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Research paper

Synthesis and biological evaluation of 20-epi-amino-20-deoxysalinomycin derivatives

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ABSTRACT

To improve the druggability of salinomycin, a 20-epi-amino-20-deoxysalinomycin derivatives library was synthesized with high efficacy from which a few salinomycin derivatives with high potency and selectivity were identified through comprehensive cytotoxicity assay, including a fluorine-19 magnetic resonance sensitive tool molecule. Using a K-ras cellular model, salinomycin and its derivatives showed different molecular mode of action from literature reports. These results would be valuable for developing salinomycin-based cancer therapy.

1. Introduction

As an easily available natural product with selective inhibition towards cancer stem cells (CSCs) [1], the polyether ionophore salinomycin is promising in the prevention of tumor growth, metastasis and recurrence [2]. It exhibits toxicity over a wide range of cancerous cells, including breast cancer cells, leukemic cancer cells, colon adenocarcinoma cells, hepatocellular carcinoma cells, lung cancer cells, and ovarian cancer cells etc. However, it suffers low druggability issues of unclear anti-cancer mechanism, narrow therapeutic index and moderate potency, etc [3]. Therefore, it is of great importance to generate salinomycin derivatives with high safety and potency through systematic structural modification as well as to clarify its molecular mode of action.

Due to its structural complexity, i.e., eighteen chiral centers, five rings, and multiple reactive groups, the site-specific modification of salinomycin has been a longstanding challenge. Initially, modification strategies for salinomycin are limited to direct derivatization of its carboxylic group, hydroxyl groups, and double bond [4]. In 2013, a strategy for site-specific acylating one of the three hydroxyl groups in salinomycin was reported by Strand et al. [5]. Among the derivatives, *C20-(R)-O*-acylated salinomycin with the least bulky substituents shows the highest potency to cancerous cells. Recently, a *C20*-site-specific azidation and derivatization strategy was developed in this group [6]. It was found that the inversion of the *C20*-configuration relieves the steric hindrance and therefore enhances ion chelation and potency [6,7]. Therefore, *C20* is a highly valuable modification site from which some high potent and selective salinomycin derivatives may be found.

Herein, we report some novel *C20-(S)*-amide derivatives of salinomycin, their comprehensive cytotoxicity assay, and mechanism study on their molecular mode of action (Fig. 1). Based on our previous site-specific modification of salinomycin *C20-(R)-OH* into *C20-(S)-N_3* [6], *C20-(S)-N_3* can be reduced into *C20-(S)-NH_2* from which a *C20-(S)*-amide library may be conveniently generated by *C20-(S)-NH_2*-specific acylation. Amide derivatives of salinomycin have many advantages over its triazol derivatives, such as higher

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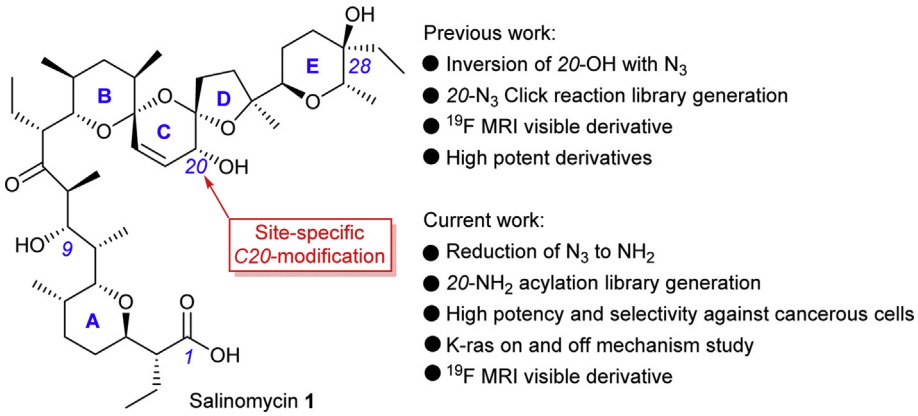


Fig. 1. *C20*-specific modification of salinomycin **1**.

water solubility and biocompatibility of amide, a broad spectrum of easily available acids and acyl chloride for structurally diverse library construction, and mild condition for amide formation without using cytotoxic copper catalyst, etc.

2. Results and discussion

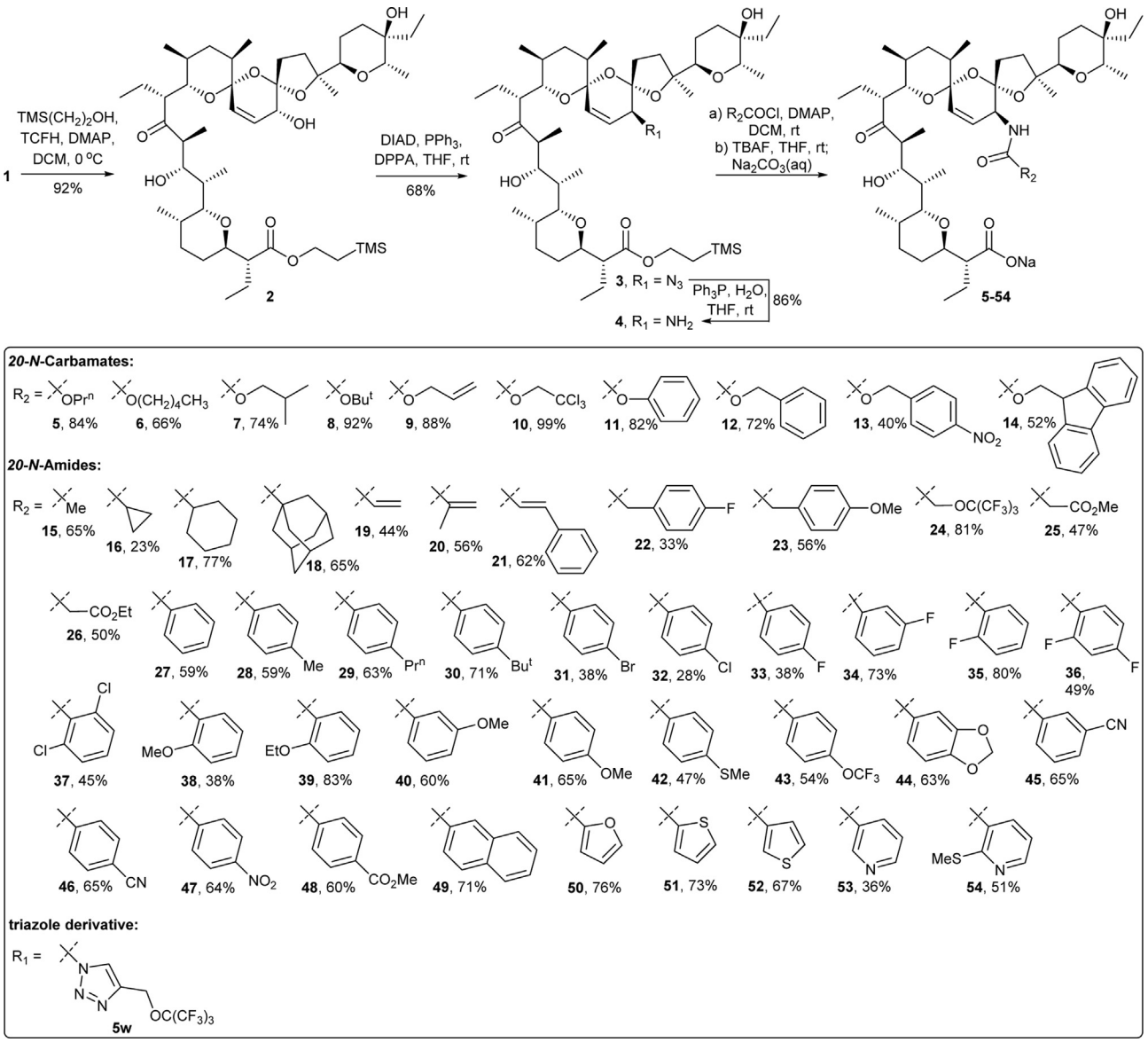
The *C20-(S)*-amide derivatives library construction commenced with protecting the carboxylic group in salinomycin (Scheme 1). Esterification of salinomycin **1** with $TMS(CH_2)_2OH$ in the presence of *N,N,N′,N′*-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *4*-dimethylamino-pyridine (DMAP) afforded ester **2** with a 92% yield [5], which was then underwent a *C20-OH*-specific Mitsunobu reaction to give azide **3** with a 68% yield [6]. Reduction of azide **3** by Staudinger reaction gave the key intermediate amine **4** with an 86% yield on a 12.8-gram scale. It is interesting to point out that amine **4** is very stable at room temperature and no side product, e.g. ester aminolysis product, was observed during the reduction. From the key intermediate **4**, a systematic derivatization with fifty carefully selected and commercially available acyl chlorides was then carried out. Selective acylation of the amine group in **4** with acyl chloride in the presence of DMAP gave the corresponding amide intermediate which was then treated with TBAF to remove the carboxylic protecting group and give the *C20-(S)*-amide derivatives **5**–**54** with high efficacy on 0.3 mmol scales. It is noteworthy that, even without optimization of the reaction conditions, high chemical selectivity was achieved and no ester by-product was observed during the acylation. In this way, a variety of side chains with structural diversity was selectively introduced into the salinomycin either as *C20-(S)-N*-carbamates or *C20-(S)*-amides.

The structure of the *C20-(S)-N*-acyl salinomycin derivative was confirmed by the single-crystal X-ray diffractogram of **44**-Na^+ (Fig. 2, CCDC No. 1519977). It was found that the introduced side chain locates at the outside of the chelation pocket and the amide group has no interaction with the chelated metal ion. Therefore, inversion of the *C20*-configuration may relieve the steric hindrance of the side chain for metal ion chelation, and provide a valuable modification site.

With the salinomycin derivative library in hand, the cytotoxicity of amides **5**–**54** together with salinomycin **1**, amine **4**, and a triazole derivative **5w** previously developed in this group were evaluated in a series of cancerous cells, including murine breast cancer cells (4T1), human promyelocytic leukemia cells (HL-60), adenocarcinomic human alveolar basal epithelial cells (A549), human cervical cancer cells (HeLa), human breast cancer cells (MCF-7), human colon adenocarcinoma cell (SW480), and human hepatocarcinoma cell (SMMC-7721). Using a MTS assay with taxol and cisplatin as positive control, many interesting cytotoxicity results were obtained (Table 1). First, amine **4** exhibited moderate potency only in HeLa cells and no appreciable potency in the others. The potency loss might be a result of ion-chelating-induced conformational change because the amine group in **4** is a strong chelating group for metal ions. Second, acylation of amine **4** into *C20-(S)-N*-carbamates **15**–**14** resulted in many high potent and selective salinomycin derivatives in which acylation of the amine group in **4** could dramatically relieve the undesired chelating. Carbamate **12** with a benzyl group showed the highest potency in SMMC-7721 cells with an IC_{50} of 0.15 μM which is over 80 folds more potent than salinomycin **1**. While, carbamate **14** with a fluorenylmethyl group showed the highest potency in A549 cells with an IC_{50} of 0.32 μM. Third, acylation of amine **4** into *C20-(S)-N*-amides **5**–**54** resulted in very complicated results. Severe potency losses were found in amides **15**, **16**, **19**, **21**, **25**, **26**, **32**, **33**, **44**, and **45**. Happily, amide **24** with a perfluoro-*tert*-butyl group exhibited high potency in all the cells and the highest potency in MCF-7 cells with an IC_{50} of 4.14 μM. Comparing to triazole **5w**, which is also bearing a perfluoro-*tert*-butyl group, amide 24 displayed similar antiproliferative activity.

According to the initial cytotoxicity results, amides **5**–**8**, **12**, **14**, **18**, **24**, **30**, and **34**–**39** were selected for further assay on normal cells, human bronchial epithelial cells (BEAS-2B), with salinomycin **1** and triazole **5w** as comparison (Table S1). Amide analogs exhibited higher or similar toxicity to salinomycin **1** except amide **18**. Comparing to triazole **5w**, the selected analogs showed 1.2- to 4.0-fold lower cytotoxicity against BEAS-2B. To evaluate the therapeutic potential of these salinomycin analogs, the selectivity index (SI) was calculated (Table 2). The analogs showed high selectivity towards a panel of cancerous cells. For example, **12** displayed the highest SI of 87.07 towards SMMC-7721 and **35** displayed the highest SI of 48.23 towards HL-60. The LogP of these compounds were also measured (Table S2).

With a singlet ^{19}F NMR signal from 9 symmetrical fluorines and a low imaging concentration of 5.6 mM, amide **24** is another valuable ^{19}F NMR and ^{19}F MRI probe for downstream study (Fig. 3a and b). It is noteworthy that the position of fluorine substitution on phenyl group plays a crucial role on the potency. Amide **35** with a 2-fluorophenyl group showed the highest potency in many selected cells, including 4T1 cells (IC_{50} of 0.92 μM), HL-60 cells (IC_{50} of 0.13 μM), HeLa cells (IC_{50} of 0.16 μM) and SW480 cells (IC_{50} of 1.04 μM). Comparing to salinomycin **1**, a 28 folds potency improvement in HeLa cells was found for amide **35**. While, amide **33** with a 4-fluorophenyl group showed no appreciable potency in



Scheme 1. Synthesis of C20-(S)-*N*-acyl salinomycin derivatives library.

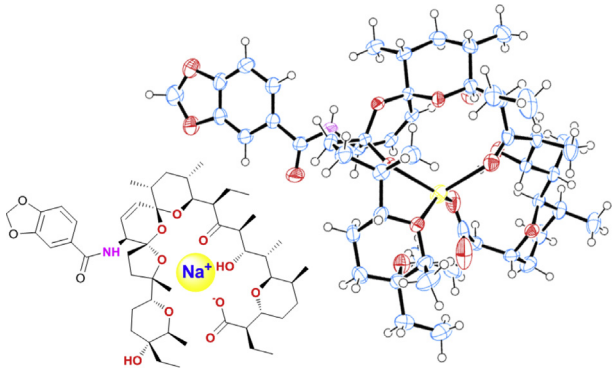


Fig. 2. Single-crystal X-ray structure of **44**-Na^+.

all the selected cells. Finally, comparing to *C20-(S)*-triazole **5w**, many of these *C20-(S)-N*-carbamates and amides exhibited further potency improvement towards the selected cells (Fig. 3c). Therefore, the *C20-(S)-N*-acylation strategy is very effective in improving the potency and selectivity of salinomycin.

