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Original article

Synthesis and biological activity of polyalthenol and pentacyclindole analogues

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ABSTRACT

A series of indole sesquiterpenes analogues of polyalthenol and pentacyclindole have been synthesized starting from *ent*-halimic acid in order to test their biological activity. These analogues include diverse oxidation levels at the sesquiterpenyl moiety and different functionalization on the indole ring. All synthetic derivatives were tested against a representative panel of Gram positive and Gram negative bacterial strains, and the human solid tumour cell lines A549 (non-small cell lung), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast) and WiDr (colon). Overall, the compounds presented activity against the cancer cell lines. The resulting lead, displaying a polyalthenol scaffold, showed GI_{50} values in the range 1.2–5.7 μM against all cell lines tested.

1. Introduction

Polyalthenol and pentacyclindole (Fig. 1) are two indole sesquiterpenes present in Nature that display significant biological activity including antimicrobial activity. Polyalthenol was isolated in 1976 from the African plant *Polyalthia oliveri* Engl. Diels (=*Greenwayodendron oliveri* Verd.) [1] and exhibits activity against clinical isolates of *Staphylococcus aureus* with a MIC_{90} of 8 μg/mL [2]. Pentacyclindole, isolated in 2010 along with polyalthenol from *Polyalthia suaveolens* (=*Greenwayodendron suaveolens*), demonstrated a MIC_{90} of 4 μg/mL [2].

In the past, our research group started diverse synthetic studies on terpene alkaloids such as (+)-agelasine C [3] and (+)-thiersindole C [4] (Fig. 2) among others. In the past few years, we have focused our attention into indole sesquiterpenes. We have reported earlier the synthesis of two polyalthenol analogues: 12-epi-*ent*-polyalthenol and 12,19-bisepi-*ent*-polyalthenol, and the pentacyclindole epimer 12-epi-*ent*-pentacyclindole [5]. Furthermore, we demonstrated the biogenetic relationship between polyalthenol and pentacyclindole that had been proposed by Williams et al. [2]

As a follow up of our previous work, herein we report on the synthesis and the biological evaluation of a series of indole sesquiterpenes analogues of polyalthenol and pentacyclindole. As a model system to study the biological activity we selected antibacterial and anticancer assays. With the results of the biological tests some structure–activity relationships (SARs) could be inferred.

2. Chemistry

For the synthesis of all indole sesquiterpenes analogues described herein we used *ent*-halimic acid as starting material [6]. The synthetic methodologies have been previously tuned up by our group in the synthesis of indole diterpenes and sesquiterpenes [3–5,7].

2.1. Analogues of polyalthenol

As it has been said before starting from *ent*-halimic acid, the synthesis of different polyalthenol analogues was achieved and the

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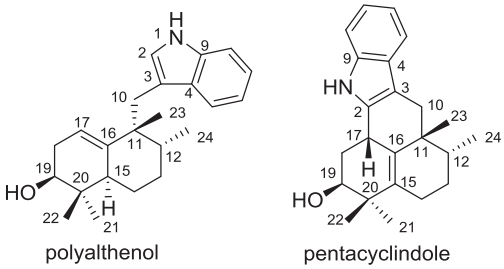


Fig. 1. Structures and stereochemistry of natural indole sesquiterpenes polyalthenol and pentacyclindole.

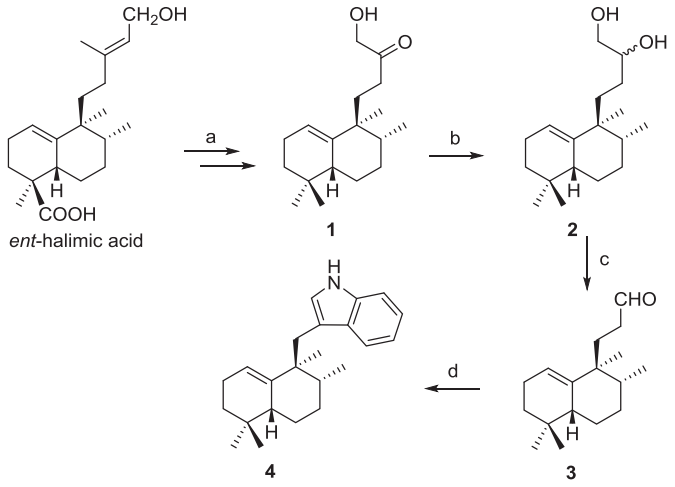
compounds were classified into: 1. C-3 desoxygenated polyalthenol analogues, 2. Analogues functionalised in the indole ring, 3. 2-methylindole analogues and 4. Polyalthenol analogues as starting materials for the synthesis of PLA2 inhibitors. Next, the synthesis of these compounds will be described in detail.

2.1.1. C-3 desoxygenated polyalthenol analogues

The first compound synthesized is a C-3 desoxygenated analogue of polyalthenol, which preparation, starting from *ent*-halimic acid, is depicted in Scheme 1. After degradation to the corresponding dinor derivative and reduction of the carboxylic group to obtain compound **1** [5,8], a further degradation to the trinor derivative aldehyde **3** is needed. This is carried out by reduction of **1** with $NaBH_4$ and reaction of the resultant diol **2** with $Pb(OAc)_4$. Then, a Fischer indolization of aldehyde **3** with phenylhydrazine in AcOH afforded the C-3 desoxygenated polyalthenol analogue **4**.

2.1.2. Analogues functionalised in the indole ring

Performing Fischer indolization reactions on aldehyde **5** using a variety of differently functionalised phenylhydrazines [9] and phenylhydrazines hydrochlorides [10] yields to the corresponding indole derivatives **6**–**15** shown in Scheme 2. Compound **5** is an important synthetic intermediate already used by our group in the synthesis of polyalthenol, pentacyclindole and a wide variety of bioactive natural products [4,5]. The synthesized polyalthenol



Scheme 1. a) See Refs. [5,8]; b) $NaBH_4$, 97%; c) $Pb(OAc)_4$, 95%; d) Phenylhydrazine, AcOH, 58%.

analogues **6**–**15** are also the synthetic precursors of the pentacyclindole analogues that we aim to obtain.

2.1.3. 2-Methylindole analogues

Analogous reactions can be performed on methylketone **16** instead of aldehyde **5** to obtain, this way, the corresponding 2-methylindoles. These compounds would permit us to obtain both a new series of polyalthenol analogues and suitable precursors for developing a series of phospholipase A_2 inhibitors ($IPLA_2$) that will be briefly commented later.

In the same manner that compound **5**, previously obtained in our group, and transformed into different bioactive natural products [4], the methylketone **16**, was treated with the adequate phenylhydrazine or phenylhydrazine hydrochloride to afford 2-methylindoles derivatives **17**–**26**.

