, C26), 7.14 (dd, 1H, J_1 = 9.1 Hz, J_2 = 2.0 Hz, C27), 4.85 (s, 1H, C7), 4.83 (d, 1H, *J* = 9.2 Hz, C6), 4.35-4.32 (m, 2H, C13), 3.59 (t, 2H, *J* = 5.2 Hz, C14), 3.51 (d, 1H, *J* = 9.2 Hz, C6), 3.34 (s, 3H, C15), 2.56 (s, 2H, C17), 2.48 (s, 2H, C19), 1.19 (s, 6H, C21 and C22), 0.93 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 188.37 (C16), 187.95 (C4), 176.66 (C2), 170.39 (C20), 166.98 (C12), 144.85 (*quart*-C), 133.41 (*quart*-C), 123.94 (*quart*-C), 123.14 (*tert*-C), 122.07 (*tert*-C), 120.29 (*tert*-C), 101.65 (C3), 98.28 (C7), 78.45 (C5), 69.81 (C14), 68.12 (C6), 65.48 (C13), 58.83 (C15), 47.86 (CH_2), 44.69 (CH_2), 35.10 (C8), 33.67 (C18), 28.75 (C21 and C22), 24.60 (C9-C11). **MS** (ES^-); 633.21 (M-H); **HRMS** (M-H); calculated for $C_{28}H_{33}ClF_3N_2O_9$; 633.1832; found 633.1836.

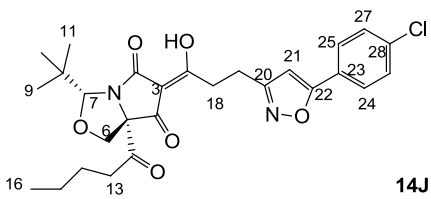
4.1.56. Synthesis of **14I**



14I

Yield: 52 %; M.P.; 89 ℃; form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 7.67 (d, 2H, *J* = 8.3 Hz, C23 and C24), 7.40 (d, 2H, *J* = 8.3 Hz, C25 and C26), 6.47 (s, 1H, C20 AB), 6.44 (s, 1H, C20 CD), 5.10 (q, 1H, *J* = 6.8 Hz, C6), 4.94 (s, 1H, C7 CD), 4.93 (s, 1H, C7 AB), 4.20 (q, 2H, *J* = 7.3 Hz, C14), 3.53-3.04 (m, 4H, C17 and C18), 1.26 (t, 3H, *J* = 6.8 Hz, C15 AB), 1.25 (t, 3H, *J* = 6.8 Hz, C15 CD), 0.99 (d, 3H, *J* = 6.8 Hz, C12 AB), 0.97 (d, 3H, *J* = 6.8 Hz, C12 CD), 0.92 (s, 9H, C9-C11 CD), 0.91 (s, 9H, C9-C11 AB). **^{13}C NMR** (125 MHz, $CDCl_3$, tautomer CD only): 188.4 (C16), 187.8 (C4), 179.4 (C2), 168.9 (C21), 167.1 (C13), 162.2 (C19), 136.2 (C27), 129.3 (C25 and C26), 127.0 (C23 and C24), 125.7 (C22), 103.2 (C3), 99.3 (C20), 95.7 (C7), 81.4 (C5), 74.8 (C6), 62.7 (C14), 35.2 (C8), 31.0 (C17), 24.7 (C9-C11), 21.9 (C18), 14.4 (CH_3), 13.9 (CH_3). **MS** (ES^+); 517.20 (M+H); **HRMS** (M+H): calculated for $C_{26}H_{30}ClN_2O_7$ 517.1736; found; 517.1740.

4.1.57. Synthesis of **14J**

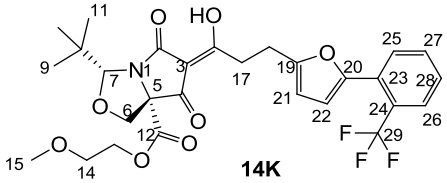


14J

Yield; 44 % (oil); form AB: CD= 20: 80; **^{1}H NMR** (400 MHz, $CDCl_3$);

7.69-7.66 (m, 2H, C24 and C25), 7.43 (d, 2H, *J* = 8.4 Hz, C26 and C27), 6.47 (s, 1H, C21 AB), 6.44 (s, 1H, C21 CD), 4.92 (d, 1H, *J* = 8.4 Hz, C6 AB), 4.89 (d, 1H, *J* = 8.8 Hz, C6 CD), 4.83 (s, 1H, C7 CD), 4.82 (s, 1H, C7 AB), 3.53-3.24 (m, 3H, C6 and C19), 3.18-3.08 (m, 2H, C18), 2.84-2.74 (m, 1H, C13), 2.33-2.25 (m, 1H, C13), 1.63-1.42 (m, 2H, C14), 1.30-1.20 (m, 2H, C15), 0.90-0.84 (m, 12H, C9-C11 and C16). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 201.03 (C12), 189.67 (C17), 188.84 (C4), 181.19 (C2), 168.97 (C22), 162.12 (C20), 136.28 (C28), 129.29 (C26 and C27), 126.98 (C24 and C25), 125.67 (C23), 102.07 (C3), 99.32 (C21), 98.71 (C7), 83.74 (C5), 66.66 (C6), 37.47 (CH_2), 35.08 (C8), 31.07 (CH_2), 25.20 (CH_2), 24.99 (C9-C11), 21.99 (CH_2), 21.80 (CH_2), 13.81 (C16). **MS** (ES^-); 513.15 (M-H); **HRMS** (M-H); calcd for $C_{27}H_{30}Cl_1N_2O_6$; 513.1798; found; 513.1794.