Finally, salinomycin **1** and its derivatives **5w**, **8**, **24**, **35** and **36** were employed to probe their molecular mechanism on a doxycycline-inducible K-ras^{G12V} expression cellular model [8]. In this cellular model, inhibitors with a molecular mechanism of action through the K-ras pathway would show lower IC_{50} value in K-ras on cells than in K-ras off cells. Inhibiting the oxidative phosphorylation in mitochondria was reported as a mechanism of salinomycin's action against cancerous cells [9]. However, it was found that salinomycin **1** and its derivatives **8**, **35**, and **36** show much lower IC_{50} value in K-ras off human embryonic kidney cells (HEK293 cells) than in K-ras on HEK293 cells (Fig. 4). Derivative **24** showed slightly lower IC_{50} value in K-ras on HEK293 cells than in K-ras off HEK293 cells. Based on these observations, salinomycin and its derivatives may eliminate cancerous cells through pathways other than inhibit oxidative phosphorylation in mitochondria as literature reported.

Table 1
Cytotoxicity of salinomycin **1**, amine **4**, triazol **5w**, and *C20-(S)-N*-acyl **5**–**54** on a series of cancerous cell.

Compd no.	Cytotoxicity (IC_{50}, μM)[a]±SD[b]						
	4T1	HL-60	A549	HeLa	MCF-7	SW480	SMMC-7721
1	3.78 ± 0.57	0.58 ± 0.02	3.98 ± 0.07	4.49 ± 0.20	9.08 ± 0.20	3.77 ± 0.25	12.04 ± 0.06
4	>20	>20	>20	6.56 ± 0.34	>20	>20	>20
5w	1.34 ± 0.11	0.25 ± 0.02	0.44 ± 0.01	0.62 ± 0.09	2.07 ± 0.09	0.90 ± 0.08	0.89 ± 0.04
5	2.92 ± 0.16	0.41 ± 0.02	1.05 ± 0.07	1.97 ± 0.12	8.70 ± 0.29	5.42 ± 0.45	5.02 ± 0.47
6	1.46 ± 0.05	0.37 ± 0.01	0.71 ± 0.05	2.77 ± 0.08	5.43 ± 0.16	2.71 ± 0.19	2.54 ± 0.17
7	1.47 ± 0.19	0.33 ± 0.01	0.58 ± 0.06	1.55 ± 0.30	8.83 ± 0.65	2.79 ± 0.29	4.45 ± 0.50
8	1.59 ± 0.21	0.14 ± 0.01	0.52 ± 0.04	0.17 ± 0.01	5.54 ± 0.42	1.37 ± 0.21	0.96 ± 0.06
9	3.00 ± 0.30	0.56 ± 0.04	1.03 ± 0.02	3.02 ± 0.38	17.33 ± 0.51	6.19 ± 0.13	5.30 ± 0.15
10	4.80 ± 0.48	1.50 ± 0.07	1.36 ± 0.07	0.40 ± 0.01	11.59 ± 0.11	4.57 ± 0.41	3.66 ± 0.32
11	9.71 ± 0.10	6.43 ± 0.08	8.94 ± 0.31	7.02 ± 0.07	8.73 ± 0.52	14.20 ± 0.40	5.73 ± 0.08
12	2.86 ± 0.11	0.26 ± 0.01	0.45 ± 0.01	4.36 ± 0.32	10.69 ± 0.10	5.61 ± 0.39	0.15 ± 0.03
13	1.70 ± 0.02	0.36 ± 0.01	0.67 ± 0.04	4.71 ± 0.11	5.50 ± 0.31	1.11 ± 0.21	2.84 ± 0.11
14	1.33 ± 0.04	0.30 ± 0.02	0.32 ± 0.01	0.30 ± 0.01	5.30 ± 0.32	2.09 ± 0.02	4.00 ± 0.33
15	>20	12.50 ± 0.31	>20	6.10 ± 0.46	>20	>20	>20
16	>20	>20	>20	>20	>20	>20	>20
17	5.14 ± 0.16	0.67 ± 0.02	0.92 ± 0.04	0.26 ± 0.01	14.13 ± 1.28	5.71 ± 0.16	4.62 ± 0.19
18	2.48 ± 0.21	0.24 ± 0.01	1.00 ± 0.03	0.38 ± 0.04	5.17 ± 0.25	1.35 ± 0.09	5.15 ± 0.36
19	19.29 ± 0.08	5.90 ± 0.33	>20	10.77 ± 0.28	>20	>20	>20
20	9.82 ± 0.22	1.27 ± 0.17	8.48 ± 1.11	>20	>20	12.19 ± 0.38	>20
21	8.99 ± 0.21	3.80 ± 0.56	6.07 ± 0.12	>20	>20	>20	>20
22	12.15 ± 0.15	4.30 ± 0.34	11.31 ± 0.15	8.69 ± 0.31	15.96 ± 0.41	>20	13.65 ± 0.31
23	15.96 ± 0.21	2.55 ± 0.27	5.55 ± 0.03	>20	38.80 ± 0.34	13.61 ± 0.85	>20
24	3.31 ± 0.35	0.43 ± 0.02	0.88 ± 0.01	0.19 ± 0.01	4.14 ± 0.08	1.82 ± 0.25	4.12 ± 0.16
25	>20	7.86 ± 0.38	>20	>20	>20	>20	>20
26	19.53 ± 0.59	1.60 ± 0.16	5.79 ± 0.20	>20	>20	>20	>20
27	2.83 ± 0.25	0.70 ± 0.04	0.74 ± 0.04	0.32 ± 0.02	8.52 ± 0.10	5.84 ± 0.32	1.42 ± 0.10
28	7.82 ± 0.16	1.77 ± 0.21	2.20 ± 0.19	2.49 ± 0.13	13.90 ± 0.70	8.20 ± 0.73	1.07 ± 0.04
29	3.39 ± 0.48	1.55 ± 0.18	4.23 ± 0.22	3.06 ± 0.45	>20	6.01 ± 0.70	5.09 ± 0.25
30	2.80 ± 0.50	1.46 ± 0.09	0.44 ± 0.04	4.48 ± 0.40	15.94 ± 0.14	3.84 ± 0.20	10.18 ± 0.17
31	4.60 ± 0.28	1.03 ± 0.02	1.64 ± 0.02	0.78 ± 0.04	9.52 ± 0.28	4.50 ± 0.05	1.72 ± 0.17
32	>20	18.26 ± 0.34	>20	>20	>20	>20	>20
33	>20	>20	>20	>20	>20	>20	>20
34	2.46 ± 0.20	0.27 ± 0.02	0.57 ± 0.01	4.55 ± 0.13	10.72 ± 0.27	6.12 ± 0.32	0.24 ± 0.01
35	0.92 ± 0.04	0.13 ± 0.01	6.91 ± 0.06	0.16 ± 0.01	4.74 ± 0.20	1.04 ± 0.03	1.23 ± 0.10
36	1.12 ± 0.07	0.16 ± 0.01	0.40 ± 0.06	0.56 ± 0.07	4.87 ± 0.17	1.25 ± 0.04	6.04 ± 0.16
37	4.73 ± 0.65	0.34 ± 0.02	0.74 ± 0.03	3.05 ± 0.42	8.50 ± 0.27	2.46 ± 0.04	1.44 ± 0.06
38	1.64 ± 0.35	0.41 ± 0.01	0.33 ± 0.03	2.52 ± 0.17	7.62 ± 0.29	4.05 ± 0.27	1.47 ± 0.01
39	3.40 ± 0.26	0.37 ± 0.02	1.55 ± 0.03	0.62 ± 0.06	5.58 ± 0.11	3.42 ± 0.21	0.92 ± 0.04
40	2.64 ± 0.20	0.82 ± 0.05	1.38 ± 0.13	2.25 ± 0.10	11.15 ± 0.28	3.98 ± 0.12	9.81 ± 0.42
41	4.59 ± 0.23	1.69 ± 0.24	4.54 ± 0.08	1.48 ± 0.22	>20	6.64 ± 0.50	15.50 ± 0.72
42	9.71 ± 0.18	2.32 ± 0.24	2.31 ± 0.03	5.23 ± 0.79	15.80 ± 0.19	10.82 ± 0.42	14.64 ± 0.72
43	4.14 ± 0.40	1.19 ± 0.07	0.87 ± 0.05	2.49 ± 0.27	11.18 ± 0.56	4.88 ± 0.12	10.53 ± 0.50
44	14.30 ± 0.14	5.00 ± 0.26	6.30 ± 0.22	>20	>20	>20	>20
45	>20	>20	>20	>20	>20	>20	>20
46	9.16 ± 0.13	1.56 ± 0.07	4.06 ± 0.21	>20	>20	10.51 ± 0.27	>20
47	5.42 ± 0.17	1.30 ± 0.04	1.51 ± 0.05	2.79 ± 0.15	17.10 ± 0.77	8.42 ± 0.17	3.96 ± 0.24
48	7.14 ± 0.15	1.53 ± 0.32	4.40 ± 0.16	9.08 ± 0.70	>20	15.21 ± 0.52	>20
49	8.72 ± 0.32	1.40 ± 0.09	4.21 ± 0.02	13.49 ± 0.52	>20	>20	15.25 ± 0.91
50	4.97 ± 0.14	0.62 ± 0.06	2.01 ± 0.06	1.20 ± 0.12	16.01 ± 1.08	7.25 ± 0.58	>20
51	4.53 ± 0.36	0.73 ± 0.04	0.94 ± 0.05	4.47 ± 0.21	12.84 ± 1.47	7.04 ± 0.21	3.99 ± 0.10
52	4.14 ± 0.49	1.03 ± 0.12	1.63 ± 0.05	0.88 ± 0.02	15.91 ± 0.70	4.86 ± 0.18	0.89 ± 0.09
53	>20	3.41 ± 0.17	10.16 ± 0.48	14.92 ± 1.53	>20	>20	2.15 ± 0.08
54	9.69 ± 0.21	0.92 ± 0.10	1.55 ± 0.16	5.38 ± 0.73	13.74 ± 0.51	6.29 ± 0.12	>20
Cisplatin	11.17 ± 0.50	3.42 ± 0.17	28.23 ± 2.95	14.14 ± 0.23	28.42 ± 3.71	14.77 ± 2.15	13.23 ± 1.17

[a] IC_{50} is the compound concentration required to inhibit cell growth by 50%.
[b] SD (standard deviation) of three independent experiments.

3. Conclusions

In summary, through a convenient salinomycin *C20-(S)-N*-acylation and comprehensive cytotoxicity assay, many novel salinomycin analogs with high potency and selectivity against cancerous cells were discovered. X-ray structural study indicated that *C20-(S)-N*-acylation provide a valuable strategy for improving the druggability of salinomycin without impairing the metal ion chelation. Fluorination of salinomycin resulted in a highly valuable tool molecular for ^{19}F NMR/MRI-guided mechanism study. With the K-ras cellular model, it was discovered that salinomycin and its derivatives' molecular mechanism may not related to the inhibition of oxidative phosphorylation as literature suggested. Discovery of druggable salinomycin derivatives and clarify the molecular mechanism of action would be the cornerstones for clinical application of salinomycin in cancer therapy. Currently, SAR study, ^{19}F NMR/MRI-guided molecular mechanism study, and animal model study are in progress and will be published in due course.

4. Experimental section

4.1. General information

Unless otherwise indicated, all reagents were obtained from

Table 2
Selectivity index (SI) of salinomycin **1**, analogs **5w**, **12**, **14**, **24**, and **35** on a panel of cancerous cells over BEAS-2B.

Compd no.	Selectivity index SI						
	4T1	HL-60	A549	HeLa	MCF-7	SW480	SMMC-7721
1	3.46	22.53	3.28	2.91	1.44	3.47	1.09
5w	3.42	18.32	10.41	7.39	2.21	5.09	5.15
12	4.57	50.23	29.02	3.00	1.22	2.33	87.07
14	7.76	34.40	32.25	34.40	1.95	4.94	2.58
24	1.69	12.98	6.34	29.37	1.35	3.07	1.35
35	6.82	48.23	0.91	39.19	1.32	6.03	5.10

The SI was calculated using formula: SI = IC_{50} (BEAS-2B)/IC_{50} (cancerous cell). It is an indication of a drug with selective efficacy against cancer cells when SI > 1.0.