2.1.4. Polyalthenol analogues as starting materials for the synthesis of PLA_2 inhibitors

PLA_2 inhibitors such as efipladib, giripladib and ecopladib are compounds of enormous interest due to its biological activity, so their analogues [11]. One of the most important considerations that

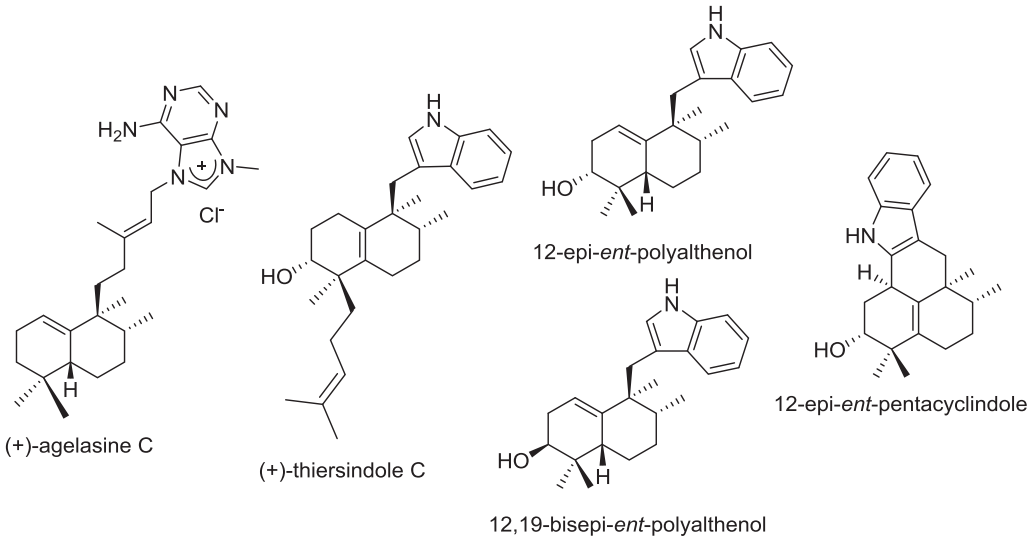
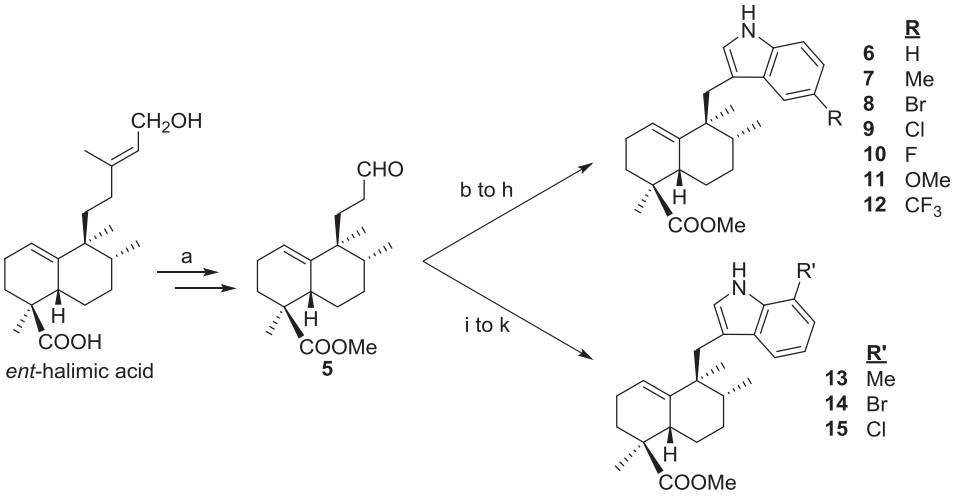
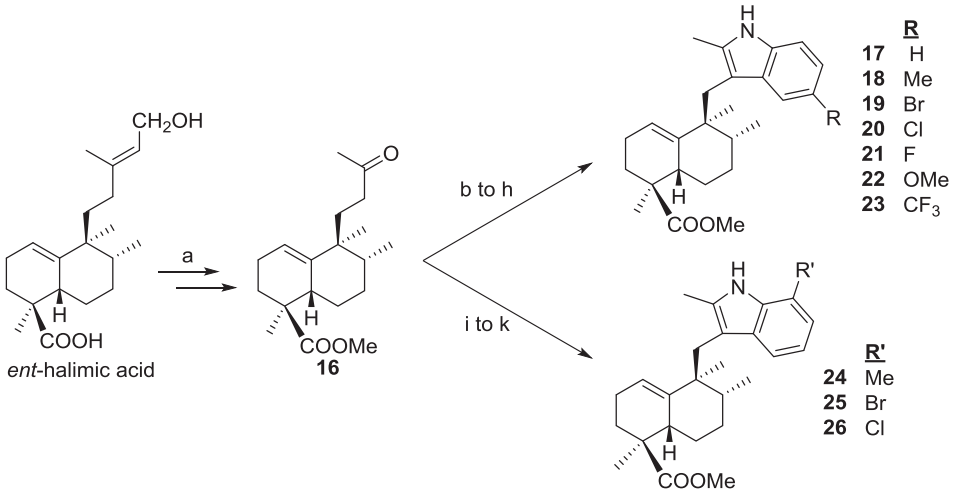


Fig. 2. Structures of (+)-agelasine C, (+)-thiersindole C and polyalthenol and pentacyclindole analogues.



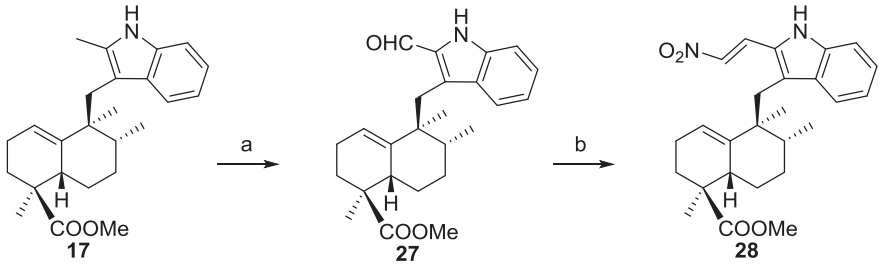
Scheme 2. a) See Ref. [4,5]; b) Phenylhydrazine, AcOH, **6** (95%); c) 4-methylphenylhydrazine hydrochloride, AcOH, **7** (45%); d) 4-bromophenylphydrazine hydrochloride, AcOH, **8** (40%); e) 4-chlorophenylhydrazine hydrochloride, AcOH, **9** (50%); f) 4-fluorophenylhydrazine hydrochloride, AcOH, **10** (53%); g) 4-methoxy phenylhydrazine hydrochloride, AcOH, **11** (44%); h) 4-trifluoromethylphenylhydrazine, AcOH, **12** (20%); i) 2-methylphenylhydrazine hydrochloride, AcOH, **13** (34%); j) 2-bromophenylhydrazine hydrochloride, AcOH, **14** (34%); k) 2-chlorophenylhydrazine hydrochloride, AcOH, **15** (27%).



