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PII: S0223-5234(19)30139-4

DOI: https://doi.org/10.1016/j.ejmech.2019.02.025

Reference: EJMECH 11117

To appear in: *European Journal of Medicinal Chemistry*

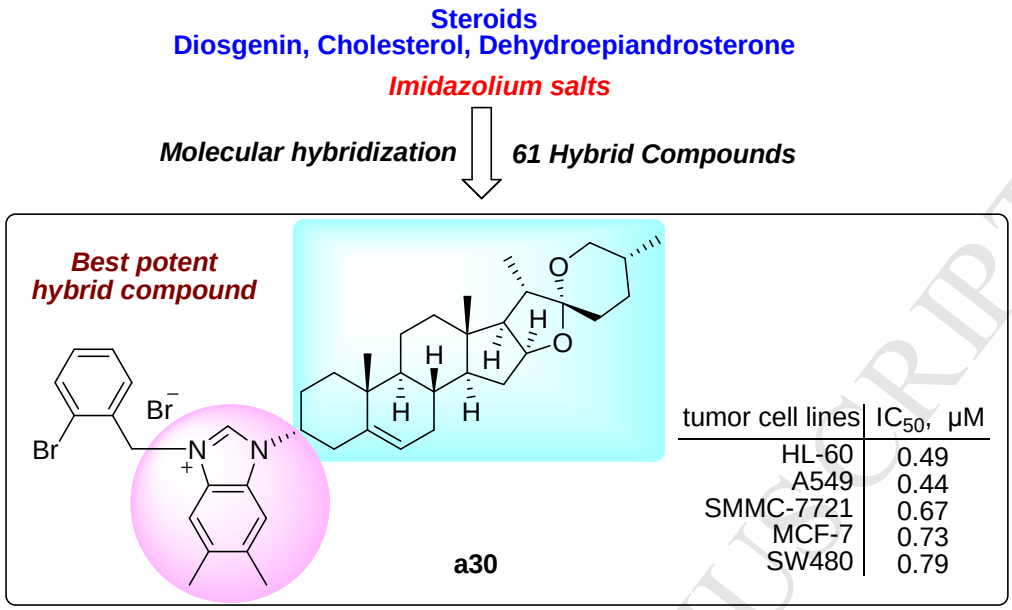
Received Date: 11 December 2018

Revised Date: 25 January 2019

Accepted Date: 8 February 2019

Please cite this article as: G. Deng, B. Zhou, J. Wang, Z. Chen, L. Gong, Y. Gong, D. Wu, Y. Li, H. Zhang, X. Yang, Synthesis and antitumor activity of novel steroidal imidazolium salt derivatives, *European Journal of Medicinal Chemistry* (2019), doi: https://doi.org/10.1016/j.ejmech.2019.02.025.

Graphical abstract



Synthesis and antitumor activity of novel steroidal imidazolium salt derivatives

Guogang Deng[a], Bei Zhou[a,c], Jing Wang[a], Zhuo Chen[a], Liang Gong[b], Yaxiao Gong[b], Dongmei Wu[b], Yan Li[b,]*, Hongbin Zhang[a,]*, Xiaodong Yang[a,]*

[a]*Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education and Yunnan Province, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China.*

[b]*State Key Laboratory for Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Science, Kunming, 650204, P. R. China.*

[c]*Key Laboratory for Forest Resources Conservation and Utilisation in the Southwest Mountains of China, Ministry of Education, Southwest Forestry University, Kunming, China*

* Corresponding author. Tel.: +86-871-65031119; fax.: +86-871-65035538. *E-mail*: xdyang@ynu.edu.cn (X. Yang); zhanghb@ynu.edu.cn (H. Zhang); liyanb@mail.kib.ac.cn (Y. Li)

Abstract—Sixty-one novel steroidal imidazolium salt derivatives were synthesized and evaluated *in vitro* against a panel of human tumor cell lines. The results showed that diosgenin–imidazolium salt derivatives displayed much higher cytotoxic activities than cholesterol–imidazolium salts and dehydroepiandrosterone–imidazolium salts. The SARs results suggested that the existence of substituted 5,6-dimethyl-benzimidazoles or benzimidazole ring and substitution of the imidazolyl-3α-position with a 2-bromobenzyl or 2-naphthylmethyl group could be critical for promoting cytotoxic activity. Diosgenin–imidazolium salt **a30** was found to be the most potent compound with IC_{50} values of 0.44–0.79 μM against five human tumor cell lines. Compound **a24** showed inhibitory activity selectively against SMMC-7721 cell lines with IC_{50} value of 0.21 μM and 54-fold more sensitive to DDP. Moreover, compound **a30** inhibited cell proliferation through inducing the G0/G1 cell cycle arrest and apoptosis in SMMC-7721 cells.

Keywords: Diosgenin; Cholesterol; Dehydroepiandrosterone; Imidazolium salt; Antitumor activities; Structure–activity relationships.

1. Introduction

Steroids are an important family of polycyclic molecules with diverse structures, which are widely existed in plants, animals and humans.[1, 2] Naturally occurring steroids exhibit a wide range of interesting biological activities. They have been traditionally used as physiological regulators and hormones, as well as antitumour, cardiotonic, diuretic and local anaesthetic agents.[3-6] Steroid-based drugs possess a broad range of clinical treatments and remain one of the highest marketed classes of pharmaceuticals.[7] Recently, the structurally modified steroids have attracted a great deal of attention, particularly the incorporation of heterocycles into the steroid core.[8, 9] As shown in Fig. 1, steroidal pyridine Abiraterone has been used for the clinical therapeutics of advanced prostate cancers[10], while steroidal spiro aminooxazoline (SSA) was prepared as potential antiproliferative drug against human breast and colon carcinoma cells (T-47D and WiDr).[8]

On the other hand, *N*-heterocycles are of great interest to medicinal chemists because of their widespread occurrence in active natural products and drug molecules.[10-14] Of them, imidazolium salts have obtained

significant concerns owing to their important and extensive biological and pharmacological activities,[15-19] particularly antitumor activity.[20-23] For instance, two novel imidazolium salts, Lepidiline A and B (Fig. 1), presented effective cytotoxic activity against human tumor cell lines (UMUC3, PACA2, MDA231, and FDIGROV).[24] In this context, our group has long been devoted to the synthesis of novel imidazolium salt derivatives and their potential antitumor activity, aiming to discover new steroid-based antitumor agents.[25-30] One representative example is the imidazolium salt NMIB (Fig. 1) which exerts potent *in vitro* and *in vivo* antitumor activity.[31, 32] Further mechanism research verified that these imidazolium salt derivatives induced the cell cycle arrest and apoptosis in tumor cells.[33-35] In previous structure-activity relationships (SARs) studies, we found that the existence of substituted benzimidazole (such as 5,6-dimethyl-benzimidazole) ring and substitution of the imidazolyl-3-position with a substituted benzyl or phenacyl group (such as 2-bromobenzyl or 2-naphthylacyl) could be vital for antitumor activity, which provides the valuable information for further rational design and synthesis of imidazolium salts.

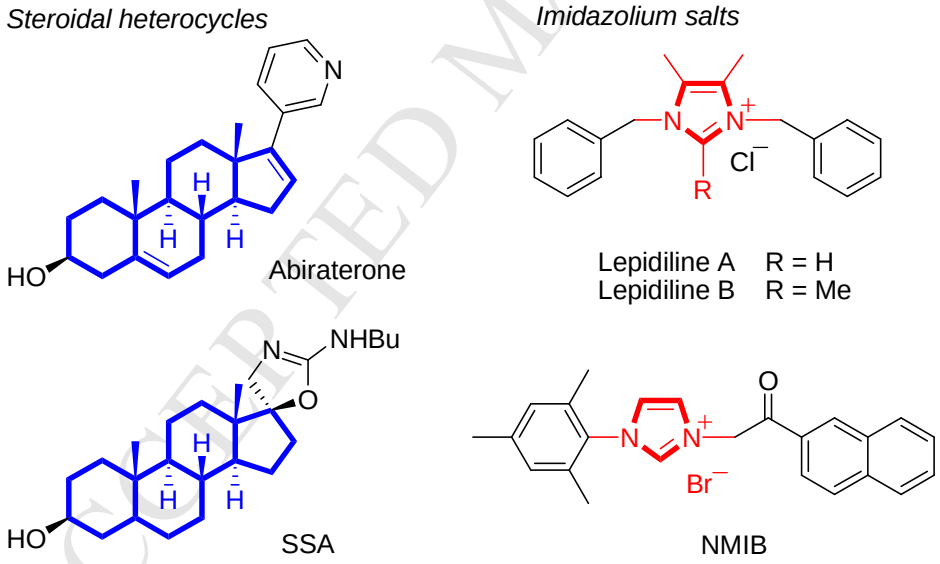


Fig. 1 Representative structures of antitumour activity steroidal derivatives and imidazolium salts.

Molecular hybridization has played an important role in drug discovery during the past two decades. Thus, it is clear that new pharmacologically interesting hybrid compounds will directly benefit the pharmaceutical industry.[36-39] In view of the potential anticancer activity of steroidal derivatives and imidazolium salts, we

launched the synthesis of hybridizing compounds bearing steroidal moieties and imidazolium salts. Although 17-(1-benzimidazole) substituted steroidal derivative was prepared and found to display anticancer activity,[40] and some steroidal derivatives bearing substituted pyrazoles and triazoles pyrazoles and triazoles were synthesized as neuroactive steroids,[41] to the best of our knowledge, no reports regarding synthesis and biological activity for steroidal imidazolium salt hybrid derivatives have been reported. With this in mind, we turned our attention to synthesis and antitumor activity of a series of novel steroidal imidazolium salt derivatives and report our results herein.

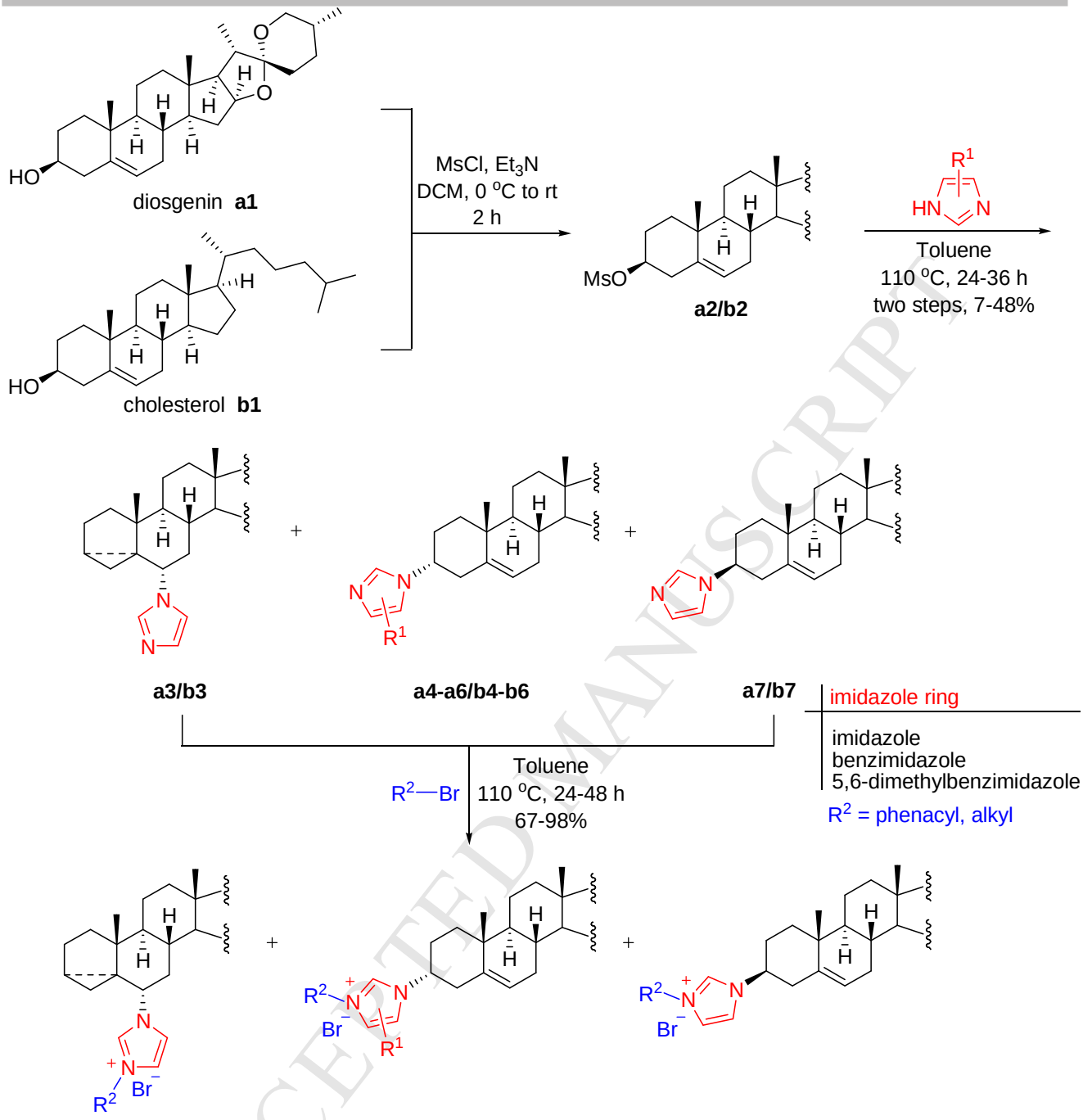
2. Results and discussion

2.1 Chemistry

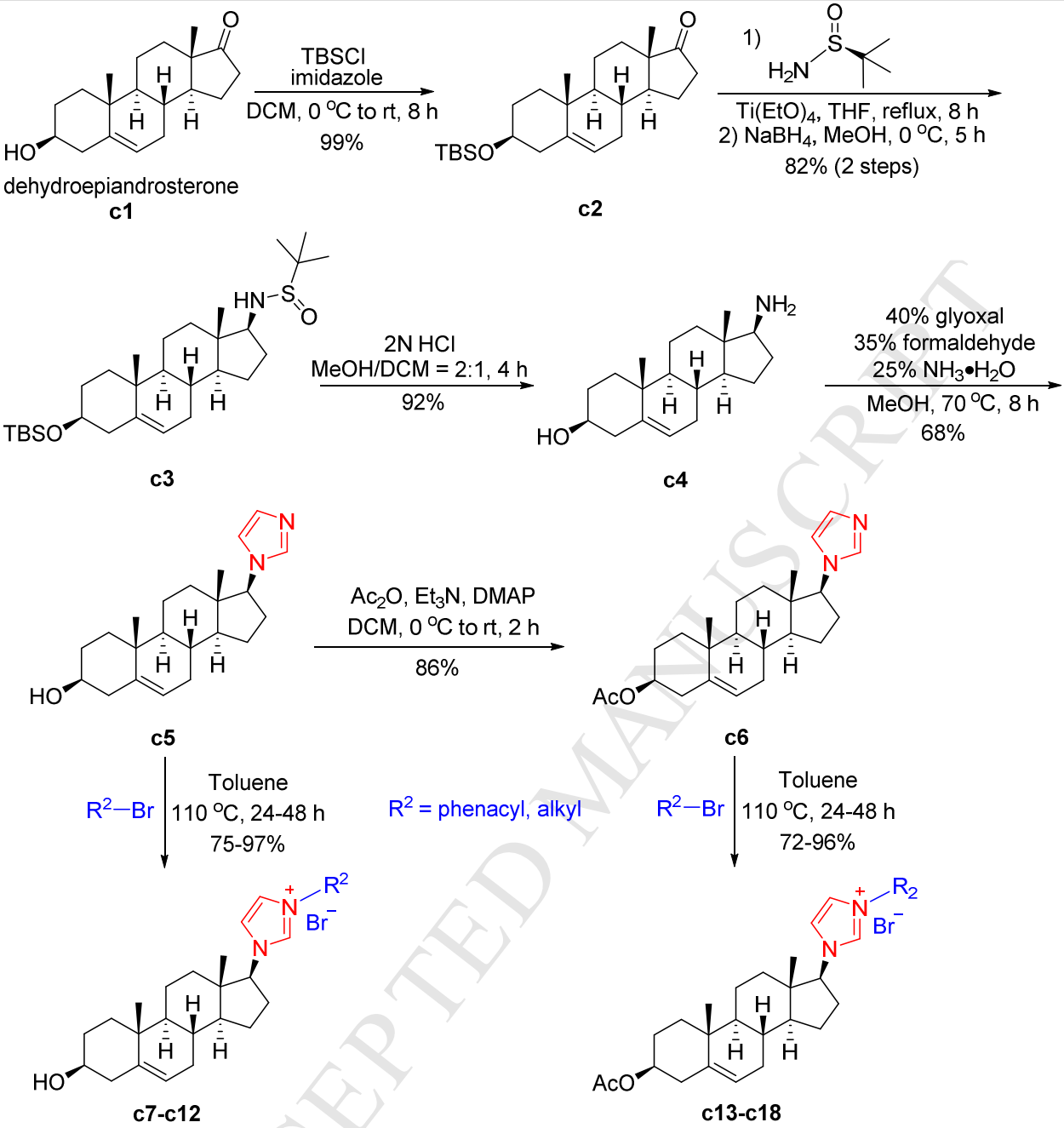
To synthesize the steroidal imidazolium salts, we used various substituted imidazole derivatives that were alkylated with activated 3-hydroxyl steroids, which were synthesized from abundant steroids (diosgenin, cholesterol and dehydroepiandrosterone) in nature. As shown in Scheme 1, commercially available steroids diosgenin **a1** or cholesterol **b1** was transformed via the mesylate derivatives (**a2/b2**) to give the respective 6α-imidazolyl steroidal derivative (**a3/b3**), 3α-imidazolyl steroidal derivative (**a4-a6/b4-b6**) and 3β-imidazolyl steroidal derivative (**a7/b7**) by refluxing with various substituted imidazole (imidazole, benzimidazole or 5,6-dimethyl-benzimidazole) under toluene with 7-48% yields (two steps). The nucleophilic substitution reactions generally led to three stereoisomers products. Major product was 6α-imidazolyl steroidal product (such as **a3/b3**, 42%/48%), and minor products were 3α-imidazolyl steroidal product (such as **a4/b4**, 15%/18%) and 3β-imidazolyl steroidal product (such as **a7/b7**, 8%/7%). Thus, some stereoisomers (3α- or 3β-imidazolyl steroidal derivative) were synthesized in relatively larger quantities. Finally, forty-nine diosgenin–imidazolium salt derivatives **a8-a35** and cholesterol–imidazolium salt derivatives **b8-b28** were synthesized from coupling of imidazolyl substituted steroidal derivatives (**a3-a7/b3-b7**) with various alkyl and phenacyl bromides at excellent yields (67–98%).

As shown in Scheme 2, after 3β-OH group was protected with *tert*-butyl(dimethyl)silyl of commercial steroid dehydroepiandrosterone **c1**, treatment of **c2** with (R)-(+)-2-methyl-2-propanesulfinamide in the presence of

tetraethyl titanate led to corresponding imine, then reduction of imine gave the 17β-*tert*-butylsulfinamido derivative **c3** in 82% yield (two steps). Subsequently, acid mediated deprotection of *N*-*tert*-butanesulfinyl and OH group yielded amine **c4** in 92% yield. Based on our previous synthetic method,[42] an imidazole ring were installed at C-17 to give key intermediate 17β-imidazolyl steroidal derivative **c5**. 3β-OH group was further protected with acetyl to give 3β-AcO-17β-imidazolyl steroid **c6**. Finally, twelve dehydroepiandrosterone–imidazolium salt derivatives **c7-c12** and **c13-c18** were synthesized from coupling of imidazolyl steroids **c5** and **c6** with various alkyl and phenacyl bromides at 75–97% and 72–96% yields, respectively. The structures and yields of all new steroidal imidazolyl derivative and steroidal imidazolium salt derivatives are shown in Table 1.



Scheme 1 Synthesis of diosgenin– and cholesterol–imidazolium salt derivatives **a8-a35/b8-b28**.



Scheme 2 Synthesis of dehydroepiandrosterone–imidazolium salt derivatives **c7-c18**.