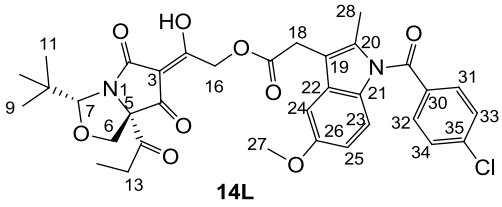
4.1.58. Synthesis of **14K**



14K

Yield; 39 % (oil); Form AB: CD = 20: 80**; ^{1}HNMR** (400 MHz, $CDCl_3$): 7.71 (t, 2H, *J* = 7.2 Hz, C25 and C26), 7.56 (t, 1H, *J* = 7.6 Hz, C27), 7.39 (t, 1H, *J* = 7.7 Hz, C28), 6.60 (d, 1H, *J* = 3.1 Hz, C22), 6.18 (d, 1H, *J* = 3.1 Hz, C21), 4.85 (s, 1H, C7 AB), 4.83 (s, 1H, C7 CD), 4.80 (d, 1H, *J* = 8.8 Hz, C6), 4.36-4.29 (m, 2H, C13), 3.60-3.54 (m, 2H, C14), 3.44 (d, 1H, *J* = 8.8 Hz, C6), 3.34-3.21 (m, 5H, C15 and C17), 3.11 (t, 2H, *J* = 7.2 Hz, C18), 0.94 (s, 9H, C9-C11 CD). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only): 189.84 (C16), 187.60 (C4), 180.13 (C2), 166.89 (C12), 153.64 (C19), 149.42 (C20), 131.69 (*tert*-C), 129.52 (*tert*-C), 127.43 (*tert*-C), 126.63 (*quart*-C), 126.57 (*quart*-C), 110.83 (C21), 108.22 (C22), 101.52 (C3), 98.35 (C7), 78.39 (C5), 69.80 (C14), 68.10 (C6), 65.49 (C13), 58.82 (C15), 35.12 (C8), 33.57 (CH_2), 31.53 (CH_2), 24.64 (C9-C11). **MS** (ES^-); 564.20 (M-H); **HRMS** (M-H); calculated for $C_{28}H_{29}F_3NO_8$; 564.1851; found; 564.1854.

4.1.59. Synthesis of **14L**

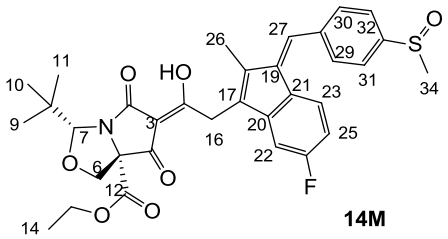


14L

Yield; 39 %; M.P.; 102 ℃; form AB: CD= 35: 65. **^{1}H NMR** (500 MHz, $CDCl_3$); 9.16 (brs, 1H, OH), 7.67 (d, 2H, *J* = 8.5 Hz, C31 and C32), 7.48 (d, 2H, *J* = 8.5 Hz, C33 and C34), 6.99 (s, 1H, C24 AB), 6.97 (s, 1H, C24 CD), 6.88 (d, 1H, *J* = 8.5 Hz, C23), 6.68 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz, C25), 5.30 (s, 2H, C16 AB), 5.23 (s, 2H, C16 CD), 4.97 (d, 1H, *J* = 9.0 Hz, C6 AB), 4.91 (d, 1H, *J* = 9.0 Hz, C6 CD), 4.81 (s, 1H, C7 CD), 4.76 (s, 1H, C7 AB), 3.84 (s, 3H, C27), 3.81 (s, 2H, C18), 3.47 (d, 1H, *J* = 8.0 Hz, C6), 2.98-2.84 (m, 1H, C13), 2.40 (s, 3H, C28), 2.36-2.27 (m, 1H, C13), 1.07 (t, 3H, *J* = 7.0 Hz, C14), 0.90 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 200.92 (C12 CD), 200.71 (C12 AB), 191.90 (C4 AB), 188.56 (C15 AB), 187.87 (C15 CD), 185.47 (C4 CD), 181.69 (C2 CD), 173.47 (C2 AB), 170.10 (C17), 168.24 (C29), 156.02 (C26), 139.30 (quart C), 136.19 (quart C), 133.77 (quart C), 131.16 (tert-C), 130.75 (quart C), 130.42 (quart C), 129.10 (tert-C), 114.94 (tert-C), 111.68 (tert-C), 105.36 (C3 AB), 101.16 (C24), 100.42 (C3 CD), 98.69 (C7 AB), 97.98 (C7 CD),

83.55 (C5 CD), 79.65 (C5 AB), 66.92 (C6 AB), 66.56 (C6 CD), 64.95 (C16 AB), 61.83 (C16 CD), 55.66 (C27), 35.05 (C8), 31.07 (C18), 29.50 (C13), 24.90 (C9-C11 AB), 13.29 (C28), 7.29 (C14). **MS** (ES^-); 649.15 (M-H); **HRMS** (M-H); calcd for $C_{34}H_{34}Cl_1N_2O_9$; 649.1958; found; 649.1955.