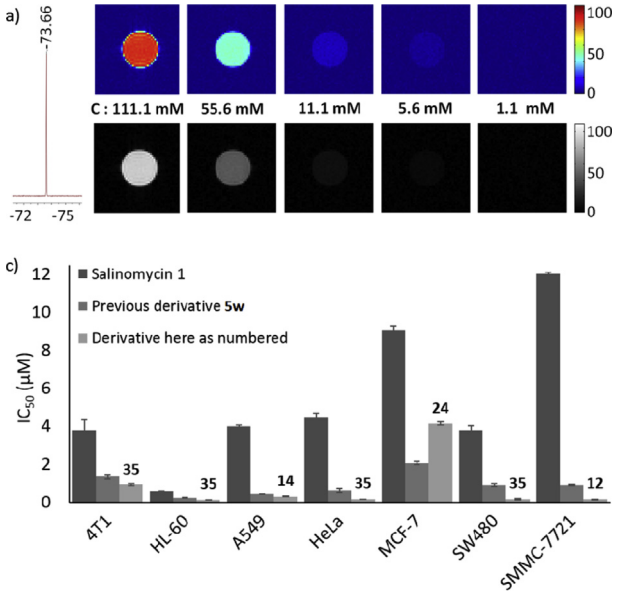


Fig. 3. (a) ^{19}F NMR of **24**. (b) ^{19}F MRI of **24**. (c) Cytotoxicity comparison among **1**, **5w**, **12**, **14**, **24**, and **35**.

commercial supplier and used without prior purification. Salinomycin was extracted and purified from a commercial veterinary feed additive with 15% of salinomycin concentration. DCM, Et_3N and THF were dried and freshly distilled prior to use. Salinomycin was extracted and purified from a commercial veterinary feed additive with 15% of salinomycin concentration. Flash chromatography was performed on silica gel (200–300 mesh) with either EtOAc/petroleum ether (PE, 60–90 °C) or MeOH/DCM as eluents. ^1H, ^{19}F and ^{13}C NMR spectra were recorded on a 400 MHz Bruker NMR spectrometer. Chemical shifts are expressed in ppm and coupling constants (*J*) are in Hertz (Hz). ^1H NMR spectra were referenced to tetramethylsilane (d, 0.00 ppm) using $CDCl_3$ as solvent. ^{13}C NMR spectra were referenced to solvent carbons (77.16 ppm for $CDCl_3$ and 49.00 ppm for CD_3OD). ^{19}F NMR spectra were referenced to 2% perfluorobenzene (s, −164.90 ppm) in $CDCl_3$. The splitting patterns for ^1H NMR spectra are denoted as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). ESI Mass spectra were recorded on a Thermo Scientific Q Exactive Focus mass spectrometer.

Salinomycin TMSEt ester 2. To a stirring solution of salinomycin **1** (15.02 g, 20.00 mmol) in DCM (300 mL), DMAP (11.22 g, 100.00 mmol), $TMS(CH_2)_2OH$ (14.20 g, 120.00 mmol) and *N,N,N′,N′*-tetramethyl chloroformamidinium hexafluorophosphate (TCFH) (6.74 g, 24.00 mmol) was added at 0 °C. The resulting mixture was stirred at rt overnight. Then it was diluted with DCM and washed with brine. The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel flash chromatography (5–33% EtOAc/PE) to afford ester **2** as white amorphous solid (15.74 g, 92% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.12–6.05 (m, 1H), 6.02–5.95 (m, 1H), 4.54–4.34 (m, 2H), 4.10–3.96 (m, 3H), 3.92–3.79 (m, 2H), 3.75–3.63 (m, 2H), 3.61–3.51 (m, 1H), 3.25–3.15 (m, 1H), 3.11–3.05 (m, 1H), 3.04–2.94 (m, 1H), 2.77–2.69 (m, 1H), 2.47–2.34 (m, 2H), 2.26–2.16 (m, 1H), 2.08–0.63 (m, 54H), 0.08 (s, 9H).

***C20-(S)*-azide-salinomycin-TMSEt-ester 3**. Under an atmosphere of argon, to a stirring solution of triphenylphosphine (4.46 g, 17.01 mmol) in anhydrous THF (100 mL) was added diisopropyl azodicarboxylate (3.44 g, 17.01 mmol, in 20 mL THF) at 0 °C. After the resulting solution was stirred for 10 min at this temperature, ester **2** (7.24 g, 8.50 mmol, in 30 mL THF) was added. The mixture was allowed to warm to rt and stirred for another 10 min. Then diphenylphosphoryl azide (4.68 g, 17.01 mmol, in 20 mL THF) was added and the resulting mixture was stirred at rt overnight. The solution was concentrated and the residue was purified by silica gel flash chromatography (0–33% EtOAc/PE) to afford azide **3** as white amorphous solid (5.08 g, 68% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.52–6.46 (m, 1H), 6.15 (dd, *J* = 10.5, 5.3 Hz, 1H), 4.55–4.35 (m, 2H), 4.10–4.01 (m, 2H), 3.90–3.87 (m, 1H), 3.82–3.75 (m, 1H), 3.72–3.67 (m, 1H), 3.59–3.52 (m, 1H), 3.46–3.40 (m, 1H), 3.20–3.08 (m, 2H), 3.04–2.94 (m, 1H), 2.75–2.66 (m, 2H), 2.21–0.69 (m, 56H), 0.08 (s, 9H).

***C20-(S)*-amine-salinomycin-TMSEt-ester 4**. To a stirring solution of azide **3** (15.31 g, 17.47 mmol) in THF (150 mL) was added Ph_3P (13.75 g, 52.41 mmol), and the solution was stirred at rt for 30 min. Then H_2O (3.15 mL) was added to the reaction. The resulting mixture was stirred at rt overnight. The solution was removed under vacuum and the residue was purified by silica gel flash chromatography (0–10% MeOH/DCM) to afford amine **4** as white amorphous solid (12.80 g, 86% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.25–6.14 (m, 2H), 4.59–4.49 (m, 1H), 4.48–4.33 (m, 1H), 4.12–4.02 (m, 2H), 3.81–3.66 (m, 2H), 3.58–3.42 (m, 2H), 3.25–3.09 (m, 2H), 3.06–2.95 (m, 1H), 2.79–2.70 (m, 1H), 2.21–0.65 (m, 60H), 0.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 175.7, 131.0, 122.6, 109.4, 98.7, 87.9, 81.3, 76.6, 74.9, 73.7, 71.6, 70.7, 68.6, 63.5, 57.0, 50.3, 48.6, 48.0, 39.2, 39.0, 36.5, 36.3, 32.6, 31.7, 30.5, 29.3, 28.0, 26.2, 24.9, 22.6, 21.8, 21.5, 19.6, 17.3, 17.0, 14.4, 13.7, 13.0, 11.8, 10.9, 7.2, 6.4, −1.6. HRMS (ESI) calcd for $C_{47}H_{84}NO_{10}Si^+$ ($[M+H]^+$), 850.5859; found, 850.5834.

General procedure for the preparation of compounds 5–54 (Using the synthesis of **5** as an example). To a stirring solution of amine **4** (0.25 g, 0.29 mmol) in dry DCM (8 mL) was added DMAP (0.072 g, 0.59 mmol) and propyl carbonochloridate (0.072 g, 0.59 mmol). The resulting mixture was stirred at rt for 4 h, then the solution was removed under vacuum and the residue was purified by silica gel flash chromatography to afford the intermediate amide product as white amorphous solid. To a stirred solution of the intermediate product in THF (8 mL), was added TBAF (3.0 equiv., 1.0 M in THF). The resulting pale yellow solution was stirred at rt and monitored by TLC. The mixture solution was diluted with EtOAc and washed with Na_2CO_3 (0.1 M in water). The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel flash chromatography (10–100% EtOAc/PE) to afford compound **5** as white amorphous solid (0.21 g, 84% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.34–6.26 (m, 1H), 6.22 (dd, *J* = 5.6, 10.4 Hz, 1H), 4.40–4.34 (m, 1H), 4.30–4.17 (m, 2H), 4.06–3.95 (m, 2H), 3.94–3.86 (m, 1H), 3.72–3.65 (m, 1H), 3.63–3.54 (m, 1H), 3.40–3.33 (m, 1H), 2.90–2.78 (m, 1H), 2.73–2.58 (m, 2H), 2.30–2.17 (m, 1H), 2.10–0.61 (m, 61H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 183.9, 155.8, 125.8, 124.8, 108.3, 98.7, 89.6, 75.5, 74.7, 74.1, 71.2, 69.6, 66.9, 66.5, 55.0, 50.9, 50.2, 47.7, 39.6, 38.4,

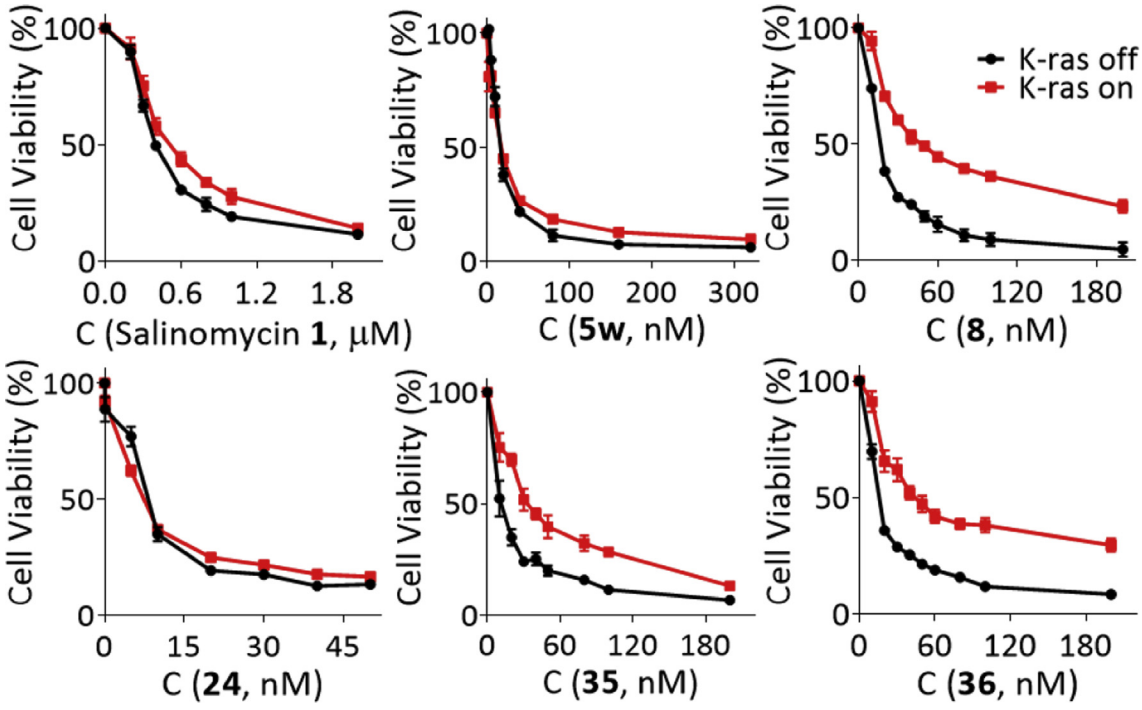


Fig. 4. K-ras on and off HEK293 cellular model study of salinomycin **1**, triazol **5w**, *20-N*-acyl **8**, **24**, **35**, and **36**.

35.7, 32.4, 32.2, 32.1, 28.7, 27.7, 27.6, 26.7, 23.6, 22.1 20.3, 19.7, 17.3, 16.9, 15.8, 14.4, 13.0, 12.3, 11.6, 10.4, 10.0, 6.5, 6.2. HRMS (ESI) calcd for $C_{46}H_{77}NNaO_{12}^{+}$ ([M+H] $^{+}$), 858.5338; found, 858.5315.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 6** was prepared from amine **4** and pentyl carbonochloridate by following the general procedure for amides with a 66% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34–6.13 (m, 2H), 4.44–4.30 (m, 2H), 4.30–4.17 (m, 2H), 4.09–3.98 (m, 2H), 3.96–3.86 (m, 1H), 3.76–3.64 (m, 1H), 3.63–3.53 (m, 1H), 3.46–3.33 (m, 1H), 2.94–2.77 (m, 1H), 2.77–2.57 (m, 2H), 2.39–2.16 (m, 1H), 2.11–0.60 (m, 64H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.0, 184.3, 156.2, 126.1, 125.0, 108.5, 98.9, 89.9, 75.8, 75.0, 74.3, 71.4, 67.0, 67.2, 65.4, 55.2, 51.1, 50.4, 48.0, 39.9, 38.6, 35.9, 32.6, 32.4, 29.7, 28.8, 28.6, 27.94, 27.88, 27.8, 26.9, 23.8, 22.3, 20.5, 19.9, 17.5, 17.1, 16.0, 14.6, 14.0, 13.2, 12.5, 11.8, 10.6, 6.7, 6.4. HRMS (ESI) calcd for $C_{42}H_{71}NNaO_{10}^{+}$ ([M+H]$^{+}$), 772.4970; found, 772.4935.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 7** was prepared from amine **4** and isobutyl carbonochloridate by following the general procedure for amides with a 74% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34–6.26 (m, 1H), 6.20 (dd, J = 5.6, 10 Hz, 1H), 4.41–4.30 (m, 2H), 4.29–4.18 (m, 2H), 3.94–3.76 (m, 3H), 3.76–3.66 (m, 1H), 3.61–3.52 (m, 1H), 3.42–3.32 (m, 1H), 2.90–2.76 (m, 1H), 2.74–2.54 (m, 2H), 2.30–2.18 (m, 1H), 2.17–0.60 (m, 62H). ^{13}C NMR (100 MHz, CD_3OD) δ 218.4, 158.4, 127.8, 126.5, 110.1, 100.2, 90.4, 78.3, 77.5, 76.7, 75.3, 73.0, 72.3, 71.9, 69.6, 57.2, 51.4, 50.1, 40.9, 39.7, 37.2, 36.7, 34.0, 33.2, 32.8, 30.8, 30.2, 29.4, 29.2, 27.5, 27.2, 24.3, 22.0, 20.9, 19.4, 18.4, 17.9, 17.1, 15.2, 13.5, 13.3, 12.8, 11.3, 7.4, 6.8. HRMS (ESI) calcd for $C_{47}H_{79}NNaO_{12}^{+}$ ([M+H]$^{+}$), 872.5494; found, 872.5456.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 8** was prepared from amine **4** and di-*tert*-butyl dicarbonate by following the general procedure for amides with a 92% yield as white amorphous solid, except that Et_3N was used instead of DMAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39–5.98 (m, 2H), 4.42–4.29 (m, 1H), 4.32–4.08 (m, 2H), 3.92–3.87 (m, 1H), 3.78–3.66 (m, 1H), 3.61–3.52 (m, 1H), 3.42–3.29 (m, 1H), 2.90–2.77 (m, 1H), 2.71–2.55 (m, 2H), 2.31–2.18 (m, 1H), 2.10–0.61 (m, 65H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 183.9, 154.8, 126.1, 124.4, 79.4, 75.6, 75.5, 74.7, 74.1, 71.2, 69.7, 67.0, 55.0, 50.9, 50.1, 47.2, 39.6, 38.4, 35.7, 35.4, 32.4, 32.2, 32.0, 29.4, 29.1, 28.5, 28.0, 27.7, 27.5, 26.7, 23.6, 20.3, 19.7, 17.2, 16.8, 15.8, 14.3, 12.9, 12.2, 11.9, 11.6, 10.4, 6.4, 6.2. HRMS (ESI) calcd for $C_{47}H_{79}NNaO_{12}^{+}$ ([M+H]$^{+}$), 872.5494; found, 872.5464.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 9** was prepared from amine **4** and allyl carbonochloridate by following the general procedure for amides with an 88% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40–6.11 (m, 2H), 5.98–5.79 (m, 1H), 5.35–5.12 (m, 2H), 4.67–4.49 (m, 2H), 4.48–4.39 (m, 1H), 4.39–4.31 (m, 1H), 4.28–4.17 (m, 2H), 4.00–3.84 (m, 1H), 3.75–3.50 (m, 2H), 3.43–3.29 (m, 1H), 2.94–2.79 (m, 1H), 2.75–2.56 (m, 2H), 2.35–2.19 (m, 1H), 2.15–0.61 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 183.9, 155.4, 132.5, 125.8, 125.0, 117.7, 108.2, 98.8, 89.7, 75.8, 75.5, 74.8, 74.1, 71.2, 69.6, 67.1, 65.6, 55.1, 50.9, 50.2, 47.9, 39.7, 38.4, 35.7, 32.3, 29.5, 29.2, 28.8, 27.8, 27.6, 26.7, 23.6, 20.4, 19.8, 17.3, 16.9, 15.8, 14.4, 13.0, 12.3, 11.6, 10.5, 6.5, 6.3. HRMS (ESI) calcd for $C_{46}H_{75}NNaO_{12}^{+}$ ([M+H]$^{+}$), 856.5181; found, 856.5215.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 10** was prepared from amine **4** and 2,2,2-trichloroethyl carbonochloridate by following the general procedure for amides with a 99% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37–6.28 (m, 1H), 6.22 (dd, J = 5.6, 10.4 Hz, 1H), 4.87–4.79 (m, 1H), 4.72–4.60 (m, 2H), 4.41–4.18 (m, 3H), 3.95–3.85 (m, 1H), 3.74–3.65 (m, 1H), 3.63–3.56 (m, 1H), 3.40–3.34 (m, 1H), 2.88–2.77 (m, 1H), 2.73–2.57 (m, 2H), 2.25–2.15 (m, 1H), 2.10–0.63 (m, 55H). ^{13}C NMR (100 MHz, CD_3OD) δ 219.3, 185.5, 127.1, 126.5, 110.0, 100.3, 97.1, 90.7, 77.6, 77.2, 76.9, 75.6, 75.5, 72.9, 71.8, 69.3, 56.8, 52.2, 50.5, 50.1, 41.2, 39.7, 37.1, 36.9, 33.8, 33.4, 33.0, 30.0, 29.3, 28.2, 27.6, 24.7, 21.8, 21.0, 17.8, 17.2, 15.1, 13.4, 13.0, 12.8, 11.2, 7.2, 6.8. HRMS (ESI) calcd for $C_{45}H_{72}Cl_3NNaO_{12}^{+}$ ([M+H]$^{+}$), 946.4012; found, 946.3984.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 11** was prepared from amine **4** and phenyl carbonochloridate by following the general procedure for amides with an 82% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 2H),