Table 1

Structures and yields of steroidal imidazolyl derivatives and steroidal imidazolium salt derivatives

Entry	Compound No.	Steroid	Imidazole ring	R^2	Molecular formula	Yields (%)
1	**a3**	diosgenin	imidazole	–	$C_{30}H_{44}N_2O_2$	42%
2	**a4**	diosgenin	imidazole	–	$C_{30}H_{44}N_2O_2$	15%
3	**a5**	diosgenin	benzimidazole	–	$C_{34}H_{46}N_2O_2$	9%
4	**a6**	diosgenin	5,6-dimethyl-benzimidazole	–	$C_{36}H_{50}N_2O_2$	10%
5	**a7**	diosgenin	imidazole	–	$C_{30}H_{44}N_2O_2$	8%
6	**b3**	cholesterol	imidazole	–	$C_{30}H_{48}N_2$	48%
7	**b4**	cholesterol	imidazole	–	$C_{30}H_{48}N_2$	18%
8	**b5**	cholesterol	benzimidazole	–	$C_{34}H_{50}N_2$	10%
9	**b6**	cholesterol	5,6-dimethyl-benzimidazole	–	$C_{36}H_{54}N_2$	9%
10	**b7**	cholesterol	imidazole	–	$C_{30}H_{48}N_2$	7%
11	**c5**	dehydroepiandrosterone	imidazole	–	$C_{22}H_{32}N_2O$	68%
12	**c6**	dehydroepiandrosterone	imidazole	–	$C_{24}H_{34}N_2O_2$	86%
13	**a8**	diosgenin	imidazole	phenacyl	$C_{38}H_{51}BrN_2O_3$	93%
14	**a9**	diosgenin	imidazole	4-methoxyphenacyl	$C_{39}H_{53}BrN_2O_4$	92%
15	**a10**	diosgenin	imidazole	3-bromophenacyl	$C_{38}H_{50}Br_2N_2O_3$	97%
16	**a11**	diosgenin	imidazole	2-naphthylacyl	$C_{42}H_{53}BrN_2O_3$	98%
17	**a12**	diosgenin	imidazole	2-bromobenzyl	$C_{37}H_{50}Br_2N_2O_2$	82%
18	**a13**	diosgenin	imidazole	2-naphthylmethyl	$C_{41}H_{53}BrN_2O_2$	75%
19	**a14**	diosgenin	imidazole	phenacyl	$C_{38}H_{51}BrN_2O_3$	72%
20	**a15**	diosgenin	imidazole	4-methoxyphenacyl	$C_{39}H_{53}BrN_2O_4$	83%
21	**a16**	diosgenin	imidazole	3-bromophenacyl	$C_{38}H_{50}Br_2N_2O_3$	73%
22	**a17**	diosgenin	imidazole	2-naphthylacyl	$C_{42}H_{53}BrN_2O_3$	94%
23	**a18**	diosgenin	imidazole	2-bromobenzyl	$C_{37}H_{50}Br_2N_2O_2$	88%
24	**a19**	diosgenin	imidazole	2-naphthylmethyl	$C_{41}H_{53}BrN_2O_2$	90%
25	**a20**	diosgenin	benzimidazole	phenacyl	$C_{42}H_{53}BrN_2O_3$	74%
26	**a21**	diosgenin	benzimidazole	4-methoxyphenacyl	$C_{43}H_{55}BrN_2O_4$	72%
27	**a22**	diosgenin	benzimidazole	3-bromophenacyl	$C_{42}H_{52}Br_2N_2O_3$	79%
28	**a23**	diosgenin	benzimidazole	2-naphthylacyl	$C_{46}H_{55}BrN_2O_3$	90%
29	**a24**	diosgenin	benzimidazole	2-bromobenzyl	$C_{41}H_{52}Br_2N_2O_2$	96%
30	**a25**	diosgenin	benzimidazole	2-naphthylmethyl	$C_{45}H_{55}BrN_2O_2$	87%
31	**a26**	diosgenin	5,6-dimethyl-benzimidazole	phenacyl	$C_{44}H_{57}BrN_2O_3$	79%
32	**a27**	diosgenin	5,6-dimethyl-benzimidazole	4-methoxyphenacyl	$C_{45}H_{59}BrN_2O_4$	72%
33	**a28**	diosgenin	5,6-dimethyl-benzimidazole	3-bromophenacyl	$C_{44}H_{56}Br_2N_2O_3$	86%
34	**a29**	diosgenin	5,6-dimethyl-benzimidazole	2-naphthylacyl	$C_{48}H_{59}BrN_2O_3$	87%
35	**a30**	diosgenin	5,6-dimethyl-benzimidazole	2-bromobenzyl	$C_{42}H_{53}Br_2N_2O_2$	68%
36	**a31**	diosgenin	5,6-dimethyl-benzimidazole	2-naphthylmethyl	$C_{47}H_{59}BrN_2O_2$	94%
37	**a32**	diosgenin	imidazole	phenacyl	$C_{38}H_{51}BrN_2O_3$	69%
38	**a33**	diosgenin	imidazole	4-methoxyphenacyl	$C_{39}H_{53}BrN_2O_4$	92%
39	**a34**	diosgenin	imidazole	2-naphthylacyl	$C_{42}H_{53}BrN_2O_3$	87%
40	**a35**	diosgenin	imidazole	2-bromobenzyl	$C_{37}H_{50}Br_2N_2O_2$	89%

41	**b8**	cholesterol	imidazole	phenacyl	$C_{38}H_{55}BrN_2O$	78%
42	**b9**	cholesterol	imidazole	4-methoxyphenacyl	$C_{39}H_{57}BrN_2O_2$	81%
43	**b10**	cholesterol	imidazole	3-bromophenacyl	$C_{38}H_{54}Br_2N_2O$	78%
44	**b11**	cholesterol	imidazole	2-naphthylacyl	$C_{42}H_{57}BrN_2O$	84%
45	**b12**	cholesterol	imidazole	2-bromobenzyl	$C_{37}H_{54}Br_2N_2$	67%
46	**b13**	cholesterol	imidazole	2-naphthylmethyl	$C_{41}H_{57}BrN_2$	75%
47	**b14**	cholesterol	imidazole	phenacyl	$C_{38}H_{55}BrN_2O$	85%
48	**b15**	cholesterol	imidazole	4-methoxyphenacyl	$C_{39}H_{57}BrN_2O_2$	76%
49	**b16**	cholesterol	imidazole	3-bromophenacyl	$C_{38}H_{54}Br_2N_2O$	79%
50	**b17**	cholesterol	imidazole	2-naphthylacyl	$C_{42}H_{57}BrN_2O$	93%
51	**b18**	cholesterol	imidazole	2-bromobenzyl	$C_{37}H_{54}Br_2N_2$	90%
52	**b19**	cholesterol	benzimidazole	phenacyl	$C_{42}H_{57}BrN_2O$	97%
53	**b20**	cholesterol	benzimidazole	4-methoxyphenacyl	$C_{43}H_{59}BrN_2O_2$	86%
54	**b21**	cholesterol	benzimidazole	2-bromobenzyl	$C_{41}H_{56}Br_2N_2$	78%
55	**b22**	cholesterol	5,6-dimethyl-benzimidazole	phenacyl	$C_{44}H_{61}BrN_2O$	82%
56	**b23**	cholesterol	5,6-dimethyl-benzimidazole	2-bromobenzyl	$C_{43}H_{60}Br_2N_2$	74%
57	**b24**	cholesterol	imidazole	phenacyl	$C_{38}H_{55}BrN_2O$	89%
58	**b25**	cholesterol	imidazole	4-methoxyphenacyl	$C_{39}H_{57}BrN_2O_2$	95%
59	**b26**	cholesterol	imidazole	2-naphthylacyl	$C_{42}H_{57}BrN_2O$	84%
60	**b27**	cholesterol	imidazole	2-bromobenzyl	$C_{37}H_{54}Br_2N_2$	78%
61	**b28**	cholesterol	imidazole	2-naphthylmethyl	$C_{41}H_{57}BrN_2$	72%
62	**c7**	dehydroepiandrosterone	imidazole	phenacyl	$C_{30}H_{39}BrN_2O_2$	75%
63	**c8**	dehydroepiandrosterone	imidazole	4-methoxyphenacyl	$C_{31}H_{41}BrN_2O_3$	89%
64	**c9**	dehydroepiandrosterone	imidazole	3-bromophenacyl	$C_{30}H_{38}Br_2N_2O_2$	89%
65	**c10**	dehydroepiandrosterone	imidazole	2-naphthylacyl	$C_{34}H_{41}BrN_2O_2$	97%
66	**c11**	dehydroepiandrosterone	imidazole	2-bromobenzyl	$C_{29}H_{38}Br_2N_2O$	78%
67	**c12**	dehydroepiandrosterone	imidazole	2-naphthylmethyl	$C_{33}H_{41}BrN_2O$	87%
68	**c13**	dehydroepiandrosterone	imidazole	phenacyl	$C_{32}H_{41}BrN_2O_3$	92%
69	**c14**	dehydroepiandrosterone	imidazole	4-methoxyphenacyl	$C_{33}H_{43}BrN_2O_4$	94%
70	**c15**	dehydroepiandrosterone	imidazole	3-bromophenacyl	$C_{32}H_{40}Br_2N_2O_3$	96%
71	**c16**	dehydroepiandrosterone	imidazole	2-naphthylacyl	$C_{36}H_{43}BrN_2O_3$	93%
72	**c17**	dehydroepiandrosterone	imidazole	2-bromobenzyl	$C_{31}H_{40}Br_2N_2O_2$	92%
73	**c18**	dehydroepiandrosterone	imidazole	2-naphthylmethyl	$C_{35}H_{43}BrN_2O_2$	72%

To confirm the structures of the steroidal imidazolium salt derivatives, compound **c11** was selected as a representative compound and characterized using X-ray crystallography (CCDC 1880928),[43] as shown in Fig. 2.

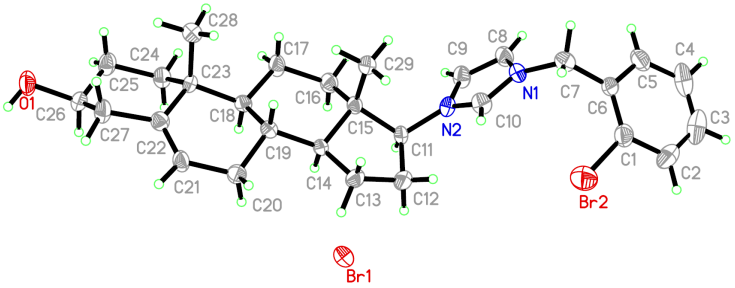


Fig. 2 X-ray crystal structure of compound **c11**.

2.2 Biological evaluation and structure-activity relationship analysis

The cytotoxic potential for the seventy-three synthesized steroidal imidazolyl derivatives and steroidal imidazolium salt derivatives against five human cancer cell lines including myeloid leukaemia (HL-60), liver carcinoma (SMMC-7721), lung carcinoma (A-549), breast carcinoma (MCF-7) and colon carcinoma (SW480) were determined using the MTS assay. DDP (Cisplatin), as well as diosgenin (**a1**), cholesterol (**b1**), dehydroepiandrosterone (**c1**), imidazole, benzimidazole and 5,6-dimethyl-benzimidazole, were chosen as positive controls. The results were listed in Table 2.

Table 2

Cytotoxic activities of steroidal imidazolyl derivatives and steroidal imidazolium salt derivatives *in vitro*[b] (IC_{50}, μM[a])

Entry	Compound No.	HL-60	SMMC-7721	A-549	MCF-7	SW480
1	**a1**	>20	>20	>20	>20	>20
2	**b1**	>20	>20	>20	>20	>20
3	**c1**	>20	>20	>20	>20	>20
4	imidazole	>20	>20	>20	>20	>20
5	benzimidazole	>20	>20	>20	>20	>20
6	5,6-dimethyl-benzimidazole	>20	>20	>20	>20	>20
7	**a3**	8.33	10.04	10.29	19.67	>20
8	**a4**	>20	>20	>20	>20	>20
9	**a5**	>20	>20	>20	>20	>20
10	**a6**	>20	>20	>20	>20	>20
11	**a7**	9.51	9.74	9.92	14.49	>20
12	**b3**	2.00	2.12	11.65	>20	16.44
13	**b4**	>20	>20	>20	>20	>20
14	**b5**	>20	>20	>20	>20	>20
15	**b6**	0.18	>20	>20	>20	>20

16	**b7**	>20	>20	>20	>20	>20
17	**c5**	>20	>20	>20	>20	>20
18	**c6**	>20	>20	>20	>20	>20
19	**a8**	2.69	7.38	7.76	5.50	7.39
20	**a9**	1.25	7.32	7.18	4.49	7.03
21	**a10**	1.28	7.28	7.03	5.21	6.46
22	**a11**	1.03	3.46	7.27	2.26	4.01
23	**a12**	1.24	4.58	6.60	3.86	6.33
24	**a13**	1.22	2.45	4.92	1.95	4.03
25	**a14**	1.09	7.15	7.30	5.18	8.18
26	**a15**	1.25	1.51	1.94	1.47	2.59
27	**a16**	1.25	1.71	1.55	1.43	1.65
28	**a17**	0.96	1.89	3.34	2.27	3.62
29	**a18**	0.43	0.95	1.22	1.41	1.66
30	**a19**	1.01	1.15	1.12	1.09	1.59
31	**a20**	1.19	1.81	2.55	2.49	2.59
32	**a21**	1.22	1.45	2.45	2.11	2.55
33	**a22**	1.36	1.75	1.77	1.53	1.74
34	**a23**	1.10	1.33	1.32	1.67	1.75
35	**a24**	0.34	0.21	4.47	2.14	2.10
36	**a25**	1.02	0.88	1.25	2.31	1.80
37	**a26**	0.44	0.90	9.57	2.91	3.22
38	**a27**	0.74	0.44	5.02	2.31	2.01
39	**a28**	0.98	1.39	7.15	2.78	2.22
40	**a29**	0.45	0.57	5.53	3.05	3.10
41	**a30**	0.49	0.44	0.67	0.73	0.79
42	**a31**	0.42	0.59	5.12	1.90	1.60
43	**a32**	1.18	2.14	1.86	5.66	7.96
44	**a33**	0.94	1.61	1.21	1.96	4.15
45	**a34**	1.37	5.49	3.49	5.83	6.55
46	**a35**	0.92	2.27	2.99	1.88	5.37
47	**b8**	1.53	1.29	7.28	6.98	6.06
48	**b9**	1.52	1.10	6.68	6.54	7.18
49	**b10**	1.42	1.22	7.84	8.70	8.23
50	**b11**	2.41	1.23	8.53	8.00	6.25
51	**b12**	5.53	1.16	7.65	10.83	10.90
52	**b13**	1.64	1.04	7.67	8.04	7.48
53	**b14**	6.85	1.49	8.42	8.41	9.03
54	**b15**	6.00	2.90	13.22	5.25	4.87
55	**b16**	9.91	1.70	7.22	8.51	6.33
56	**b17**	10.63	1.88	8.82	>20	10.54
57	**b18**	1.59	0.94	7.36	6.02	8.32
58	**b19**	0.88	1.65	7.51	7.18	10.18

59	**b20**	4.41	1.45	7.66	9.85	10.10
60	**b21**	4.47	1.56	7.31	8.97	10.60
61	**b22**	0.28	1.77	8.11	9.87	10.44
62	**b23**	6.96	1.81	8.44	14.25	13.16
63	**b24**	7.73	1.42	8.10	8.84	6.56
64	**b25**	7.97	1.52	8.75	8.71	10.66
65	**b26**	7.26	2.10	9.65	>20	11.28
66	**b27**	2.35	1.44	8.05	7.62	7.75
67	**b28**	5.39	1.41	6.95	8.35	9.29
68	**c7**	>20	>20	>20	>20	>20
69	**c8**	>20	>20	>20	>20	>20
70	**c9**	6.42	14.90	>20	7.25	9.78
71	**c10**	2.00	3.50	9.69	4.38	5.59
72	**c11**	6.30	7.63	>20	9.61	>20
73	**c12**	2.68	4.41	7.87	5.08	6.47
74	**c13**	6.42	12.03	>20	9.07	11.12
75	**c14**	2.20	4.31	10.70	3.46	6.06
76	**c15**	4.35	5.47	7.20	4.88	7.26
77	**c16**	1.26	1.75	4.39	2.10	4.45
78	**c17**	1.48	3.83	6.52	4.84	6.87
79	**c18**	1.22	2.45	4.74	2.53	5.64
80	**DDP**	2.11	11.27	6.94	17.43	17.05

[a] Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTS assay.

[b] Data represent the mean values of three independent determinations.

As displayed in Table 2, single steroidal compounds (diosgenin (**a1**), cholesterol (**b1**) and dehydroepiandrosterone (**c1**)) and single imidazole compounds (imidazole, benzimidazole and 5,6-dimethyl-benzimidazole), as controls, lacked activity against all tumor cell lines investigated at the concentration of 20 μM (Entries 1-6). The structures of imidazole and imidazolium salt in steroidal derivatives have an important effect on the cytotoxic potential. Most of steroidal imidazolyl derivatives **a3-a7/b3-b7/c5-c6** (Entries 7-18) lacked activities against all tumor cell lines tested at the concentration of 20 μM, except **a3**, **a7**, **b3** and **b6** with weak cytotoxic activities. Interestingly, compound **b6**, bearing a benzimidazole ring at position-3β of cholesterol, showed obvious cytotoxic activity selectively against HL-60 cell lines with IC_{50} value of 0.18 μM.

However, their steroidal imidazolium salt derivatives (Entries 19-79) exhibited higher cytotoxic activities. For three kinds of steroids, diosgenin–imidazolium salt derivatives **a8-a35** displayed the highest cytotoxic activities

with IC_{50} values of 0.21–9.57 μM *in vitro*. Cholesterol–imidazolium salt derivatives **b8-b28** exhibited the higher activities with IC_{50} values of 0.28–14.25 μM, while dehydroepiandrosterone–imidazolium salt derivatives **c7-c18** showed the lowest activities with IC_{50} values of 1.22–14.90 μM or higher than 20 μM.

For the substituent's position of imidazolium salt moiety in steroids, imidazolium salts at position-3α of steroidal derivatives (**a14-a31/b14-b23**) possessed the highest cytotoxic activities and most of them exhibited potent inhibitory activities. 3β-Imidazolium salt steroidal derivatives (**a32-a35/b24-b28**) and 6α-imidazolium salt steroidal derivatives (**a8-a13/b8-b13**) showed medium or high inhibitory activities. In dehydroepiandrosterone derivatives (**c7-c18**), imidazolium salts at position-17β of dehydroepiandrosterone derivatives had the lowest activities, and imidazolium salts with 3β-AcO group (**c7-c12**) were better than with 3β-OH group (**c13-c18**).

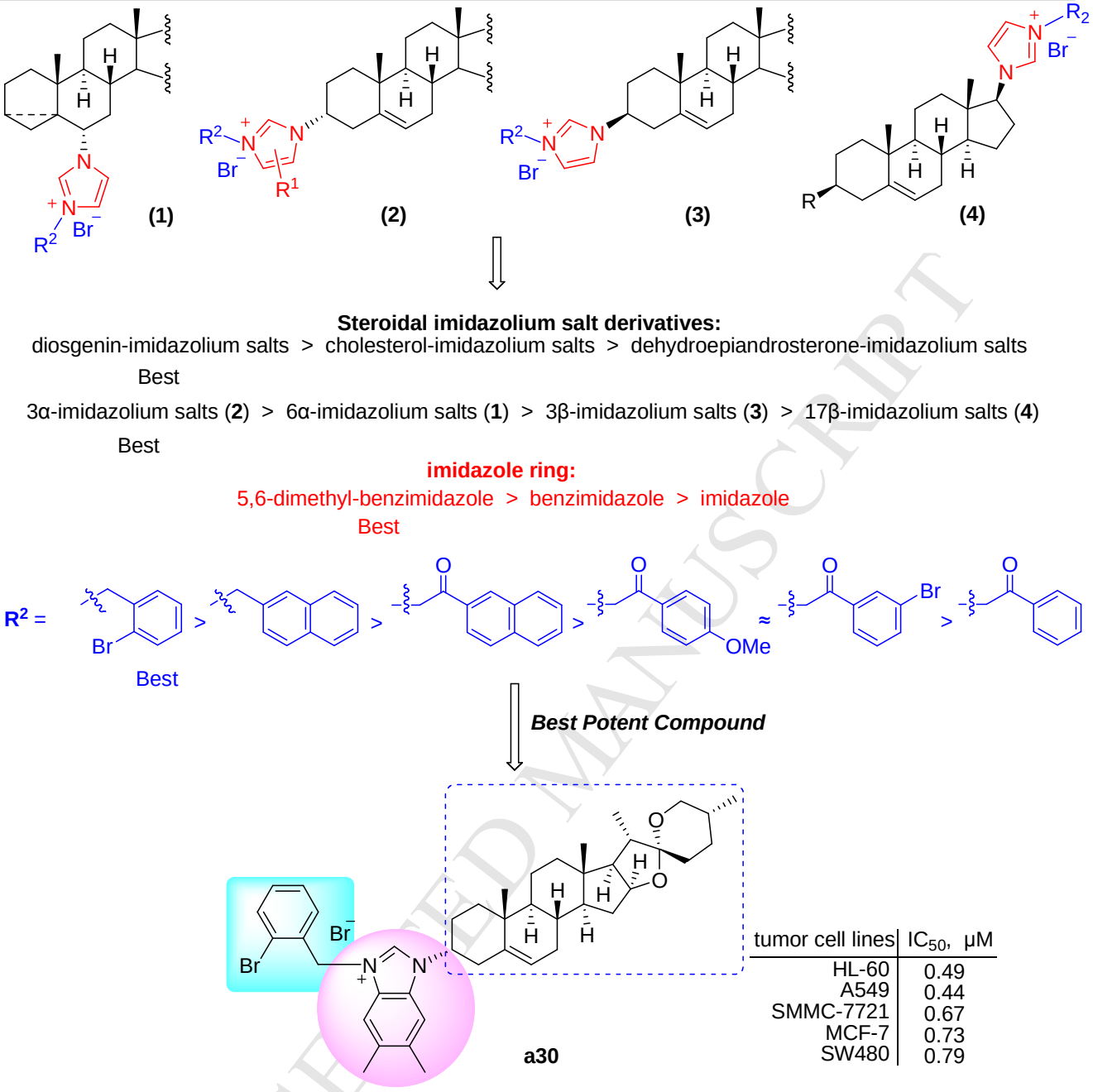
Many literatures have reported that bioactivities of natural products and drug molecules have been closely related to the stereo structures.[44-46] As shown in Table 2, the stereochemistry at position-3 in steroidal imidazolium salt derivatives has a great influence on the cytotoxic potential. Although both isomers (3α- and 3β-) in steroidal derivatives possessed cytotoxic activities, imidazolium salts at position-3α displayed higher inhibitory activities than 3β-isomer in most cell lines. For example, steroidal imidazolium salt **a17** (3α-isomer) and **a18** (3α-isomer) showed higher inhibitory activities against SMMC-7721 cell lines with 2.9- and 2.4-fold than **a34** (3β-isomer) and **a35** (3β-isomer), respectively. Similarly, steroidal imidazolium salt **a18** (3α-isomer) and **b15** (3α-isomer) showed higher inhibitory activities against SW-480 cell lines with 3.2- and 2.2-fold than **a35** (3β-isomer) and **b25** (3β-isomer), respectively.

In the case of imidazole ring, steroidal imidazolium salt derivatives (**a8-a19/b8-b18/c7-c18**) with imidazole ring displayed medium inhibitory activities. Steroidal derivatives (**a20-a25/b19-b21**) with benzimidazole ring possessed higher inhibitory activity. Interestingly, Steroidal derivatives (**a26-a31/b22-b23**) with 5,6-dimethyl-benzimidazole rings exhibited significant inhibitory activities. Among them, diosgenin derivatives **a26-a31**, with 5,6-dimethyl-benzimidazole rings, showed powerful inhibitory activity with IC_{50} values of 0.42-3.22 μM against HL-60, A-549, MCF-7 and SW480 cell lines.