4.1.60. Synthesis of **14M**

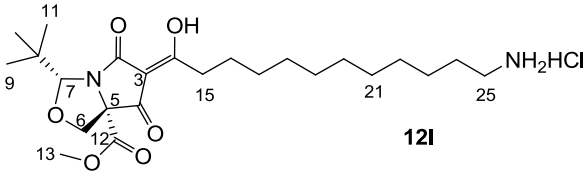


14M

Yield; 84 %; M.P.; 115 ℃; Form AB: CD= 20: 80**; ^{1}H NMR** (400 MHz, $CDCl_3$); 7.73 (d, 2H, *J* = 8.4 Hz, C29 and C30), 7.67 (d, 2H, *J* = 8.4 Hz, C31 and C32), 7.19 (s, 1H, C27 CD), 7.18 (s, 1H, C27 AB), 7.15 (dd, 1H, $J_{H\text{-}H}$ = 8.8 Hz, $J_{H\text{-}F}$ = 5.2 Hz, C23), 6.97 (dd, 1H, $J_{H\text{-}F}$ = 9.2 Hz, $J_{H\text{-}H}$ = 2.4 Hz, C22 AB), 6.97 (dd, 1H, $J_{H\text{-}F}$ = 9.2 Hz, $J_{H\text{-}H}$ = 2.4 Hz, C22 CD), 6.57 (dd, 1H, $J_{H\text{-}H}$ = 8.8 Hz, $J_{H\text{-}H}$ = 2.4 Hz, $J_{H\text{-}F}$ = 9.2 Hz, C25), 4.97 (s, 1H, C7 AB), 4.90 (d, 1H, *J* = 8.8 Hz, C6 CD), 4.88-4.86 (m, 1H, C7 CD, 1H C6 AB), 4.35-4.23 (m, 3H, C13 and C16), 4.03 (d, 1H, *J* = 14.8 Hz, C16), 3.56 (d, 1H, *J* = 8.8 Hz, C6), 2.81 (s, 3H, C34), 2.26 (s, 3H, C26 AB), 2.25 (s, 3H, C26 CD), 1.30 (t, 3H, *J* = 7.6 Hz, C14), 0.99 (s, 9H, C9-11 AB), 0.94 (s, 9H, C9-11 CD). **^{13}C NMR** (100 MHz, $CDCl_3$, CD form only); 188.45 (C15), 187.11 (C4), 179.87 (C2), 166.73 (C12), 163.3 (d**,** $J_{C\text{-}F}$ = 245 Hz, C24), 146.25 (tert Ar-C), 145.57 (tert Ar-C), 141.42 (tert Ar-C), 139.79 (tert Ar-C), 139.45 (tert Ar-C), 131.47 (tert Ar-C), 130.17 (C29 and C30), 129.29 (C21), 128.79 (C27), 123.81 (C31 and C32), 123.66 (d, $J_{C\text{-}F}$ = 9.5 Hz, C23), 110.96 (d, $J_{C\text{-}F}$ = 22.3 Hz, C25), 106.22 (d, $J_{C\text{-}F}$ = 23.8 Hz, C22), 101.80 (C3), 98.28 (C7), 78.48 (C5), 68.09 (C6), 62.88 (C13), 43.84 (C34), 35.15 (C8), 28.90 (C16), 24.64 (C9-11), 13.93 (C14), 10.83 (C26). **MS** (ES^-); 606.17 (M-H); **HRMS** (M-H); calcd for $C_{33}H_{33}F_1N_1O_7S_1$; 606.1967; found; 606.1961.

4.2. Synthesis of 12I and 12J from 12H

In order to prepare HCl solution, acetyl chloride (4.0 ml) was slowly added to methanol (10 ml) under nitrogen atmosphere and at 0 ℃. Then, the HCl solution made obove was slowly added to the solution of tetramic acid **12H** (200 mg, 0.362 mmol) in methanol (10 ml) under nitrogen atmosphere and at 0 ℃. After strring for 1 hr at 0 ℃, monitoring the reaction by TLC, the solvent was evaporated in vacuo and dissoved in dichloromethane. The mixture was washed with acidic water (2 M HCl) and the organic layer was dried over $MgSO_4$. Tetramic acid **12I** (165 mg, 0.340 mmol, 94 % yield, oil) was obtained after removing the solvent in vacuo.

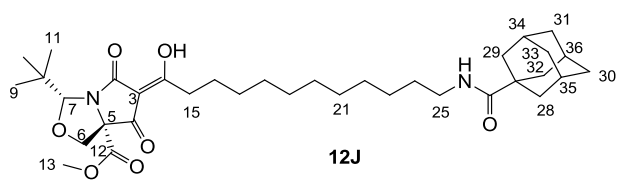


12I

Form AB: CD= not determined; **^{1}H NMR** (500 MHz, CD_3OD); 4.71-4.66 (m, 2H, C6 and C7), 3.73 (s, 3H, C13), 3.41-3.36 (m, 1H, C6), 2.92 (t, 2H, *J* = 7.5 Hz, C15), 2.79-2.73 (m, 2H, C25), 1.69-1.55 (m, 4H, C16 and C24), 1.40-1.30 (m, 14H, C17-C23), 1.87 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, CD_3OD, tautomer CD only); 191.24 (C14), 184.95 (C4), 176.06 (C2), 170.65 (C12), 101.14 (C3), 99.06 (C7), 78.64 (C5), 69.97 (C6), 53.41 (C13), 40.85

(C25), 36.22 (C8), 34.83 (C15), 30.69 (CH_2), 30.55 (CH_2), 30.25 (CH_2), 28.62 (CH_2), 27.49 (CH_2), 26.14 (CH_2), 26.05 (CH_2), 25.49 (C9-11). **MS** (ES^-); 451.29 (M-H); **HRMS** (M+Na); calcd for $C_{24}H_{40}N_2Na_1O_6$; 475.2779; found; 475.2768.

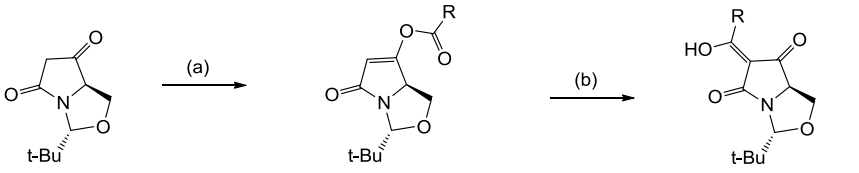
1-Adamantylcarbonyl chloride (50 mg, 0.245 mmol) was added to the mixture of tetramic acid **12I** (100 mg, 0.204 mmol) and triethylamine (45 mg, 0.450 mmol) in dichloromethane (15 ml), and the mixture was stirred for 2 hr. After completion of reaction, concentration in vacuo followed by flash column chromatography gave metal-chelated product. The compound was dissolved in dichloromethane (20 mL) and washed with aqueous HCl (3< pH <5, 50 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give free form of 3-acyltetramic acid **12J** (80 mg, 0.131 mmol, 64 % yield, oil).