7.23–7.16 (m, 1H), 7.13–7.07 (m, 2H), 6.43–6.23 (m, 2H), 4.83–4.70 (m, 1H), 4.40–4.28 (m, 2H), 4.27–4.18 (m, 1H), 3.98–3.85 (m, 1H), 3.79–3.54 (m, 3H), 3.41–3.31 (m, 1H), 2.92–2.58 (m, 3H), 2.46–2.18 (m, 1H), 2.14–0.63 (m, 54H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 184.3, 154.1, 150.7, 129.2, 125.6, 125.4, 121.5, 121.4, 108.3, 98.9, 90.0, 75.9, 75.6, 75.0, 74.2, 71.4, 69.9, 67.2, 55.1, 51.0, 50.2, 48.2, 39.8, 38.5, 35.9, 32.4, 29.6, 27.9, 27.6, 27.0, 26.8, 19.9, 17.9, 17.5, 17.1, 16.6, 16.0, 14.5, 13.2, 13.0, 12.4, 11.8, 10.6, 6.7, 6.4. HRMS (ESI) calcd for $C_{49}H_{75}NNaO_{12}^{+}$ ([M+H]$^+$), 892.5181; found, 892.5138.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 12** was prepared from amine **4** and benzyl carbonochloridate by following the general procedure for amides with a 72% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 6.33–6.25 (m, 1H), 6.23–6.11 (m, 1H), 5.17–4.99 (m, 2H), 4.51–4.43 (m, 1H), 4.43–4.31 (m, 1H), 4.30–4.15 (m, 2H), 3.94–3.85 (m, 1H), 3.77–3.66 (m, 1H), 3.60–3.50 (m, 1H), 3.42–3.34 (m, 1H), 2.93–2.79 (m, 1H), 2.74–2.58 (m, 2H), 2.35–2.20 (m, 1H), 2.08–0.62 (m, 54H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.1, 155.6, 135.9, 128.3, 127.9, 125.8, 124.9, 108.2, 98.7, 89.6, 75.7, 75.4, 74.9, 74.0, 71.2, 69.9, 67.1, 66.8, 55.1, 50.8, 50.0, 48.0, 39.6, 38.3, 35.7, 32.2, 29.4, 28.6, 27.7, 27.4, 26.6, 23.5, 20.4, 19.7, 17.3, 16.8, 15.8, 14.3, 12.9, 12.2, 11.7, 10.4, 6.4, 6.2. HRMS (ESI) calcd for $C_{50}H_{77}NNaO_{12}^{+}$([M+H]$^+$), 906.5338; found, 906.5355.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 13** was prepared from amine **4** and 4-nitrobenzyl carbonochloridate by following the general procedure for amides with a 40% yield as white amorphous solid. ^{1}H NMR (400 MHz, MeOD) δ 8.21 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 6.44–6.34 (m, 1H), 6.10 (dd, J = 10.5, 5.4 Hz, 1H), 5.19 (s, 2H), 4.29–4.21 (m, 2H), 4.20–4.09 (m, 1H), 3.93–3.86 (m, 1H), 3.70–3.56 (m, 2H), 3.53–3.45 (m, 1H), 3.33–3.28 (m, 6H), 2.90–2.78 (m, 3H), 2.25–0.70 (m, 51H). ^{13}C NMR (100 MHz, CD_3OD) δ 219.2, 185.4, 157.7, 148.8, 145.9, 129.2, 126.9, 126.7, 124.5, 110.0, 100.3, 90.7, 77.6, 77.2, 76.8, 75.6, 73.0, 71.8, 69.3, 66.3, 56.8, 52.2, 50.5, 50.0, 41.1, 39.7, 37.1, 36.9, 33.8, 33.4, 33.0, 30.0, 29.3, 28.1, 27.6, 24.7, 21.8, 21.0, 17.8, 17.4, 17.2, 15.1, 13.4, 13.0, 12.8, 11.1, 7.1, 6.8. HRMS (ESI) calcd for $C_{50}H_{76}N_2NaO_{14}^{+}$ ([M+H]$^+$), 951.5189; found, 951.5231.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 14** was prepared from amine **4** and (9*H*-fluoren-9-yl)methyl carbonochloridate by following the general procedure for amides with a 52% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.1 Hz, 2H), 7.34–7.27 (m, 2H), 6.36–6.26 (m, 1H), 6.22 (dd, J = 10.4, 5.8 Hz, 1H), 4.56–4.45 (m, 1H), 4.44–4.30 (m, 3H), 4.29–4.17 (m, 3H), 3.97–3.86 (m, 1H), 3.77–3.55 (m, 2H), 3.40–3.32 (m, 1H), 2.94–2.80 (m, 1H), 2.75–2.56 (m, 2H), 2.27–2.12 (m, 1H), 2.08–0.63 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 184.0, 155.4, 143.7, 143.6, 141.2, 127.6, 126.9, 124.9, 119.8, 108.3, 98.9, 89.8, 75.8, 74.9, 74.2, 71.3, 69.6, 67.1, 66.7, 55.1, 51.0, 50.3, 48.0, 47.1, 39.8, 38.5, 35.8, 32.4, 29.6, 28.9, 27.9, 26.8, 23.8, 22.6, 20.4, 19.8, 17.4, 17.0, 15.9, 14.4, 13.1, 12.4, 11.7, 10.6, 6.6, 6.4. HRMS (ESI) calcd for $C_{57}H_{81}NNaO_{12}^{+}$ ([M+H]$^+$), 994.5651; found, 994.5650.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 15** was prepared from amine **4** and acetyl chloride by following the general procedure for amides with a 65% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36–6.26 (m, 1H), 6.18 (dd, J = 10.3, 5.8 Hz, 1H), 5.15–5.05 (m, 1H), 4.61–4.48 (m, 1H), 4.42–4.30 (m, 1H), 4.27–4.16 (m, 1H), 3.96–3.86 (m, 1H), 3.74–3.65 (m, 1H), 3.61–3.53 (m, 1H), 3.41–3.30 (m, 1H), 2.88–2.76 (m, 1H), 2.74–2.56 (m, 2H), 2.28–2.13 (m, 1H), 2.06–0.61 (m, 58H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 183.7, 169.0, 126.0, 124.8, 108.0, 98.8, 89.6, 75.7, 74.8, 74.0, 71.2, 69.5, 67.0, 55.0, 50.8, 50.2, 46.0, 39.6, 38.4, 35.7, 32.2, 29.4, 28.8, 27.7, 26.7, 23.6, 23.2, 20.2, 19.7, 17.3, 16.8, 15.8, 14.3, 13.0, 12.2, 11.6, 10.4, 6.5, 6.2. HRMS (ESI) calcd for $C_{44}H_{73}NNaO_{11}^{+}$ ([M+H]$^+$), 814.5076; found, 814.5075.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 16** was prepared from amine **4** and cyclopropanecarbonyl chloride by following the general procedure for amides with a 23% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77–6.58 (m, 1H), 6.13 (dd, J = 9.9, 3.6 Hz, 1H), 5.58 (dd, J = 9.9, 1.5 Hz, 1H), 4.47–4.39 (m, 1H), 4.47–4.39 (m, 2H), 3.88–3.77 (m, 2H), 3.68–3.60 (m, 1H), 3.57–3.50 (m, 1H), 3.39–3.27 (m, 1H), 3.07–2.90 (m, 3H), 2.80–2.70 (m, 1H), 2.54–2.42 (m, 1H), 2.26–2.02 (m, 3H), 2.01–0.64 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.6, 177.8, 174.2, 129.9, 129.7, 108.3, 99.0, 87.2, 76.2, 75.2, 74.2, 71.7, 71.6, 69.0, 56.5, 50.8, 49.0, 48.9, 39.0, 36.6, 36.1, 33.3, 32.8, 31.4, 30.8, 29.8, 29.1, 28.1, 26.2, 25.5, 22.4, 21.9, 20.7, 19.8, 18.3, 15.9, 14.8, 14.8, 13.8, 13.1, 12.0, 11.0, 7.3, 7.2, 7.1, 6.5. HRMS (ESI) calcd for $C_{46}H_{75}NNaO_{11}^{+}$([M+H]$^+$),840.5232; found, 840.5258.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 17** was prepared from amine **4** and cyclohexanecarbonyl chloride by following the general procedure for amides with a 77% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39–6.24 (m, 1H), 6.17 (dd, J = 10.5, 6.0 Hz, 1H), 5.17–5.06 (m, 1H), 4.61–4.49 (m, 1H), 4.39–4.29 (m, 1H), 4.27–4.16 (m, 1H), 3.96–3.83 (m, 1H), 3.75–3.66 (m, 1H), 3.64–3.53 (m, 1H), 3.41–3.28 (m, 1H), 2.91–2.76 (m, 1H), 2.74–2.57 (m, 2H), 2.29–2.13 (m, 1H), 2.08–0.65 (m, 66H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 184.1, 175.1, 126.0, 124.8, 108.0, 98.7, 89.6, 75.6, 75.3, 74.8, 73.8, 71.2, 70.0, 67.1, 55.1, 49.9, 45.7, 45.1, 39.6, 38.3, 35.8, 32.2, 29.6, 29.4, 28.9, 28.5, 27.7, 26.5, 25.4, 25.2, 23.4, 20.4, 19.7, 17.3, 16.9, 15.9, 14.2, 13.0, 12.1, 11.7, 10.4, 6.4, 6.2. HRMS (ESI) calcd for $C_{49}H_{81}NNaO_{11}^{+}$ ([M+H]$^+$), 882.5702; found, 882.5712.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 18** was prepared from amine **4** and (3*r*, 5*r*, 7*r*)-adamantane-1-carbonyl chloride by following the general procedure for amides with a 65% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36–6.27 (m, 1H), 6.17 (dd, J = 10.5, 6.1 Hz, 1H), 5.36–5.29 (m, 1H), 4.61–4.52 (m, 1H), 4.41–4.28 (m, 1H), 4.26–4.18 (m, 1H), 3.96–3.85 (m, 1H), 3.76–3.66 (m, 1H), 3.64–3.55 (m, 1H), 3.40–3.32 (m, 1H), 2.88–2.77 (m, 1H), 2.73–2.58 (m, 2H), 2.26–2.13 (m, 1H), 2.10–0.59 (m, 70H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 183.9, 176.8, 126.3, 124.8, 108.2, 98.8, 89.8, 75.7, 75.6, 74.7, 74.1, 71.2, 69.6, 67.0, 55.1, 50.9, 50.3, 45.4, 40.5, 39.7, 39.0, 38.4, 36.2, 35.7, 35.6, 32.4, 32.3, 32.1, 28.6, 27.9, 27.8, 27.6, 26.7, 23.7, 20.3, 19.8, 17.3, 17.0, 15.9, 14.4, 13.0, 12.3, 11.6, 10.4, 6.5, 6.2. HRMS (ESI) calcd for $C_{53}H_{85}NNaO_{11}^{+}$ ([M+H]$^+$), 934.6015; found, 934.5987.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 19** was prepared from amine **4** and acryloyl chloride by following the general procedure for amides with a 44% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41–6.15 (m, 3H), 5.99 (dd, J = 16.9, 10.3 Hz, 1H), 5.72–5.58 (m, 1H), 5.27–5.18 (m, 1H), 4.70–4.59 (m, 1H), 4.41–4.29 (m, 1H), 4.27–4.15 (m, 1H), 3.97–3.86 (m, 1H), 3.76–3.65 (m, 1H), 3.64–3.54 (m, 1H), 3.43–3.32 (m, 1H), 2.92–2.78 (m, 1H), 2.75–2.57 (m, 2H), 2.32–2.14 (m, 1H), 2.10–0.58 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 184.7, 165.1, 130.4, 127.2, 126.0, 125.2, 108.2, 98.8, 89.8, 75.8, 75.5, 75.0, 74.0, 71.4, 70.4, 67.3, 55.3, 50.8, 50.1, 46.4, 39.8, 38.6, 36.0, 32.4, 29.6, 28.6, 27.9, 26.6, 23.6, 20.7, 19.8, 17.5, 17.1, 16.1, 14.4, 13.1, 12.3, 10.6, 6.7, 6.3. HRMS (ESI) calcd for $C_{45}H_{73}NNaO_{11}^{+}$ ([M+H]$^+$), 826.5076; found, 826.5071.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 20** was prepared from amine **4** and methacryloyl chloride by following the general procedure for amides with a 56% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38–6.29 (m, 1H), 6.22 (dd, J = 10.5, 6.0 Hz, 1H), 5.62 (s, 1H), 5.51 (d, J = 9.2 Hz, 1H), 5.32 (s, 1H), 4.67–4.59 (m, 1H), 4.43–4.29 (m, 1H), 4.27–4.19 (m, 1H), 3.96–3.85 (m, 1H), 3.75–3.66 (m, 1H), 3.64–3.55 (m, 1H), 3.42–3.32 (m, 1H), 2.90–2.76 (m, 1H), 2.76–2.57 (m, 2H), 2.31–2.16 (m, 1H), 2.11–0.62 (m, 58H). ^{13}C NMR (100 MHz, CD_3OD) δ 218.6, 170.4, 141.1, 127.2,