For the substituent at position-3 of imidazole ring, imidazolium salts with phenacyl substituent such as **a8**, **a14**, **a20**, **a26** and **a32**, as well as steroidal derivatives with 4-methoxyphenacyl or 3-bromophenacyl substituent

such as **a9**, **a10**, **a15**, **a16**, **a21**, **a22**, **a27**, **a28** and **a33** had relative weak inhibitory activities against five tumor cell lines. Meanwhile, imidazolium salts with 2-naphthylacyl substituent such as **a11**, **a17**, **a23**, **a29** and **a34** showed medium cytotoxic activities (IC_{50} = 0.44–9.57 μM). However, imidazolium salts with 2-bromobenzyl substituent such as **a12**, **a18**, **a24**, **a30** and **a35**, as well as 2-naphthylmethyl substituent such as **a13**, **a19**, **a25** and **a31** exhibited much higher inhibitory activity (IC_{50} = 0.21–6.60 μM). Notably, diosgenin–imidazolium salt **a30**, bearing a 2-bromobenzyl substituent at position-3 of 5,6-dimethyl-benzimidazole, was found to be the most potent compound with IC_{50} values of 0.44–0.79 μM against five human tumor cell lines investigated. Particularly, diosgenin–imidazolium salt **a24**, with a 2-bromobenzyl substituent at position-3 of benzimidazole, showed inhibitory activity selectively against SMMC-7721 cell lines with IC_{50} value of 0.21 μM and 54-fold more sensitive to DDP.

The results suggest that the existence of substituted 5,6-dimethyl-benzimidazoles ring and substitution of the imidazolyl-3α-position with a 2-bromobenzyl or 2-naphthylmethyl group could be critical for promoting cytotoxic activity. Then, the structure-activity relationships (SARs) results were exemplified in Scheme 3.

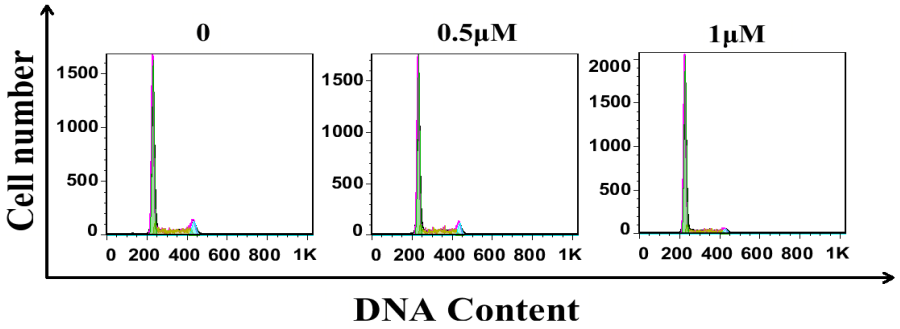


Scheme 3 Structure-activity relationships of steroidal imidazolium salt derivatives.

*2.3 Steroidal imidazolium salt **a30** induces G0/G1 cell cycle arrest and apoptosis in SMMC-7721 cells*

To determine whether the proliferation inhibitory effect of imidazolium salt **a30** was caused by cell cycle arrest, propidium iodide (PI) staining and flow cytometry analysis of cells was performed in SMMC-7721 cells treated with indicated concentrations of imidazolium salt **a30** (0, 0.5, 1 μM). As shown in Fig. 3, imidazolium

salt **a30** induced G0/G1 cell cycle arrest in a dose dependent manner, while the G0/1 phase cell population increased to 73.61 % and 78.10 % in cells treated with 2 μM and 4 μM imidazolium salt **a30** as compared to control showing 62.58 %. Inversely, S phase and G2/M phase cell population were respectively decreased to 14.22% and 4.67 % in 4 μM imidazolium salt **a30** treated group as compared to control having 24.50 % and 8.72% , while the proportion of sub-G1 phase cells showed no significant change.



Treatment	Cells (%)			
	sub-G1	G0/G1	S	G2/M
DMSO	2.33±0.17	62.58±0.35	24.50±0.05	8.72±0.42
Compound **a30** (0.5 μM)	2.40±0.23	73.61±0.50	19.23±0.54	3.49±0.35
Compound **a30** (1 μM)	2.43±0.12	78.10±1.15	14.22±0.36	4.67±0.05

Fig. 3 Compound **a30** induces G0/G1 phase arrest in SMMC-7721 cells. (A) Cells were treated with 0.5 and 1 μM of compound **a30** for 24 h. Cell cycle was determined by PI staining and cell cytometry. (B) The percentages of cells in different phases were quantified. At least three independent experiments were performed and data of one representative experiment is shown.

The steroidal imidazolium salt **a30** induced cell apoptosis was determined with Annexin V-FITC/PI double-labeled cell cytometry. As shown in Fig. 4, after treatment of cells with imidazolium salt **a30** at 1 μM and 2 μM for 48 h, cell apoptosis in SMMC-7721 cells remarkably elevated to 19.07 % and 65.59 %, respectively. The data suggested that illustrated that steroidal imidazolium salt **a30** inhibited cell proliferation through induction of G0/G1 cell cycle arrest and apoptosis of the SMMC-7721 cells.

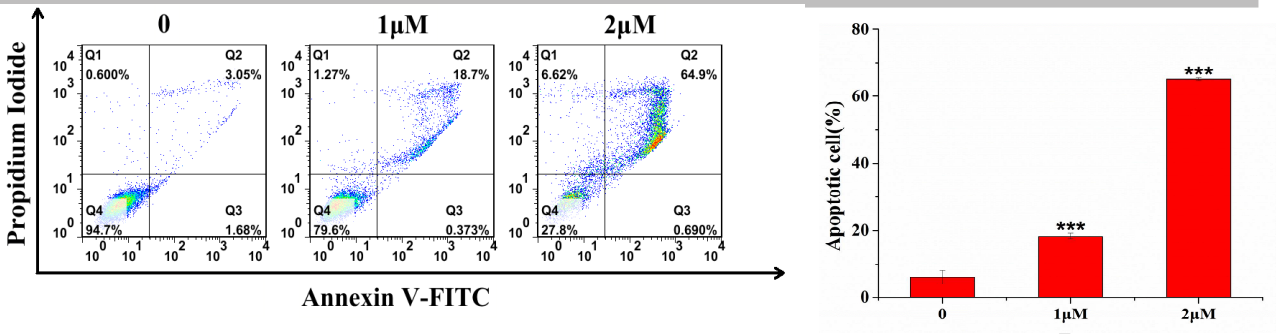


Fig. 4 Compound **a30** caused significant apoptosis of SMMC-7721 cells. (A) Cells were treated with 1 and 2 μM compound imidazolium salt **a30** for 48 h. Cell apoptosis was determined by Annexin V-FITC/PI double-staining assay. (B) The quantification of cell apoptosis.

3. Conclusion

In summary, a number of novel steroidal imidazolium salt derivatives synthesized in this work proved to be potent antitumor agents. The results showed that diosgenin–imidazolium salt derivatives displayed much higher cytotoxic activities than holesterol–imidazolium salts and dehydroepiandrosterone–imidazolium salts. The SARs results suggested that the existence of substituted 5,6-dimethyl-benzimidazoles or benzimidazole ring and substitution of the imidazolyl-3α-position with a 2-bromobenzyl or 2-naphthylmethyl group could be critical for promoting cytotoxic activity. The diosgenin–imidazolium salt derivatives **a18**, **a19**, **a24**, **a25**, **a30** and **a31**, with 5,6-dimethyl-benzimidazoles ring and a 2-bromobenzyl or 2-naphthylmethyl group at imidazolyl-3-position, exhibited powerful inhibitory activity. Particularly, diosgenin–imidazolium salt **a30** was found to be the most potent compound with IC_{50} values of 0.44–0.79 μM against five human tumor cell lines investigated. Diosgenin–imidazolium salt **a24** showed inhibitory activity selectively against SMMC-7721 cell lines with IC_{50} value of 0.21 μM and 54-fold more sensitive to DDP. Compound **a30** can induce the G0/G1 phase cell cycle arrest and apoptosis in SMMC-7721 cells. The steroidal imidazolium salts derivatives **a18**, **a19**, **a24**, **a25**, **a30** and **a31** could serve as a new starting point to explore promising lead compounds for the development of new anticancer agents.

4. Experimental Section

4.1. Chemistry

4.1.1. General

Melting points were obtained on a XT-4 melting-point apparatus and were uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) was recorded on Bruker Avance 400 spectrometer at 100 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. Low-resolution Mass spectra were recorded on a VG Auto Spec-3000 magnetic sector MS spectrometer. High Resolution Mass spectra were taken on AB QSTAR Pulsar mass spectrometer. Silica gel (200–300 mesh) for column chromatography and silica GF_{254} for TLC were produced by Qingdao Marine Chemical Company (China). All air- or moisture-sensitive reactions were conducted under an argon atmosphere. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Fluka and were used without purification, unless otherwise indicated.

*4.1.2. Synthesis of compounds **a3-a7/b3-b7***

To a solution of diosgenin **a1** (4.2 g, 10.0 mmol)/cholesterol **b1** (3.9 g, 10.0 mmol) in dichloromethane (30.0 mL) was added methanesulfonyl chloride (0.9 mL, 12.0 mmol) and triethylamine (2.8 mL, 20.0 mmol) at 0 ^{o}C. The resulting mixture was stirred at room temperature for 12 h. After quenching the reaction with water (50.0 mL), the layers were separated. The organic phase was dried over anhydrous Na_2SO_4 and concentrated, and used for the next synthetic step. A mixture of the previous methanesulfonate and imidazole or substituted imidazole (30.0 mmol) was stirred in toluene (20.0 ml) at reflux for 24–36 h (monitored by TLC). After cooling to room temperature, the solvent was concentrated, and the residue was diluted with EtOAc (20.0 mL). The organic layer was washed with water (20.0 mL) and brine (20.0 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether 60–90 ^{o}C : ethyl acetate = 3:1→1:1) to afford **a3-a7/b3-b7** in 7–48% yield (two steps) as yellow or white powder.

*4.1.2.1 1-((2S,2aR,3aR,5aR,5'R,7aS,8S,9R)-5a,5',7a,8-tetramethylicosahydro-2H-spiro[cyclopropa[1', 7a']indeno[5',4':4,5]indeno[2,1-b]furan-9,2'-pyran]-2-yl)-1H-imidazole（**a3**）*. Yield 42%. White powder, m.p. 199 – 201 ^{o}C. IR ν_{max} (cm^{-1}): 3424, 2949, 1454, 1378, 1299, 1073, 982, 850, 819, 738, 662. ^{1}H

NMR (400 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.11 (s, 1H), 7.02 (s, 1H), 4.43 (q, *J* = 8.0 Hz, 1H), 3.55 (t, *J* = 3.2 Hz, 1H), 3.49 – 3.44 (m, 1H), 3.37 (t, *J* = 10.8 Hz, 1H), 2.36 (dt, *J* = 14.4, 2.8 Hz, 1H), 2.14 – 2.08 (m, 1H), 1.88 – 1.68 (m, 5H), 1.66 – 1.54 (m, 7H), 1.47 – 1.11 (m, 8H), 0.99 – 0.90 (m, 6H), 0.78 (d, *J* = 6.0 Hz, 3H), 0.73 (s, 3H), 0.70 (s, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.5, 128.5, 117.9, 109.3, 80.6, 66.9, 62.2, 58.7, 55.8, 48.0, 43.2, 41.6, 40.7, 39.9, 35.2, 34.7, 33.4, 31.6, 31.4, 30.4, 30.3, 28.8, 24.5, 24.3, 22.3, 19.7, 17.1, 16.6, 14.5, 14.4 ppm.HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{44}N_2O_2$ $[M+H]^+$ 465.3476, found 465.3477.

4.1.2.2 1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a, 12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazole （***a4***）. Yield 15%. White powder, m.p. 199 – 201 °C. IR ν_{max} (cm^{-1}): 3424, 2949, 1453, 1376, 1242, 1109, 1069, 980, 899, 662. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 7.05 (s, 1H), 6.98 (s, 1H), 5.42 (d, *J* = 5.6. Hz, 1H), 4.42 (q, *J* = 7.6 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.49 – 3.45 (m, 1H), 3.37 (t, *J* = 10.8 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.45 – 2.40 (m, 1H), 2.03 – 1.98 (m, 4H), 1.84 – 1.74 (m, 4H), 1.69 – 1.42 (m, 10H), 1.31 – 1.16 (m, 4H), 1.09 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.80 – 0.78 (m, 6H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 139.7, 135.3, 129.1, 122.6, 116.8, 109.3, 80.7, 66.9, 62.1, 57.5, 56.5, 50.1, 41.6, 40.5, 40.3, 39.7, 38.0, 36.8, 32.0, 31.8, 31.4, 31.3, 30.3, 29.9, 28.8, 20.8, 19.4, 17.1, 16.3, 14.5 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{44}N_2O_2$ $[M+H]^+$ 465.3476, found 465.3475.

4.1.2.3 1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a, 12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d] imidazole （***a5***）. Yield 9%. White powder, m.p. 225 – 227 °C. IR ν_{max} (cm^{-1}): 3416, 2948, 1484, 1456, 1386, 1280, 1052, 1008, 901, 747. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.83 – 7.80 (m, 1H), 7.44 – 7.42 (m, 1H), 7.29 – 7.27 (m, 2H), 5.47 (d, *J* = 3.2 Hz, 1H), 4.44 (q, *J* = 7.4 Hz, 1H), 4.21 – 4.14 (m, 1H), 3.41 – 3.30 (m, 1H), 2.77 (t, *J* = 12.8 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.17 – 1.99 (m, 5H), 1.91 – 1.85 (m, 1H), 1.83 – 1.77 (m, 2H), 1.73 – 1.57 (m, 7H), 1.52 – 1.22 (m, 6H), 1.16 (s, 3H), 1.13 – 1.06 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.82 – 0.79 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 140.2, 139.8, 133.4, 122.8, 122.6, 122.1, 120.5, 110., 109.3, 80.8, 66.9, 62.1, 56.5, 56.2, 50.1, 41.6, 40.3, 39.7, 39.3, 38.2, 37.0, 32.0, 31.8, 31.4, 30.3,

28.8, 20.8, 19.6, 17.2, 16.3, 14.6 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{34}H_{46}N_2O_2$ $[M+H]^+$ 515.3632, found 515.3631.

4.1.2.4 5,6-dimethyl-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazole （***a6***）. Yield 10%. Pale yellow powder, m.p. 211 – 213 °C. IR ν_{max} (cm^{-1}): 3439, 2941, 1486, 1458, 1374, 1223, 1171, 1050, 980, 901. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.90 (s, 1H), 7.56 (s, 1H), 7.17 (s, 1H), 5.46 (d, *J* = 5.6 Hz, 1H), 4.47 – 4.40 (m, 1H), 4.15 – 4.09 (m, 1H), 3.50 – 3.46 (m, 1H), 3.41 – 3.32 (m, 1H), 2.78 – 2.70 (m, 1H), 2.54 – 2.49 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 2.11 – 1.98 (m, 6H), 1.91 – 1.87 (m, 1H), 1.82 – 1.76 (m, 2H), 1.72 – 1.56 (m, 7H), 1.51 – 1.41 (m, 2H), 1.36 – 1.22 (m, 4H), 1.15 (s, 3H), 1.01 – 0.98 (m, 3H), 0.82 – 0.79 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 140.1, 139.5, 132.1, 131.8, 131.1, 129.2, 128.3, 125.4, 122.8, 120.5, 110.3, 109.9, 109.4, 81.0, 67.0, 62.2, 56.6, 56.2, 50.3, 41.8, 40.4, 39.9, 39.5, 38.4, 37.1, 32.2, 32.0, 31.5, 30.4, 29.0, 21.0, 20.8, 20.4, 19.7, 17.3, 16.5, 14.7 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{36}H_{50}N_2O_2$ $[M+H]^+$ 543.3945, found 543.3943.

4.1.2.5 1-((4S,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazole （***a7***）. Yield 8%. White powder, m.p. 195 – 197 °C. IR ν_{max} (cm^{-1}): 3422, 2950, 1618, 1456, 1378, 1241, 1215, 1079, 1052, 982, 899, 661. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.69 (s, 1H), 7.00 (d, *J* = 10.2 Hz, 2H), 5.48 (dd, *J* = 4.8, 2.0 Hz, 1H), 4.44 – 4.35 (m, 2H), 3.49 – 3.45 (m, 1H), 3.37 (t, *J* = 10.8 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.51 (dt, *J* = 15.6, 2.4 Hz, 1H), 2.10 – 1.96 (m, 3H), 1.88 – 1.82 (m, 2H), 1.79 – 1.57 (m, 9H), 1.49 – 1.39 (m, 3H), 1.33 – 1.24 (m, 1H), 1.15 – 1.00 (m, 7H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.79 – 0.77 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.8, 128.4, 123.7, 118.7, 109.3, 80.8, 66.8, 62.0, 56.4, 53.0, 49.7, 41.6, 40.2, 39.6, 37.1, 35.9, 32.3, 32.0, 31.8, 31.4, 31.2, 30.3, 28.8, 28.5, 20.4, 19.4, 17.1, 16.3, 14.5 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{44}N_2O_2$ $[M+H]^+$ 465.3476, found 465.3476.

4.1.2.6 1-((1aR,3aR,5aR,10S,10aR)-3a,5a-dimethyl-6-((R)-6-methylheptan-2-yl)hexadecahydrocyclopenta[a]cyclopropa[2,3]cyclopenta[1,2-f]naphthalen-10-yl)-1H-imidazole （***b3***）. Yield 48%. Brown powder, m.p. 99 – 101 °C. IR ν_{max} (cm^{-1}): 3424, 2938, 1469, 1383, 1223, 1112, 1079, 906, 828, 718, 664.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (s, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 5.29 (s, 1H), 3.54 (s, 1H), 2.39 – 2.31 (m, 1H), 2.00 – 1.95 (m, 1H), 1.89 – 1.78 (m, 2H), 1.72 – 1.67 (m, 1H), 1.61 – 1.47 (m, 5H), 1.41 – 1.25 (m, 6H), 1.23 – 1.19 (m, 1H), 1.17 – 1.07 (m, 7H), 1.01 – 0.92 (m, 4H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.85 (dd, *J* = 6.8, 2.0 Hz, 6H), 0.69 (s, 3H), 0.62 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 128.5, 118.2, 58.9, 56.3, 56.2, 48.1, 43.2, 42.8, 40.1, 39.6, 36.2, 35.9, 35.4, 34.7, 33.6, 30.9, 28.3, 28.1, 24.7, 24.4, 24.3, 23.9, 22.9, 22.7, 22.6, 19.8, 18.8, 14.4, 12.3 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{30}H_{48}N_2$ $[M+1]^+$ 437.389, found 437.389.

4.1.2.7 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15, 16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-1H-imidazole（***b4***）. Yield 18%. Brown powder, m.p. 136 – 138 °C. IR ν_{max} (cm^{-1}): 3435, 2937, 1724, 1434, 1417, 1239, 1117, 1027, 905, 823, 744, 664, 611. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 7.05 (s, 1H), 6.98 (s, 1H), 5.43 – 5.42 (m, 1H), 3.92 – 3.84 (m, 1H), 2.65 – 2.58 (m, 1H), 2.44 – 2.39 (m, 1H), 2.06 – 1.79 (m, 7H), 1.61 – 1.46 (m, 6H), 1.39 – 1.31 (m, 3H), 1.29 – 1.22 (m, 2H), 1.19 – 1.11 (m, 5H), 1.07 (s, 3H), 1.04 – 0.96 (m, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.86 (dd, *J* = 6.8, 2.0 Hz, 6H), 0.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 135.4, 129.2, 123.0, 116.9, 57.7, 56.8, 56.3, 50.3, 42.4, 40.7, 39.8, 39.6, 38.1, 36.8, 36.3, 35.9, 32.0, 31.9, 30.1, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.1, 19.5, 18.9, 12.0 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{30}H_{48}N_2$ $[M+H]^+$ 437.389, found 437.389.

4.1.2.8 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15, 16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-1H-benzo[d]imidazole（***b5***）. Yield 10%. Pale yellow powder, m.p. 209 – 211 °C. IR ν_{max} (cm^{-1}): 3429, 2941, 1496, 1466, 1439, 1383, 1234, 1113, 1071, 819, 729, 662. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.81 – 7.77 (m, 1H), 7.43 – 7.39 (m, 1H), 7.27 – 7.24 (m, 2H), 5.45 – 5.44 (m, 1H), 4.20 – 4.12 (m, 1H), 2.79 – 2.72 (m, 1H), 2.54 – 2.49 (m, 1H), 2.16 – 1.99 (m, 5H), 1.86 – 1.79 (m, 1H), 1.63 – 1.48 (m, 6H), 1.37 – 1.18 (m, 7H), 1.13 (s, 3H), 1.11 – 0.96 (m, 7H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.85 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 140.3, 139.8, 133.5, 123.2, 122.7, 122.2, 120.6, 110.2, 56.9, 56.4, 56.3, 50.3, 42.5, 39.8, 39.6, 39.5, 38.4, 37.0, 36.3, 35.9, 32.0, 32.0, 29.0, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.2, 19.7, 18.9, 12.0 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{34}H_{50}N_2$ $[M+H]^+$ 487.4047, found 487.4048.

4.1.2.9 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-5,6-dimethyl-1H-benzo[d]imidazole (***b6***). Yield 9%. White powder, m.p. 241 – 243 °C. IR ν_{max} (cm^{-1}): 3432, 2932, 1614, 1484, 1456, 1373, 1285, 1160, 1006, 889, 861, 741. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (s, 1H), 7.56 (s, 1H), 7.18 (s, 1H), 5.48 – 5.45 (m, 1H), 4.15 – 4.07 (m, 1H), 2.77 – 2.71 (m, 1H), 2.53 – 2.49 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 2.11 – 2.01 (m, 5H), 1.88 – 1.81 (m, 1H), 1.64 – 1.49 (m, 6H), 1.38 – 1.18 (m, 9H), 1.13 (s, 3H), 1.11 – 1.01 (m, 5H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.87 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.71 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 140.0, 139.5, 132.1, 131.8, 131.0, 123.1, 120.5, 110.3, 56.9, 56.3, 56.2, 53.5, 50.4, 42.5, 39.9, 39.7, 39.5, 38.4, 37.0, 36.3, 35.9, 32.0, 32.0, 29.0, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.2, 20.8, 20.4, 19.7, 18.9, 12.0 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{36}H_{54}N_2$ $[M+H]^+$ 515.436, found 515.4361.