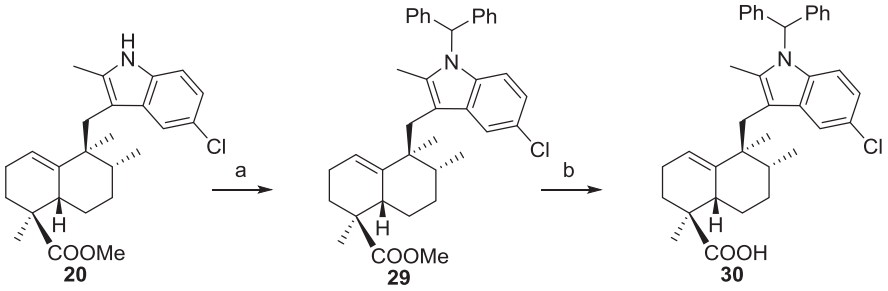
Scheme 3. a) See Ref. [4]; b) Phenylhydrazine, AcOH, **17** (90%); c) 4-methylphenylhydrazine hydrochloride, AcOH, **18** (78%); d) 4-bromophenylphydrazine hydrochloride, AcOH, **19** (95%); e) 4-chlorophenylhydrazine hydrochloride, AcOH, **20** (94%); f) 4-fluorophenylhydrazine hydrochloride, AcOH, **21** (63%); g) 4-methoxy phenylhydrazine hydrochloride, AcOH, **22** (47%); h) 4-trifluoromethylphenylhydrazine, AcOH, **23** (27%); i) 2-methylphenylhydrazine hydrochloride, AcOH, **24** (62%); j) 2-bromophenylhydrazine hydrochloride, AcOH, **25** (87%); k) 2-chlorophenylhydrazine hydrocloride, AcOH, **26** (95%).

must be taken into account in order to ensure the biological activity of these $IPLA_2$ is that they must be functionalised at the C-2 position of the indole. So we decided to add functionality to the methyl group of the side chain on C-2. This can be achieved by oxidizing the 2-methylindoles obtained with Na_2CrO_4 [7f], as depicted in Scheme 4. Once aldehyde **27** is obtained in this way, it was condensed with nitromethane in presence of ammonium acetate [11d] to afford compound **28**.

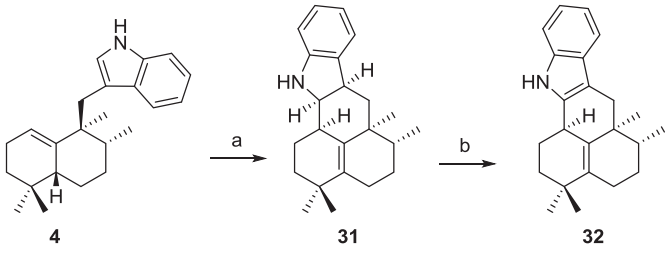
Other important requirement for the bioactivity of these compounds is that the indole moiety should be functionalised and the N



Scheme 4. a) Na_2CrO_4, NaOAc, Ac_2O, AcOH, 55 °C, 30%; b) NH_4OAc, CH_3NO_2, 100 °C, 66%.



Scheme 5. a) Bromodiphenylmethane, NaH, 38%; b) ^{t}BuOK/^{t}BuOH, 90 °C, 95%.



Scheme 6. a) HI 57%, benzene, 85 °C, 81%; b) TPAP, NMO, 63%.

must bear a bulky protective group; the presence of a carboxylic acid in the molecule is also essential. Taking this into account, we decided to synthesize **30** (Scheme 5).

Reaction of **20** with bromodiphenylmethane [11b,11c] afforded the *N*-protected indole derivative **29** which was hydrolysed [12] to give **30**. In this manner has been achieved the synthesis of compounds **27**–**30** that are good starting materials for the synthesis of PLA_2 inhibitors analogues.

2.2. Analogues of pentacyclindole

Our group has recently described the biomimetic synthesis of a pentacyclindole by cyclisation of a polyalthenol derivative induced in acid conditions. So all the analogues described for polyalthenol can be easily transformed into pentacyclindoles by acidic treatment. Following a similar classification as before, it is described the synthesis of the different pentacyclindole analogues.

2.2.1. C-3 desoxygenated pentacyclindole analogues

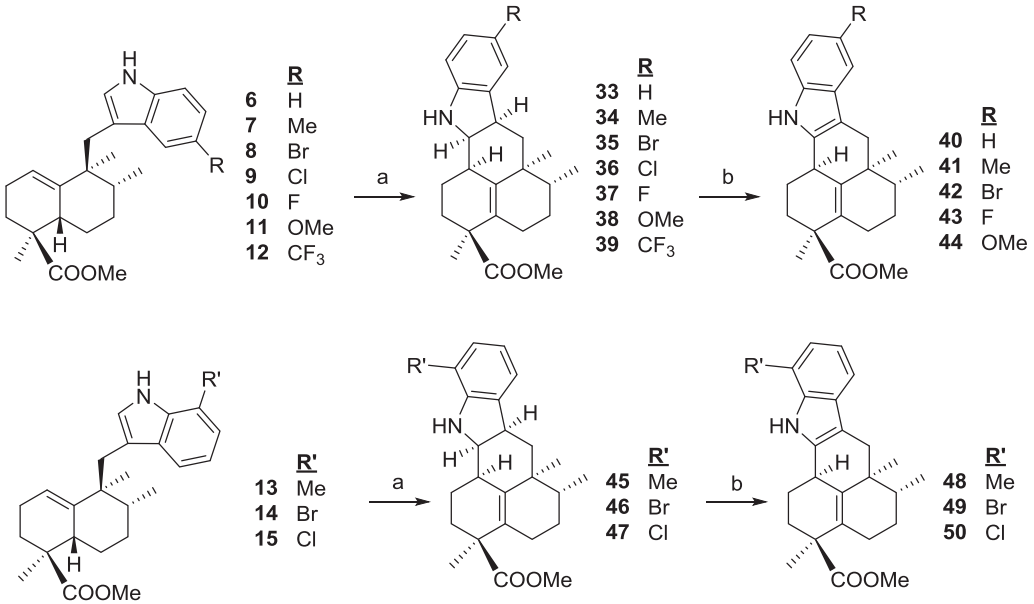
Using polyalthenol analogue **4** as a starting material, a C-3 desoxygenated analogue of pentacyclindole can be obtained, as seen in Scheme 6. Heating up compound **4** in C_6H_6 in the presence of HI [7i,8] gave a pentacyclic compound with hexahydrocarbazole structure **31**. In order to regain the double bound, a mild oxidation with TPAP [13] was performed, affording the pentacyclindole analogue **32**.