127.0, 120.9, 109.6, 100.4, 90.7, 78.2, 77.6, 76.8, 75.3, 73.0, 71.9, 69.6, 57.2, 51.6, 50.2, 48.2, 41.0, 39.6, 37.3, 37.0, 34.0, 33.3, 32.8, 30.2, 29.4, 27.5, 27.3, 24.4, 22.0, 21.0, 18.7, 17.8, 17.3, 15.1, 13.5, 13.2, 12.8, 11.3, 7.4, 6.8. HRMS (ESI) calcd for$C_{46}H_{75}NNaO_{11}^{+}$ ([M+H]$^{+}$),840.5232; found, 840.5270.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 21** was prepared from amine **4** and cinnamoyl chloride by following the general procedure for amides with a 62% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 15.6 Hz, 1H), 7.56–7.42 (m, 2H), 7.41–7.30 (m, 3H), 6.47–6.08 (m, 3H), 5.37–5.15 (m, 1H), 4.80–4.65 (m, 1H), 4.46–4.32 (m, 1H), 4.26–4.16 (m, 1H), 4.03–3.85 (m, 1H), 3.75–3.56 (m, 2H), 3.44–3.35 (m, 1H), 2.95–2.78 (m, 2H), 2.73–2.57 (m, 3H), 2.38–2.20 (m, 1H), 2.15–0.57 (m, 53H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 184.1, 165.2, 141.8, 134.3, 129.6, 128.5, 127.7, 126.1, 125.0, 119.8, 108.2, 98.8, 89.6, 75.7, 75.4, 74.9, 74.0, 71.2, 70.0, 67.2, 55.1, 50.8, 50.0, 46.4, 39.6, 38.4, 35.9, 32.3, 29.4, 28.7, 27.8, 27.5, 26.6, 23.5, 20.4, 19.7, 17.4, 17.0, 15.8, 14.3, 13.0, 12.2, 11.7, 10.5, 6.5, 6.2. HRMS (ESI) calcd for $C_{51}H_{77}NNaO_{11}^{+}$ ([M+H]$^{+}$), 902.5389; found, 902.5373.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 22** was prepared from amine **4** and 2-(4-fluorophenyl)acetyl chloride by following the general procedure for amides with a 33% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 2H), 7.04–6.95 (m, 2H), 6.77–6.61 (m, 1H), 6.05 (dd, J = 9.7, 5.8 Hz, 1H), 5.86–5.74 (m, 1H), 4.52–4.42 (m, 1H), 4.34–4.26 (m, 1H), 4.23–4.15 (m, 1H), 4.07–3.98 (m, 1H), 3.92–3.82 (m, 1H), 3.80–3.69 (m, 2H), 3.54–3.37 (m, 3H), 3.11–3.00 (m, 1H), 2.87–2.68 (m, 3H), 2.43–0.68 (m, 54H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −119.67. ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.4, 177.6, 173.6, 161.8 (d, J = 244.7 Hz), 132.7, 131.8 (d, J = 3.0 Hz), 130.7 (d, J = 7.9 Hz), 128.8, 115.4, 115.2, 108.6, 97.1, 86.6, 75.2, 74.7, 72.7, 71.6, 71.2, 68.4, 55.3, 49.6, 49.4, 47.8, 41.8, 39.3, 36.6, 35.8, 33.9, 32.8, 31.9, 30.5, 29.7, 29.3, 28.0, 25.9, 23.5, 22.7, 21.9, 21.2, 19.9, 19.2, 18.2, 16.0, 14.4, 13.6, 13.0, 12.0, 11.6, 7.4, 6.4. HRMS (ESI) calcd for $C_{50}H_{76}FNNaO_{11}^{+}$ ([M+H]$^{+}$), 908.5295; found, 908.5276.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 23** was prepared from amine **4** and 2-(4-methoxyphenyl)acetyl chloride by following the general procedure for amides with a 56% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.24–6.12 (m, 1H), 6.12–6.00 (m, 1H), 5.12–4.98 (m, 1H), 4.56–4.45 (m, 1H), 4.40–4.28 (m, 1H), 4.26–4.14 (m, 1H), 3.95–3.84 (m, 1H), 3.78 (s, 3H), 3.72–3.63 (m, 1H), 3.56–3.44 (m, 3H), 3.39–3.29 (m, 1H), 2.87–2.76 (m, 1H), 2.69–2.56 (m, 2H), 2.20–2.07 (m, 1H), 2.03–0.60 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 183.9, 170.9, 158.9, 130.5, 126.0, 125.7, 124.8, 114.4, 107.8, 98.7, 89.7, 75.7, 75.4, 75.0, 74.0, 71.3, 70.2, 67.3, 55.2, 55.0, 51.0, 49.9, 46.0, 42.6, 39.4, 38.2, 36.9, 36.0, 35.7, 32.6, 32.3, 31.8, 29.9, 29.5, 29.2, 28.5, 27.9, 27.2, 26.9, 26.6, 23.6, 22.5, 20.5, 19.9, 19.6, 17.3, 16.0, 14.4, 14.0, 13.0, 12.2, 11.8, 10.7, 6.6, 6.2. HRMS (ESI) calcd for $C_{51}H_{79}NNaO_{12}^{+}$ ([M+H]$^{+}$), 920.5494; found, 920.5457.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 24** was prepared from amine **4** and 2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)acetyl chloride by following the general procedure for amides with an 81% yield as white amorphous solid, except that Et_3N was used instead of DMAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39–6.32 (m, 1H), 6.21–6.11 (m, 1H), 6.08 (dd, J = 10.5, 6.1 Hz, 1H), 4.65–4.56 (m, 1H), 4.49 (s, 2H), 4.16–4.09 (m, 1H), 4.00–3.86 (m, 3H), 3.70–3.58 (m, 2H), 2.94–2.82 (m, 1H), 2.78–2.57 (m, 2H), 2.31–0.62 (m, 56H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.56. ^{13}C NMR (100 MHz, CD_3OD) δ 219.5, 186.0, 127.6, 126.2, 109.6, 100.5, 91.2, 77.7, 77.0, 76.9, 75.7, 73.0, 71.8, 69.3, 56.8, 52.4, 50.8, 48.0, 41.3, 39.6, 37.4, 37.1, 33.8, 33.5, 33.0, 30.0, 29.3, 28.4, 27.7, 24.9, 21.8, 21.0, 17.8, 17.1, 15.1, 13.4, 13.1, 12.6, 11.1, 7.1, 6.9. HRMS (ESI) calcd for $C_{48}H_{72}F_9NNaO_{12}^{+}$([M+H]$^{+}$), 1048.4803; found, 1048.4783.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 25** was prepared from amine **4** and methyl 3-chloro-3-oxopropanoate by following the general procedure for amides with a 47% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, J = 9.2 Hz, 1H), 6.37–6.27 (m, 1H), 6.16 (dd, J = 10.5, 6.0 Hz, 1H), 4.68–4.50 (m, 1H), 4.46–4.31 (m, 1H), 4.27–4.12 (m, 1H), 3.98–3.82 (m, 1H), 3.79–3.66 (m, 4H), 3.62–3.54 (m, 1H), 3.38–3.32 (m, 1H), 3.32–3.26 (m, 2H), 2.90–2.78 (m, 1H), 2.74–2.59 (m, 2H), 2.23–2.08 (m, 1H), 2.08–0.60 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 184.1, 169.4, 164.2125.4, 125.1, 107.8, 98.9, 89.8, 75.6, 75.5, 74.8, 74.1, 71.2, 69.8, 67.1, 55.1, 52.2, 50.8, 50.2, 46.1, 40.6, 39.8, 38.5, 36.0, 35.7, 32.4, 32.3, 32.0, 29.5, 28.6, 27.8, 27.5, 26.7, 23.6, 20.4, 19.8, 17.3, 16.6, 15.8, 14.4, 13.0, 12.2, 11.6, 10.4, 6.5, 6.2. HRMS (ESI) calcd for $C_{46}H_{75}NNaO_{13}^{+}$ ([M+H]$^{+}$), 872.5131; found, 872.5120.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 26** was prepared from amine **4** and ethyl 3-chloro-3-oxopropanoate by following the general procedure for amides with a 50% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 9.3 Hz, 1H), 6.40–6.28 (m, 1H), 6.17 (dd, J = 10.4, 5.9 Hz, 1H), 4.67–4.57 (m, 1H), 4.43–4.31 (m, 1H), 4.27–4.11 (m, 3H), 3.96–3.87 (m, 1H), 3.75–3.66 (m, 1H), 3.63–3.54 (m, 1H), 3.43–3.31 (m, 1H), 3.32–3.25 (m, 2H), 2.92–2.80 (m, 1H), 2.74–2.58 (m, 2H), 2.29–0.65 (m, 59H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.1, 168.9, 164.3, 125.5, 125.1, 107.8, 98.9, 89.7, 75.6, 75.5, 74.8, 74.1, 71.2, 69.8, 67.0, 61.3, 55.1, 50.8, 50.2, 46.1, 40.9, 39.8, 38.5, 36.0, 35.7, 32.4, 32.2, 32.0, 29.4, 28.6, 27.8, 27.5, 26.7, 23.6, 20.4, 19.8, 17.3, 16.6, 15.8, 14.4, 13.8, 13.0, 12.2, 11.6, 10.4, 6.5, 6.2. HRMS (ESI) calcd for $C_{47}H_{77}NNaO_{13}^{+}$ ([M+H]$^{+}$), 886.5287; found, 886,5263.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 27** was prepared from amine **4** and benzoyl chloride by following the general procedure for amides with a 59% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.64 (m, 2H), 7.55–7.46 (m, 1H), 7.46–7.37 (m, 2H), 6.45–6.35 (m, 1H), 6.32–6.24 (m, 1H), 5.92–5.77 (m, 1H), 4.88–4.74 (m, 1H), 4.47–4.33 (m, 1H), 4.28–4.20 (m, 1H), 4.00–3.86 (m, 2H), 3.76–3.67 (m, 1H), 3.67–3.58 (m, 1H), 3.43–3.33 (m, 1H), 2.99–2.80 (m, 2H), 2.77–2.60 (m, 3H), 2.38–2.25 (m, 2H), 2.15–0.61 (m, 51H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.0, 166.4, 133.9, 131.6, 128.5, 126.6, 126.2, 125.2, 108.2, 98.9, 89.9, 75.8, 75.5, 74.9, 74.0, 71.2, 69.8, 67.2, 55.2, 50.9, 50.2, 46.4, 39.7, 38.4, 36.0, 32.4, 28.7, 27.8, 26.6, 23.6, 20.4, 19.8, 17.4, 17.1, 16.0, 14.3, 13.0, 12.3, 11.7, 10.6, 6.5, 6.3. HRMS (ESI) calcd for $C_{49}H_{75}NNaO_{11}^{+}$([M+H]$^{+}$), 876.5232; found, 876.5219.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 28** was prepared from amine **4** and 4-methylbenzoyl chloride by following the general procedure for amides with a 59% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.40–6.34 (m, 1H), 6.27 (dd, J = 10.5, 6.0 Hz, 1H), 5.80 (d, J = 9.2 Hz, 1H), 4.81–4.73 (m, 1H), 4.46–4.33 (m, 1H), 4.30–4.19 (m, 1H), 3.98–3.88 (m, 1H), 3.75–3.68 (m, 1H), 3.67–3.59 (m, 1H), 3.40–3.34 (m, 1H), 2.91–2.78 (m, 1H), 2.76–2.59 (m, 2H), 2.40–2.26 (m, 4H), 2.16–0.65 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.0, 166.2, 142.0, 131.0, 129.1, 126.5, 126.2, 125.1, 108.2, 98.9, 89.8, 75.8, 75.5, 74.8, 74.0, 71.2, 69.7, 67.1, 55.1, 50.9, 50.2, 46.3, 39.7, 38.4, 35.9, 35.8, 32.3, 29.5, 28.7, 27.8, 27.5, 26.6, 23.6, 21.2, 20.4, 19.8, 17.3, 17.0, 15.9, 14.3, 13.0, 12.3, 11.6, 10.5, 6.5, 6.3. HRMS (ESI) calcd for $C_{50}H_{77}NNaO_{11}^{+}$ ([M+H]$^{+}$), 890.5389; found, 890.5430.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 29** was prepared from amine **4** and 4-propylbenzoyl chloride by following the general procedure for amides with a 63% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 6.41–6.34 (m, 1H), 6.27 (dd, J = 10.5, 6.0 Hz, 1H), 5.82 (d, J = 9.3 Hz, 1H), 4.88–4.72 (m, 1H), 4.43–4.33 (m, 1H), 4.29–4.19 (m, 1H), 3.99–3.88 (m, 1H), 3.78–3.68 (m, 1H), 3.66–3.58 (m, 1H), 3.51–3.34 (m, 1H), 2.90–2.78 (m, 1H), 2.76–2.56 (m, 5H), 2.37–2.25 (m, 1H), 2.14–0.62 (m, 59H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 216.9, 184.3, 166.4, 146.8, 131.2, 128.6, 126.6, 126.1, 125.2, 108.2, 98.9, 89.9, 75.7, 74.9, 74.0, 71.3, 70.0, 67.2, 55.1, 50.9, 50.2, 46.3, 39.7, 38.4, 37.6, 36.0, 35.8, 32.4, 29.5, 28.6, 27.8, 27.5, 26.7, 24.1, 23.7, 20.5, 19.8, 17.4, 17.1, 15.9, 14.4, 13.6, 13.1, 12.3, 11.7, 10.5, 6.6, 6.3. HRMS (ESI) calcd for $C_{52}H_{81}NNaO_{11}^{+}$ ([M+H]$^+$), 918.5702; found, 918.5734.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 30** was prepared from amine **4** and 4-(*tert*-butyl)benzoyl chloride by following the general procedure for amides with a 71% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.43–6.33 (m, 1H), 6.27 (dd, J = 10.5, 6.0 Hz, 1H), 5.83 (d, J = 9.3 Hz, 1H), 4.86–4.72 (m, 1H), 4.46–4.32 (m, 1H), 4.27–4.19 (m, 1H), 3.97–3.84 (m, 1H), 3.76–3.68 (m, 1H), 3.66–3.57 (m, 1H), 3.44–3.33 (m, 1H), 2.88–2.80 (m, 1H), 2.74–2.62 (m, 2H), 2.35–2.27 (m, 1H), 2.15–0.64 (m, 64H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.2, 166.3, 155.1, 130.8, 126.5, 126.1, 125.4, 125.1, 108.2, 98.9, 89.9, 75.7, 75.6, 74.8, 74.0, 71.2, 70.0, 67.1, 55.1, 50.8, 50.2, 46.3, 39.6, 38.4, 36.0, 35.7, 34.7, 32.3, 30.9, 29.5, 28.5, 27.8, 27.5, 26.6, 23.6, 20.5, 19.8, 17.4, 17.1, 15.9, 14.4, 13.0, 12.3, 11.7, 10.5, 6.5, 6.3. HRMS (ESI) calcd for $C_{53}H_{83}NNaO_{11}^{+}$([M+H]$^+$), 932.5858; found, 932.5853.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 31** was prepared from amine **4** and 4-bromobenzoyl chloride by following the general procedure for amides with a 38% yield as white amorphous solid, except that Et_3N was used instead of DMAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.49 (m, 4H), 6.41–6.14 (m, 2H), 6.13–5.72 (m, 1H), 4.82–4.71 (m, 1H), 4.43–4.31 (m, 1H), 4.28–4.13 (m, 1H), 4.01–3.83 (m, 2H), 3.76–3.58 (m, 2H), 3.42–3.34 (m, 1H), 2.94–2.60 (m, 3H), 2.35–2.19 (m, 1H), 2.15–0.63 (m, 54H). ^{13}C NMR (100 MHz, CD_3OD) δ 217.9, 169.0, 134.6, 132.9, 130.2, 128.3, 127.3, 127.2, 110.0, 100.5, 90.2, 78.6, 77.5, 76.7, 75.2, 73.0, 71.9, 69.7, 57.1, 51.2, 50.1, 40.8, 39.7, 37.3, 36.6, 34.0, 33.2, 32.8, 30.4, 29.4, 27.4, 26.8, 24.3, 22.1, 20.9, 18.6, 17.9, 17.1, 15.1, 13.5, 12.7, 11.3, 7.5, 6.8. HRMS (ESI) calcd for $C_{49}H_{74}BrNNaO_{11}^{+}$ ([M+H]$^+$), 954.4337; found, 954.4303.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 32** was prepared from amine **4** and 4-chlorobenzoyl chloride by following the general procedure for amides with a 28% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 2.9 Hz, 1H), 6.17 (dd, J = 10.1, 1.8 Hz, 1H), 5.51 (dd, J = 10.1, 2.6 Hz, 1H), 4.57–4.38 (m, 1H), 4.18–3.99 (m, 2H), 3.88–3.63 (m, 2H), 3.57–3.45 (m, 2H), 3.18–3.05 (m, 1H), 3.04–2.86 (m, 1H), 2.78–2.66 (m, 2H), 2.47–2.28 (m, 1H), 2.17–2.00 (m, 1H), 1.99–0.57 (m, 53H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.6, 178.2, 168.3, 137.5, 134.3, 129.2, 129.0, 128.8, 128.7, 107.8, 99.9, 87.5, 76.2, 75.2, 74.7, 71.8, 71.6, 68.7, 57.2, 51.8, 49.4, 48.9, 38.7, 36.6, 36.1, 33.3, 32.1, 31.0, 30.5, 29.8, 29.7, 28.0, 26.5, 26.2, 22.5, 22.2, 21.4, 19.7, 18.3, 15.8, 13.8, 13.7, 13.2, 12.1, 10.8, 7.1, 6.2. HRMS (ESI) calcd for $C_{49}H_{74}ClNNaO_{11}^{+}$ ([M+H]$^+$), 910.4843; found, 910.4798.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 33** was prepared from amine **4** and 4-fluorobenzoyl chloride by following the general procedure for amides with a 38% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.6, 5.4 Hz, 2H), 7.11 (t, J = 8.5 Hz, 2H), 7.02–6.92 (m, 1H), 6.18 (dd, J = 10.1, 1.7 Hz, 1H), 5.50 (dd, J = 10.1, 2.5 Hz, 1H), 4.54–4.43 (m, 1H), 4.12–4.04 (m, 2H), 3.80–3.66 (m, 2H), 3.56–3.45 (m, 2H), 3.18–3.02 (m, 1H), 3.02–2.88 (m, 1H), 2.80–2.64 (m, 2H), 2.46–2.34 (m, 1H), 2.16–2.01 (m, 1H), 2.00–0.59 (m, 53H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.52. ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.5, 178.2, 168.2, 164.7 (d, J = 251.7 Hz), 132.0, 129.7, 129.6, 129.1, 129.0, 115.5, 115.3, 107.8, 99.9, 87.4, 77.4, 77.1, 76.1, 75.2, 74.7, 71.8, 71.5, 68.6, 57.2, 51.7, 49.3, 48.9, 38.7, 36.6, 36.1, 33.2, 32.1, 31.0, 30.4, 29.7, 28.0, 26.5, 26.2, 22.5, 22.2, 21.4, 19.7, 18.2, 15.8, 13.8, 13.7, 13.2, 12.1, 10.8, 7.0, 6.3. HRMS (ESI) calcd for $C_{49}H_{74}FNNaO_{11}^{+}$ ([M+H]$^+$), 894.5138; found, 894.5143.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 34** was prepared from amine **4** and 3-fluorobenzoyl chloride by following the general procedure for amides with a 73% yield as white amorphous solid, except that Et_3N was used instead of DMAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.35 (m, 3H), 7.23–7.16 (m, 1H), 6.47–6.35 (m, 1H), 6.27 (dd, J = 10.4, 6.0 Hz, 1H), 5.81 (d, J = 9.1 Hz, 1H), 4.84–4.71 (m, 1H), 4.44–4.31 (m, 1H), 4.30–4.20 (m, 1H), 4.03–3.87 (m, 1H), 3.76–3.67 (m, 1H), 3.67–3.56 (m, 1H), 3.44–3.32 (m, 1H), 2.91–2.76 (m, 1H), 2.75–2.59 (m, 2H), 2.36–2.22 (m, 1H), 2.14–0.62 (m, 55H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.61. ^{13}C NMR (100 MHz, CD_3OD) δ 219.3, 185.8, 168.5, 164.0 (d, J = 246.2 Hz), 137.8 (d, J = 6.8 Hz), 131.7 (d, J = 8.0 Hz), 127.5, 126.6, 124.0 (d, J = 2.8 Hz), 119.7 (d, J = 21.0 Hz), 115.4 (d, J = 23.2 Hz), 109.9, 100.4, 90.8, 77.7, 77.0, 76.9, 75.6, 72.9, 71.8, 69.2, 56.7, 52.4, 50.7, 48.4, 41.2, 39.6, 37.1, 36.9, 33.8, 33.5, 33.0, 29.9, 29.3, 28.2, 27.6, 24.8, 21.8, 21.0, 17.8, 17.3, 17.1, 15.1, 13.5, 13.0, 12.7, 11.1, 7.1, 6.9. HRMS (ESI) calcd for $C_{49}H_{74}FNNaO_{11}^{+}$([M+H]$^+$), 894.5138; found, 894.5117.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 35** was prepared from amine **4** and 2-fluorobenzoyl chloride by following the general procedure for amides with an 80% yield as white amorphous solid, except that Et_3N was used instead of DMAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (td, J = 7.9, 1.8 Hz, 1H), 7.52–7.41 (m, 1H), 7.26–7.22 (m, 1H), 7.07 (dd, J = 11.9, 8.0 Hz, 1H), 6.55 (dd, J = 12.9, 9.2 Hz, 1H), 6.42–6.34 (m, 1H), 6.25 (dd, J = 10.5, 6.0 Hz, 1H), 4.88–4.80 (m, 1H), 4.44–4.34 (m, 1H), 4.30–4.19 (m, 1H), 3.97–3.87 (m, 1H), 3.75–3.68 (m, 1H), 3.66–3.58 (m, 1H), 3.43–3.33 (m, 1H), 2.89–2.80 (m, 1H), 2.75–2.59 (m, 2H), 2.37–0.62 (m, 56H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.65. ^{13}C NMR (100 MHz, CD_3OD) δ 219.4, 185.8, 164.9 (d, J = 2.2 Hz), 161.7 (d, J = 247.1 Hz), 135.0 (d, J = 9.4 Hz), 132.4, 127.4, 126.2, 126.1 (d, J = 2.9 Hz), 122.2, 122.1, 117.4, 117.1, 109.5, 100.4, 91.2, 77.6, 76.9, 76.8, 75.6, 72.9, 71.7, 69.2, 56.7, 52.3, 50.7, 47.8, 41.2, 39.6, 37.4, 37.1, 33.8, 33.5, 33.0, 29.9, 29.2, 28.4, 27.6, 24.8, 21.8, 21.0, 17.8, 17.2, 15.1, 13.5, 13.0, 12.7, 11.1, 7.1, 6.9. HRMS (ESI) calcd for $C_{49}H_{74}FNNaO_{11}^{+}$([M+H]$^+$), 894.5138; found, 894.5117.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 36** was prepared from amine **4** and 2,4-difluorobenzoyl chloride by following the general procedure for amides with a 49% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.07 (m, 1H), 7.02–6.93 (m, 1H), 6.87–6.77 (m, 1H), 6.51–6.40 (m, 1H), 6.41–6.30 (m, 1H), 6.24 (dd, J = 10.5, 6.0 Hz, 1H). 4.90–4.76 (m, 1H), 4.45–4.34 (m, 1H), 4.29–4.18 (m, 1H), 3.98–3.86 (m, 1H), 3.76–3.59 (m, 2H), 3.45–3.35 (m, 1H), 2.90–2.79 (m, 1H), 2.75–2.58 (m, 2H), 2.35–2.23 (m, 1H), 2.14–0.64 (m, 55H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.79 (d, J = 11.1 Hz), −112.38 (d, J = 10.9 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ 219.5, 186.0, 166.3 (dd, J = 253.8, 13.0 Hz), 164.3, 162.23 (dd, J = 249.9, 12.4 Hz), 134.3 (m), 127.6, 126.1, 119.1 (dd, J = 12.5, 3.7 Hz), 113.4 (dd, J = 21.8, 3.2 Hz), 109.6, 105.4 (m), 100.5, 91.2, 77.7, 76.94, 76.88, 75.7, 73.0, 71.8, 69.3, 56.8, 52.4, 50.8, 48.0, 41.3, 39.6, 37.4, 37.1, 33.8, 33.5, 33.0, 29.9, 29.3, 28.4, 27.7, 24.9, 21.8, 21.0, 17.8, 17.13, 17.09, 15.1, 13.4, 13.1, 12.6, 11.1, 7.1, 6.9. HRMS (ESI) calcd for $C_{49}H_{73}F_2NNaO_{11}^{+}$ ([M+H]$^+$), 912.5044; found, 912.5015.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 37** was prepared from amine **4** and 2,6-dichlorobenzoyl chloride by following the general procedure for amides with a 45% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.34–7.28 (m, 2H), 7.27–7.21 (m, 1H), 6.54–6.15 (m, 2H), 5.62–5.48 (m, 1H), 4.79–4.67 (m, 1H), 4.19–4.11 (m, 1H), 4.01–3.81 (m, 2H), 3.74–3.58 (m, 2H), 2.95–2.81 (m, 1H), 2.81–2.59 (m, 2H), 2.52–2.39 (m, 1H), 2.17–0.62 (m, 56H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 178.2, 163.7, 135.5, 131.9, 130.8, 128.1, 125.8, 125.5, 107.6, 99.0, 89.7, 76.3, 75.7, 74.8, 73.4, 71.5, 71.0, 68.0, 55.8, 49.6, 47.5, 39.7, 38.5, 36.8, 36.2, 32.6, 31.8, 29.6, 27.9, 26.2, 25.4, 22.9, 21.5, 19.9, 17.7, 17.1, 14.3, 13.2, 12.8, 12.1, 10.9, 6.7, 6.4. HRMS (ESI) calcd for $C_{49}H_{73}Cl_2NNaO_{11}^{+}$ ([M+H]$^+$), 944.4453; found, 944.4493.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 38** was prepared from amine **4** and 2-methoxybenzoyl chloride by following the general procedure for amides with a 38% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26–8.16 (m, 1H), 7.84–7.71 (m, 1H), 7.50–7.40 (m, 1H), 7.12–7.01 (m, 1H), 6.99–6.89 (m, 1H), 6.42–6.33 (m, 1H), 6.28 (dd, J = 10.6, 5.7 Hz, 1H), 4.93–4.81 (m, 1H), 4.43–4.34 (m, 1H), 4.26–4.19 (m, 1H), 3.97–3.87 (m, 1H), 3.83 (s, 3H), 3.76–3.55 (m, 2H), 3.45–3.34 (m, 1H), 2.95–2.81 (m, 1H), 2.77–2.59 (m, 2H), 2.38–0.62 (m, 56H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.0, 184.1, 164.8, 157.3, 132.9, 132.6, 126.4, 124.6, 121.2, 120.9, 111.2, 108.5, 98.9, 89.9, 75.8, 75.7, 74.9, 74.2, 71.4, 69.9, 67.2, 55.6, 55.3, 51.0, 50.4, 46.4, 39.9, 38.6, 36.2, 35.9, 32.4, 32.2, 29.6, 28.7, 27.9, 27.6, 26.8, 23.7, 20.6, 19.9, 17.5, 16.9, 16.0, 14.4, 13.2, 12.4, 11.8, 10.6, 6.6, 6.4. HRMS (ESI) calcd for $C_{50}H_{77}NNaO_{12}^+$([M+H]$^+$), 906.5338; found, 906.5381.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 39** was prepared from amine **4** and 2-ethoxybenzoyl chloride by following the general procedure for amides with an 83% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.09 (m, 1H), 7.61–7.53 (m, 1H), 7.45–7.34 (m, 1H), 7.07–7.00 (m, 1H), 6.95–6.88 (m, 1H), 6.39–6.24 (m, 2H), 4.90–4.79 (m, 1H), 4.43–4.32 (m, 1H), 4.28–4.09 (m, 3H), 3.99–3.87 (m, 1H), 3.74–3.58 (m, 2H), 3.45–3.35 (m, 1H), 2.90–2.80 (m, 1H), 2.72–2.61 (m, 2H), 2.49–0.62 (m, 59H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 183.8, 165.1, 156.2, 132.6, 132.3, 126.0, 124.6, 121.6, 120.9, 112.5, 108.3, 98.7, 89.5, 75.7, 75.4, 74.8, 74.0, 71.2, 69.9, 67.1, 64.6, 55.2, 50.8, 50.0, 46.6, 39.6, 38.5, 36.1, 35.7, 32.2, 29.4, 28.5, 27.7, 26.6, 23.5, 20.5, 19.7, 17.3, 16.9, 15.8, 14.5, 14.3, 13.0, 12.2, 11.7, 10.5, 6.5, 6.2. HRMS (ESI) calcd for $C_{51}H_{79}NNaO_{12}^+$([M+H]$^+$), 920.5494; found, 920.5478.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 40** was prepared from amine **4** and 3-methoxybenzoyl chloride by following the general procedure for amides with a 60% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 2H), 7.18–7.10 (m, 1H), 7.05–6.99 (m, 1H), 6.44–6.33 (m, 1H), 6.28 (dd, J = 10.4, 6.0 Hz, 1H), 5.85 (d, J = 9.2 Hz, 1H), 4.83–4.75 (m, 1H), 4.44–4.32 (m, 1H), 4.32–4.19 (m, 1H), 3.98–3.88 (m, 1H), 3.82 (s 3H), 3.75–3.68 (m, 1H), 3.65–3.57 (m, 1H), 3.44–3.32 (m, 1H), 2.97–2.76 (m, 1H), 2.79–2.56 (m, 2H), 2.41–2.21 (m, 1H), 2.17–0.63 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.0, 166.1, 159.7, 135.4, 129.5, 126.1, 125.3, 118.0, 111.9, 108.2, 99.0, 90.0, 75.8, 75.6, 74.9, 74.2, 71.3, 69.6, 67.1, 55.2, 55.1, 51.0, 50.4, 46.4, 39.8, 38.4, 36.0, 35.8, 32.4, 32.2, 29.6, 28.8, 27.8, 27.6, 26.8, 23.7, 20.4, 19.8, 17.4, 17.1, 16.0, 14.5, 13.1, 12.4, 11.7, 10.5, 6.6, 6.4. HRMS (ESI) calcd for $C_{50}H_{77}NNaO_{12}^+$([M+H]$^+$), 906.5338; found, 906.5361.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 41** was prepared from amine **4** and 4-methoxybenzoyl chloride by following the general procedure for amides with a 65% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.44–6.32 (m, 1H), 6.27 (dd, J = 10.5, 6.0 Hz, 1H), 5.75 (d, J = 9.2 Hz, 1H), 4.85–4.70 (m, 1H), 4.43–4.33 (m, 1H), 4.28–4.18 (m, 1H), 3.98–3.88 (m, 1H), 3.84 (s, 3H), 3.75–3.68 (m, 1H), 3.66–3.59 (m, 1H), 3.43–3.33 (m, 1H), 2.90–2.80 (m, 1H), 2.75–2.59 (m, 2H), 2.36–2.24 (m, 1H), 2.14–0.64 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 184.3, 166.0, 162.2, 128.5, 126.2, 125.9, 125.1, 113.7, 108.3, 98.9, 89.9, 75.7, 74.9, 74.1, 71.3, 70.0, 67.1, 55.3, 55.1, 50.9, 50.2, 46.3, 39.7, 38.4, 36.0, 35.8, 32.4, 29.5, 28.6, 27.8, 27.6, 26.7, 23.7, 20.5, 19.8, 17.4, 17.1, 16.0, 14.4, 13.1, 12.3, 11.7, 10.5, 6.6, 6.3. HRMS (ESI) calcd for $C_{50}H_{77}NNaO_{12}^+$([M+H]$^+$), 906.5338; found, 906.5350.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 42** was prepared from amine **4** and 4-(methylthio)benzoyl chloride by following the general procedure for amides with a 67% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.41–6.33 (m, 1H), 6.27 (dd, J = 10.5, 6.0 Hz, 1H), 5.77 (d, J = 9.3 Hz, 1H), 4.82–4.73 (m, 1H), 4.43–4.32 (m, 1H), 4.28–4.21 (m, 1H), 3.99–3.88 (m, 1H), 3.76–3.68 (m, 1H), 3.68–3.58 (m, 1H), 3.41–3.36 (m, 1H), 2.89–2.79 (m, 1H), 2.76–2.58 (m, 2H), 2.49 (s, 3H), 2.36–0.65 (m, 56H). ^{13}C NMR (100 MHz, CD_3OD) δ 219.4, 185.9, 169.2, 145.8, 131.1, 128.6, 127.4, 126.6, 126.3, 109.9, 100.4, 90.9, 77.7, 76.9, 75.6, 73.0, 71.8, 69.2, 56.7, 52.4, 50.7, 48.2, 41.2, 39.6, 37.1, 37.0, 33.8, 33.5, 33.0, 29.9, 29.3, 28.3, 27.6, 24.8, 21.8, 21.0, 17.8, 17.4, 17.1, 15.1, 14.8, 13.5, 13.0, 12.7, 11.1, 7.1, 6.9. HRMS (ESI) calcd for $C_{50}H_{77}NNaO_{11}S^+$ ([M+H]$^+$), 922.5110; found, 922.5141.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 43** was prepared from amine **4** and 4-(trifluoromethoxy)benzoyl chloride by following the general procedure for s with a 54% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.8 Hz, 2H), 7.26–7.23 (m, 2H), 6.43–6.35 (m, 1H), 6.27 (dd, J = 10.5, 6.0 Hz, 1H), 5.79 (d, J = 9.3 Hz, 1H), 4.82–4.75 (m, 1H), 4.44–4.33 (m, 1H), 4.28–4.19 (m, 1H), 3.99–3.87 (m, 1H), 3.78–3.68 (m, 1H), 3.66–3.59 (m, 1H), 3.48–3.35 (m, 1H), 2.90–2.78 (m, 1H), 2.77–2.60 (m, 2H), 2.36–2.22 (m, 1H), 2.16–0.64 (m, 55H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.97. ^{13}C NMR (100 MHz, CD_3OD) δ 218.2, 183.5, 168.6, 152.8, 134.4, 130.6, 127.9, 127.3, 121.8, 121.7 (q, J = 255 Hz), 110.0, 100.5, 90.3, 78.1, 77.5, 76.7, 75.2, 73.0, 71.8, 69.6, 58.2, 56.9, 51.5, 50.2, 49.1, 40.9, 39.7, 37.2, 36.6, 34.0, 33.3, 32.8, 30.8, 30.2, 29.3, 27.5, 27.2, 24.4, 22.0, 20.9, 18.2, 17.8, 17.1, 15.1, 13.5, 13.3, 12.7, 11.3, 7.4, 6.8. HRMS (ESI) calcd for $C_{50}H_{74}F_3NNaO_{12}^+$([M+H]$^+$), 960.5055; found, 960.5099.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 44** was prepared from amine **4** and benzo[*d*] [1,3]dioxole-5-carbonyl chloride by following the general procedure for amides with a 63% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.11 (m, 2H), 6.83–6.76 (m, 1H), 6.44–6.33 (m, 1H), 6.26 (dd, J = 10.5, 6.0 Hz, 1H), 6.02 (s, 2H), 5.69 (d, J = 9.1 Hz, 1H), 4.80–4.67 (m, 1H), 4.45–4.32 (m, 1H), 4.30–4.18 (m, 1H), 3.99–3.85 (m, 1H), 3.77–3.57 (m, 2H), 3.43–3.32 (m, 1H), 2.91–2.78 (m, 1H), 2.74–2.58 (m, 2H), 2.43–2.23 (m, 1H), 2.14–0.61 (m, 55H). ^{13}C NMR (100 MHz, CD_3OD) δ 218.2, 183.5, 168.9, 152.2, 149.4, 129.2, 128.0, 127.1, 123.1, 110.0, 109.0, 108.5, 103.3, 100.4, 90.3, 78.0, 77.5, 76.7, 75.2, 73.0, 71.9, 69.6, 57.0, 51.4, 50.2, 40.9, 39.6, 37.2, 36.7, 34.0, 33.2, 32.8, 30.2, 29.3, 27.4, 27.2, 24.4, 22.0, 20.9, 18.2, 17.8, 17.2, 15.1, 13.5, 13.2, 12.8, 11.3, 7.4, 6.8. HRMS (ESI) calcd for $C_{50}H_{75}NNaO_{13}^+$([M+H]$^+$), 920.5131; found, 920.5100.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 45** was prepared from amine **4** and 3-cyanobenzoyl chloride by following the general procedure for amides with a 65% yield as white amorphous solid, except that Et_3N was used instead of DMAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.02 (m, 1H), 8.00–7.94 (m, 1H), 7.82–7.75 (m, 1H), 7.62–7.54 (m, 1H), 7.05 (d, J = 3.4 Hz, 1H), 6.17 (dd, J = 10.1, 2.0 Hz, 1H), 5.54 (dd, J = 10.1, 2.5 Hz, 1H), 4.55–4.48 (m, 1H), 4.10–4.00 (m, 2H), 3.79–3.71 (m, 1H), 3.67–3.61 (m, 1H), 3.55–3.48 (m, 1H), 3.47–3.40 (m, 1H), 3.12–3.03 (m, 1H), 2.96–2.87 (m, 1H), 2.78–2.64 (m, 2H), 2.38–2.30 (m, 1H), 2.13–2.01 (m, 1H), 1.99–0.61 (m, 53H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 177.8, 166.9, 136.8, 134.5, 131.3, 131.1, 129.4, 128.5, 117.8, 112.8, 107.6, 99.8, 87.4, 76.6, 76.1, 75.1, 74.6, 71.7, 71.4, 68.5, 56.8, 51.8, 49.2, 49.0, 38.6, 36.5, 35.9, 33.3, 32.0, 30.9, 30.4, 29.6, 29.4, 27.9, 26.4, 26.1, 22.4, 22.0, 21.1, 19.5, 18.2, 15.7, 13.8, 13.6, 13.0, 12.0, 10.7, 7.0, 6.3. HRMS (ESI) calcd for $C_{50}H_{74}N_2NaO_{11}^+$ ([M+H]$^+$), 901.5185; found, 901.5159.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 46** was prepared from amine **4** and 4-cyanobenzoyl chloride by following the general procedure for amides with a 47% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.76 (m, 2H), 7.76–7.70 (m, 2H), 6.40–6.31 (m, 1H), 6.21 (dd, J = 10.4, 5.6 Hz, 1H), 6.14 (d, J = 9.0 Hz, 1H), 4.81–4.68 (m, 1H), 4.20–4.13 (m, 1H), 4.02–3.92 (m, 1H), 3.93–3.83 (m, 2H), 3.70–3.59 (m, 2H), 2.94–2.83 (m, 1H), 2.76–2.61 (m, 2H), 2.32–2.22 (m, 1H), 2.13–0.66 (m, 55H). ^{13}C NMR (100 MHz, CD_3OD) δ 218.3, 168.4, 139.7, 133.6,