12J

Form AB: CD= 20: 80; **^{1}H NMR** (400 MHz, $CDCl_3$); 5.60 (brs, 1H, NH), 4.87 (s, 1H, C7 AB), 4.84 (s, 1H, C7 CD), 4.81 (d, 1H, *J* = 9.2 Hz, C6), 3.79 (s, 3H, C13 AB), 3.78 (s, 3H, C13 CD), 3.48 (d, 1H, *J* = 9.2 Hz, C6), 3.23-3.18 (m, 2H, C25), 3.01-2.88 (m, 2H, C15 AB), 2.83 (t, 2H, *J* = 8.0 Hz, C15 CD), 2.02 (brs, 3H, C34-C36), 1.91-1.83 (m, 8H, adamantyl CH_2), 1.75-1.62 (m, 6H, C16 and adamantyl CH_2), 1.48-1.25 (m, 16H, C17-C24), 0.92 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$, tautomer CD only); 192.45 (C14), 187.70 (C4), 180.22 (C2), 177.84 (C26), 167.44 (C12), 100.97 (C3), 98.17 (C7), 78.26 (C5), 68.17 (C6), 53.23 (C13), 40.49 (C27), 39.23 (CH_2), 38.60 (CH_2), 36.48 (CH_2), 36.39 (CH_2), 35.10 (C8), 29.56 (CH_2), 29.38 (CH_2), 29.26 (CH_2), 29.20 (CH_2), 29.11 (CH_2), 29.06 (CH_2), 28.09 (CH), 27.80 (CH), 26.81 (CH_2), 25.81 (CH_2), 24.57 (C9-11). **MS** (ES^-); 613.31 (M-H); **HRMS** (M+Na); calcd for $C_{35}H_{54}N_2Na_1O_7$; 637.3823; found; 637.3813.

4.3. Synthesis of 3-acyl tetramic acids via acyl migration



T20

O-13H; R = cyclohexyl
O-14A; R = Phenyl

13H; R = cyclohexyl
14A; R = Phenyl

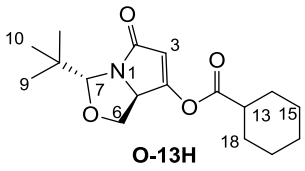
(a) carboxylic acid (1.1 eq), DCC (1.05 eq), DMAP (0.1 eq), CH_2Cl_2, r.t.;
(b) $(CH_3)_2C(OH)CN$ (0.5 eq), Et_3N (2.0 eq), CH_3CN, r.t..

General methods for *O*-acylation: To a mixture of tetramic acid (1 equivalent) and carboxylic acid (1.1 equivalent) in dichloromethane was added DCC (1.1 equivalent) and DMAP (0.1 equivalent). The mixture was stirred 24 hr at r.t. The crude reaction mixture was filtered with dichloromethane. Concentration in *vacuo* followed by flash column chromatography gave the *O*-acyl tetramic acid.

General method for acyl migration: To a mixture of *O*-acyl tetramic acid (1.0 equivalent) and triethyl amine (2.0 equivalents) in acetonitrile was added acetone cyanohydrin (0.5 equivalent) at room temperature. The

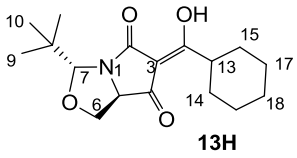
reaction mixture was stirred for 12 hr at room temperature. The crude reaction mixture was concentrated in *vacuo*. The crude product was disoved in ether then wash with basic water solution (0.25 N NaOH) and acidic water solution (1N HCl). The organic layer was dried with $MgSO_4$ and concentrated to afford 3-acyl tetramic acid.

4.3.1. Synthesis of **O-13H** and **13H**



O-13H

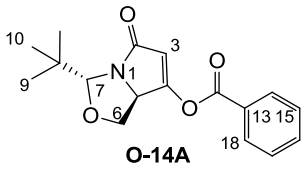
O-13H; Yield; 55 %; **^{1}H NMR** (400 MHz, $CDCl_3$); 5.83 (s, 1H, C3), 4.79 (s, 1H, C7), 4.47 (dd, 1H, J_1 = 9.2 Hz, J_2 = 6.4 Hz, C5), 4.26 (dd, 1H, J_1 = 8.0 Hz, J_2 = 6.4 Hz, C6) 3.36 (dd, 1H, J_1 = 9.2 Hz, J_2 = 8.0 Hz, C6), 2.49-2.42 (m, 1H, C13), 1.96-1.93 (m, 2H, (CH_2)), 1.79-1.75 (m, 2H, CH_2), 1.67-1.64 (m, 1H, CH_2), 1.51-1.42 (m, 2H, CH_2), 1.35-1.21 (m, 3H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$); 176.06 (quart C), 171.22 (quart C), 165.65 (quart C), 107.88 (C3), 94.31 (C7), 68.95 (C6), 64.17 (C5), 43.06 (C13), 35.81 (C8), 28.63 (CH_2), 28.59 (CH_2), 25.43 (CH_2), 25.10 (CH_2), 24.65 (C9-11).



13H

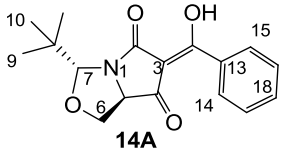
13H; Yield; 75 % (Oil); Form AB: CD= 30: 70; $[\alpha]_D^{22}$ = +51.6 (c = 2.0 in MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$); 4.93 (s, 1H, C7 AB), 4.90 (s, 1H, C7 CD), 4.25-4.21 (m, 1H, C5, 1H C6 AB), 4.10 (dd, 2H, J_1 = 9.6 Hz, J_2 = 7.2 Hz, C6 CD), 3.46-3.31 (m, 2H, C6 and C13), 1.80-1.18 (m, 10H, C14-18), 0.94 (s, 9H, C9-11). **^{13}C NMR** (100 MHz, $CDCl_3$); 198.63 (C4 AB), 197.47 (C12 AB), 194.23 (C12 CD), 191.35 (C4 CD), 179.77 (C2 CD), 171.91 (C2 AB), 103.88 (C3 AB), 100.89 (C3 CD), 95.84 (C7 AB), 95.75 (C7 CD), 67.08 (C6), 67.08 (C5 CD), 64.38 (C5 AB), 41.42 (C13 AB), 41.01 (C13 CD), 36.01 (C8 AB), 35.90 (C8 CD), 28.97 (CH_2), 28.85 (CH_2), 28.77 (CH_2), 28.53 (CH_2), 28.35 (CH_2), 25.51 (CH_2), 25.45 (CH_2), 25.35 (CH_2), 24.73 (C9-11 AB), 24.67 (C9-11 CD). **MS** (ES^-); 306.2 (M-H); **HRMS** (M-H); calcd for $C_{17}H_{24}N_1O_4$; 306.1711; found; 306.1711.