2.2.2. Analogues functionalised in the indole ring

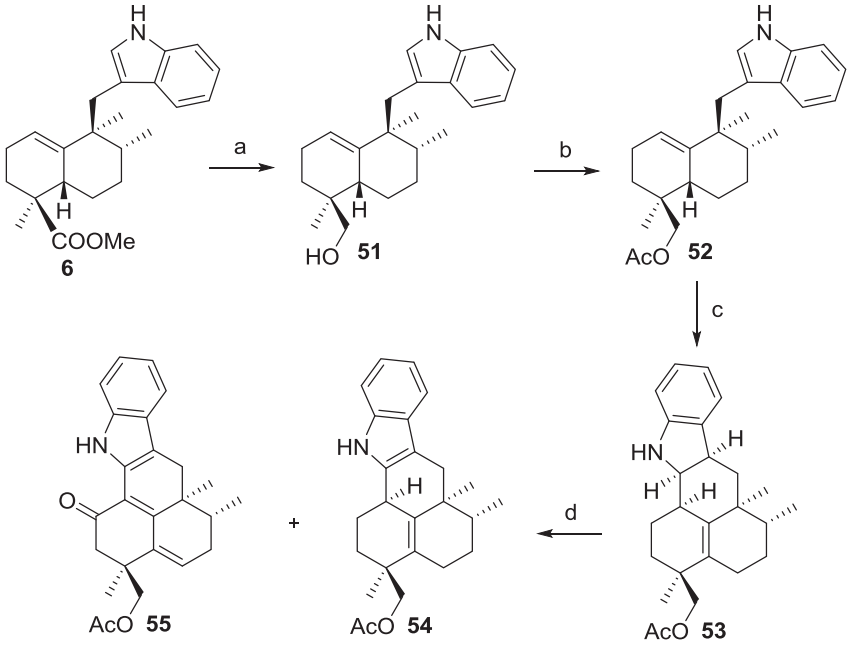
The same sequence of reactions can be performed with the aforementioned polyalthenol analogues **6**–**15**, as depicted in Scheme 7. Compounds **6**–**15**, by heating with HI in C_6H_6, were transformed into a series of hexahydrocarbazoles **33**–**39** and **45**–**47**. These compounds by TPAP oxidation led the corresponding pentacyclindole analogues, **40**–**44** and **48**–**50**.

2.3. Analogues functionalised in C-21

Finally, a series of analogues with a different substituent at C-21 position were made, as seen in Scheme 8. Indole derivative **6** was



Scheme 7. a) HI 57%, benzene, 85 °C; **33** (97%), **34** (99%), **35** (92%), **36** (91%), **37** (93%), **38** (90%), **39** (87%), **45** (93%), **46** (99%), **47** (99%); b) TPAP, NMO; **40** (36%), **41** (66%), **42** (50%), **43** (59%), **44** (79%), **48** (85%), **49** (46%), **50** (47%).



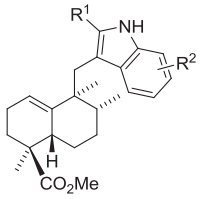
Scheme 8. a) LAH, Et_2O, 97%; b) Ac_2O, Py, 95%; c) HI 57%, C_6H_6, 98%; d) TPAP, NMO, **54** (27%), **55** (5%).

transformed into the hydroxyderivative **51** by reduction with LAH. Compound **51** was acetylated to afford **52**, which under cyclisation conditions, by heating with HI in C_6H_6, yielded hexahydrocarbazole derivative **53**. Oxidation of **53** with TPAP in presence of NMO afforded **54** and **55**.

3. Biological activity

Since antibacterial activity has been reported for naturally occurring polyalthenol [1,2] and pentacyclindol [2], and we have observed some preliminary antitumour activity for related

Table 1
Antiproliferative activity (GI_{50}) against human solid tumour cells of compounds produced via Schemes 2–4.[a]



Compound			Cell line					
	R^1	R^2	A549	HBL-100	SW1573	HeLa	T-47D	WiDr
6	H	H	5.0 (±0.5)	4.5 (±0.5)	7.3 (±1.3)	3.6 (±0.6)	4.2 (±0.7)	8.7 (±3.7)
7	H	6-Me	17 (±1.0)	18 (±1.3)	15 (±3.4)	14 (±1.2)	20 (±2.0)	22 (±2.0)
8	H	6-Br	15 (±0.2)	16 (±1.0)	12 (±1.6)	10 (±2.0)	16 (±2.1)	20 (±1.0)
9	H	6-Cl	16 (±1.0)	17 (±1.6)	11 (±3.3)	11 (±1.6)	17 (±0.8)	20 (±0.5)
10	H	6-F	6.2 (±0.6)	4.8 (±0.5)	7.3 (±1.1)	3.7 (±0.4)	3.9 (±0.4)	8.0 (±2.6)
11	H	6-OMe	2.2 (±0.9)	2.1 (±1.1)	1.3 (±0.2)	1.2 (±0.7)	3.7 (±0.3)	5.7 (±1.1)
12	H	6-CF_3	15 (±1.2)	15 (±2.5)	14 (±1.5)	11 (±1.8)	15 (±2.0)	18 (±1.2)
13	H	8-Me	11 (±0.4)	8.0 (±2.3)	7.8 (±1.2)	4.9 (±0.8)	18 (±2.0)	26 (±2.2)
14	H	8-Br	22 (±3.4)	18 (±5.1)	14 (±4.8)	13 (±2.8)	24 (±4.7)	32 (±3.4)
15	H	8-Cl	22 (±2.6)	19 (±4.9)	14 (±2.6)	14 (±1.8)	24 (±4.6)	31 (±2.9)
17	Me	H	15 (±0.5)	14 (±3.7)	14 (±5.0)	11 (±3.3)	17 (±2.7)	19 (±0.7)
18	Me	6-Me	26 (±1.4)	25 (±9.3)	18 (±5.5)	17 (±4.5)	31 (±5.3)	28 (±2.9)
19	Me	6-Br	15 (±0.4)	15 (±0.9)	14 (±2.2)	11 (±1.5)	16 (±1.2)	15 (±0.4)
20	Me	6-Cl	17 (±1.0)	15 (±0.6)	14 (±2.5)	12 (±1.7)	17 (±2.0)	18 (±1.4)
21	Me	6-F	15 (±0.3)	14 (±0.7)	12 (±1.6)	11 (±0.9)	15 (±1.1)	17 (±0.6)
22	Me	6-OMe	16 (±0.9)	16 (±1.6)	15 (±1.2)	12 (±0.9)	15 (±1.1)	17 (±2.1)
23	Me	6-CF_3	17 (±0.8)	16 (±0.3)	15 (±2.6)	12 (±1.4)	21 (±3.2)	21 (±1.3)
24	Me	8-Me	14 (±1.6)	16 (±2.2)	15 (±0.9)	14 (±0.7)	19 (±4.3)	21 (±4.0)
25	Me	8-Br	27 (±2.4)	27 (±5.1)	25 (±2.7)	22 (±3.0)	31 (±5.8)	38 (±1.8)
26	Me	8-Cl	20 (±6.1)	22 (±8.4)	19 (±1.8)	17 (±2.6)	27 (±9.3)	29 (±6.1)
27	CHO	H	45 (±1.1)	7.5 (±0.9)	7.9 (±1.4)	4.4 (±0.6)	17 (±4.4)	20 (±2.1)
28	[b]	H	13 (±2.3)	16 (±0.9)	13 (±3.1)	6.9 (±2.1)	15 (±3.3)	21 (±2.7)

[a] Values are given in μM and are means of two to five experiments; standard deviation is given in parentheses.
[b] R^1: CH=CH–NO_2.