4.1.2.10 1-((3S,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-1H-imidazole (***b7***). Yield 7%. Pale brown powder, m.p. 150 – 152 °C. IR ν_{max} (cm^{-1}): 3439, 2933, 1625, 1485, 1464, 1383, 1223, 872, 838, 618. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (s, 1H), 7.02 (s, 1H), 7.00 (s, 1H), 5.50 – 5.47 (m, 1H), 4.38 – 4.36 (m, 1H), 2.91 – 2.84 (m, 1H), 2.53 – 2.49 (m, 1H), 2.11 – 1.96 (m, 4H), 1.88 – 1.82 (m, 2H), 1.65 – 1.57 (m, 3H), 1.53 – 1.42 (m, 4H), 1.40 – 1.21 (m, 5H), 1.16 – 1.09 (m, 5H), 1.07 (s, 3H), 1.03 – 0.97 (m, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.86 (dd, *J* = 6.6, 2.0 Hz, 6H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.9, 128.5, 124.2, 118.9, 56.8, 56.2, 53.3, 49.9, 42.4, 39.7, 39.6, 37.2, 36.3, 36.1, 35.9, 32.5, 32.1, 31.8, 28.6, 28.3, 28.1, 24.4, 24.0, 23.0, 22.7, 20.8, 19.5, 18.8, 12.0 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{30}H_{48}N_2$ $[M+H]^+$ 437.389, found 437.389.

4.1.3. Synthesis of (3S,8R,9S,10R,13S,14S)-3-((tert-butyldimethylsilyl)oxy)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (***c2***)

To a solution of dehydroepiandrosterone **c1** (2.9 g, 10.0 mmol) in dichloromethane (30.0 mL) was added *tert*-Butyldimethylsilyl chloride (1.8 g, 12.0 mmol) and imidazole (1.4 g, 20.0 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 8 h. After quenching the reaction with water (50.0 mL), the layers were separated. The organic layer was washed with water (20.0 mL) and brine (20.0 mL), dried over anhydrous

Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether 60–90 ^oC : ethyl acetate = 20:1) to afford **c2** (3.96 g, 99%) as white powder.

Yield 99%. White powder, m.p. 153 – 155 ^oC. IR ν_{max} (cm^{-1}): 3423, 2934, 1494, 1382, 1303, 1238, 1082, 811, 662. ^1H NMR (400 MHz, Chloroform-*d*) δ 5.34 (d, *J* = 4.8 Hz, 1H), 3.52 – 3.44 (m, 1H), 2.46 (dd, *J* = 19.2, 8.8 Hz, 1H), 2.28 (t, *J* = 12.8 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.13 – 2.04 (m, 2H), 1.98 – 1.91 (m, 1H), 1.86 – 1.79 (m, 2H), 1.75 – 1.60 (m, 4H), 1.58 – 1.42 (m, 3H), 1.31 – 1.25 (m, 2H), 1.09 – 0.95 (m, 5H), 0.89 (s, 12H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.3, 141.9, 120.5, 72.6, 52.0, 50.5, 47.7, 42.9, 37.5, 36.9, 36.0, 32.16, 31.7, 31.6, 31.0, 26.1, 22.0, 20.5, 19.6, 18.4, 13.7, -4.4 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{42}O_2Si$ $[M+H]^+$ 425.2846, found 425.2846.

*4.1.4. Synthesis of N-((3S,8R,9S,10R,13S,14S,17S)-3-((tert-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-methylpropane-2-sulfinamide (**c3**)*

To a mixture of ketone **c2** (2.0 g, 5.0 mmol) and (*R*)-(+)-*tert*-Butylsulfinamide (909.0 mg, 7.5 mmol) in tetrahydrofuran (30.0 mL) was added titanium (IV) ethoxide (2.1 mL, 10.0 mmol). Heat the resulting mixture at reflux and monitor the reaction progress by TLC. After cooling to room temperature, methyl alcohol (20.0 mL) was added to the mixture and cooled to 0 ^oC. To the mixture was then added sodium borohydride (2.8 g, 75.0 mmol), and the resulting solution was stirres at 0 ^oC for 5 h. The reaction mixture was filtered through a small pad of Celite to remove Ti salts. The filtrate was treated with EtOAc (100.0 mL), saturated sodium potassium tartrate (50.0 mL), and brine (50.0 mL) and the mixture stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite and the organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether 60–90 ^oC : ethyl acetate = 3:1) to afford **c3** (2.1 g, 82%, two steps) as white powder.

Yield 82%. White powder, m.p. 221 – 223 ^oC. IR ν_{max} (cm^{-1}): 3431, 2930, 1598, 1474, 1375, 1068, 976, 799. ^1H NMR (400 MHz, Chloroform-*d*) δ 5.37 – 5.27 (m, 1H), 3.50 – 3.45 (m, 1H), 3.15 (q, *J* = 8.8 Hz, 1H), 2.91 (d, *J* = 7.8 Hz, 1H), 2.29 – 2.14 (m, 3H), 2.02 – 1.94 (m, 1H), 1.83 – 1.64 (m, 5H), 1.59 – 1.37 (m, 6H), 1.21 (s, 9H), 1.14 – 1.03 (m, 2H), 1.02 – 0.94 (m, 5H), 0.88 (s, 9H), 0.69 (s, 3H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

141.7, 121.0, 72.7, 66.9, 55.9, 52.8, 50.5, 43.3, 42.9, 37.5, 37.1, 36.8, 32.2, 31.7, 31.2, 26.1, 24.0, 22.9, 20.7, 19.6, 18.4, 11.8, -4.4 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{29}H_{53}NO_2SSi$ $[M+H]^+$ 530.3458, found 530.3457.

4.1.5. Synthesis of (3S,8R,9S,10R,13S,14S,17S)-17-amino-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol ***(c4)***

To a solution of secondary amine **c3** (1.0 g, 2.0 mmol) in methyl alcohol/dichloromethane = 2:1 (30.0 mL) was added 2N HCl in dioxane (12.0 mL). The resulting mixture was stirred at room temperature for 4 h. The crude reaction was diluted with methyl alcohol (20.0 mL) and filtered. The filtrate was concentrated and the solid obtained was washed with petroleum ether (3 × 10.0 ml), then dried to afford **c4** (534.8 mg, 92%) as white powder.

Yield 92%. White powder, m.p. 144 – 146 °C. IR ν_{max} (cm^{-1}): 3450, 2947, 1747, 1472, 1369, 1254, 1091, 887, 837, 774. ^{1}H NMR (400 MHz, Methanol-d_4) δ 5.37 – 5.35 (m, 1H), 3.44 – 3.35 (m, 1H), 3.05 (t, *J* = 9.2 Hz, 1H), 2.28 – 2.13 (m, 3H), 2.05 – 1.96 (m, 2H), 1.89 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.83 – 1.74 (m, 2H), 1.71 – 1.46 (m, 6H), 1.43 – 1.32 (m, 1H), 1.27 – 1.09 (m, 3H), 1.05 (s, 3H), 1.03 – 0.98 (m, 1H), 0.85 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 140.9, 120.6, 70.9, 60.2, 52.5, 50.0, 41.6, 41.6, 37.1, 36.3, 35.7, 31.6, 31.1, 30.8, 26.1, 23.3, 20.1, 18.5, 10.4 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{31}NO$ $[M+H]^+$ 290.2478, found 290.2478.

4.1.6. Synthesis of (3S,10R,13S,17S)-17-(1H-imidazol-1-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol ***(c5)***

To a solution of amine **c4** (500.0 mg, 1.7 mmol) in methyl alcohol (20 mL) was added 40% glyoxal (1.1 mL, 8.5 mmol), 35% formaldehyde (0.9 mL, 8.5 mmol) and 25% ammonium hydroxide (0.6 mL, 8.5 mmol). Heat the resulting mixture at reflux and monitor the reaction progress by TLC. After cooling to room temperature, the solvent was concentrated, and the residue was diluted with EtOAc (20.0 mL). The organic layer was washed with water (20.0 mL) and brine (20.0 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate) to afford **c5** (400.0 mg, 68%) as pale yellow powder.

Yield 68%. Pale yellow powder, m.p. 282 – 284 °C. IR ν_{max} (cm^{-1}): 3423, 2925, 1497, 1353, 1225, 1067, 811, 737, 663. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (s, 1H), 7.03 (s, 1H), 6.94 (s, 1H), 5.35 (d, *J* = 5.4 Hz, 1H),

3.94 (t, *J* = 9.6 Hz, 1H), 3.56 – 3.48 (m, 1H), 2.32 – 2.15 (m, 5H), 2.07 – 2.00 (m, 1H), 1.86 – 1.72 (m, 4H), 1.63 – 1.34 (m, 6H), 1.28 – 1.08 (m, 3H), 1.00 (s, 3H), 0.57 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 136.6, 128.6, 121.1, 118.8, 71.6, 67.9, 53.1, 50.3, 43.9, 42.4, 37.4, 36.9, 36.7, 32.2, 31.7, 31.6, 26.2, 23.4, 20.8, 19.5, 12.0 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{22}H_{32}N_2O$ $[M+H]^+$ 341.2587, found 341.2587.

*4.1.7. Synthesis of (3S,10R,13S,17S)-17-(1H-imidazol-1-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (**c6**)*

To a solution of alcohol **c5** (200.0 mg, 0.6 mmol) in dichloromethane (20.0 mL) was added acetic anhydride (85.0 μL, 0.9 mmol), triethylamine (250.0 μL, 1.8 mmol) and 4-dimethylaminopyridine (3.6 mg, 3 mol%) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. After quenching the reaction with saturated sodium bicarbonate (20.0 mL), the layers were separated. The organic layer was washed with water (20.0 mL) and brine (20.0 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether 60–90 °C : ethyl acetate = 1:1) to afford **c6** (193.2 mg, 86%) as white powder.

Yield 86%. Pale yellow powder, m.p. 166 – 168 °C. IR ν_{max} (cm^{-1}): 3439, 2930, 1472, 1383, 1361, 1254, 1073, 887, 839, 773. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (s, 1H), 7.01 (s, 1H), 6.93 (s, 1H), 5.36 (d, *J* = 4.8 Hz, 1H), 4.62 – 4.54 (m, 1H), 3.92 (t, *J* = 9.6 Hz, 1H), 2.35 – 2.10 (m, 4H), 2.05 – 1.98 (m, 4H), 1.87 – 1.70 (m, 4H), 1.62 – 1.32 (m, 6H), 1.28 – 1.09 (m, 3H), 0.99 (s, 4H), 0.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 139.9, 136.6, 128.6, 122.1, 118.7, 73.8, 67.8, 52.9, 50.1, 43.8, 38.1, 37.0, 36.8, 36.7, 32.0, 31.5, 27.7, 26.2, 23.4, 21.5, 20.6, 19.4, 12.0 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{24}H_{34}N_2O_2$ $[M+H]^+$ 383.2695, found 383.2695.

*4.1.8. General procedure for the preparation of steroidal imidazolium salts **a8-a35**/**b8-b28**/**c7-c18***

A mixture of imidazole compounds **a3-a7/b3-b7/c5-c6** (1.0 mmol) and phenacyl bromide or alkyl halide (1.2 mmol) was stirred in toluene (10.0 ml) at reflux for 24-48 h. An insoluble substance was formed. After completion of the reaction as indicated by TLC, the precipitate was filtered through a small pad of Celite, and washed with toluene (3 × 10.0 ml), then dried to afford imidazolium salts **a8-a35/b8-b28/c7-c18** in 67–98% yields.

4.1.8.1 3-(2-oxo-2-phenylethyl)-1-((2S,2aR,3aR,5aR,5'R,7aS,8S,9R)-5a,5',7a,8-tetramethylicosahydro-2H-spiro [cyclopropa[1',7a']indeno[5',4':4,5]indeno[2,1-b]furan-9,2'-pyran]-2-yl)-1H-imidazol-3-ium bromide ***(a8)***. Yield 93%. White powder, m.p. 280 – 282 °C. IR ν_{max} (cm^{-1}): 3540, 3438, 2953, 2927, 1700, 1449, 1226, 1154, 1050, 1003, 809, 754, 618. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.09 – 8.07 (m, 2H), 7.93 (s, 1H), 7.80 – 7.76 (m, 2H), 7.67 – 7.63 (m, 2H), 6.12 (d, *J* = 2.84 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 1H), 4.09 (s, 1H), 3.43 – 3.40 (m, 1H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.43 – 2.40 (m, 1H), 2.07 – 2.01 (m, 1H), 1.87 – 1.78 (m, 2H), 1.72 – 1.32 (m, 14H), 1.30 – 1.13 (m, 4H), 1.01 (d, *J* = 7.2 Hz, 1H), 0.98 – 0.95 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.73 – 0.70 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 137.4, 135.0, 134.1, 129.6, 128.6, 124.2, 121.6, 108.8, 80.7, 66.4, 62.4, 61.7, 56.1, 55.3, 47.3, 43.2, 41.6, 34.7, 33.3, 33.2, 31.7, 31.5, 30.3, 29.9, 29.0, 24.5, 24.2, 22.3, 19.7, 17.6, 16.7, 15.2, 14.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{38}H_{51}N_2O_3$ $[M\text{-}Br]^+$ 583.3894, found 585.3893.

4.1.8.2 3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-((2S,2aR,3aR,5aR,5'R,7aS,8S,9R)-5a,5',7a,8-tetramethylicosa hydro-2H-spiro[cyclopropa[1',7a']indeno[5',4':4,5]indeno[2,1-b]furan-9,2'-pyran]-2-yl)-1H-imidazol-3-ium bromide ***(a9)***. Yield 92%. White powder, m.p. 248 – 250 °C. IR ν_{max} (cm^{-1}): 3448, 2953, 2928, 1685,1604, 1269, 1243, 1176, 1153, 984, 600. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.06 – 8.04 (m, 2H), 7.92 (s, 1H), 7.77 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.06 – 6.03 (m, 2H), 4.33 (q, *J* = 7.2 Hz, 1H), 4.08 (s, 1H), 3.89 (s, 3H), 3.44 – 3.40 (m, 1H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.41 (d, *J* = 12.8 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.86 – 1.78 (m, 2H), 1.71 – 1.47 (m, 10H), 1.45 – 1.35 (m, 4H), 1.30 – 1.12 (m, 4H), 1.01 (d, *J* = 7.2 Hz, 1H), 097 – 0.95 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.74 – 0.70 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.0, 164.5, 137.4, 131.0, 126.9, 124.6, 121.5, 114.8, 108.8, 80.7, 66.4, 62.4, 61.6, 56.2, 55.7, 55.3, 47.3, 43.2, 41.6, 34.7, 33.3, 31.7, 31.5, 30.3, 29.9, 29.0, 24.5, 24.2, 22.3, 19.7, 17.6, 16.7, 15.1, 14.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{39}H_{53}N_2O_4$ $[M\text{-}Br]^+$ 613.4, found 613.4001.

4.1.8.3 3-(2-(3-bromophenyl)-2-oxoethyl)-1-((2S,2aR,3aR,5aR,5'R,7aS,8S,9R)-5a,5',7a,8-tetramethylicosa hydro-2H-spiro[cyclopropa[1',7a']indeno[5',4':4,5]indeno[2,1-b]furan-9,2'-pyran]-2-yl)-1H-imidazol-3-ium bromide ***(a10)***. Yield 97%. White powder, m.p. 268 – 270 °C. IR ν_{max} (cm^{-1}): 3440, 2953, 2927, 1705, 1564, 1455, 1382, 1240, 1153, 1129, 1053, 984, 899, 675. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.20 (d, *J* = 11.2 Hz, 1H), 8.09 – 8.03 (m, 1H), 7.99 – 7.90 (m, 2H), 7.76 (d, *J* = 12.4 Hz, 1H), 7.64 – 87.57 (m, 1H), 6.11

(d, *J* = 11.6 Hz, 2H), 4.32 (q, *J* = 6.8 Hz, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 3.42 (d, *J* = 11.6 Hz, 1H), 3.24 – 3.19 (m, 1H), 2.40 (t, *J* = 13.6 Hz, 1H), 2.04 – 2.01 (m, 1H), 1.84 – 1.77 (m, 2H), 1.69 – 1.34 (m, 13H), 1.26 – 1.12 (m, 4H), 1.02 – 0.85 (m, 7H), 0.73 – 0.66 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.9, 137.5, 137.4, 136.2, 131.9, 131.1, 127.6, 124.2, 122.8, 121.6, 108.8, 80.7, 66.4, 62.4, 61.7, 56.1, 55.3, 47.3, 43.2, 41.6, 34.6, 33.2, 31.7, 31.5, 30.2, 29.9, 28.9, 24.5, 24.2, 22.3, 19.7, 17.6, 16.7, 15.1, 14.0 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{38}H_{50}BrN_2O_3$ $[M\text{-}Br]^+$ 661.2999, found 661.2997.

*4.1.8.4 3-(2-(naphthalen-2-yl)-2-oxoethyl)-1-((2S,2aR,3aR,5aR,5'R,7aS,8S,9R)-5a,5',7a,8-tetramethylicosahydro-2H-spiro[cyclopropa[1',7a']indeno[5',4':4,5]indeno[2,1-b]furan-9,2'-pyran]-2-yl)-1H-imidazol-3-ium bromide (**a11**)*. Yield 98%. White powder, m.p. 265 – 267 °C. IR ν_{max} (cm^{-1}): 3447, 2953, 1693, 1629, 1455, 1153, 1126, 1053, 982, 898, 746. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, *J* = 1.6 Hz, 1H), 8.88 (d, *J* = 1.6 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.08 – 8.04 (m, 2H), 7.96 (t, *J* = 1.6 Hz, 1H), 7.84 (t, *J* = 1.6 Hz, 1H), 7.77 – 7.68 (m, 2H), 6.25 (s, 2H), 4.33 (q, *J* = 7.2 Hz, 1H), 4.10 (d, *J* = 3.2 Hz, 1H), 3.44 – 3.40 (m, 1H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.45 – 2.42 (m, 1H), 2.08 – 2.02 (m, 1H), 1.86 – 1.78 (m, 2H), 1.70 – 1.53 (m, 8H), 1.48 – 1.36 (m, 4H), 1.32 – 1.12 (m, 5H), 1.03 – 0.95 (m, 4H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.75 – 0.71 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 137.5, 136.0, 132.5, 131.4, 130.9, 130.1, 129.8, 129.3, 128.4, 127.9, 124.3, 123.6, 121.6, 108.8, 80.7, 66.4, 62.4, 61.7, 56.1, 55.3, 47.3, 43.2, 41.6, 34.7, 33.2, 31.7, 31.5, 30.2, 30.0, 29.0, 24.6, 24.2, 22.3, 19.7, 17.6, 16.7, 15.2, 14.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{42}H_{53}N_2O_3$ $[M\text{-}Br]^+$ 633.4051, found 633.4051.

*4.1.8.5 3-(2-bromobenzyl)-1-((2S,2aR,3aR,5aR,5'R,7aS,8S,9R)-5a,5',7a,8-tetramethylicosahydro-2H-spiro[cyclopropa[1',7a']indeno[5',4':4,5]indeno[2,1-b]furan-9,2'-pyran]-2-yl)-1H-imidazol-3-ium bromide (**a12**)*. Yield 82%. White powder, m.p. 220 – 222 °C. IR ν_{max} (cm^{-1}): 3426, 2952, 1629, 1452, 1149, 1051, 983, 749. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 7.94 (s, 1H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.49 – 7.45 (m, 1H), 7.39 – 7.36 (m, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 5.62 (s, 2H), 4.32 (q, *J* = 7.2 Hz, 1H), 4.04 (s, 1H), 3.44 – 3.40 (m, 1H), 3.22 (t, *J* = 10.8 Hz, 1H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.85 – 1.77 (m, 2H), 1.70 – 1.46 (m, 10H), 1.42 – 1.13 (m, 9H), 1.01 (d, *J* = 7.2 Hz, 1H), 0.97 – 0.88 (m, 7H), 0.69 (s, 3H), 0.63 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.7, 134.4, 133.6, 131.4, 130.8, 128.9, 123.2, 122.8, 122.7, 108.8, 80.7, 66.4,

62.3, 61.8, 55.3, 52.7, 47.2, 43.1, 41.6, 34.5, 33.2, 31.7, 31.5, 30.3, 29.9, 29.0, 24.7, 24.7, 22.2, 19.7, 17.6, 16.8, 15.2, 14.0 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{37}H_{50}BrN_2O_2$ $[M\text{-}Br]^+$ 633.305, found 633.305.

*4.1.8.6 3-(naphthalen-2-ylmethyl)-1-((2S,2aR,3aR,5aR,5'R,7aS,8S,9R)-5a,5',7a,8-tetramethylicosahydro-2H-spiro[cyclopropa[1',7a']indeno[5',4':4,5]indeno[2,1-b]furan-9,2'-pyran]-2-yl)-1H-imidazol-3-ium bromide (**a13**).* Yield 75%. White powder, m.p. 256 – 258 °C. IR ν_{max} (cm^{-1}): 3408, 2952, 1454, 1382,1148, 1126, 1099, 983, 899, 818, 759. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.25 (s, 1H), 8.06 (s, 1H), 7.87 – 7.78 (m, 3H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.29 (d, *J* = 3.6 Hz, 1H), 6.05 – 5.86 (m, 2H), 4.40 (s, 1H), 3.94 (s, 1H), 3.48 – 3.27 (m, 2H), 2.41 – 2.11 (m, 3H), 1.84 – 1.33 (m, 15H), 1.28 – 1.02 (m, 7H), 0.98 – 0.94 (m, 4H), 0.80 – 0.78 (m, 2H), 0.66 – 0.62 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 133.3, 133.1, 131.2, 129.3, 128.7, 128.2, 127.7, 126.9, 126.7, 125.9, 121.6, 120.3, 109.6, 109.1, 80.4, 66.8, 65.1, 62.6, 62.1, 61.9, 55.3, 53.4, 47.4, 43.2, 42.0, 41.5, 40.6, 39.5, 34.3, 34.0, 33.1, 31.6, 31.4, 30.2, 30.2, 28.7, 27.0, 26.0, 25.7, 25.3, 24.0, 22.1, 19.9, 17.2, 16.4, 16.0, 14.7, 14.5, 14.3 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{41}H_{53}N_2O_2$ $[M\text{-}Br]^+$ 605.4102, found 605.4103.