4.3.2. Synthesis of **O-14A** and **14A**



O-14A

O-14A; Yield; 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$); 8.08 (d, 2H, J = 7.4 Hz, C14, C18), 7.68 (t, 1H, J = 7.4 Hz, C21), 7.51 (t, 2H, J = 7.4 Hz, C19 and C20), 6.01 (s, 1H, C3), 4.86 (s, 1H, C7), 4.68 (dd, 1H, J_1 = 9.0 Hz, J_2 = 6.4 Hz, C5), 4.39 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.8 Hz, C6), 3.49 (dd, 1H, J_1 = 7.8 Hz, J_2 = 6.4 Hz, C6), 0.98 (s, 9H, C9-11).

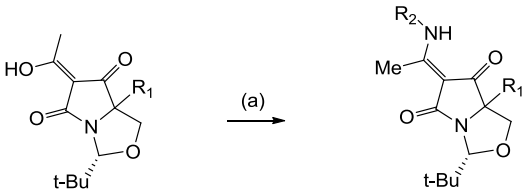


14A

14A; Yield; 85 %; M.P.; 94 ℃; Form AB: CD= 25: 75; $[\alpha]_D^{22}$ = +184.1 (c = 2.0 in MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$); 8.24 (d, 2H, J = 7.6 Hz, C14 and C15 AB), 8.20 (d, 2H, J = 7.6 Hz, C14 and C15 CD), 7.62 (t, 1H, J = 7.6 Hz, C18), 7.50 (t, 2H, J = 7.6 Hz, C16 and C17), 5.02 (s, 1H, C7), 4.41-4.20 (m, 2H, C5 and C6), 3.48 (dd, 1H, J_1 = 9.2 Hz, J_2 = 8.8 Hz, C5), 1.01 (s, 9H, C9-11 CD), 0.99 (s, 9H, C9-11 AB). **^{13}C NMR** (100 MHz, $CDCl_3$);

200.56 (C4 AB), 189.72 (C12 CD), 185.10 (C12 AB), 182.02 (C4 CD), 181.37 (C2 CD), 171.08 (C2 AB), 134.33 (C18), 131.22 (C13), 129.95 (C16 and C17), 128.25 (C14 and C15), 104.40 (C3 AB), 101.02 (C3 CD), 96.24 (C7 CD), 96.16 (C7 AB), 67.04 (C6 CD), 66.95 (C6 AB), 66.60 (C5 CD), 64.27 (C5 AB), 36.15 (C8 AB), 35.98 (C8 CD), 24.85 (C9-11 AB), 24.75 (C9-11 CD). **MS** (ES^-); 300.1 (M-H), **HRMS** (M-H); calcd for $C_{17}H_{18}N_1O_4$; 300.1241; found; 300.1240.

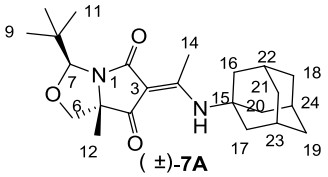
5. Synthesis of 3-enamine tetramic acids



(a) amine (1.0 eq), toluene, reflux;

General procedure: To the solution of 3-acetyl tetramic acid (1.0 eq) in toluene was added amine (1.1 eq) and the mixture was reflux for 4 hr. After completion of reaction checking with TLC, flash column chromatography gave 3-enamine tetramic acid.

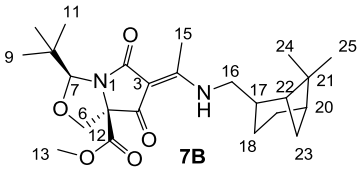
5.1. Synthesis (±)-**7A**



(±)-**7A**

Yield; 64% (oil); form AB: CD = 45: 55**;** **^{1}H NMR** (400 MHz, $CDCl_3$); 11.26 (br s, 1H, NH B), 10.91 (br s, 1H, NH D), 4.74 (s, 1H, C7 B), 4.70 (s, 1H, C7 D), 3.77 (d, 1H, *J* = 8.3 Hz, C6), 3.36 (d, 1H, *J* = 8.3 Hz, C6), 2.70 (s, 3H, C14 B), 2.69 (s, 3H, C14 D), 2.17 (brs, 3H, C22-C24), 2.09-2.04 (m, 6H, adamantyl CH_2), 1.77-1.64 (m, 6H, adamantyl CH_2), 1.47 (s, 3H, C12 B), 1.45 (s, 3H, C12 D), 1.01 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$); 198.2 (C4 B), 196.1 (C4 D), 180.4 (C2 D), 177.3 (C2 B), 170.1 (C13 B), 169.7 (C13 D), 98.2 (C7 B), 98.1 (C7 D), 96.9 (C3 B), 95.1 (C3 D), 72.3 (C6 B), 72.1 (C6 D), 71.3 (C5 B), 70.2 (C5 D), 55.5 (C15 B), 55.3 (C15 D), 42.5 (adamantyl CH_2), 42.4 (adamantyl CH_2), 35.8 (adamantyl CH_2), 35.7 (adamantyl CH_2), 34.7 (C8 B), 34.6 (C8 D), 29.3 (C22-C24), 25.8 (C9-C11), 21.5 (C12 B), 21.4 (C12 D), 17.3 (C14 B), 16.7 (C14 D). **MS** (ES^+); 387.29 (M+H); **HRMS** (M+Na); calculated for $C_{23}H_{34}N_2NaO_3$; 409.2462; found; 409.2458.