Table 2
Antiproliferative activity (GI_{50}) against human solid tumour cells of compounds produced via Scheme 5.[a]

Compound	Cell line					
	A549	HBL-100	SW1573	HeLa	T-47D	WiDr
20	17 (±1.0)	15 (±0.6)	14 (±2.5)	12 (±1.7)	17 (±2.0)	18 (±1.4)
29	>100	>100	>100	>100	>100	>100
30	9.1 (±1.6)	13 (±0.9)	13 (±2.3)	5.5 (±0.7)	13 (±1.1)	16 (±1.7)

[a] Values are given in μM and are means of two to five experiments; standard deviation is given in parentheses.

compounds [5], we decided to study the biological activity of the synthetic analogues in two whole-cell screening models: a representative panel of human solid tumour cell lines and a set of clinically relevant bacteria species. The selected microbes included two strains of Gram-positive and three Gram-negative bacteria.

3.1. Antibacterial activity

Compounds were screened against strains of the Gram-positive *S. aureus* and *Enterococcus faecalis*, and the Gram-negative *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Despite the fact of being analogues of known antimicrobial compounds, the screening of compounds revealed some irrelevant activity observed solely for compound **27** (MIC 50–100 μM) and only against the bacterial strain *S. aureus*.

3.2. Antiproliferative activity

As a model to study the anticancer activity of the synthetic compounds, we used the human solid tumour cell lines A549 (non-small cell lung), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast), and WiDr (colon). The in vitro antiproliferative activity was evaluated after 48 h of drug exposure using the sulforhodamine B (SRB) assay [14]. The results expressed as GI_{50} (50% growth inhibition) are given in Tables 1–4. With the exception of compound **29**, all evaluated compounds induced cell growth inhibition in all cell lines. This is consistent with the fact that natural products possess inherent drug-likeness and have proven an extremely powerful source of potent and selective antitumour drugs [15]. Overall, the resulting GI_{50} values were in the range 1.2–78 μM.

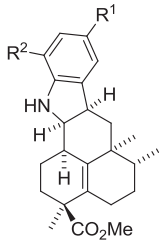
All tested compounds can be grouped in three main categories according to their chemical scaffold. Thus, we distinguish polyalthenol (Tables 1 and 2), 2,3-dihydro pentacyclindole (Table 3) and C3-unsaturated pentacyclindole analogues (Table 4). In Fig. 3, the mean graph derived from the obtained dose-response data of all tested products is displayed. In this plot, it is possible to observe that the 2,3-dihydro pentacyclindole scaffold (Table 3) originates the least active compounds (with the exception of compound **29**). Overall, the compounds show similar activity profile against drug sensitive (A549, HBL-100, HeLa and SW1573) and resistant (T-47D and WiDr) cell lines.

From the results of the antiproliferative activity some structure–activity relationships (SARs) could be inferred, and will be discussed below.

For the polyalthenol analogues (Tables 1 and 2), the following SAR was obtained. The presence of side chains (R^1) in C-2 position produces a slight loss in activity (**6**–**15** vs **17**–**28**). When considering the substituents on the benzene ring either at C-6 (**7**–**12**) or C-8 (**13**–**15**), only the presence of a methoxy group enhances the biological activity over the parent compound (**11** vs **6**). Finally, the substitution on the nitrogen atom with a diphenylmethyl produces a loss in activity (**20** vs **29**). However, if the methyl ester of compound **29** is hydrolysed the resulting carboxylic acid **30** recovers the biological activity. With this set of compounds it is not possible to establish the role in the activity of the carboxylic acid group, although we speculate that it might be favourable.

For the pentacyclindole analogues (Tables 3 and 4), the following SAR was obtained. As aforementioned, the 2,3-dihydro pentacyclindole derivatives (Table 3) show less activity than the corresponding C3-unsaturated pentacyclindole analogues (Table 4). Similar to what was observed for the polyalthenol analogues, the presence of a methoxy group on the benzene ring provides a minor enhancement on the antiproliferative activity, but not in all cell lines (**38** vs **33** and **44** vs **40**).

Table 3
Antiproliferative activity (GI_{50}) against human solid tumour cells of compounds produced via Scheme 7.[a]



Compound			Cell line					
	R^1	R^2	A549	HBL-100	SW1573	HeLa	T-47D	WiDr
33	H	H	39 (±17)	78 (±22)	30 (±20)	19 (±5.3)	35 (±12)	50 (±27)
34	Me	H	27 (±3.2)	15 (±0.5)	23 (±5.5)	18 (±3.2)	23 (±4.3)	32 (±2.2)
35	Br	H	40 (±3.2)	34 (±0.8)	45 (±15)	25 (±0.7)	31 (±7.1)	55 (±11)
36	Cl	H	35 (±0.7)	28 (±3.8)	38 (±11)	23 (±4.4)	28 (±5.1)	48 (±5.4)
37	F	H	25 (±1.9)	18 (±1.4)	27 (±5.7)	20 (±4.1)	27 (±5.2)	32 (±2.5)
38	OMe	H	22 (±9.7)	15 (±2.9)	25 (±5.5)	20 (±2.0)	19 (±6.8)	25 (±5.8)
45	H	Me	30 (±0.5)	32 (±3.7)	31 (±4.7)	22 (±1.3)	29 (±2.9)	43 (±4.7)
46	H	Br	42 (±2.7)	40 (±8.3)	44 (±9.5)	22 (±2.4)	37 (±6.3)	54 (±10)
47	H	Cl	54 (±4.9)	52 (±8.2)	49 (±5.9)	31 (±5.2)	50 (±5.8)	67 (±11)

[a] Values are given in μM and are means of two to five experiments; standard deviation is given in parentheses.