*4.1.8.7 3-(2-oxo-2-phenylethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a14**).* Yield 72%. Pale yellow powder, m.p. 265 – 267 °C. IR ν_{max} (cm^{-1}): 3423, 2948, 1696, 1599, 1512, 1375, 1355, 1238, 1171, 1056, 988, 833. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.11 – 8.05 (m, 3H), 7.79 – 7.75 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 2H), 6.08 (s, 2H), 5.47 (d, *J* = 4.8 Hz, 1H), 4.40 – 4.27 (m, 2H), 3.22 (t, *J* = 12.0 Hz 1H), 2.76 (t, *J* = 12.4 Hz, 1H), 2.06 – 1.90 (m, 5H), 1.86 – 1.77 (m, 2H), 1.74 – 1.67 (m, 2H), 1.65 – 1.46 (m, 7H), 1.36 – 1.27 (m, 2H), 1.21 – 1.14 (m, 3H), 1.11 (s, 3H), 1.02 – 0.91 (m, 6H), 0.76 – 0.73 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.8, 139.6, 136.8, 135.0, 134.1, 129.6, 128.6, 124.5, 123.0, 120.9, 80.6, 66.4, 62.3, 59.8, 56.2, 55.9, 49.9, 41.6, 38.8, 37.6, 36.8, 31.9, 31.4, 30.3, 28.9, 20.8, 19.5, 17.5, 16.6, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{38}H_{51}N_2O_3$ $[M\text{-}Br]^+$ 583.3894, found 583.3894.

*4.1.8.8 3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a15**).* Yield 83%. White powder, m.p. 280 – 282 °C. IR ν_{max} (cm^{-1}): 3428, 2949, 1703, 1563, 1452, 1224, 1166, 1051, 1007, 674. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.12 – 8.04 (m,

3H), 7.77 (d, *J* = 12.0 Hz, 1H), 7.19 – 7.14 (m, 2H), 6.03 (d, *J* = 13.2 Hz, 2H), 5.50 (s, 1H), 4.42 – 4.26 (m, 2H), 3.90 (d, *J* = 13.2 Hz, 3H), 3.26 – 3.21 (m, 1H), 2.77 (d, *J* = 10.8 Hz, 1H), 2.05 – 1.81 (m, 6H), 1.76 – 1.45 (m, 10H), 1.34 – 1.30 (m, 1H), 1.23 – 1.18 (m, 3H), 1.11 (d, *J* = 11.6 Hz, 4H), 1.05 – 0.90 (m, 6H), 0.79 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.0, 164.6, 139.5, 136.8, 131.1, 126.9, 124.5, 123.0, 120.8, 114.8, 108.9, 80.6, 66.4, 62.3, 59.8, 56.3, 56.2, 56.1, 55.5, 49.8, 41.6, 38.8, 37.6, 36.8, 31.9, 31.4, 30.3, 28.9, 20.8, 19.5, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{39}H_{53}N_2O_4$ $[M\text{-}Br]^+$ 613.4, found 613.3999.

*4.1.8.9 3-(2-(3-bromophenyl)-2-oxoethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a16**)*. Yield 73%. Pale brown powder, m.p. 170 – 172 °C. IR ν_{max} (cm^{-1}): 3424, 2949, 1695, 1627, 1596, 1454, 1370, 1167, 1096, 1007, 898, 750. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 6.08 (s, 2H), 5.47 (d, *J* = 4.8 Hz, 1H), 4.40 – 4.27 (m, 2H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.06 – 1.95 (m, 4H), 1.94 – 1.89 (m, 1H), 1.86 – 1.77 (m, 2H), 1.73 – 1.42 (m, 11H), 1.36 – 1.26 (m, 2H), 1.23 – 1.15 (m, 2H), 1.11 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 2H), 0.95 – 0.91 (m, 3H), 0.76 – 0.73 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.9, 139.5, 137.5, 136.7, 136.2, 131.8, 131.1, 127.6, 124.5, 123.0, 121.0, 108.9, 80.6, 66.4, 62.3, 59.9, 56.2, 55.9, 49.8, 41.6, 38.8, 37.6, 36.8, 32.0, 31.4, 30.3, 29.0, 28.9, 20.8, 19.5, 17.6, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{38}H_{50}BrN_2O_3$ $[M\text{-}Br]^+$ 661.2999, found 661.2999.

*4.1.8.10 3-(2-(naphthalen-2-yl)-2-oxoethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6, 6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a17**)*. Yield 94%. White powder, m.p. 270 – 272 °C. IR ν_{max} (cm^{-1}): 3415, 2949, 1695, 1560, 1454, 1370, 1167, 1125, 1007, 898, 863, 750. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.15 – 8.12 (m, 2H), 8.08 – 8.02 (m, 2H), 7.83 (s, 1H), 7.77 – 7.67 (m, 2H), 6.23 (s, 2H), 5.48 (d, *J* = 4.8 Hz, 1H), 4.42 – 4.27 (m, 2H), 3.43 – 3.40 (m, 1H), 3.24 – 3.19 (m, 1H), 2.82 – 2.75 (m, 1H), 2.08 – 1.95 (m, 4H), 1.94 – 1.89 (m, 1H), 1.85 – 1.80 (m, 1H), 1.71 – 1.48 (m, 11H), 1.35 – 1.27 (m, 2H), 1.23 – 1.16 (m, 3H), 1.11 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.76 – 0.73 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 139.6, 136.8, 136.0, 132.5, 131.4, 131.0, 130.2, 129.8, 129.3, 128.3, 127.9, 124.6, 123.6, 123.0, 121.0, 108.9, 80.6, 66.4, 62.3, 59.9, 56.2, 55.9,

49.8, 41.6, 38.8, 37.6, 36.8, 32.0, 31.4, 30.3, 28.9, 20.8, 19.5, 17.6, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{42}H_{53}N_2O_3$ $[M\text{-}Br]^+$ 633.4051, found 611.4052.

*4.1.8.11 3-(2-bromobenzyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a, 8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a18**).* Yield 88%. White powder, m.p. 266 – 268 °C. IR ν_{max} (cm^{-1}): 3430, 2949, 1618, 1561, 1451, 1377, 1158, 1067, 982, 746. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.10 (d, *J* = 2.8 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.41 – 7.36 (m, 2H), 5.53 (s, 2H), 5.44 (d, *J* = 4.8 Hz, 1H), 4.31 – 4.23 (m, 2H), 3.42 – 3.39 (m, 1H), 3.20 (t, *J* = 10.4 Hz, 1H), 2.74 (t, *J* = 12.8 Hz, 1H), 2.47 – 2.44 (m, 1H), 2.04 – 1.88 (m, 5H), 1.84 – 1.78 (m, 1H), 1.72 – 1.44 (m, 10H), 1.35 – 1.29 (m, 1H), 1.19 – 1.15 (m, 3H), 1.09 (s, 3H), 1.01 – 0.90 (m, 5H), 0.75 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.6, 136.3, 134.0, 133.6, 131.5, 131.3, 129.0, 123.5, 123.2, 122.9, 121.7, 108.9, 80.6, 66.4, 62.3, 60.0, 56.1, 52.7, 49.8, 41.6, 38.8, 37.6, 36.8, 31.9, 31.4, 31.4, 30.3, 28.9, 28.8, 20.8, 19.5, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{37}H_{50}BrN_2O_2$ $[M\text{-}Br]^+$ 633.305, found 633.3051.

*4.1.8.12 3-(naphthalen-2-ylmethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b, 6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a19**).* Yield 90%. White powder, m.p. 325 – 327 °C. IR ν_{max} (cm^{-1}): 3431, 2949, 1561, 1451, 1157, 1051, 1028, 746. H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 8.02 (s, 1H), 7.97 – 7.92 (m, 4H), 7.59 – 7.55 (m, 3H), 5.61 (s, 2H), 5.43 (d, *J* = 4.8 Hz, 1H), 4.32 – 4.19 (m, 2H), 3.20 (t, *J* = 11.2 Hz, 1H), 2.73 (t, *J* = 12.4 Hz, 1H), 2.01 – 1.88 (m, 5H), 1.83 – 1.78 (m, 1H), 1.71 – 1.43 (m, 11H), 1.36 – 1.28 (m, 1H), 1.18 – 1.13 (m, 3H), 1.08 (s, 3H), 1.01 – 0.90 (m, 6H), 0.74 – 0.71 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 139.6, 136.9, 136.8, 136.0, 132.5, 131.4, 131.0, 130.2, 129.8, 129.3, 128.3, 127.9, 124.6, 123.6, 123.0, 121.0, 108.8, 80.7, 66.4, 62.3, 59.9, 56.2, 55.9, 49.8, 41.6, 38.8, 37.6, 36.8, 32.0, 31.4, 30.3, 29.0, 20.8, 19.5, 17.6, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{41}H_{53}N_2O_2$ $[M\text{-}Br]^+$ 605.4102, found 605.41.

*4.1.8.13 3-(2-oxo-2-phenylethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b, 6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a20**).* Yield 74%. Pale yellow powder, m.p. 279 – 281 °C. IR ν_{max} (cm^{-1}):

3431, 2949, 1697, 1598, 1449, 1224, 1052, 983, 755, 685. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.19 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 2H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 7.2 Hz, 1H), 7.72 – 7.65 (m, 4H), 6.44 (s, 2H), 5.54 (d, *J* = 4.8 Hz, 1H), 4.79 – 4.71 (m, 1H), 4.32 (q, *J* = 6.8 Hz, 1H), 3.25 – 3.19 (m, 1H), 2.90 (t, *J* = 12.8 Hz, 1H), 2.64 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.18 – 2.12 (m, 2H), 2.04 – 1.99 (m, 2H), 1.96 – 1.91 (m, 1H), 1.87 – 1.79 (m, 1H), 1.75 – 1.69 (m, 2H), 1.67 – 1.45 (m, 8H), 1.41 – 1.30 (m, 3H), 1.23 – 1.19 (m, 2H), 1.14 (s, 3H), 1.09 – 1.00 (m, 2H), 0.97 – 0.92 (m, 3H), 0.77 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 142.6, 139.5, 135.1, 134.2, 132.4, 130.7, 129.6, 128.9, 127.3, 127.0, 123.2, 114.5, 108.9, 80.7, 66.4, 62.3, 57.8, 56.2, 53.7, 49.9, 41.6, 38.0, 37.5, 37.0, 32.0, 31.9, 31.4, 30.3, 29.0, 28.4, 20.9, 19.5, 17.6, 16.5, 15.2 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{42}H_{53}N_2O_3$ $[M\text{-}Br]^+$ 633.4051, found 633.405.

*4.1.8.14 3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a21**)*. Yield 72%. White powder, m.p. 220 – 222 °C. IR ν_{max} (cm^{-1}): 3424, 2949, 1687, 1601, 1561, 1242, 1174, 1052, 983, 829, 760. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 – 10.08 (m, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.36 (s, 2H), 5.53 (d, *J* = 4.8 Hz, 1H), 4.78 – 4.70 (m, 1H), 4.31 (q, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.89 (t, *J* = 12.8 Hz, 1H), 2.64 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.17 – 2.08 (m, 2H), 2.03 – 1.99 (m, 2H), 1.94 – 1.91 (m, 1H), 1.85 – 1.81 (m, 1H), 1.75 – 1.69 (m, 2H), 1.64 – 1.26 (m, 10H), 1.23 – 1.15 (m, 3H), 1.14 (s, 3H), 1.09 – 1.01 (m, 2H), 0.96 – 0.92 (m, 3H), 0.86 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.8, 164.7, 142.6, 139.5, 132.4, 131.4, 130.7, 127.3, 127.0, 123.2, 114.8, 114.4, 108.9, 80.7, 66.4, 62.3, 57.8, 56.3, 56.2, 49.9, 41.6, 38.1, 37.5, 37.0, 32.0, 31.4, 30.3, 28.9, 28.5, 21.2, 20.9, 19.5, 17.5, 16.5, 15.1, 14.6 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{43}H_{55}N_2O_4$ $[M\text{-}Br]^+$ 663.4156, found 663.4156.

*4.1.8.15 3-(2-(3-bromophenyl)-2-oxoethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a22**)*. Yield 79%. Pale yellow powder, m.p. 218 – 220 °C. IR ν_{max} (cm^{-1}): 3424, 2949, 1702, 1562, 1451, 1218, 1051, 982, 919, 759, 678. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.30 (s, 1H), 8.20 – 8.18 (m, 1H), 8.13 – 8.07 (m, 2H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.72 – 7.62 (m, 3H), 6.43 (d, *J*

= 4.8 Hz, 2H), 5.54 (d, *J* = 4.8 Hz, 1H), 4.79 – 4.71 (m, 1H), 4.31 (q, *J* = 7.6 Hz, 1H), 3.21 (t, *J* = 11.2 Hz, 1H), 2.89 (t, *J* = 13.2 Hz, 1H), 2.66 – 2.62 (m, 1H), 2.17 – 2.11 (m, 2H), 2.05 – 1.99 (m, 2H), 1.96 – 1.91 (m, 1H), 1.87 – 1.79 (m, 1H), 1.75 – 1.69 (m, 2H), 1.67 – 1.48 (m, 7H), 1.42 – 1.26 (m, 3H), 1.23 – 1.15 (m, 3H), 1.13 (s, 3H), 1.09 – 1.00 (m, 2H), 0.96 – 0.91 (m, 3H), 0.77 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.8, 142.5, 139.5, 137.6, 136.2, 132.4, 131.8, 131.4, 130.7, 127.8, 127.3, 127.1, 123.2, 122.8, 114.5, 108.9, 80.7, 66.4, 62.3, 60.2, 57.9, 56.2, 53.7, 49.9, 41.6, 38.0, 37.5, 36.9, 32.0, 31.9, 31.4, 30.3, 28.9, 28.4, 21.2, 20.9, 19.5, 17.6, 16.5, 15.1, 14.6 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{42}H_{52}BrN_2O_3$ $[M\text{-}Br]^+$ 711.3156, found 711.3156.

*4.1.8.16 3-(2-(naphthalen-2-yl)-2-oxoethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a23**)*. Yield 90%. Pale yellow powder, m.p. 237 – 239 °C. IR ν_{max} (cm^{-1}): 3407, 2949, 1694, 1626, 1595, 1452, 1364, 1258, 1180, 1051, 982, 919, 748. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.98 (s, 1H), 8.25 – 8.20 (m, 2H), 8.16 – 8.12 (m, 2H), 8.09 – 8.06, 2H), 7.78 – 7.66 (m, 4H), 6.58 (s, 2H), 5.54 (d, *J* = 5.2 Hz, 1H), 4.81 – 4.72 (m, 1H), 4.31 (q, *J* = 7.6 Hz, 1H), 3.25 – 3.19 (m, 1H), 2.92 (t, *J* = 12.8 Hz, 1H), 2.66 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.19 – 2.13 (m, 1H), 2.05 – 2.01 (m, 2H), 1.96 – 1.92 (m, 1H), 1.85 – 1.80 (m, 1H), 1.75 – 1.44 (m, 10H), 1.41 – 1.26 (m, 3H), 1.23 – 1.14 (m, 6H), 1.09 – 1.00 (m, 2H), 0.97 – 0.92 (m, 3H), 0.77 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 142.7, 139.5, 136.1, 132.5, 131.5, 130.7, 130.2, 129.9, 129.2, 128.4, 127.9, 127.3, 127.0, 123.8, 123.2, 114.5, 108.9, 80.7, 66.4, 62.3, 57.9, 56.2, 53.7, 49.9, 41.6, 38.1, 37.5, 36.9, 32.0, 31.9, 31.4, 30.3, 29.0, 28.5, 20.9, 19.5, 17.6, 16.5, 15.2 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{46}H_{55}N_2O_3$ $[M\text{-}Br]^+$ 683.4207, found 683.4207.

*4.1.8.17 3-(2-bromobenzyl)-1-((4R,6aR,8aS,9S,10R)-6a,8a,9-trimethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a, 12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a24**)*. Yield 96%. White powder, m.p. 205 – 207 °C. IR ν_{max} (cm^{-1}): 3425, 2951, 1618, 1559, 1447, 1379, 1096, 981, 746. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.19 (t, *J* = 7.6 Hz, 1H), 7.82 – 7.62 (m, 4H), 7.42 – 7.32 (m, 3H), 5.86 (s, 2H), 5.51 (d, *J* = 6.0 Hz, 1H), 4.69 (q, *J* = 7.6 Hz, 1H), 4.32 – 4.26 (m, 1H), 3.21 (t, *J* = 10.0 Hz, 1H), 2.98 – 2.90 (m, 1H), 2.63 – 2.59 (m, 1H), 2.20 – 1.92 (m, 5H), 1.84 – 1.80 (m, 1H), 1.72 – 1.46 (m, 9H), 1.40 – 1.30 (m, 3H), 1.21 – 1.13 (m, 6H),

1.05 – 0.99 (m, 2H), 0.95 – 0.89 (m, 3H), 0.77 – 0.70 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.5, 139.6, 133.7, 133.2, 131.4, 131.3, 131.2, 130.7, 128.9, 127.4, 127.16 , 127.2, 123.2, 123.1, 114.7, 114.2, 108.9, 80.7, 66.4, 62.3, 58.0, 56.2, 51.0, 49.9, 41.6 , 38.0, 37.5, 36.9, 32.0, 31.9, 31.4, 30.3, 28.9, 28.4, 20.9, 19.6, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{41}H_{52}BrN_2O_2$ $[M\text{-}Br]^+$ 683.3207, found 683.3206.

*4.1.8.18 3-(naphthalen-2-ylmethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a25**).* Yield 87%. White powder, m.p. 216 – 218 °C. IR ν_{max} (cm^{-1}): 3439, 2945, 1554, 1449, 1383, 1240, 1097, 1075, 1034, 736. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.15 (s, 2H), 7.97 – 7.91 (m, 4H), 7.66 – 7.53 (m, 5H), 5.96 (s, 2H), 5.52 (d, *J* = 4.8 Hz, 1H), 4.71 – 4.65 (m, 1H), 4.31 (q, *J* = 7.6 Hz, 1H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.98 (t, *J* = 12.8 Hz, 1H), 2.67 – 2.63 (m, 1H), 2.22 – 2.16 (m, 2H), 2.03 – 1.99 (m, 2H), 1.95 – 1.80 (m, 2H), 1.74 – 1.48 (m, 10H), 1.38 – 1.29 (m, 2H), 1.22 – 1.13 (m, 6H), 1.07 – 0.99 (m, 2H), 0.96 – 0.91 (m, 3H), 0.77 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.8, 139.7, 133.2, 132.0, 131.4, 131.3, 129.2, 128.4, 128.1, 127.9, 127.2 , 127.1, 126.0, 123.1, 114.6, 114.4, 108.9, 80.7, 66.4, 62.3, 60.2, 57.9, 56.2, 50.8, 49.9, 41.6, 38.0, 37.5, 37.0, 32.0, 31.9, 31.4, 30.3, 28.9, 28.4, 20.9, 19.7, 17.5, 16.5, 15.1, 14.5 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{45}H_{55}N_2O_2$ $[M\text{-}Br]^+$ 655.4258, found 655.4261.

*4.1.8.19 5,6-dimethyl-3-(2-oxo-2-phenylethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a26**).* Yield 79%. Pale brown powder, m.p. 284 – 286 °C. IR ν_{max} (cm^{-1}): 3425, 2949, 1698, 1560, 1449, 1375, 1224, 1051, 981, 757, 688, 616. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.13 (d, *J* = 7.6 Hz, 2H), 7.99 (s, 1H), 7.87 (s, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 2H), 6.36 (s, 2H), 5.54 (d, *J* = 4.8 Hz, 1H), 4.69 – 4.61 (m, 1H), 4.31 (q, *J* = 7.6 Hz, 1H), 3.22 (d, *J* = 11.2 Hz, 1H), 2.87 (t, *J* = 13.2 Hz, 1H), 2.64 – 2.60 (m, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 2.15 – 2.09 (m, 2H), 2.02 – 1.98 (m, 1H), 1.96 – 1.90 (m, 1H), 1.87 – 1.79 (m, 1H), 1.74 – 1.47 (m, 11H), 1.41 – 1.30 (m, 3H), 1.22 – 1.16 (m, 2H), 1.13 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.86 – 0.80 (m, 1H), 0.76 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 141.2, 139.5, 137.0, 136.8, 135.1, 134.2, 130.9, 129.5, 129.2, 128.9, 123.2, 113.9, 108.9, 80.66 , 66.4, 62.3, 57.7, 56.2, 53.6, 49.9, 41.6, 38.1, 37.6, 36.9, 32.0, 31.9, 31.4, 30.3, 28.9,

28.5, 20.8, 20.4, 19.5, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{44}H_{57}N_2O_3$ $[M\text{-}Br]^+$ 661.4364, found 661.4364.

*4.1.8.20 3-(2-(4-methoxyphenyl)-2-oxoethyl)-5,6-dimethyl-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a27**).* Yield 72%. Pale brown powder, m.p. 237 – 239 °C. IR ν_{max} (cm^{-1}): 3424, 2948, 1685, 1600, 1560, 1241, 1172, 1096, 1008, 837. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.98 (s, 1H), 7.84 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.29 (s, 2H), 5.53 (d, *J* = 4.8 Hz, 1H), 4.68 – 4.60 (m, 1H), 4.30 (q, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.86 (t, *J* = 13.2 Hz, 1H), 2.642– 2.59 (m, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 2.14 – 2.08 (m, 2H), 2.02 – 1.99 (m, 1H), 1.95 – 1.90 (m, 1H), 1.85 – 1.80 (m, 1H), 1.74 – 1.47 (m, 11H), 1.40 – 1.29 (m, 3H), 1.21 – 1.18 (m, 2H), 1.12 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.85 – 0.80 (m, 1H), 0.76 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.8, 164.7, 141.3, 139.5, 137.0, 136.7, 131.3, 130.9, 129.2, 127.0, 123.2, 114.8, 113.8, 108.9, 80.7, 62.3, 57.6, 56.3, 53.2, 49.9, 41.6, 38.2, 37.6, 36.9, 32.0, 31.4, 30.3, 29.0, 28.5, 20.8, 20.4, 19.5, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{45}H_{59}N_2O_4$ $[M\text{-}Br]^+$ 691.4469, found 691.4468.