5.2. Synthesis of **7B**

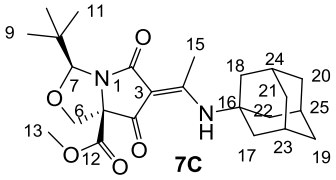


7B

Yield; 96 %; M.P.; 88 ℃; form AB: CD = 45: 55; **^{1}H NMR** (400 MHz, $CDCl_3$); 10.85 (brs, 1H, NH B), 10.67 (brs, 1H, NH D), 4.84-4.79 (m, 2H, C6 and C7), 3.78 (s, 3H, C13 B), 3.77 (s, 3H, C13 D), 3.47-3.44 (m, 1H, C6), 3.43-3.30 (m, 2H, C16), 2.55 (s, 3H, C15 B), 2.51 (s, 3H, C15 D), 2.45-2.29 (m, 2H, C17 and C19), 2.09-1.69 (m, 5H, C18, C20, C22 and C23), 1.54-1.44 (m, 1H, C18), 1.22 (s, 3H, CH_3 D), 1.21 (s, 3H, CH_3 B), 1.03 (s, 3H, CH_3 B), 1.02 (s, 3H, CH_3 D), 0.94-0.93 (m, 1H, C19), 0.92 (s, 9H, C9-C11). **^{13}C NMR** (100 MHz, $CDCl_3$); 191.9 (C4 B), 188.9 (C4 D), 180.6 (C2 D), 176.8 (C2 B), 170.5 (C14 B), 170.0 (C14

D), 169.0 (C12 B), 169.0 (C12 D), 98.0 (C7 B), 97.9 (C7 D), 95.8 (C3 B), 93.8 (C3 D), 77.6 (C5 D), 76.5 (C5 B), 68.8 (C6 D), 68.7 (C6 B), 53.0 (C13 B), 52.9 (C13 D), 48.9 (C16 B), 48.9 (C16 D), 43.4 (C20 or C22 D), 43.3 (C20 or C22 B), 41.1 (C20 or C22 D), 41.0 (C17), 40.9 (C20 or C22 B), 38.6 (C21), 35.2 (C8 B), 35.2 (C8 D), 33.2 (C19 D), 33.1 (C19 B), 27.8 (C24 or C25), 25.7 (C23 D), 25.7 (C23 B), 24.8 (C9-C11 B), 24.7 (C9-C11 D), 23.1 (C24 or C25), 19.9 (C18 D), 19.8 (C18 B), 14.5 (C15 D), 13.9 (C15 B). **MS** (ES^-); 431.28 (M-H); MS (ES^+); 433.31 (M+H), 455.27 (M+Na); **HRMS** (M+Na); calcd for $C_{24}H_{36}N_2Na_1O_5$; 455.2516; found; 455.2508.

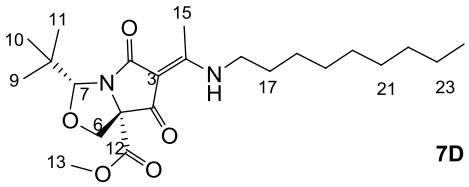
5.3. Synthesis of **7C**



7C

Yield; 28 %; M.P.; 200 ℃; form AB: CD = 45: 55**; ^{1}H NMR** (500 MHz, $CDCl_3$); 10.99 (brs, 1H, NH B), 10.86 (brs, 1H, NH D), 4.84-4.79 (m, 2H, C6 and C7), 3.79 (s, 3H, C13 B), 3.78 (s, 3H, C13 D), 3.47-3.44 (m, 1H, C6), 2.73 (s, 3H, C15 B), 2.68 (s, 3H, C15 D), 2.19 (brs, 3H, C23-C25), 2.07 (brs, 6H, adamantyl CH_2), 1.76-1.69 (m, 6H, adamantyl CH_2), 0.92 (s, 9H, C9-C11). **^{13}C NMR** (125 MHz, $CDCl_3$); 191.5 (C4 B), 189.2 (C4 D), 180.7 (C2 D), 177.2 (C2 B), 170.8 (C14 B), 170.3 (C14 D), 169.1 (C12), 98.0 (C7), 96.0 (C3 B), 94.0 (C3 D), 77.3 (C5 D), 76.5 (C5 B), 68.9 (C6 D), 68.8 (C6 B), 56.0 (C16 B), 55.8 (C16 D), 53.0 (C13 B), 52.9 (C13 D), 42.5 (adamantyl CH_2), 42.4 (adamantyl CH_2), 35.7 (adamantyl CH_2), 35.7 (adamantyl CH_2), 35.2 (C8 B), 35.2 (C8 D), 29.3 (C23-C25), 24.8 (C9-C11), 17.5 (C15 D), 16.8 (C15 B). **MS** (ES^+); 453.25 (M+Na); MS (ES^-); 429.28 (M-H); **HRMS** (M+Na); calcd for $C_{24}H_{34}N_2Na_1O_5$; 453.2360; found; 453.2360.

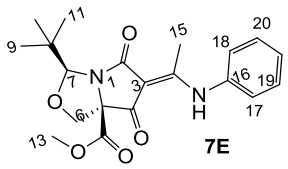
5.4. Synthesis of **7D**



7D

Yield; 36 % (oil); form AB: CD = 40: 60. **^{1}H NMR** (500 MHz, $CDCl_3$); 10.79 (brs, 1H, NH B), 10.65 (brs, 1H, NH D), 4.84-4.80 (m, 2H, C6 and C7), 3.78 (s, 3H, C13 B), 3.77 (s, 3H, C13 D), 3.47-3.44 (m, 1H, C6), 3.41-3.33 (m, 2H, C16), 2.56 (s, 3H, C15 B), 2.52 (s, 3H, C15 D), 1.70-1.64 (m, 2H, C17), 1.41-1.24 (m, 12H, C18-C23), 0.92-0.96 (m, 12H, C9-C11 and C24). **^{13}C NMR** (125 MHz, $CDCl_3$); 191.9 (C4 B), 188.9 (C4 D), 180.6 (C2 D), 176.8 (C2 B), 170.6 (C14 B), 170.1 (C14 D), 169.0 (C12 B), 169.0 (C12 D), 98.0 (C7 B), 97.9 (C7 D), 95.8 (C3 B), 93.9 (C3 D), 77.6 (C5 D), 76.5 (C5 B), 68.8 (C6 D), 68.7 (C6 B), 53.0 (C13 B), 52.9 (C13 D), 43.5 (C16 B), 43.3 (C16 D), 35.2 (C8 B), 35.2 (C8 D), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 24.8 (C9-C11 B), 24.7 (C9-C11 D), 22.6 (CH_2), 14.3 (C15 D), 14.0 (C24), 13.7 (C15 B). **MS** (ES^+); 423.2 (M+H), 445.25 (M+Na); MS (ES^-); 421.27 (M-H); **HRMS** (M-H); calcd for $C_{23}H_{37}N_2O_5$; 421.2708; found; 421.2709.