4. Conclusions

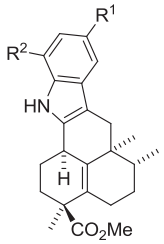
In summary, we have described a straightforward synthetic methodology to obtain a series of polyalthenol and pentacyclindole analogues, with different functionalisation in sesquiterpenic and indole fragments starting from *ent*-halimic acid. We evaluated their ability to inhibit tumour cell growth and from the results some structure–activity relationships have been derived. Although the experiments are preliminary, these compounds show remarkable biological activity towards human cancer cell lines. Overall, the compounds show active against drug sensitive and resistant cell lines. More experiments are needed to establish the scope and limitations of the methoxy group present in the most active compound of the series.

5. Experimental

5.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical

Table 4
Antiproliferative activity (GI_{50}) against human solid tumour cells of compounds produced via Scheme 7.[a]



Compound			Cell line					
	R^1	R^2	A549	HBL-100	SW1573	HeLa	T-47D	WiDr
40	H	H	4.6 (±0.1)	3.5 (±0.2)	8.3 (±1.1)	3.2 (±0.2)	3.4 (±0.7)	4.0 (±0.6)
41	Me	H	16 (±0.6)	11 (±2.0)	15 (±1.1)	11 (±0.8)	16 (±1.5)	19 (±1.0)
42	Br	H	17 (±0.3)	16 (±2.2)	12 (±1.1)	14 (±0.5)	21 (±2.1)	22 (±1.2)
44	OMe	H	7.7 (±2.3)	5.0 (±0.6)	5.9 (±1.1)	3.9 (±0.5)	6.5 (±1.4)	1.2 (±2.2)
48	H	Me	16 (±0.5)	13 (±0.7)	16 (±2.3)	12 (±0.7)	23 (±1.8)	22 (±1.1)
49	H	Br	35 (±5.0)	26 (±5.2)	26 (±2.4)	18 (±4.9)	31 (±1.4)	37 (±2.8)
50	H	Cl	21 (±2.4)	16 (±0.8)	17 (±0.2)	12 (±0.8)	21 (±1.7)	21 (±1.6)

[a] Values are given in μM and are means of two to five experiments; standard deviation is given in parentheses.

shifts are reported in δ parts per million and coupling constants (J) are given in hertz. MS were performed using a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as m/z (% rel. int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionization (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin-Elmer 241 polarimeter in 1 dm cells. Values are given in 10^{-1} deg cm^2 g^{-1}. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under Argon atmosphere.

5.2. General procedure for Fischer's indolization reaction with phenylhydrazines

To a 0.1 M solution of the corresponding aldehyde or ketone in AcOH, 1.2 eq of phenylhydrazine were added and the reaction mixture was stirred for 2 h at r.t. under Ar atmosphere; then it was heated up to 130 °C for further 2 h. It was let to cool down to r.t., diluted with EtOAc, washed with 6% $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. It was filtered and the solvent was removed. The crude was purified through column chromatography to afford the corresponding indole sesquiterpenes. Compound **17** could not be purified by column chromatography, so the crude was

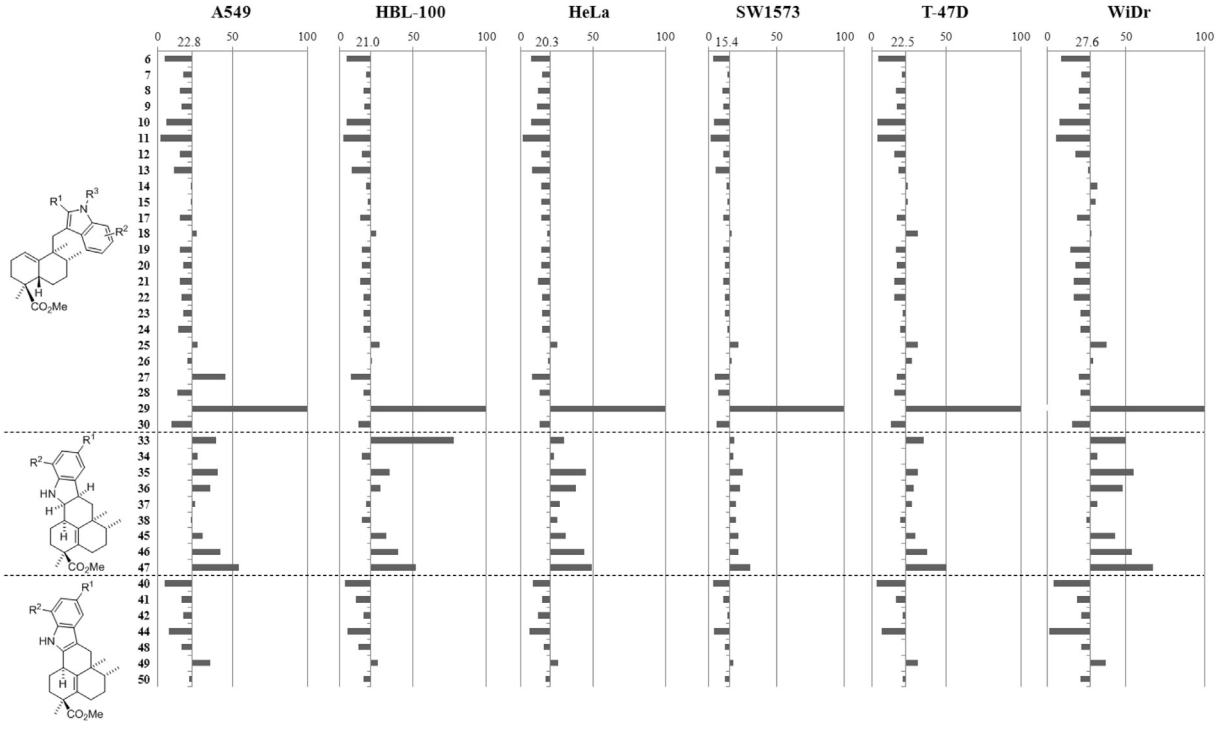


Fig. 3. Mean graph profiles for compounds **6**–**50**. The middle line represents the median GI_{50} (μM) value of the set of compounds against each individual cell line.

dissolved in EtOH, cooled down to 0 °C and 3 eq of $NaBH_4$ was added. After stirring for 40 min at r.t. it was cooled down again to 0 °C and 2 M HCl was added. It was diluted with H_2O and 1 M NaOH was added until pH = 7. It was extracted with EtOAc, washed with brine and dried over anhydrous Na_2SO_4. After filtering and removing the solvent the crude was purified by column chromatography.