129.3, 127.6, 127.4, 118.9, 116.2, 109.9, 100.4, 90.3, 78.2, 77.5, 76.7, 75.2, 73.0, 71.9, 69.6, 58.3, 57.0, 51.4, 50.2, 40.9, 39.7, 37.2, 36.7, 34.0, 33.2, 32.8, 30.3, 29.4, 27.4, 27.1, 24.3, 22.0, 20.9, 18.4, 18.3, 17.8, 17.1, 15.1, 13.4, 13.3, 12.7, 11.3, 7.4, 6.8. HRMS (ESI) calcd for $C_{50}H_{74}N_2NaO_{11}^+$ ([M+H]$^+$), 901.5185; found, 901.5200.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 47** was prepared from amine **4** and 4-nitrobenzoyl chloride by following the general procedure for amides with a 64% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 6.46–6.37 (m, 1H), 6.29 (dd, J = 10.4, 5.9 Hz, 1H), 5.89 (d, J = 9.3 Hz, 1H), 4.91–4.77 (m, 1H), 4.46–4.31 (m, 1H), 4.29–4.19 (m, 1H), 4.02–3.85 (m, 1H), 3.75–3.56 (m, 2H), 3.48–3.36 (m, 1H), 2.90–2.79 (m, 1H), 2.75–2.61 (m, 2H), 2.42–0.63 (m, 56H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.2, 164.5, 149.4, 139.5, 127.8, 125.7, 123.7, 107.9, 98.9, 89.9, 75.8, 75.4, 75.1, 74.0, 71.2, 69.9, 67.2, 55.1, 50.8, 50.0, 46.9, 39.6, 38.3, 36.0, 35.8, 32.3, 29.4, 28.7, 27.8, 27.5, 26.6, 23.5, 20.6, 19.7, 17.3, 17.0, 15.9, 14.3, 13.0, 12.2, 11.7, 10.5, 6.5, 6.2. HRMS (ESI) calcd for $C_{49}H_{74}N_2NaO_{13}^+$([M+H]$^+$), 921.5083; found, 921.5075.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 48** was prepared from amine **4** and methyl 4-(chlorocarbonyl)benzoate by following the general procedure for amides with a 60% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 6.43–6.36 (m, 1H), 6.29 (dd, J = 10.4, 5.9 Hz, 1H), 5.87 (d, J = 9.3 Hz, 1H), 4.88–4.78 (m, 1H), 4.43–4.34 (m, 1H), 4.26–4.20 (m, 1H), 3.96–3.85 (m, 4H), 3.74–3.67 (m, 1H), 3.67–3.58 (m, 1H), 3.46–3.36 (m, 1H), 2.91–2.80 (m, 1H), 2.76–2.60 (m, 2H), 2.37–0.63 (m, 56H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.0, 165.7, 165.5, 137.7, 132.7, 129.7, 126.6, 125.8, 125.4, 108.0, 98.9, 89.9, 75.8, 75.5, 74.9, 74.0, 71.2, 69.8, 67.1, 55.1, 52.1, 50.8, 50.1, 46.6, 39.6, 38.3, 36.0, 35.7, 32.3, 32.0, 29.4, 28.6, 27.7, 27.4, 26.6, 23.5, 20.4, 19.7, 17.3, 17.0, 15.9, 14.3, 13.0, 12.2, 11.7, 10.4, 6.5, 6.2. HRMS (ESI) calcd for $C_{51}H_{77}NNaO_{13}^+$ ([M+H]$^+$), 934.5287; found, 934.5241.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 49** was prepared from amine **4** and 2-naphthoyl chloride by following the general procedure for amides with a 71% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26–8.16 (m, 1H), 7.91–7.82 (m, 3H), 7.77–7.65 (m, 1H), 7.58–7.49 (m, 2H), 6.45–6.38 (m, 1H), 6.38–6.28 (m, 1H), 6.00 (d, J = 9.1 Hz, 1H), 4.94–4.81 (m, 1H), 4.45–4.34 (m, 1H), 4.29–4.20 (m, 1H), 4.00–3.86 (m, 1H), 3.78–3.57 (m, 2H), 3.47–3.33 (m, 1H), 2.92–0.56 (m, 59H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 184.2, 166.5, 134.7, 132.5, 131.1, 128.8, 128.5, 127.7, 127.6, 127.5, 126.8, 126.3, 125.3, 123.0, 108.3, 99.0, 90.0, 75.9, 75.6, 75.0, 74.1, 71.4, 70.0, 67.3, 55.3, 51.0, 50.3, 46.6, 39.8, 38.5, 36.2, 35.9, 32.4, 29.6, 28.7, 27.9, 26.7, 23.7, 20.6, 19.9, 17.5, 17.2, 16.1, 14.4, 13.1, 12.4, 11.8, 10.6, 6.6, 6.4. HRMS (ESI) calcd for $C_{53}H_{77}NNaO_{11}^+$([M+H]$^+$), 926.5389; found, 926.5320.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 50** was prepared from amine **4** and furan-2-carbonyl chloride by following the general procedure for amides with a 76% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.37 (m, 1H), 7.11 (d, J = 3.1 Hz, 1H), 6.53–6.45 (m, 1H), 6.42–6.32 (m, 1H), 6.29–6.18 (m, 1H), 6.10 (d, J = 9.4 Hz, 1H), 4.79–4.64 (m, 1H), 4.42–4.30 (m, 1H), 4.27–4.17 (m, 1H), 4.00–3.85 (m, 1H), 3.75–3.57 (m, 2H), 3.44–3.32 (m, 1H), 2.90–2.81 (m, 1H), 2.73–2.63 (m, 2H), 2.32–2.22 (m, 1H), 2.12–0.65 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 183.8, 157.4, 147.2, 144.0, 125.8, 125.3, 114.6, 112.0, 108.0, 98.9, 89.9, 75.7, 75.4, 74.8, 74.0, 71.2, 69.7, 67.1, 55.1, 50.7, 50.2, 45.6, 39.6, 38.4, 36.0, 35.7, 32.2, 29.4, 28.6, 27.7, 27.4, 26.6, 23.5, 20.3, 19.7, 17.3, 16.8, 15.9, 14.3, 13.0, 12.2, 11.6, 10.5, 6.5, 6.2. HRMS (ESI) calcd for $C_{47}H_{73}NNaO_{12}^+$ ([M+H]$^+$), 866.5025; found, 866.4998.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 51** was prepared from amine **4** and thiophene-2-carbonyl chloride by following the general procedure for amides with a 73% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 5.0, 0.9 Hz, 1H), 7.44–7.36 (m, 1H), 7.11–7.03 (m, 1H), 6.42–6.16 (m, 2H), 5.78 (dd, J = 76.5, 9.1 Hz, 1H), 4.77–4.64 (m, 1H), 4.41–4.11 (m, 2H), 4.07–3.87 (m, 2H), 3.76–3.60 (m, 2H), 3.45–3.33 (m, 1H), 2.92–2.58 (m, 3H), 2.38–2.24 (m, 1H), 2.13–0.63 (m, 54H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.1, 160.8, 138.1, 130.1, 128.0, 127.6, 126.1, 125.3, 108.0, 98.9, 89.9, 75.9, 75.4, 75.0, 73.9, 71.2, 69.9, 67.3, 55.2, 50.8, 50.1, 46.4, 39.7, 38.4, 36.1, 35.9, 32.4, 29.5, 28.7, 27.8, 26.5, 23.5, 20.4, 19.7, 17.4, 17.0, 16.0, 14.3, 13.0, 12.2, 11.8, 10.6, 6.5, 6.3. HRMS (ESI) calcd for $C_{47}H_{73}NNaO_{11}S^+$([M+H]$^+$), 882.4797; found, 882.4768.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 52** was prepared from amine **4** and thiophene-3-carbonyl chloride by following the general procedure for amides with a 67% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 1H), 7.35–7.31 (m, 1H), 7.30–7.27 (m, 1H), 6.36–6.28 (m, 1H), 6.20 (dd, J = 10.5, 5.7 Hz, 1H), 5.91 (d, J = 9.2 Hz, 1H), 4.78–4.68 (m, 1H), 4.21–4.12 (m, 1H), 4.01–3.84 (m, 3H), 3.68–3.58 (m, 2H), 2.93–2.81 (m, 2H), 2.78–2.60 (m, 3H), 2.36–2.27 (m, 1H), 2.12–0.63 (m, 53H). ^{13}C NMR (100 MHz, CD_3OD) δ 218.0, 183.0, 165.2, 137.9, 130.2, 128.4, 127.9, 127.3, 127.2, 110.2, 100.6, 90.2, 78.5, 77.6, 76.7, 75.1, 73.1, 72.0, 69.8, 58.3, 57.1, 51.3, 50.1, 40.9, 39.7, 37.3, 36.6, 34.1, 33.2, 32.8, 30.4, 29.4, 27.4, 26.7, 24.3, 22.0, 20.9, 18.6, 17.8, 17.1, 15.1, 13.4, 12.6, 11.3, 7.4, 6.8. HRMS (ESI) calcd for $C_{47}H_{73}NNaO_{11}S^+$ ([M+H]$^+$), 882.4797; found, 882.4819.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 53** was prepared from amine **4** and nicotinoyl chloride hydrochloride by following the general procedure for amides with a 36% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92–8.81 (m, 1H), 8.76–8.67 (m, 1H), 8.14–8.01 (m, 1H), 7.48–7.36 (m, 1H), 6.47–6.34 (m, 1H), 6.33–6.20 (m, 1H), 5.94–5.78 (m, 1H), 4.85–4.72 (m, 1H), 4.44–4.34 (m, 1H), 4.28–4.17 (m, 1H), 4.01–3.87 (m, 1H), 3.76–3.60 (m, 2H), 3.45–3.36 (m, 1H), 2.94–2.59 (m, 3H), 2.36–2.24 (m, 1H), 2.13–0.63 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.0, 184.2, 164.5, 152.4, 147.3, 135.2, 129.7, 125.9, 125.7, 123.6, 108.1, 99.1, 90.1, 75.9, 75.7, 75.0, 74.2, 71.4, 69.8, 67.2, 55.2, 51.0, 50.3, 46.6, 39.7, 38.4, 36.1, 35.8, 32.4, 32.2, 29.6, 28.8, 27.9, 27.7, 26.8, 23.7, 20.5, 19.9, 17.4, 17.2, 16.0, 14.5, 13.1, 12.4, 11.8, 10.6, 6.6, 6.4. HRMS (ESI) calcd for $C_{48}H_{74}N_2NaO_{11}^+$ ([M+H]$^+$), 877.5185; found, 877.5143.