5.5. Synthesis of **7E**



7E

Yield; 48 %; M.P.; 70 ℃; form AB: CD = 35: 65; **^{1}H NMR** (500 MHz, $CDCl_3$); 12.21

(brs, 1H, NH B), 12.19 (brs, 1H, NH D), 7.47-7.43 (m, 2H, C19 and C20), 7.39-7.35 (m, 1H, C21), 7.19-7.17 (m, 2H, C17 and C18), 4.89 (s, 1H, C7 B), 4.86 (s, 1H, C7 D), 4.85 (d, 1H, *J* = 8.8 Hz, C6 B), 4.84 (d, 1H, *J* = 8.8 Hz, C6 D), 3.80 (s, 3H, C13 B), 3.79 (s, 3H, C13 D), 3.52 (d, 1H, *J* = 8.5 Hz, C6), 2.55 (s, 3H, C15 B), 2.50 (s, 3H, C15 D), 0.94 (s, 9H, C9-C11 D), 0.93 (s, 9H, C9-C11 B). **^{13}C NMR** (125 MHz, $CDCl_3$); 192.2 (C4 B), 189.2 (C4 D), 179.9 (C2 D), 176.2 (C2 B), 169.7 (C14 B), 169.0 (C14 D), 168.8 (C12 B), 168.7 (C12 D), 135.3 (C16 D), 135.3 (C16 B), 129.7 (Ar-C B), 129.6 (Ar-C D), 128.4 (Ar-C B), 128.2 (Ar-C D), 125.4 (Ar-C B), 125.3 (Ar-C D), 98.1 (C7), 97.2 (C3 B), 95.4 (C3 D), 77.7 (C5 D), 76.7 (C5 B), 68.7 (C6 D), 68.6 (C6 B), 53.1 (C13 B), 53.0 (C13 D), 35.2 (C8 B), 35.2 (C8 D), 24.8 (C9-C11 B), 24.7 (C9-C11 D), 16.2 (C15 D), 15.6 (C15 B). **MS** (ES^+); 395.17 (M+Na); MS (ES^-); 371.19 (M+Na); **HRMS** (M-H); calcd for $C_{20}H_{24}N_2Na_1O_5$; 395.1577; found; 395.1572.

S-References

S-1. References for natural 3-acyltetramic acids; Kibdelomycin; Philips, J. W. et al. Discovery of Kibdelomycin, a potent new class of bacterial type II topoisomerase inhibitor by chemical-genetic profiling in Staphylococcus aureus. *Chem. Biol.* **18**, 955-965 (2011). **Bu-2313 A** and **B**; Tsukiura, H. et al. Bu-2313, a new antibiotic complex active against anaerobes 1. Production, isolation and properties of Bu-2313 A and B. *J. Antibiot.* **33**, 157-165 (1980). **BU-4514N**; Toda, S. et al. A new neuritogenetic compound BU-4514N produced by *Microtetraspora sp.*. *J. Antibiot.* **46**, 875-883 (1993). **Cissetin** and **Trichosetin**; Boros, C., Dix, A., Katz, B., Vasina, Y. & Pearce, C. Isolation and identification of cissetin-a setin-like antibiotic with a novel cis-octalin ring fusion. *J. Antibiot.* **56**, 862-865 (2003). **Coniosetin**; Segeth, M. P. et al. Coniosetin, a novel tetramic acid antibiotic from *Coniochaeta ellipsoidea* DSM 13856. *J. Antibiot.* **56**, 114-122 (2003). **C12-TA** and **C14-TA** in the unnatural analogues; Lowery, C. A. *et al.* Defining the mode of action of tetramic acid antibacterials derived from *Pseudomonas aeruginosa* quorum sensing signals. *J. Am. Chem. Soc.* **131**, 14473-14479 (2009). **Delaminomycin A, B** and **C**; Ueno, M. et al. Delaminomycins, novel nonpeptide extracellular matrix receptor antagonist and a new class of potent immunomodulator. *J. Antibiot.* **46**, 719-727 (1993). **Equisetin;** Rurmeister, H.R., Bennett, G. A.,Vesonder, R.F. & Hesseltine, C.W. Antibiotic produced by *Fusarium equiseti* NRRL 5537. *Antimicrob. Agents Chemother.* **5**, 634-639 (1974). **Ikarugamycin, Ikarugamycin epoxides** and **Ripromycin**; Bertasso, M. et al. Ripromycin and other polycyclic macrolactams from Streptomyces sp. Tü 6239: Taxonomy, fermentation, isolation and biological properties. *J. Antibiot.* **56**, 364-371 (2003). **Lydicamycin** and **TPU-0037-A, B, C** and **D**; Furumai, T. et al.TPU-0037-A, B, C and D, novel lydicamycin congeners with anti-MRSA activity from *Streptomyces platensis* TP-A0598. *J. Antibiot.* **55**, 873-880 (2002). **Ophiosetin** and **Paecilosetin**; Putri, S. P., Kinoshita, H., Ihara, F., Igarashi, Y. & Nihira, T. Ophiosetin, a new tetramic acid derivative from the mycopathogenic fungus *Elaphocordyceps ophioglossoides*. *J. Antibiot.* **63**, 195-198 (2010). **Methiosetin**; Herath, K. et al. Isolation, structure elucidation, and antibacterial activity of Methiosetin, a tetramic acid from a tropical sooty mold (Capnodium sp.). *J. Nat. Prod.* **75**, 420-424 (2012). **Oxasetin**; He, H. et al. Oxasetin, a new antibacterial polyketide produced by fungus *Vaginatispora aquatica*,