*5.2.1. Aureanindol-16-ene (**4**)*

Yield 58%; $[\alpha]_D^{22}$-59.1 (*c* 0.23, EtOH); IR (film, cm^{-1}): 3400, 3043, 2947, 2913, 1456, 1383, 746; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (1H, br s, N–H), 7.66 (1H, d, J = 7.8 Hz), 7.33 (1H, d, J = 7.8 Hz), 7.20 (1H, t, J = 7.8 Hz), 7.15 (1H, t, J = 7.8 Hz), 6.94 (1H, s), 5.32 (1H, br s), 3.12 (1H, d, J = 14.4 Hz), 2.98 (1H, d, J = 14.4 Hz), 1.02 (3H, s), 0.94 (3H, s), 0.92 (3H, s), 0.88 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 135.6, 129.3, 122.8, 121.3, 120.2, 119.5, 119.0, 113.6, 110.8, 44.5, 43.3, 38.1, 34.9, 34.8, 31.8, 29.1, 28.9, 24.6 , 23.5, 23.1, 23.0, 16.0; HRMS calcd for $C_{23}H_{32}N$ (M^+ + H) 322.5229, found 322.2512.

*5.2.2. Methyl aureanindol-16-ene-21-oate (**6**)*

Yield 95%; mp: 129–132 °C; $[\alpha]_D^{22}$-45.7 (*c* 0.81, $CHCl_3$); IR (film, cm^{-1}): 3399, 3052, 2949, 1727, 1457, 1434, 1379, 1255, 1232, 1198, 1112, 739; ^1H NMR (200 MHz, $CDCl_3$): δ 8.01 (1H, br s, N–H), 7.63 (1H, d, J = 7.6 Hz), 7.34 (1H, d, J = 7.6 Hz), 7.16 (1H, t, J = 7.6 Hz), 7.10 (1H, t, J = 7.6 Hz), 6.94 (1H, s), 5.25 (1H, br s), 3.72 (3H, s), 3.09 (1H, d, J = 14.2 Hz), 2.98 (1H, d, J = 14.2 Hz), 1.18 (3H, s), 2.39–1.04 (10H, m), 0.88 (3H, s), 0.83 (3H, d, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 179.2, 141.4, 135.6, 129.5, 123.3, 121.5, 120.2, 119.7, 119.2, 113.6, 111.0, 52.1, 45.4, 44.7, 38.9, 37.9, 35.2, 31.9, 28.7, 23.6, 23.0, 22.9, 18.8, 16.3; HRMS calcd for $C_{24}H_{31}NO_2$ (M^+) 365.2353, found 365.2355.

*5.2.3. Methyl 6-trifluoromethyl-aureanindol-16-ene-21-oate (**12**)*

Yield 5%; $[\alpha]_D^{22}$-26.9 (*c* 0.32, $CHCl_3$); IR (film, cm^{-1}): 3368, 2928, 2874, 1699, 1329, 1258, 1159, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, s, N–H), 7.90 (1H, s), 7.41 (2H, s), 7.01 (1H, s), 5.24 (1H, br s), 3.71 (3H, s), 3.18 (1H, d, J = 14.4 Hz), 3.04 (1H, m), 2.94 (1H, d, J = 14.4 Hz), 2.30–1.25 (9H, m), 1.16 (3H, s), 0.85 (3H, s), 0.84 (3H, d, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.1, 141.0, 137.1, 128.9, 124.9, 121.8 (d, J = 30.0 Hz, C-6), 120.6, 118.4, 115.3, 114.8, 111.3, 52.1, 45.4, 44.6, 38.8, 38.4, 34.9, 31.7, 28.6, 23.5, 23.0, 22.9, 19.0, 16.3; HRMS calcd for $C_{25}H_{30}NO_2F_3Na$ (M^+ + Na) 456.2121, found 456.2112.

*5.2.4. Methyl 2-methyl-aureanindol-16-ene-21-oate (**17**)*

Yield: 14%; $[\alpha]_D^{22}$-33.7 (*c* 1.04, $CHCl_3$); IR (film, cm^{-1}): 3398, 2926, 1709, 1460, 1437, 1251, 1113; ^1H NMR (200 MHz, $CDCl_3$) δ 7.84 (1H, br s, N–H), 7.53 (1H, d, J = 7.0 Hz), 7.22 (1H, d, J = 7.0 Hz), 7.08 (1H, t, J = 7.0 Hz), 7.07 (1H, t, J = 7.0 Hz), 5.22 (1H, br s), 3.75 (3H, s), 3.15 (1H, m), 3.01 (1H, d, J = 14.6 Hz), 2.92 (1H, d, J = 14.6 Hz), 2.34 (3H, s, $Me_{C\text{-}2}$), 2.10–1.25 (9H, m), 1.19 (3H, s), 0.87 (3H, s), 0.83 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.4, 141.7, 135.3, 133.0, 130.8, 120.7, 119.8, 119.7, 118.9, 110.4, 110.1, 52.2, 45.6, 45.2, 39.1, 38.6, 35.2, 32.1, 28.7, 23.6, 22.8, 22.6, 18.1, 16.6, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{25}H_{33}NO_2Na$ (M^+ + Na) 402.2404, found 402.2412.

*5.2.5. Methyl 6-trifluoro-2-methyl-aureanindol-16-ene-21-oate (**23**)*

Yield: 27% calculated from transformed reagent; $[\alpha]_D^{22}$-31.5 (*c* 0.31, $CHCl_3$); IR (film, cm^{-1}): 3367, 2926, 2872, 1701, 1449, 1331, 1256, 1157, 1111; ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (1H, br s, N–H), 7.78 (1H, s), 7.29 (2H, m), 5.19 (1H, br s), 3.74 (3H), 3.05 (1H, d, J = 14.4 Hz), 2.86 (1H, d, J = 14.4 Hz), 2.37 (3H, s, $Me_{C\text{-}2}$), 2.15–1.30 (9H, m), 1.17 (3H, s), 0.83 (3H, s), 0.82 (3H, d, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2, 141.2, 138.0, 136.7, 134.7, 130.2, 120.2, 117.7, 117.2, 111.6, 110.2, 52.1, 45.5, 45.0, 39.2, 39.0, 35.1, 32.0, 28.5, 23.6, 22.7, 22.4, 17.9, 16.5, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{26}H_{32}NO_2NaF_3$ (M^+ + Na) 470.2277, found 470.2281.

5.3. General procedure for Fischer's indolization with phenylhydrazine hydrochlorides

To 1.2 eq. of the corresponding phenylhydrazine hydrochloride under Ar atmosphere, 1.2 eq of aqueous 1 M NaOH were added and the mixture was stirred for 10 min. Then, a 0.1 M solution of aldehyde **5** or ketone **16** in AcOH was added and the mixture was stirred under Ar atmosphere and at r.t. for 2 h and then heated up to 130 °C for further 2 h. In the case of the reactions with ketone **16** the mixture was stirred at r.t. for 7 h and at 130 °C for 16 h. It was let to cool down to r.t. and diluted with EtOAc. The organic layer was washed with 6% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed. The crude was purified through column chromatography affording the corresponding indole derivatives.