***C20-(S)-N*-acyl-salinomycin sodium salt derivative 54** was prepared from amine **4** and 2-(methylthio)nicotinoyl chloride by following the general procedure for amides with a 51% yield as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53–8.45 (m, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 7.6, 4.8 Hz, 1H), 6.45–6.32 (m, 1H), 6.25 (dd, J = 10.4, 5.9 Hz, 1H), 6.11 (d, J = 9.1 Hz, 1H), 4.88–4.75 (m, 1H), 4.44–4.33 (m, 1H), 4.30–4.20 (m, 1H), 4.00–3.86 (m, 1H), 3.77–3.68 (m, 1H), 3.65–3.57 (m, 1H), 3.48–3.30 (m, 1H), 2.94–2.80 (m, 1H), 2.75–2.60 (m, 2H), 2.55 (s, 3H), 2.41–2.27 (m, 1H), 2.22–0.65 (m, 55H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 184.0, 165.6, 156.5, 150.5, 136.5, 129.2, 125.6, 118.8, 108.1, 99.0, 89.9, 75.9, 75.6, 75.0, 74.3, 71.2, 69.7, 67.1, 55.2, 51.0, 50.2, 46.7, 39.9, 38.6, 36.9, 36.3, 35.8, 32.6, 32.3, 32.2, 31.8, 29.9, 29.6, 29.2, 28.8, 27.8, 27.6, 26.9, 26.8, 23.8, 22.5, 20.5, 19.8, 19.6, 17.4 16.9, 15.9, 14.4, 14.0, 13.4, 13.1, 12.4, 11.7, 10.5, 6.6, 6.3. HRMS (ESI) calcd for $C_{49}H_{76}N_2NaO_{11}S^+$ ([M+H]$^+$), 923.5062; found, 923.5089.