HK1821. *J. Antibiot.* **55**, 821-825 (2002). **PF1052**; Koyama, N. et al. Spylidone, a novel inhibitor of lipid droplet accumulation in mouse macrophages produced by *Phoma sp.* FKI-1840. *J. Antibiot.* **58**, 338-345 (2005). **Ravenic acid**; Michael, A. P., Grace, E. J., Kotiw, M. & Barrow, R. A. Ravenic acid, a new tetramic acid isolated from a cultured microfungus, *Penicillium sp*. *J. Nat. Prod.* **65**, 1360-1362 (2002). **Reutericyclin**; Gänzle, M. G., Höltzel, A., Walter, J., Jung, G. & Hammes, W. P. Characterization of reutericyclin produced by *Lactobacillus reuteri* LTH2584. *Appl. Environ. Microbiol.* **66**, 4325-4333 (2000). **Streptolygin, Tirandamycin A** and **Tirandalydigin**; Karwowski, J. P. et al. Tirandalydigin, a novel tetramic acid of the tirandamycin-streptolydigin type. 1. Taxonomy of the producing organism, fermentation and biological activity. *J. Antibiot.* **45**, 1125-1132 (1992). **Vancoresmycin**; Hopmann, C., Kurz, M., Brönstrup, M., Wink, J. & LeBeller, D., Isolation and structure elucidation of vancoresmycin—a new antibiotic from *Amycolatopsis* sp. ST 101170. *Tetrahedron Lett.* **43**, 435-438 (2002). **Vermisporin**; Chin, N. X. & Neu, H. C. In vitro antimicrobial activity of the new antibiotic vermisporin. *Eur. J. Clin. Microbiol. Infect. Dis.* **11**, 755-757 (1992). **Virgineone**; Ondeyka, J. et al. Isolation, structure elucidation, and biological activity of virgineone from *Lachnum virgineum* using the genome-wide *Candida albicans* Fitness Test. *J. Nat. Prod.* **72**, 136-141 (2009). **49F233α;** Singh, M. P., Zaccardi, J. & Greenstein, M. LL-49F233α, novel antibiotic produced by an unknown fungus: biological and mechanistic activities. *J. Antibiot.* **51**, 1109-1112 (1998).

S-2. References for unnatural 3-acyltetramic acids; CPB-2 - **CPB-32**; Katsuo, K., Kimura, M., Kinuta, T., Takai, N. & Tanaka, K. Synthesis and antimicrobial activities of 3-acyltetramic acid derivatives. *Chem. Pharm. Bull.* **32**, 4197-4204 (1984). **CPB2-3** – **CPB2-17**; Katsuo, K., Kitaguchi, T., Takata, Y. & Tanaka, K. Structure-activity relationships in tetramic acids and their copper (II) complexes. *Chem. Pharm. Bull.* **28**, 2494-2502 (1980). **JMC-A** – **TMC-N**; Yendapally, R., Hurdle, J. G., Carson, E. I., Lee, R. & Lee, R. E. N-Substituted 3-acetyltetramic acid derivatives as antibacterial agents. *J. Med. Chem.* **51**, 1487-1491 (2008). **JMC-T** – **TMC-U**; Rosen, T., Fernandes, P. B., Marovich, M. A., Shen, L., Mao, J. & Pernet, A. G. Aromatic dienoyl tetramic acids. Novel antibacterial agents with activity against anaerobes and Staphylococci. *J. Med. Chem.* **32**, 1062-1069 (1989). **T-4a** – **T-6**; Wilson, J. B. Synthesis and evaluation of tetramic acids as antimicrobial agents. *Master thesis (2008)*; the university of Tennessee.

S-3. Peukert, S. *et al.* Design and structure–activity relationships of potent and selective inhibitors of undecaprenyl pyrophosphate synthase (UPPS): Tetramic, tetronic acids and dihydropyridin-2-ones. *Bioorg. Med. Chem. Lett*. 18, 1840–1844 (2008).

S-4. (a) Bikadi, Z & Hazai, E. Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock. *J. Cheminf.* **1**, 15 (2009). (b) Halgren, T. A. Merck molecular force field. 1. Basis, form, scope, parametrization, and performance of MMFF94. *J. Comput. Chem.* **17**, 490-519 (1996). (c) Stewart, J. P. Computer code MOPAC2009, *Stewart Computational Chemistry*, 2009. (d) Morris, G. M., Goodsell, D. S., Halliday, R. S., Huey, R., Hart, W. E., Belew, R. K. & Olson, A. J. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *J. Comput. Chem.* **19**, 1639-1662 (1998). (e) Solis, F. J. & Wets, R. J. B. Minimization by random search techniques. *Math. Oper. Res.* **6**, 19-30

This journal is © The Royal Society of Chemistry 2013

(1981).

S-5. (a) Gentry, D. R. et. al. A rapid microtiter plate assay for measuring the effect of compounds on Staphylococcus aureus membrane potential. *J. Microbiol. Methods.* **2010**, *83*, 254-256. (b) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved Standard- seventh edition. **2006**, M7-A7, CLSI, Wayne PA. (c) Reference method for broth dilution antifungal susceptibility testing of yeasts; Approved standard - third edition. **2006**, M27-A2, CLSI, Wayne PA.

S-6. (a) Andrews, M. D. *et al.* Regioselective Dieckmann cyclisations leading to enantiopure highly functionalised tetramic acid derivatives. *J. Chem. Soc., Perkin Trans. 1,* 223-235 (1998). (b) Jeong, Y.-C. & Moloney, M. G. Tetramic acids as scaffolds: synthesis, tautomeric and antibacterial behavior. *Synlett* 2487-2491 (2009). (c) Jeong, Y.-C., Anwar, M., Nguyen, T. M., Tan, B. S. W., Chai, C. L. L. & Moloney, M. G. Control of chemoselectivity in Dieckmann ring closures leading to tetramic acids. *Org. Biomol. Chem.* **9**, 6663-6669 (2011). (d) Andrews, M. D., Brewster, A. G. & Moloney, M. G. Diastereocontrolled synthesis of hydroxylated lactams. *J. Chem. Soc., Perkin Trans. 1,* 80-90 (2002).