*4.1.8.21 3-(2-(3-bromophenyl)-2-oxoethyl)-5,6-dimethyl-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a28**).* Yield 86%. Pale yellow powder, m.p. 240 – 242 °C. IR ν_{max} (cm^{-1}): 3423, 2949, 1702, 1560, 1452, 1218, 1051, 981, 899. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.29 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.88 (s, 1H), 7.64 (t, *J* = 80 Hz, 1H), 6.36 (s, 2H), 5.53 (d, *J* = 4.8 Hz, 1H), 4.69 – 4.61 (m, 1H), 4.30 (q, *J* = 7.6 Hz, 1H), 3.22 (t, *J* = 10.8 Hz, 1H), 2.87 (t, *J* = 12.8 Hz, 1H), 2.63 – 2.59 (m, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 2.14 – 2.08 (m, 2H), 2.01 – 1.98 (m, 1H), 1.94 – 1.90 (m, 1H), 1.85 – 1.78 (m, 1H), 1.74 – 1.47 (m, 11H), 1.40 – 1.28 (m, 3H), 1.21 – 1.72 (m, 2H), 1.12 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 1H), 0.92 (d, *J* = 6.88 Hz, 3H), 0.84 – 0.80 (m, 1H), 0.76 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.8, 141.2, 139.5, 137.6, 137.1, 136.8, 136.2, 131.8, 131.4, 130.8, 129.2, 127.8, 123.2, 122.8, 113.9, 108.9, 80.7, 66.4, 62.3, 57.7, 56.2, 53.7, 49.9, 41.6, 38.1, 37.6, 36.9, 31.9, 31.4, 30.3, 28.9, 28.5, 20.8, 20.5, 20.4, 19.5, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{44}H_{56}BrN_2O_3$ $[M\text{-}Br]^+$ 739.3469, found 739.3469.

*4.1.8.22 5,6-dimethyl-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a29**).* Yield 87%. Pale brown powder, m.p. 231 – 233 ^{o}C. IR ν_{max} (cm^{-1}): 3416, 2949, 1690, 1626, 1560, 1451, 1373, 1178, 1051, 981, 821. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.96 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.07 (t, *J* = 6.8 Hz, 2H), 8.00 (s, 1H), 7.92 (s, 1H), 7.78 – 7.69 (m, 2H), 6.50 (s, 2H), 5.54 (d, *J* = 4.8 Hz, 1H), 4.71 – 4.64 (m, 1H), 4.30 (q, *J* = 7.6 Hz, 1H), 3.21 (t, *J* = 10.8 Hz, 1H), 2.89 (t, *J* = 12.8 Hz, 1H), 2.66 – 2.61 (m, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 2.16 – 2.10 (m, 2H), 2.05 – 1.99 (m, 1H), 1.96 – 1.92 (m, 1H), 1.86 – 1.80 (m, 1H), 1.74 – 1.47 (m, 11H), 1.44 – 1.25 (m, 5H), 1.13 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.86 – 0.80 (m, 1H), 0.76 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 141.3, 139.5, 137.0, 136.8, 136.1, 132.5, 131.5, 131.4, 130.9, 130.2, 129.9, 129.3, 129.2, 128.4, 127.9, 123.7, 123.2, 113.9, 108.9, 80.7, 66.4, 62.3, 57.7, 56.2, 53.6, 49.9, 41.6, 38.2 , 37.6, 36.9, 32.0, 31.9, 31.4, 30.3, 29.0, 28.5, 20.8, 20.4, 19.5, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{48}H_{59}N_2O_3$ [M-Br]$^{+}$ 711.452, found 711.4522.

*4.1.8.23 3-(2-bromobenzyl)-5,6-dimethyl-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a30**).* Yield 68%. White powder, m.p. 228 – 230 ^{o}C. IR ν_{max} (cm^{-1}): 3548, 3474, 3414, 2947, 1617, 1553, 1450, 1218, 1026, 981, 765, 602. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.39 (s, 1H), 7.66 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.33 – 7.28 (m, 2H), 7.21 – 7.18 (m, 1H), 6.01 (s, 2H), 5.45 (d, *J* = 4.8 Hz, 1H), 4..43 – 4.32 (m, 2H), 3.47 – 3.32 (m, 2H), 3.14 – 3.07 (m, 1H), 2.62 – 2.52 (m, 2H), 2.38 (s, 3H), 2.33 (s, 3H), 2.22 – 2.19 (m, 1H), 2.10 – 1.95 (m, 4H), 1.89 – 1.81 (m, 2H), 1.79 – 1.73 (m, 2H), 1.69 – 1.58 (m, 5H), 1.52 – 1.49 (m, 2H), 1.34 – 1.26 (m, 2H), 1.20 (s, 3H), 1.13 – 1.04 (m, 3H), 0.99 – 0.94 (m, 3H), 0.78 – 0.75 (m, 6H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 141.0, 138.9, 137.3, 137.1, 133.3, 132.4, 131.3, 130.7, 129.9, 129.3, 129.0, 128.6, 128.2, 123.6, 123.5, 113.7, 112.8, 109.3, 80.8, 66.8, 62.1, 59.1, 56.5, 50.7, 50.0, 41.6, 40.3, 39.7, 39.0, 37.9, 37.1, 32.0, 31.8, 31.4, 31.3, 30.3, 28.8, 28.5, 20.7, 19.7, 17.1, 16.3, 14.5 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{43}H_{56}BrN_2O_2$ [M-Br]$^{+}$ 711.352, found 711.352.

4.1.8.24 5,6-dimethyl-3-(naphthalen-2-ylmethyl)-1-((4R,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-

*4-yl)-1H-benzo[d]imidazol-3-ium bromide (**a31**)*. Yield 94%. Pale yellow powder, m.p. 230 – 232 °C. IR ν_{max} (cm^{-1}): 3415, 2948, 1556, 1451, 1376, 1218, 1051, 981, 920, 777. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.48 (s, 1H), 8.00 (s, 1H), 7.83 – 7.80 (m, 1H), 7.77 – 7.72 (m, 2H), 7.60 – 7.56 (m, 1H), 7.45 – 7.42 (m, 2H), 7.37 – 7.35 (m, 2H), 6.07 (s, 2H), 5.45 (d, *J* = 4.8 Hz, 1H), 4.42 – 4.29 (m, 2H), 3.46 – 3.26 (m, 2H), 3.07 (t, *J* = 13.2 Hz, 1H), 2.62 – 2.57 (m, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 2.25 – 2.20 (m, 2H), 2.08 – 1.97 (m, 3H), 1.89 – 1.84 (m, 1H), 1.78 – 1.70 (m, 2H), 1.66 – 1.53 (m, 5H), 1.50 – 1.40 (m, 4H), 1.31 – 1.22 (m, 3H), 1.17 (d, *J* = 3.2 Hz, 3H), 1.07 – 1.04 (m, 1H), 1.01 – 0.98 (m, 1H), 0.97 – 0.94 (m, 3H), 0.82 – 0.76 (m, 6H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.4, 138.9, 137.3, 137.1, 133.1, 133.2, 130.8, 129.9, 129.5, 129.2, 128.2, 127.9, 127.7, 126.7, 126.6, 125.5, 123.6, 113.6, 112.8, 109.3, 80.8, 66.9, 62.1, 59.0, 56.5, 51.3, 50.0, 41.6, 40.3, 39.7, 39.0, 37.9, 37.1, 32.0, 31.8, 31.4, 31.2, 30.3, 28.8, 28.6, 20.7, 19.6, 17.1, 16.3, 14.5 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{47}H_{59}N_2O_2$ $[M\text{-}Br]^+$ 683.4571, found 683.4571.

*4.1.8.25 3-(2-oxo-2-phenylethyl)-1-((4S,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a32**)*. Yield 69%. Pale yellow powder, m.p. 279 – 281 °C. IR ν_{max} (cm^{-1}): 3549, 3478, 3415, 2946, 1700, 1617, 1449, 1229, 1135, 1049, 983, 757, 618. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.05 (s, 2H), 7.90 (s, 1H), 7.78 – 7.71 (m, 2H), 7.66 – 7.59 (m, 2H), 6.09 (s, 2H), 5.54 (d, *J* = 12.4 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.26 (d, *J* = 7.6 Hz, 1H), 3.23 – 3.16 (m, 1H), 3.01 – 2.93 (m, 1H), 2.61 (t, *J* = 14.8 Hz, 1H), 2.20 – 2.04 (m, 2H), 1.98 – 1.77 (m, 4H), 1.67 – 1.43 (m, 10H), 1.36 – 1.29 (m, 2H), 1.19 – 1.11 (m, 2H), 1.05 (d, *J* = 13.4 Hz, 4H), 0.99 – 0.94 (m, 2H), 0.91 – 0.83 (m, 3H), 0.74 – 0.68 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 137.3, 137.2, 135.0, 134.1, 129.6, 128.6, 124.7, 124.2, 122.0, 108.9, 80.6, 66.4, 62.2, 56.3, 56.2, 56.0, 49.6, 41.5, 37.1, 34.6, 32.4, 31.8, 31.4, 31.2, 30.3, 28.9, 26.3, 20.5, 19.4, 17.5, 16.4, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{38}H_{51}N_2O_3$ $[M\text{-}Br]^+$ 583.3894, found 583.3895.

*4.1.8.26 3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-((4S,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a33**)*. Yield 92%. White powder, m.p. 273 – 275 °C. IR ν_{max} (cm^{-1}): 3422, 2948, 1691, 1602, 1242, 1178, 1049, 983, 839. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.89 (s, 1H), 7.75 (s, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.03 (d, *J* = 3.6 Hz, 2H), 5.56 (d, *J* = 4.8 Hz, 1H), 4.71

(s, 1H), 4.27 (q, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 3.19 (t, *J* = 10.4 Hz, 1H), 2.98 (d, *J* = 15.6 Hz, 1H), 2.63 (d, *J* = 16.0 Hz, 1H), 2.19 – 2.07 (m, 2H), 1.92 – 1.87 (m, 2H), 1.82 – 1.78 (m, 1H), 1.70 – 1.44 (m, 11H), 1.39 – 1.28 (m, 4H), 1.11 (d, *J* = 4.0 Hz, 1H), 1.06 (s, 3H), 1.00 (d, *J* = 7.2 Hz, 1H), 0.94 (s, 1H), 0.92 – 0.89 (m, 3H), 0.73 – 0.71 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 137.3, 137.2, 136.0, 132.5, 131.4, 130.9, 130.1, 129.8, 129.3, 128.4, 127.9, 124.7, 124.3, 123.6, 122.1, 108.9, 80.6, 66.4, 62.2, 56.4, 56.2, 56.0, 49.7, 41.6, 37.1, 34.6, 32.5, 31.9, 31.4, 31.2, 30.3, 28.9, 26.3, 20.5, 19.4, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{39}H_{53}N_2O_4$ $[M\text{-}Br]^+$ 613.4, found 613.3999.

*4.1.8.27 3-(2-(naphthalen-2-yl)-2-oxoethyl)-1-((4S,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a34**)*. Yield 87%. White powder, m.p. 310 – 311 °C. IR ν_{max} (cm^{-1}): 3427, 2941, 1694, 1627, 1561, 1456, 1366, 1169, 1131, 1096, 982, 898, 864, 823, 750. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.84 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.08 – 8.02 (m, 2H), 7.91 (s, 1H), 7.79 – 7.77, 1H), 7.75 – 7.68 (m, 2H), 6.20 (d, *J* = 4.8 Hz, 2H), 5.56 (d, *J* = 4.8 Hz, 1H), 4.73 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 1H), 3.20 (t, *J* = 10.8 Hz, 1H), 3.00 (d, *J* = 15.6 Hz, 1H), 2.64 (d, *J* = 16.0 Hz, 1H), 2.25 – 2.07 (m, 2H), 1.99 – 1.79 (m, 4H), 1.72 – 1.47 (m, 11H), 1.40 – 1.29 (m, 2H), 1.22 – 1.15 (m, 2H), 1.08 (s, 3H), 1.00 (d, *J* = 7.2 Hz, 1H), 0.97 – 0.94 (m, 1H), 0.92 – 0.89 (m, 3H), 0.76 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 137.3, 137.2, 136.0, 132.5, 131.4, 130.9, 130.1, 129.8, 129.3, 128.4, 127.9, 124.7, 124.3, 123.6, 122.1, 108.9, 80.6, 66.4, 62.2, 56.4, 56.2, 56.0, 49.7, 41.6, 37.1, 34.6, 32.5, 31.9, 31.4, 31.2, 30.3, 28.9, 26.3, 20.5, 19.4, 17.5, 16.5, 15.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{42}H_{53}N_2O_3$ $[M\text{-}Br]^+$ 633.4051, found 633.4051.

*4.1.8.28 3-(2-bromobenzyl)-1-((4S,5'R,6aR,8aS,9S,10R)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)-1H-imidazol-3-ium bromide (**a35**)*. Yield 89%. White powder, m.p. 205 – 207 °C. IR ν_{max} (cm^{-1}): 3416, 2945, 1640, 1555, 1451, 1376, 1241, 1160, 1076, 1027, 899, 865, 758, 744, 620. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.89 (s, 1H), 7.78 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 6.4 Hz, 2H), 5.54 (s, 2H), 4.65 (s, 1H), 4.30 (q, *J* = 7.2 Hz, 1H), 3.21 (t, *J* = 10.4 Hz, 1H), 2.94 (d, *J* = 15.8 Hz, 1H), 2.64 (d, *J* = 16.0 Hz, 1H), 2.18 – 2.06 (m, 2H), 1.95 – 1.88 (m, 2H), 1.82 – 1.79 (m, 1H), 1.70 – 1.47 (m, 8H), 1.41 – 1.26 (m, 4H), 1.21 –

1.13 (m, 2H), 1.09 – 0.99 (m, 6H), 0.94 – 0.89 (m, 3H), 0.86 – 0.76 (m, 2H), 0.74 – 0.72 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.5, 136.6, 134.1, 133.7, 131.6, 131.5, 128.9, 124.6, 123.6, 123.0, 122.7, 108.9, 80.6, 66.4, 62.2, 60.2, 56.3, 52.8, 49.8, 41.6, 37.0, 34.4, 32.4, 31.9, 31.8, 31.4, 31.0, 30.3, 28.9, 26.1, 20.5, 19.4, 17.54 16.4, 15.1, 14.5 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{37}H_{50}BrN_2O_2$ $[M\text{-}Br]^+$ 633.305, found 633.305.

4.1.8.29 1-((1aR,3aR,5aR,10S,10aR)-3a,5a-dimethyl-6-((R)-6-methylheptan-2-yl)hexadecahydrocyclopenta [a]cyclopropa[2,3]cyclopenta[1,2-f]naphthalen-10-yl)-3-(2-oxo-2-phenylethyl)-1H-imidazol-3-ium bromide ***(b8)***. Yield 78%. White powder, m.p. 208 – 210 °C. IR ν_{max} (cm^{-1}): 3439, 2953, 1698, 1630, 1448, 1384, 1230, 1160, 1131, 811, 682, 620. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.92 (s, 1H), 7.80 – 7.76 (m, 2H), 7.64 (t, *J* = 8.0 Hz, 2H), 6.14 (s, 2H), 4.08 (s, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 1.95 (d, *J* = 11.6 Hz, 1H), 1.85 – 1.77 (m, 2H), 1.69 – 1.62 (m, 2H), 1.59 – 1.48 (m, 3H), 1.45 – 1.31 (m, 6H), 1.27 – 1.08 (m, 10H), 1.02 – 0.93 (m, 4H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.84 (dd, *J* = 6.4, 2.0 Hz, 6H), 0.72 (s, 3H), 0.64 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 137.5, 135.0, 134.2, 129.6, 128.6, 124.3, 121.5, 61.8, 56.1, 55.8, 47.4, 43.1, 42.7, 36.1, 35.7, 34.4, 33.4, 30.3, 28.3, 27.9, 24.8, 24.2, 23.7, 23.1, 22.9, 22.5, 19.8, 19.0, 14.0, 12.4 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{38}H_{55}N_2O$ $[M\text{-}Br]^+$ 555.4309, found 555.4309.

4.1.8.30 1-((1aR,3aR,5aR,10S,10aR)-3a,5a-dimethyl-6-((R)-6-methylheptan-2-yl)hexadecahydrocyclopenta [a]cyclopropa[2,3]cyclopenta[1,2-f]naphthalen-10-yl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide ***(b9)***. Yield 81%. White powder, m.p. 153 – 155 °C. IR ν_{max} (cm^{-1}): 3418, 2953, 1686, 1602, 1465, 1383, 1242, 1160, 1140, 1030, 989, 834, 600. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.05 (d, *J* = 10.0 Hz, 2H), 7.91 – 7.78 (m, 2H), 7.15 (d, *J* = 10.0 Hz, 2H), 6.08 (d, *J* = 10.0 Hz, 2H), 4.07 (d, *J* = 9.6 Hz, 1H), 3.89 (s, 3H), 2.42 – 2.36 (m, 1H), 1.96 – 1.76 (m, 3H), 1.64 – 1.48 (m, 4H), 1.39 – 1.10 (m, 16H), 0.96 – 0.80 (m, 14H), 0.71 – 0.61 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.0, 164.5, 137.5, 131.0, 127.0, 124.3, 121.4, 114.8, 61.7, 56.2, 56.1, 55.8, 55.7, 47.4, 43.0, 42.7, 36.1, 35.7, 34.4, 33.4, 30.3, 28.3, 27.9, 24.7, 24.2, 23.7, 23.1, 22.9, 22.5, 19.8, 18.9, 14.0, 12.4 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{39}H_{57}N_2O_2$ $[M\text{-}Br]^+$ 585.4415, found 585.4415.

4.1.8.31 3-(2-(3-bromophenyl)-2-oxoethyl)-1-((1aR,3aR,5aR,10S,10aR)-3a,5a-dimethyl-6-((R)-6-methylheptan-2-yl)hexadecahydrocyclopenta[a]cyclopropa[2,3]cyclopenta[1,2-f]naphthalen-10-yl)-1H-imidazol-3-ium

*bromide (**b10**)*. Yield 78%. White powder, m.p. 211 – 213 °C. IR ν_{max} (cm^{-1}): 3420, 2953, 1703, 1564, 1466, 1420, 1222, 1160, 1131, 678, 621. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8. Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 7.79 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 6.16 (s, 2H), 4.09 (s, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 1.94 (d, *J* = 11.6 Hz, 1H), 1.87 – 1.80 (m, 2H), 1.67 – 1.49 (m, 7H), 1.43 – 1.31 (m, 6H), 1.27 – 1.10 (m, 8H), 0.99 – 0.94 (m, 4H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 6H), 0.71 (s, 3H), 0.64 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.9, 137.5, 136.2, 131.9, 131.1, 127.6, 124.2, 122.8, 121.5, 61.8, 56.2, 55.8, 47.4, 43.0, 42.7, 36.1, 35.7, 34.4, 33.4, 30.3, 28.3, 27.9, 24.8, 24.2, 23.7, 23.1, 22.9, 22.6, 19.8, 19.0, 14.0, 12.4 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{38}H_{54}BrN_2O$ $[M\text{-}Br]^+$ 633.3414, found 633.3416.

*4.1.8.32 1-((1aR,3aR,5aR,10S,10aR)-3a,5a-dimethyl-6-((R)-6-methylheptan-2-yl)hexadecahydrocyclopenta [a]cyclopropa[2,3]cyclopenta[1,2-f]naphthalen-10-yl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**b11**)*. Yield 84%. White powder, m.p. 212 – 214 °C. IR ν_{max} (cm^{-1}): 3424, 2952, 1692, 1628, 1468, 1383, 1179, 1124, 857, 746. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.87 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.08 – 8.04 (m, 2H), 7.94 (t, *J* = 1.6 Hz, 1H), 7.83 (t, *J* = 2.0 Hz, 1H), 7.77 – 7.68 (m, 2H), 6.25 (s, 2H), 4.09 (s, 1H), 2.42 (d, *J* = 14.8 Hz, 1H), 1.95 (d, *J* = 11.6 Hz, 1H), 1.85 – 1.78 (m, 2H), 1.679 – 1.48 (m, 5H), 1.45 – 1.19 (m, 10H), 1.17 – 1.01 (m, 6H), 1.02 – 0.94 (m, 4H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.84 (dd, *J* = 6.4, 2.0 Hz, 6H), 0.74 (s, 3H), 0.65 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 137.5, 136.0, 132.5, 131.4, 130.9, 130.1, 129.8, 129.3, 128.4, 127.9, 124.3, 123.6, 121.5, 61.8, 56.1, 55.8, 47.3, 43.1, 42.7, 36.1, 35.7, 34.4, 33.4, 30.4, 28.3, 27.9, 24.8, 24.2, 23.7, 23.1, 22.9, 22.5, 19.8, 19.0, 14.0, 12.4 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{42}H_{57}N_2O$ $[M\text{-}Br]^+$ 605.4465, found 605.4465.

*4.1.8.33 3-(2-bromobenzyl)-1-((1aR,3aR,5aR,10S,10aR)-3a,5a-dimethyl-6-((R)-6-methylheptan-2-yl)hexadeca hydrocyclopenta[a]cyclopropa[2,3]cyclopenta[1,2-f]naphthalen-10-yl)-1H-imidazol-3-ium bromide (**b12**)*. Yield 67%. White powder, m.p. 169 – 171 °C. IR ν_{max} (cm^{-1}): 3439, 2956, 2931, 1630, 1467, 1442, 1382, 1141, 1038, 745, 623. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 7.93 (s, 1H), 7.75 – 7.72 (m, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.40 – 7.33 (m, 2H), 5.62 (s, 2H), 4.03 (s, 1H), 2.38 (d, *J* = 14.8 Hz, 1H), 1.92 (d, *J* = 10.4 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.66 – 1.48 (m, 5H), 1.41 – 1.20 (m, 8H), 1.18 – 1.08 (m, 8H), 1.01 – 0.95 (m, 4H), 0.88 (d, *J* = 6.0 Hz, 3H), 0.84 (dd, *J* = 6.8, 2.0 Hz, 6H), 0.63 (s, 3H), 0.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-

d_6) δ 136.7, 134.3, 133.6, 131.4, 131.0, 128.9, 123.3, 122.8, 122.6, 61.9, 56.0, 55.7, 52.7, 47.3, 43.0, 42.7, 36.1, 35.7, 34.3, 33.4, 30.3, 28.2, 27.9, 24.8, 24.2, 23.7, 23.1, 22.9, 22.5, 19.8, 18.9, 13.9, 12.4 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{37}H_{54}BrN_2$ $[M\text{-}Br]^+$ 605.3465, found 605.3466.