4.2. Cell cytotoxicity assay

4T1, HL-60, A549, HeLa, MCF-7, SW480 and SMMC-7721 were used to test the cytotoxicity of the library compounds. Cells were plated at a density of 3–15 × 10^3 cells/well into 96-well plates and cultured in DMEM or RPMI-1640 media supplemented with 10% fetal bovine serum. The cells were allowed to attach to the wells for 24 h at 37 °C, 5% CO_2. Then the cells were incubated with different concentrations of the compounds (100 μL) for 48 h. After that, each

well was added 20 μL of MTS reagent and incubated for 4 h. The OD at 492 nm of the solution were read with a microplate reader (MULTISKAN FC).

4.3. K-ras on and off cell model

The doxycycline inducible T-Rex/K-RasG12V cells were cultured in DMEM media supplemented with 10% tetracycline-free FBS. 2.5×10^3 cells/well were seeded in triplicate in 96-well plates. After 24 h of incubation, the cells activated by doxycycline (K-ras on) or not (K-ras off) were exposed to various concentrations of compounds respectively for 72 h. At the end of the incubation, 20 μL of MTT reagent was added to each well and incubated at 37 °C for 4 h. After removal of the culture medium, 200 μL DMSO was added to each well to dissolve the formazan precipitates. The OD was measured at 570 nm with a microplate reader (Bio-Rad Laboratories, Hercules, CA, USA). The IC_{50} values were listed in Table S2.

Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejmech.2018.02.004.

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