*4.1.8.34 1-((1aR,3aR,5aR,10S,10aR)-3a,5a-dimethyl-6-((R)-6-methylheptan-2-yl)hexadecahydrocyclopenta[a] cyclopropa[2,3]cyclopenta[1,2-f]naphthalen-10-yl)-3-(naphthalen-2-ylmethyl)-1H-imidazol-3-ium bromide (**b13**)*. Yield 75%. White powder, m.p. 204 – 206 °C. IR ν_{max} (cm^{-1}): 3416, 2948, 1618, 1466, 1383, 1128, 780, 760, 625. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 7.97 – 7.93 (m, 4H), 7.90 – 7.88 (m, 2H), 7.58 – 7.54 (m, 3H), 5.73 (s, 2H), 4.02 (s, 1H), 2.38 (d, *J* = 14.8 Hz, 1H), 1.89 – 1.77 (m, 3H), 1.64 – 1.46 (m, 5H), 1.38 – 1.22 (m, 7H), 1.20 – 1.05 (m, 9H), 0.99 – 0.90 (m, 4H), 0.87 – 0.83 (m, 9H), 0.62 (s, 3H), 0.51 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.2, 133.3, 133.1, 129.2, 128.2, 128.1, 127.7, 127.2, 127.1, 125.9, 122.7, 122.5, 61.8, 56.0, 55.7, 52.4, 47.3, 43.0, 42.6, 36.1, 35.6, 34.3, 33.3, 30.3, 28.2, 27.9, 24.7, 24.2, 23.7, 23.1, 22.9, 22.5, 19.7, 18.9, 14.1, 12.3 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{41}H_{57}N_2$ $[M\text{-}Br]^+$ 577.4516, found 577.4517.

*4.1.8.35 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-oxo-2-phenylethyl)-1H-imidazol-3-ium bromide (**b14**)*. Yield 85%. White powder, m.p. 211 – 213 °C. IR ν_{max} (cm^{-1}): 3425, 2936, 1693, 1629, 1561, 1449, 1233, 1166, 820, 759, 689, 650. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.12 – 8.05 (m, 3H), 7.78 (s, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 6.10 (s, 2H), 5.47 (s, 1H), 4.35 (s, 1H), 2.76 (t, *J* = 12.8 Hz, 1H), 2.09 – 1.95 (m, 5H), 1.82 – 1.79 (m, 1H), 1.58 – 1.43 (m, 6H), 1.34 – 1.32 (m, 3H), 1.23 – 0.98 (m, 15H), 0.92 – 0.83 (m,9H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.8, 139.5, 136.8, 135.0, 134.1, 129.6, 128.6, 124.5, 123.1, 120.9, 59.9, 56.6, 56.1, 55.9, 49.9, 42.3, 38.8, 37.6, 36.6, 36.1, 36.7, 35.7, 31.8, 28.9, 28.3, 27.9, 24.3, 23.7, 23.1, 22.9, 21.1, 19.5, 19.0, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{38}H_{55}N_2O$ $[M\text{-}Br]^+$ 555.4309, found 555.4311.

*4.1.8.36 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**b15**)*. Yield 76%. Pale yellow powder, m.p. 224 – 226 °C. IR ν_{max} (cm^{-1}): 3415, 2936, 1688, 1602, 1466, 1242, 1167, 1025, 990, 834, 600. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.10 (d, *J* = 2.0 Hz, 1H),

8.03 (d, *J* = 9.2 Hz, 2H), 7.76 (s, 1H), 7.16 – 7.14 (m, 2H), 6.02 (s, 2H), 5.47 (d, *J* = 4.8 Hz, 1H), 4.38 – 4.30 (m, 1H), 3.88 (s, 3H), 2.79 – 2.72 (m, 1H), 2.09 – 1.94 (m, 5H), 1.82 – 1.75 (m, 1H), 1.59 – 1.43 (m, 6H), 1.37 – 1.31 (m, 3H), 1.26 – 0.97 (m, 15H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.84 (dd, *J* = 6.8, 2.0 Hz, 6H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.1, 164.6, 139.5, 136.8, 131.1, 126.9, 124.5, 123.1, 120.8, 114.8, 59.8, 56.6, 56.3, 55.5, 49.9, 42.3, 38.8, 37.6, 36.6, 36.2, 35.7, 31.8, 28.9, 28.3, 27.9, 24.3, 23.7, 23.1, 22.9, 21.0, 19.5, 19.0, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{39}H_{57}N_2O_2$ $[M\text{-}Br]^+$ 585.4415, found 585.4415.

*4.1.8.37 3-(2-(3-bromophenyl)-2-oxoethyl)-1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-1H-imidazol-3-ium bromide (**b16**).* Yield 79%. Pale yellow powder, m.p. 170 – 172 °C. IR ν_{max} (cm^{-1}): 3408, 2947, 1704, 1565, 1467, 1420, 1224, 1164, 995, 827, 678. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.21 (t, *J* = 2.0 Hz, 1H), 8.12 (t, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.97 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 6.10 (s, 2H), 5.46 (d, *J* = 4.8 Hz, 1H), 4.41 – 4.32 (m, 1H), 2.80 – 2.73 (m, 1H), 2.09 – 1.94 (m, 5H), 1.84 – 1.75 (m, 1H), 1.59 – 1.31 (m, 10H), 1.26 – 1.16 (m, 4H), 1.13 – 1.08 (m, 6H), 1.06 – 0.94 (m, 4H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.84 (dd, *J* = 6.4, 2.0 Hz, 6H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.5, 136.7, 131.8, 131.2, 127.6, 124.5, 123.2, 122.8, 120.9, 59.9, 56.6, 56.1, 55.9, 49.9, 42.3, 38.8, 37.6, 36.6, 36.2, 35.7, 31.8, 28.9, 28.2, 27.9, 24.3, 23.7, 23.1, 22.9, 21.1, 19.5, 19.0, 12.2 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{38}H_{54}BrN_2O$ $[M\text{-}Br]^+$ 633.3414, found 633.3414.

*4.1.8.38 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**b17**).* Yield 93%. White powder, m.p. 287 – 289 °C. IR ν_{max} (cm^{-1}): 3415, 2951, 1697, 1628, 1561, 1468, 1367, 1261, 1166, 1124, 861, 749. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.20 (s, 1H), 8.73 (s, 1H), 7.94 (dd, *J* = 20.0, 8.0 Hz, 2H), 7.76 – 7.72 (m, 3H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.39 (s, 1H), 6.52 (s, 2H), 5.39 (s, 1H), 4.04 – 3.98 (m, 1H), 2.58 (t, *J* = 13.2 Hz, 1H), 2.44 – 2.39 (m, 1H), 2.03 – 1.82 (m, 6H), 1.61 – 1.50 (m, 3H), 1.48 – 1.22 (m, 9H), 1.19 – 1.03 (m, 8H), 0.99 (s, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 6H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 190.9, 137.7, 136.6, 132.3, 131.3, 130.1, 129.2, 128.8, 127.6, 127.0, 124.4, 123.3, 119.2, 60.6, 56.6, 56.1, 55.7, 49.8, 42.3, 39.6, 39.5, 39.2, 37.3,

36.5, 36.2, 35.8, 31.8, 31.6, 29.1, 28.2, 28.0, 24.2, 23.8, 22.8, 22.6, 20.9, 19.3, 18.7, 11.9 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{42}H_{57}N_2O$ $[M\text{-}Br]^+$ 605.4465, found 605.4465.

*4.1.8.39 3-(2-bromobenzyl)-1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-1H-imidazol-3-ium bromide (**b18**).* Yield 90%. White powder, m.p. 250 – 252 ^oC. IR ν_{max} (cm^{-1}): 3432, 2937, 1621, 1469, 1164, 1022, 751, 618. ^1H NMR (400 MHz, Chloroform-*d*) δ 10.80 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.42 – 7.37 (m, 2H), 7.31 – 7.25 (m, 1H), 5.81 (s, 2H), 5.46 – 5.45 (m, 1H), 4.30 – 4.22 (m, 1H), 2.78 (td, *J* = 12.8, 2.8 Hz, 1H), 2.58 – 2..53 (m, 1H), 2.17 – 1.82 (m, 7H), 1.59 – 1.42 (m, 6H), 1.40 – 1.12 (m, 6H), 1.18 – 1.11 (m, 3H), 1.08 (s, 3H), 1.04 – 0.95 (m, 4H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.87 (dd, *J* = 6.4, 2.0 Hz, 6H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.4, 133.3, 132.7, 131.4, 128.8, 124.4, 121.8, 120.4, 60.9, 56.6, 56.1, 52.7, 49.8, 42.3, 39.6, 39.5, 39.4, 37.4, 36.5, 36.2, 35.8, 31.8, 31.7, 29.4, 28.2, 27.9, 24.2, 23.8, 22.8, 22.6, 20.9, 19.4, 18.7, 11.9 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{37}H_{54}BrN_2$ $[M\text{-}Br]^+$ 605.3465, found 605.3466.

*4.1.8.40 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazol-3-ium bromide (**b19**).* Yield 97%. Pale yellow powder, m.p. 181 – 183 ^oC. IR ν_{max} (cm^{-1}): 3404, 2936, 1698, 1560, 1449, 1349, 1223, 985, 754, 685. ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.16 – 8.07 (m, 4H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.67 – 7.64 (m, 4H), 6.48 (s, 2H), 5.53 (s, 1H), 4.74 – 4.69 (m, 1H), 2.91 (t, *J* = 12.8 Hz, 1H), 2.63 (d, *J* = 11.6 Hz, 1H), 2.18 – 2.13 (m, 2H), 2.03 – 1.98 (m, 3H), 1.82 (d, *J* = 9.6 Hz, 1H), 1.59 – 1.45 (m, 7H), 1.39 – 1.34 (m, 4H), 1.27 – 1.22 (m, 2H), 1.12 (s, 6H), 1.07 – 1.02 (m, 4H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 6H), 0.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 142.6, 139.5, 135.1, 129.5, 128.9, 127.3, 127.0, 123.3, 114.5, 114.3, 57.9, 56.7, 56.1, 53.8, 49.9, 42.4, 38.1, 37.6, 36.8, 36.2, 35.8, 31.8, 28.4, 28.3, 27.9, 24.4, 23.8, 23.1, 22.9, 21.1, 19.5, 19.0, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{42}H_{57}N_2O$ $[M\text{-}Br]^+$ 605.4465, found 605.4464.

*4.1.8.41 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**b20**).* Yield 86%. White powder, m.p. 210 – 212 ^oC. IR ν_{max} (cm^{-1}): 3462, 2935, 1686, 1608, 1559, 1246, 1176, 987, 830, 761. ^1H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.18 – 8.05 (m, 4H), 7.70 –

7.63 (m, 2H), 7.18 (d, *J* = 9.2 Hz, 2H), 6.39 (s, 2H), 5.54 – 5.52 (m, 1H), 4.76 – 4.69 (m, 1H), 3.91 (s, 3H), 2.95 – 2.88 (m, 1H), 2.65 – 2.61 (m, 1H), 2.15 – 1.99 (m, 4H), 1.83 – 1.81 (m, 1H), 1.62 – 1.19 (m, 13H), 1.17 – 1.10 (m, 6H), 1.07 – 1.00 (m, 5H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.85 (dd, *J* = 6.4, 2.0 Hz, 6H), 0.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.8, 164.7, 142.6, 131.4, 130.7, 127.3, 127.0, 123.3, 114.8, 114.5, 114.3, 57.9, 56.7, 56.3, 56.1, 53.3, 49.9, 42.4, 38.1, 37.6, 36.8, 36.2, 35.7, 31.8, 28.5, 28.3, 27.9, 24.36 , 23.7, 23.1, 22.9, 21.1, 19.5, 19.0, 12.2 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{43}H_{59}N_2O_2$ $[M\text{-}Br]^+$ 635.4571, found 635.4571.

*4.1.8.42 3-(2-bromobenzyl)-1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12, 13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-1H-benzo[d]imidazol-3-ium bromide (**b21**).* Yield 78%. White powder, m.p. 224 – 226 °C. IR ν_{max} (cm^{-1}): 3435, 2931, 1615, 1553, 1469, 1441, 1382, 1026, 763, 753. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.60 (s, 1H), 7.81 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.52 (m, 4H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.23 (td, *J* = 7.6, 1.6 Hz, 1H), 6.14 (s, 2H), 5.50 (d, *J* = 5.2 Hz, 1H), 4.50 – 4.41 (m, 1H), 3.18 (td, *J* = 12.8, 2.8 Hz, 1H), 2.68 – 2.56 (m, 2H), 2.31 – 2.26 (m, 1H), 2.17 – 2.11 (m, 1H), 2.08 – 1.99 (m, 2H), 1.90 – 1.80 (m, 2H), 1.62 – 1.46 (m, 6H), 1.43 – 1.28 (m, 5H), 1.22 (s, 3H), 1.19 – 0.99 (m, 8H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.87 (dd, *J* = 6.8, 1.6 Hz, 6H), 0.71 (s, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 142.3, 133.3, 132.2, 131.7, 130.9, 130.8, 128.7, 127.2, 126.9, 124.1, 114.1, 113.2, 59.5, 56.7, 56.2, 50.9, 50.1, 42.3, 39.7, 39.5, 38.9, 37.9, 36.9, 36.2, 35.8, 31.9, 31.7, 28.5, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.0, 19.6, 18.7, 11.9 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{41}H_{56}BrN_2$ $[M\text{-}Br]^+$ 655.3621, found 655.3623.

*4.1.8.43 1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-5,6-dimethyl-3-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazole-3-ium bromide (**b22**).* Yield 82%. Pale yellow powder, m.p. 193 – 195 °C. IR ν_{max} (cm^{-1}): 3408, 2952, 1454, 1382, 1148, 1126, 1099, 1052, 983, 782. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.14 (d, *J* = 7.6 Hz, 2H), 7.98 (s, 1H), 7.89 (s, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 2H), 6.38 (s, 2H), 5.54 (d, *J* = 4.8 Hz, 1H), 4.69 – 4.61 (m, 1H), 2.88 (t, *J* = 12.8 Hz, 1H), 2.62 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 2.14 (d, *J* = 9.2 Hz, 2H), 2.01 (d, *J* = 13.2 Hz, 3H), 1.86 – 1.77 (m, 1H), 1.61 – 1.33 (m, 11H), 1.27 – 1.18 (m, 2H), 1.14 – 1.11 (m, 4H), 1.04 – 0.99 (m, 6H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.85 (dd, *J* = 6.4, 1.6 Hz, 6H), 0.68 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 141.3, 139.5, 136.9, 136.7, 135.1,

134.2, 130.9, 129.5, 128.9, 123.3, 113.9, 113.8, 57.7, 56.7, 56.1, 53.6, 50.0, 42.4, 38.2, 37.6, 36.8, 36.2, 35.7, 31.8, 28.5, 28.3, 27.9, 24.3, 23.7, 23.1, 22.9, 21.1, 20.4, 20.4, 19.5, 19.0, 12.2 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{44}H_{61}N_2O$ $[M\text{-}Br]^+$ 633.4778, found 633.4778.

*4.1.8.44 3-(2-bromobenzyl)-1-((3R,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-5,6-dimethyl-1H-benzo[d]imidazol-3-ium bromide (**b23**)*. Yield 74%. White powder, m.p. 300 – 302 °C. IR ν_{max} (cm^{-1}): 3431, 2942, 1553, 1468, 1438, 1384, 1219, 1135, 1023, 760, 748. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.98 (s, 1H), 7.74 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.63 (s, 1H), 7.43 – 7.33 (m, 2H), 7.26 (d, *J* = 7.6 Hz, 1H), 5.79 (s, 2H), 5.51 (d, *J* = 5.2 Hz, 1H), 4.66 – 4.58 (m, 1H), 2.95 – 2.89 (m, 1H), 2.59 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 2.20 – 2.11 (m, 2H), 2.03 – 1.99 (m, 3H), 1.85 – 1.76 (m, 1H), 1.61 – 1.18 (m, 13H), 1.15 – 1.10 (m, 6H), 1.07 – 0.99 (m, 4H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.85 (dd, *J* = 6.8, 2.0 Hz, 6H), 0.68 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.2, 139.6, 137.2, 137.0, 133.7, 133.4, 131.2, 130.3, 129.9, 129.7, 128.9, 123.2, 123.0, 114.1, 113.6, 57.8, 56.7, 56.0, 50.9, 49.9, 42.4, 38.2, 37.6, 36.8, 36.2, 35.7, 31.8, 28.5, 28.3, 27.9, 24.4, 23.7, 23.1, 22.9, 21.1, 20.5, 20.4, 19.6, 19.1, 12.2 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{43}H_{60}BrN_2$ $[M\text{-}Br]^+$ 683.3934, found 683.3934.

*4.1.8.45 1-((3S,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-oxo-2-phenylethyl)-1H-imidazol-3-ium bromide (**b24**)*. Yield 89%. White powder, m.p. 268 – 270 °C. IR ν_{max} (cm^{-1}): 3433, 2941, 1700, 1450, 1229, 1141, 757, 687, 652. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 2H), 7.93 (s, 1H), 7.78 (d, *J* = 4.8 Hz, 2H), 7.64 (t, *J* = 8.0 Hz, 2H), 6.14 (s, 2H), 5.58 (d, *J* = 4.4 Hz, 1H), 4.72 (s, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.64 (d, *J* = 16.0 Hz, 1H), 2.24 – 2.09 (m, 1H), 1.99 – 1.90 (m, 2H), 1.79 – 1.73 (m, 1H), 1.67 (d, *J* = 13.6 Hz, 1H), 1.60 – 1.30 (m, 10H), 1.23 – 1.05 (m, 10H), 0.97 – 0.93 (m, 4H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 6H), 0.65 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 137.3, 137.1, 135.0, 134.1, 129.6, 128.6, 124.9, 124.2, 121.9, 56.5, 56.3, 56.0, 49.6, 42.3, 37.0, 36.1, 35.7, 34.5, 32.5, 31.7, 31.6, 28.2, 27.9, 24.3, 23.8, 22.8, 20.7, 19.3, 19.0, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{38}H_{55}N_2O$ $[M\text{-}Br]^+$ 555.4309, found 555.4309.

*4.1.8.46 1-((3S,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**b25**)*. Yield 95%. Pale yellow powder, m.p. 209 – 211 °C. IR ν_{max} (cm^{-1}): 3416, 2938, 1685, 1602, 1466, 1244, 1174, 1025, 988, 835. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.04 – 8.02 (m, 2H), 7.89 (s, 1H), 7.74 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 2H), 5.55 (s, 1H), 4.70 (s, 1H), 3.88 (s, 3H), 2.97 (d, *J* = 15.6 Hz, 1H), 2.63 (d, *J* = 16.0 Hz, 1H), 2.19 – 2.07 (m, 2H), 1.97 – 1.90 (m, 2H), 1.77 – 1.66 (m, 3H), 1.56 – 1.31 (m, 10H), 1.09 – 0.96 (m, 12H), 0.88 (s, 3H), 0.83 (s, 6H), 0.64 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.9, 164.5, 137.3, 137.1, 131.0, 126.9, 124.9, 124.2, 121.8, 114.8, 56.5, 56.2, 56.1, 55.6, 49.6, 42.3, 37.0, 36.1, 35.7, 34.5, 32.5, 31.7, 28.3, 27.9, 26.3, 24.3, 23.7, 23.1, 22.8, 20.7, 19.4, 19.0, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{39}H_{57}N_2O_2$ $[M\text{-}Br]^+$ 585.4415, found 585.4415.

*4.1.8.47 1-((3S,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**b26**)*. Yield 84%. Pale yellow powder, m.p. 231 – 233 °C. IR ν_{max} (cm^{-1}): 3431, 2935, 1695, 1626, 1159, 821, 750. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.85 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.06 (dd, *J* = 12.8, 8.4 Hz, 2H), 7.93 (s, 1H), 7.82 (s, 1H), 7.77 – 7.68 (m, 2H), 6.26 (d, *J* = 2.8 Hz, 2H), 5.58 (d, *J* = 4.4 Hz, 1H), 4.75 (s, 1H), 3.00 (d, *J* = 15.6 Hz, 1H), 2.66 (d, *J* = 16.0 Hz, 1H), 2.25 – 2.11 (m, 2H), 1.99 – 1.92 (m, 2H), 1.80 – 1.68 (m, 2H), 1.61 – 1.15 (m, 11H), 1.13 – 1.06 (m, 8H), 1.02 – 0.93 (m, 4H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.84 (dd, *J* = 6.8, 2.0 Hz, 6H), 0.66 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 137.4, 137.1, 136.0, 132.5, 131.4, 131.0, 130.1, 129.8, 129.3, 128.4, 127.9, 124.9, 124.3, 123.6, 122.0, 56.5, 56.3, 56.1, 49.7, 42.3, 37.0, 36.1, 35.7, 34.5, 32.5, 31.8, 31.7, 28.3, 27.9, 26.3, 24.3, 23.5, 23.1, 22.9, 20.7, 19.4, 19.0, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{42}H_{57}N_2O$ $[M\text{-}Br]^+$ 605.4464, found 605.4465.

*4.1.8.48 3-(2-bromobenzyl)-1-((3S,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-1H-imidazol-3-ium bromide (**b27**)*. Yield 78%. White powder, m.p. 214 – 216 °C. IR ν_{max} (cm^{-1}): 3414, 2935, 1637, 1466, 1136, 1029, 745, 615. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.90 (s, 1H), 7.95 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.54 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.28 (m, 1H), 5.83 (d, *J* = 14.4 Hz, 1H), 5.71 (d, *J* = 14.4 Hz, 1H), 5.61 (d, *J* = 4.8 Hz, 1H), 4.89 (d, *J* = 4.4 Hz, 1H), 2.95 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.70 – 2.65 (m, 1H), 2.24 – 2.10 (m,

3H), 2.04 – 1.98 (m, 2H), 1.90 – 1.81 (m, 1H), 1.74 – 1.69 (m, 1H), 1.61 – 1.23 (m, 12H), 1.67 – 1.07 (m, 5H), 1.05 (s, 3H), 1.00 – 0.95 (m, 2H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.87 (dd, *J* = 6.4, 1.6 Hz, 6H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.7, 133.4, 133.0, 131.4, 128.8, 125.7, 121.7, 121.6, 56.70, 56.5, 56.2, 53.1, 50.1, 42.3, 39.6, 39.5, 37.0, 36.2, 35.8, 34.8, 32.1, 31.9, 31.5, 28.2, 28.0, 27.6, 24.2, 23.9, 22.8, 22.5, 20.6, 19.2, 18.7, 11.8 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{37}H_{54}BrN_2$ $[M\text{-}Br]^+$ 605.3465, found 605.3465.

*4.1.8.49 1-((3S,10R,13R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-(naphthalen-2-ylmethyl)-1H-imidazol-3-ium bromide **(b28)***. Yield 72%. White powder, m.p. 284 – 286 °C. IR ν_{max} (cm^{-1}): 3432, 2947, 1556, 1467, 1130, 821, 755, 625. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.01 (s, 1H), 8.03 (s, 1H), 7.90 – 7.83 (m, 3H), 7.56 – 7.52 (m, 4H), 7.27 (s, 1H), 5.90 – 5.75 (m, 2H), 5.51 – 5.50 (m, 1H), 4.84 (s, 1H), 2.89 (d, *J* = 16.4 Hz, 1H), 2.60 (d, *J* = 16.0 Hz, 1H), 2.19 – 2.05 (m, 3H), 1.97 – 1.92 (m, 1H), 1.82 – 1.77 (m, 3H), 1.66 (d, *J* = 14.4 Hz, 1H), 1.57 – 1.49 (m, 2H), 1.43 – 1.30 (m, 6H), 1.24 (d, *J* = 12.0 Hz, 2H), 1.20 – 1.12 (m, 3H), 1.07 – 1.01 (m, 4H), 0.99 (s, 4H), 0.91 – 0.86 (m, 9H), 0.61 (s, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.9, 136.7, 133.4, 133.2, 130.5, 129.6, 129.1, 128.2, 127.8, 127.2, 126.9, 125.9, 125.8, 121.7, 121.4, 56.6, 56.3, 56.1, 53.6, 50.1, 42.1, 39.5, 36.9, 36.2, 35.7, 34.9, 32.1, 31.5, 31.2, 28.1, 28.0, 27.6, 24.0, 23.8, 22.8, 22.6, 20.5, 19.2, 18.7, 11.8 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{41}H_{57}N_2$ $[M\text{-}Br]^+$ 577.4516, found 577.4516.

*4.1.8.50 1-((3S,10R,13S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-oxo-2-phenylethyl)-1H-imidazol-3-ium bromide **(c7)***. Yield 75%. Pale yellow powder, m.p. 232 – 234 °C. IR ν_{max} (cm^{-1}): 3386, 2937, 1701, 1597, 1449, 1353, 1232, 1175, 1047, 1001, 754, 686, 644. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.96 (s, 1H), 7.78 (t, *J* = 8.4 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 2H), 6.07 (s, 2H), 5.29 (d, *J* = 4.8 Hz, 1H), 4.46 (t, *J* = 9.6 Hz, 1H), 3.31 – 3.24 (m, 1H), 2.33 – 2.22 (m, 2H), 2.20 – 2.06 (m, 2H), 2.02 – 1.97 (m, 1H), 1.80 – 1.75 (m, 2H), 1.68 (d, *J* = 12.4 Hz, 1H), 1.61 – 1.55 (m, 3H), 1.50 (dd, *J* = 10.6, 4.4 Hz, 1H), 1.46 – 1.44 (m, 1H), 1.42 – 1.23 (m, 5H), 1.04 – 0.99 (m, 1H), 0.96 (s, 3H), 0.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ191.8, 141.8, 137.6, 135.0, 134.1, 129.6, 129.5, 128.6, 124.1, 122.2, 120.5, 70.4, 69.3, 56.0, 52.4, 50.0, 44.0, 42.6, 37.4, 36.6, 35.8, 32.0, 31.8, 31.3, 25.5, 23.5, 20.6, 19.6, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{30}H_{39}N_2O_2$ $[M\text{-}Br]^+$ 459.3006, found 459.3007.

*4.1.8.51 1-((3S,10R,13S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**c8**).* Yield 89%. Pale yellow powder, m.p. 203 – 205 °C. IR ν_{max} (cm^{-1}): 3423, 2931, 1691, 1602, 1241, 1170, 627. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.94 (s, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.99 (s, 2H), 5.29 (d, *J* = 4.8 Hz, 1H), 4.44 (t, *J* = 9.6 Hz, 1H), 3.89 (s, 3H), 3.30 – 3.24 (m, 1H), 2.33 – 2.23 (m, 2H), 2.20 – 2.09 (m, 2H), 2.02 – 1.98 (m, 1H), 1.77 (d, *J* = 12.6 Hz, 2H), 1.68 (d, *J* = 12.4 Hz, 1H), 1.61 – 1.54 (m, 3H), 1.50 (dd, *J* = 10.8, 4.2 Hz, 1H), 1.46 – 1.43 (m, 1H), 1.40 – 1.23 (m, 5H), 1.03 – 0.99 (m, 1H), 0.96 (s, 3H), 0.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.0, 164.6, 141.8, 137.6, 131.1, 131.0, 126.9, 124.1, 122.2, 120.5, 114.9, 114.8, 70.4, 69.3, 56.3, 56.2, 55.6, 52.4, 50.0, 44.0, 42.6, 37.4, 36.6, 35.8, 32.0, 31.8, 31.3, 25.5, 23.4, 20.6, 19.6, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{31}H_{41}N_2O_3$ [M-Br]$^+$ 489.3112, found 489.3112.

*4.1.8.52 3-(2-(3-bromophenyl)-2-oxoethyl)-1-((3S,10R,13S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-1H-imidazol-3-ium bromide (**c9**).* Yield 89%. Pale yellow powder, m.p. 296 – 298 °C. IR ν_{max} (cm^{-1}): 3424, 2926, 1701, 1631, 1226, 1172, 1059, 789, 672. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.21 (s, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 8.00 – 7.96 (m, 2H), 7.78 (s, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 6.09 (s, 2H), 5.29 (d, *J* = 4.8 Hz, 1H), 4.47 (t, *J* = 9.6 Hz, 1H), 3.31 – 3.23 (m, 1H), 2.33 – 2.22 (m, 2H), 2.19 – 2.07 (m, 2H), 2.03 – 1.96 (m, 1H), 1.79 – 1.75 (m, 2H), 1.68 (d, *J* = 11.6 Hz, 1H), 1.61 – 1.54 (m, 3H), 1.50 (dd, *J* = 10.6, 4.8 Hz, 1H), 1.44 (dd, *J* = 7.8, 4.8 Hz, 1H), 1.41 – 1.23 (m, 5H), 1.03 – 0.99 (m, 1H), 0.95 (s, 3H), 0.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.0, 141.8, 137.5, 136.1, 131.9, 131.2, 127.6, 124.1, 122.8, 122.3, 120.5, 70.4, 69.4, 56.0, 52.4, 50.0, 44.0, 42.6, 37.4, 36.6, 35.8, 32.0, 31.8, 31.3, 25.5, 23.5, 20.6, 19.6, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{30}H_{38}BrN_2O_2$ [M-Br]$^+$ 537.2111, found 537.2111.

*4.1.8.53 1-((3S,10R,13S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**c10**).* Yield 97%. Pale yellow powder, m.p. 242 – 244 °C. IR ν_{max} (cm^{-1}): 3417, 2933, 1696, 1628, 1470, 1362, 1173, 1123, 745, 631. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.86 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.08 – 8.05 (m, 2H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 1.8 Hz, 1H), 7.79 – 7.68 (m, 2H), 6.24

(s, 2H), 5.29 (d, *J* = 4.8 Hz, 1H), 4.48 (t, *J* = 9.2 Hz, 1H), 3.33 – 3.24 (m, 1H), 2.36 – 2.24 (m, 2H), 2.20 – 2.07 (m, 2H), 2.01 – 1.97 (m, 1H), 1.77 (d, *J* = 12.6 Hz, 2H), 1.69 (d, *J* = 11.8 Hz, 1H), 1.62 – 1.54 (m, 3H), 1.50 (dd, *J* = 10.6, 4.6 Hz, 1H), 1.46 (d, *J* = 5.2 Hz, 1H), 1.43 – 1.21 (m, 5H), 1.03 – 0.99 (m, 1H), 0.96 (s, 3H), 0.60 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 141.8, 137.6, 136.0, 132.5, 131.4, 131.1, 130.2, 129.8, 129.3, 128.4, 127.9, 124.2, 123.6, 122.3, 120.5, 70.4, 69.4, 56.0, 52.4, 50.0, 44.0, 42.7, 37.4, 36.6, 35.8, 32.0, 31.9, 31.3, 25.5, 23.5, 20.8, 19.6, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{34}H_{41}N_2O_2$ $[M\text{-}Br]^+$ 509.3163, found 509.3164.

*4.1.8.54 3-(2-bromobenzyl)-1-((3S,10R,13S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-1H-imidazol-3-ium bromide (**c11**).* Yield 78%. Pale yellow powder, m.p. 309 – 311 °C. IR ν_{max} (cm^{-1}): 3417, 2931, 1617, 1161, 1121, 774, 623. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.83 (s, 1H), 7.72 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.38 (m, 2H), 5.58 (s, 2H), 5.27 (d, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 9.8 Hz, 1H), 3.30 – 3.23 (m, 1H), 2.39 – 2.30 (m, 1H), 2.23 – 2.05 (m, 3H), 2.01 – 1.95 (m, 1H), 1.76 – 1.65 (m, 3H), 1.57 – 1.52 (m, 3H), 1.49 – 1.45 (m, 1H), 1.41 (d, *J* = 6.2 Hz, 1H), 1.39 – 1.19 (m, 5H), 1.02 – 0.97 (m, 1H), 0.93 (s, 3H), 0.53 (d, *J* = 6.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.8, 138.0, 136.9, 134.0, 133.6, 131.6, 131.3, 129.0, 123.6, 123.56, 123.50, 123.2, 122.8, 120.5, 70.4, 69.5, 52.9, 52.4, 50.0, 43.9, 43.8, 42.6, 37.4, 36.6, 35.9, 32.0, 31.8, 31.3, 25.7, 23.4, 20.6, 19.6, 12.2 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{29}H_{38}BrN_2O$ $[M\text{-}Br]^+$ 509.2162, found 509.2162.

*4.1.8.55 1-((3S,10R,13S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(naphthalen-2-ylmethyl)-1H-imidazol-3-ium bromide (**c12**).* Yield 87%. Pale yellow powder, m.p. 281 – 283 °C. IR ν_{max} (cm^{-1}): 3416, 2923, 1630, 1553, 1451, 1155, 1053, 827, 778, 753. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.01 – 7.91 (m, 6H), 7.57 – 7.55 (m, 3H), 5.64 (s, 2H), 5.27 (d, *J* = 4.8 Hz, 1H), 4.36 (t, *J* = 9.6 Hz, 1H), 3.30 – 3.22 (m, 1H), 2.38 – 2.28 (m, 1H), 2.24 – 2.05 (m, 3H), 1.99 – 1.92 (m, 1H), 1.75 – 1.66 (m, 3H), 1.56 – 1.49 (m, 3H), 1.46 (dd, *J* = 10.6, 4.6 Hz, 1H), 1.40 (d, *J* = 6.2 Hz, 1H), 1.37 – 1.17 (m, 5H), 1.01 – 0.96 (m, 1H), 0.92 (s, 3H), 0.51 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.8, 136.3, 133.2, 132.8, 129.3, 128.4, 128.2, 128.0, 127.2, 126.0, 123.2, 122.8, 120.5, 70.4, 69.5, 52.7, 52.4, 50.0, 43.9, 42.6, 37.4, 36.6, 35.8, 32.2, 31.8, 31.3, 25.6, 23.4, 20.5, 19.6, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{33}H_{41}BrN_2O$ $[M\text{-}Br]^+$ 481.3213, found 482.3213.

*4.1.8.56 1-((3S,10R,13S,17S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-oxo-2-phenylethyl)-1H-imidazol-3-ium bromide (**c13**).* Yield 92%. White powder, m.p. 263 – 265 °C. IR ν_{max} (cm^{-1}): 3439, 2940, 1732, 1699, 1351, 1239, 1175, 1030, 758, 685. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, *J* = 16.8 Hz, 1H), 8.08 – 8.01 (m, 2H), 7.95 (d, *J* = 16.0 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.66 – 7.58 (m, 2H), 6.08 (d, *J* = 16.8 Hz, 2H), 5.38 – 5.33 (m, 1H), 4.50 – 4.41 (m, 2H), 2.29 – 2.20 (m, 4H), 1.96 (d, *J* = 16.0 Hz, 3H), 1.87 – 1.73 (m, 4H), 1.61 – 1.23 (m, 10H), 1.12 – 1.04 (m, 1H), 0.97 (d, *J* = 16.0 Hz, 3H), 0.57 (d, *J* = 16.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.8, 170.2, 140.1, 137.6, 135.0, 134.1, 129.6, 128.6, 124.1, 122.2, 73.6, 69.3, 56.0, 52.3, 49.8, 44.0, 38.1, 36.9, 36.6, 35.7, 31.9, 31.3, 27.8, 25.5, 23.4, 21.5, 20.5, 19.4, 12.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{32}H_{41}N_2O_3$ $[M\text{-}Br]^+$ 501.3112, found 501.3111.

*4.1.8.57 1-((3S,10R,13S,17S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**c14**).* Yield 94%. White powder, m.p. 280 – 282 °C. IR ν_{max} (cm^{-1}): 3423, 2942, 1735, 1685, 1601, 1245, 1173, 1028, 840, 628. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (d, *J* = 14.6 Hz, 1H), 8.08 – 7.96 (m, 3H), 7.81 (d, *J* = 14.0 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.06 (d, *J* = 14.0 Hz, 2H), 5.39 – 5.34 (m, 1H), 4.51 – 4.38 (m, 2H), 3.88 (d, *J* = 15.2 Hz, 3H), 3.36 (d, *J* = 14.4 Hz, 2H), 2.34 – 2.21 (m, 4H), 1.98 (d, *J* = 14.8 Hz, 3H), 1.84 – 1.75 (m, 2H), 1.62 – 1.25 (m, 10H), 1.14 – 1.07 (m, 1H), 0.99 (d, *J* = 13.2 Hz, 3H), 0.58 (d, *J* = 14.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.0, 170.2, 140.1, 137.6, 131.1, 126.9, 124.1, 122.2, 114.9, 73.6, 69.3, 56.3, 55.6, 52.3, 49.8, 44.0, 38.1, 36.9, 36.6, 35.8, 31.9, 31.3, 27.8, 25.5, 23.4, 21.5, 20.5, 19.5, 12.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{33}H_{43}N_2O_4$ $[M\text{-}Br]^+$ 531.3217, found 531.3217.

*4.1.8.58 1-((3S,10R,13S,17S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-(3-bromophenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**c15**).* Yield 96%. White powder, m.p. 188 – 190 °C. IR ν_{max} (cm^{-1}): 3432, 2951, 1719, 1561, 1253, 1179, 1029, 813, 739. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.21 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.99 – 7.97 (m, 2H), 7.78 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 6.09 (s, 2H), 5.38 – 5.37 (m, 1H), 4.50 – 4.45 (m, 2H), 2.37 – 2.24 (m, 4H), 1.98 (s, 3H), 1.87 – 1.75 (m, 3H), 1.64 – 1.24 (m, 10H), 1.15 – 1.03 (m, 2H), 0.99 (s, 3H), 0.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.0, 170.2, 140.1, 137.5, 136.2, 131.9, 131.2, 127.6, 124.1, 122.8,

122.3, 122.2, 73.6, 69.3, 56.0, 52.3, 49.8, 44.0, 38.1, 37.0, 36.6, 35.7, 31.9, 31.3, 27.8, 25.5, 23.4, 21.5, 20.5, 19.5, 12.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{32}H_{40}BrN_2O_3$ $[M\text{-}Br]^+$ 579.2217, found 579.2217.

*4.1.8.59 1-((3S,10R,13S,17S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**c16**).* Yield 94%. White powder, m.p. 267 – 269 °C. IR ν_{max} (cm^{-1}): 3424, 2942, 1731, 1698, 1364, 1248, 1173, 1030, 818, 752. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (d, *J* = 10.8 Hz, 1H), 8.86 (d, *J* = 11.2 Hz, 1H), 8.22 – 8.17 (m, 1H), 8.15 – 7.98 (m, 4H), 7.85 (d, *J* = 11.2 Hz, 1H), 7.77 – 7.65 (m, 2H), 6.25 (d, *J* = 11.2 Hz, 2H), 5.36 (q, *J* = 7.2 Hz, 1H), 4.52 – 4.41 (m, 2H), 2.34 – 2.21 (m, 4H), 2.03 – 1.93 (m, 4H), 1.86 – 1.74 (m, 3H), 1.60 – 1.19 (m, 10H), 1.12 – 1.05 (m, 1H), 0.98 (d, *J* = 10.4 Hz, 3H), 0.59 (d, *J* = 11.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.7, 170.2, 140.1, 137.6, 136.0, 132.5, 131.4, 131.1, 130.2, 129.8, 129.3, 128.4, 127.9, 124.2, 123.6, 122.3, 122.2, 73.6, 69.3, 56.0, 52.3, 49.8, 44.0, 38.1, 36.9, 36.6, 35.8, 31.9, 31.3, 27.8, 25.5, 23.4, 21.5, 20.5, 19.5, 12.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{36}H_{43}N_2O_3$ $[M\text{-}Br]^+$ 551.3268, found 551.3269.

*4.1.8.60 1-((3S,10R,13S,17S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-bromobenzyl)-1H-imidazol-3-ium bromide (**c17**).* Yield 92%. White powder, m.p. 175 – 177 °C. IR ν_{max} (cm^{-1}): 3431, 2951, 1724, 1438, 1245, 1029, 749, 658. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 – 9.54 (m, 1H), 7.97 – 7.94 (m, 1H), 7.79 – 7.69 (m, 2H), 7.49 – 7.34 (m, 3H), 5.56 – 5.52 (m, 2H), 5.36 (t, *J* = 4.8 Hz, 1H), 4.48 – 4.35 (m, 2H), 2.36 – 2.20 (m, 4H), 1.97 (d, *J* = 8.4 Hz, 3H), 1.86 – 1.75 (m, 3H), 1.62 – 1.18 (m, 10H), 1.12 – 1.02 (m, 2H), 0.96 (d, *J* = 8.0 Hz, 3H), 0.54 (d, *J* = 10.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 140.0, 136.9, 134.0, 133.6, 131.5, 131.3, 129.0, 123.5, 123.2, 122.9, 122.2, 73.6, 69.4, 52.9, 52.4, 49.8, 43.9, 38.1, 36.9, 36.6, 35.7, 31.9, 31.3, 27.8, 25.5, 23.4, 21.5, 20.5, 19.4, 12.1 ppm. HRMS (ESI-TOF) *m/z* Calcd for $C_{31}H_{40}BrN_2O_2$ $[M\text{-}Br]^+$ 551.2268, found 551.2268.

*4.1.8.61 1-((3S,10R,13S,17S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(naphthalen-2-ylmethyl)-1H-imidazol-3-ium bromide (**c18**).* Yield 72%. White powder, m.p. 174 – 176 °C. IR ν_{max} (cm^{-1}): 3416, 2943, 1728, 1365, 1247, 1163, 1030, 759, 614. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.02 – 7.91 (m, 6H), 7.59 – 7.55 (m, 3H), 5.65 (s, 2H), 5.35 (d, *J* = 4.8 Hz, 1H), 4.49 – 4.35 (m, 2H), 2.39 – 2.14 (m, 4H), 1.98 (s, 3H), 1.83 – 1.70 (m, 3H), 1.60 – 1.168(m, 10H), 1.11 – 1.01 (m, 2H), 0.95 (s, 3H), 0.52 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 140.0, 136.4,

133.2, 132.9, 129.3, 128.4, 128.2, 128.0, 127.2, 126.1, 123.2, 122.8, 122.2, 73.6, 69.5, 52.7, 52.3, 49.8, 43.9, 38.1, 36.9, 36.6, 35.8, 31.9, 31.3, 27.8, 25.6, 23.4, 21.5, 20.5, 19.4, 12.1 ppm. HRMS (ESI-TOF) *m*/*z* Calcd for $C_{35}H_{43}N_2O_2$ $[M\text{-}Br]^+$ 523.3320, found 523.3319.

4.2 Cytotoxicity assay

Cytotoxicity of compounds was determined by MTS method. All the compounds tested were absolutely dissolved to 10 mM in DMSO in stock. 5×10^3 cells were plated in 96-well plates 12 h before treatment and continuously exposed to 0.032, 0.16, 0.8, 4 and 20 μM test compounds for 48 h. Then MTS (Promega) was added to each well. The samples were incubated at 37 °C for 1~4 h and the optical density (OD) was measured at 490 nm using a microplate reader (Bio-Rad Laboratories). The IC_{50} values are calculated from appropriate dose-response curves.

4.3 Cell cycle analysis.

To analyze the DNA content by flow cytometry, cells were collected and washed twice with PBS. Cells were fixed with 70% ethanol overnight. Fixed cells were washed with PBS, and then stained with a 50 μg/ml propidium iodide (PI) solution containing 50 μg/ml RNase A for 30 min at room temperature. Fluorescence intensity was analyzed by FACSCalibur flow cytometer (BD Biosciences, San Jose, CA, USA). The percentages of the cells distributed in different phases of the cell cycle were determined using FlowJo V 7.6.1 software.

4.4 Cell apoptosis analysis.

Cell apoptosis was analyzed using the Annexin V-FITC/PI Apoptosis kit (BD Biosciences, Franklin Lakes, NJ) according to the manufacturer's protocols. Cells were seeded in 6-well plates at a density of 3×10^5 cells/well. After 48 h of compound treatment at the indicated concentrations, cells were collected and then washed twice with cold PBS, and then resuspended in a binding buffer containing Annexin V-FITC and propidium iodine (PI). After incubation for 15 min at room temperature in the dark, the fluorescent intensity was measured using a FACSCalibur flow cytometer (BD Biosciences, Franklin Lakes, NJ).

Acknowledgments

This work was supported by grants from the Natural Science Foundation of China (21662043, U1402227 and U1702286), Program for Changjiang Scholars and Innovative Research Team in University (IRT17R94), YunLing Scholar of Yunnan Province and Donglu Scholar & Excellent Young Talents of Yunnan University, State Key Laboratory of Phytochemistry and Plant Resources in West China (P2017-KF12).

Appendix A. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech. 2018.xx.xxx.

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Highlights

► A series of sixty-one novel steroidal imidazolium salt derivatives were prepared.

► Compound **a30** was found to be the most potent compound with antitumor activity.

► Compound **a24** showed inhibitory activity selectively against SMMC-7721 cells.

► The structure-activity relationship results of imidazolium salts were summarized.

► Compound **a30** induced the G0/G1 phase cell cycle arrest and apoptosis in SMMC-7721.