*5.3.1. Methyl 6-metil-aureanindol-16-ene-21-oate (**7**)*

Yield 45%; $[\alpha]_D^{22}$-47.6° (*c* 0.34, $CHCl_3$); IR (film, cm^{-1}): 3408, 2949, 2924, 2872, 1701, 1431, 1256, 1232, 1113; ^1H NMR (200 MHz, $CDCl_3$): δ 7.91 (1H, br s), 7.41 (1H, s), 7.22 (1H, d, J = 8.0 Hz), 6.99 (1H, dd, J = 8.0, 1.0 Hz), 6.89 (1H, d, J = 2.2 Hz), 5.25 (1H, br s), 3.72 (3H, s), 3.07 (1H, d, J = 14.4 Hz), 2.94 (1H, d, J = 14.4 Hz), 2.48 (3H, s, $Me_{C\text{-}6}$), 2.30–1.20 (10H, m), 1.19 (3H, s), 0.90 (3H, s), 0.85 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.3, 141.4, 134.2, 129.8, 128.3, 123.6, 123.2, 120.2, 119.3, 113.1, 110.7, 52.1, 45.5, 44.6, 38.9, 38.0, 35.2, 31.9, 28.7, 23.7, 23.0, 22.9, 21.8 ($Me_{C\text{-}6}$), 18.7, 16.3; HRMS calcd for $C_{25}H_{33}NO_2Na$ (M^+ + Na) 402.2403, found 402.2385.

*5.3.2. Methyl 6-bromo-aureanindol-16-ene-21-oate (**8**)*

Yield 40%; $[\alpha]_D^{22}$-44.5 (*c* 0.38, $CHCl_3$); IR (film, cm^{-1}): 3421, 3373, 2949, 2928, 2872, 1709, 1458, 1379, 1251, 1113, 739; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (1H, br s, N–H), 7.72 (1H, s), 7.21 (1H, d, J = 8.3 Hz), 7.17 (1H, d, J = 8.3 Hz), 6.91 (1H, s), 5.20 (1H, br s), 3.71 (3H, s), 3.06 (1H, d, J = 14.5 Hz), 3.01 (1H, br s), 2.82 (1H, d, J = 14.4 Hz), 2.20–1.20 (9H, m), 1.17 (3H, s), 0.84 (3H, s), 0.83 (3H, d, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.3, 141.0, 134.5, 131.3, 124.7, 124.3, 122.2, 120.5, 113.4, 112.6, 112.5, 52.1, 45.5, 44.5, 38.8, 38.2, 35.1, 31.8, 28.6, 23.5, 22.9, 22.8, 18.9, 16.3; HRMS calcd for $C_{24}H_{30}NO_2NaBr$ (M^+ + Na) 466.1352, found 466.1368.

*5.3.3. Methyl 6-chloro-aureanindol-16-ene-21-oate (**9**)*

Yield 50%; $[\alpha]_D^{22}$-46.9 (*c* 0.29, $CHCl_3$); IR (film, cm^{-1}): 3373, 2949, 1708, 1458, 1251, 1113, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 8.06 (1H, br s, N–H), 7.56 (1H, d, J = 1.8 Hz), 7.23 (1H, d, J = 8.0 Hz), 7.09 (1H, dd, J = 8.4, 1.8 Hz), 6.95 (1H, dd, J = 2.2 Hz), 5.21 (1H, br s), 3.70 (3H, s), 3.07 (1H, d, J = 13.8 Hz), 2.85 (1H, d, J = 13.8 Hz), 2.30–1.25 (10H, m), 1.16 (3H, s), 0.85 (3H, s), 0.83 (3H, d, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2, 141.0, 134.2, 130.7, 125.1, 124.8, 121.8, 120.5, 119.2, 113.6, 112.0, 52.1, 45.4, 44.5, 38.8, 38.2, 35.1, 31.8, 28.6, 23.5, 23.0, 22.9, 18.9, 16.3; HRMS calcd for $C_{24}H_{30}NO_2NaCl$ (M^+ + Na) 422.1857, found 422.1843.

*5.3.4. Methyl 6-fluoro-aureanindol-16(17)-ene-21-oate (**10**)*

Yield 53%; $[\alpha]_D^{22}$-45.1 (*c* 0.34, $CHCl_3$), IR (film, cm^{-1}): 3383, 2949, 1712, 1485, 1456, 1251, 1114, 910, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 7.97 (1H, br s, N–H), 7.25–7.20 (2H, m), 6.98 (1H, s), 6.89 (1H, m), 5.23 (1H, br s), 3.71 (3H, s), 3.08–3.06 (1H, m); 3.04 (1H, d, J = 14.2 Hz), 3.03 (1H, m), 2.88 (1H, d, J = 14.2 Hz), 2.30–1.25 (9H, m), 1.17 (3H, s), 0.86 (3H, s), 0.83 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 157.6 (d, J = 115.0 Hz, C6-F), 141.0, 132.1, 129.7 (d, J = 5.0 Hz, C-4), 125.0, 120.1, 113.5, 111.4, 111.2 (J = 10.0 Hz,

C-7), 104.2 (d, J = 10.0 Hz, C-5), 51.8, 45.2, 44.4, 38.6, 37.7, 35.0, 31.5, 28.4, 23.3, 22.8, 22.6, 18.6, 16.0; HRMS calcd for $C_{24}H_{31}NO_2F$ (M^+ + H) 384.2333, found 384.2336.

*5.3.5. Methyl 6-methoxy-aureanindol-16-ene-21-oate (**11**)*

Yield 44%; $[\alpha]_D^{22}$-52.6 (*c* 0.27, $CHCl_3$); IR (film, cm^{-1}): 3412, 3949, 2872, 1718, 1485, 1256, 1213, 1113, 910, 733; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (1H, br s, N–H), 7.20 (1H, d, J = 8.8 Hz), 7.06 (1H, d, J = 2.2 Hz), 6.91 (1H, d, J = 2.2 Hz), 6.83 (1H, dd, J = 8.8, 2.2 Hz), 5.27 (1H, br s), 3.88 (3H, s, –O<u>Me</u>), 3.71 (3H, s, –COO<u>Me</u>), 3.02 (1H, d, J = 14.4 Hz), 2.95 (1H, d, J = 14.4 Hz), 2.30–1.25 (9H, m), 1.18 (3H, s), 0.89 (3H, s), 0.83 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2, 154.0, 141.5, 131.1, 130.0, 124.3, 120.1, 113.4, 111.7, 111.6, 101.8, 56.2 (–O<u>Me</u>), 52.1 (–COO<u>Me</u>), 45.4, 44.8, 38.9, 37.8, 35.3, 31.9, 28.7, 23.7, 23.0, 22.9, 18.9, 16.3; HRMS calcd for $C_{25}H_{33}NO_3Na$ (M^+ + Na) 418.2364, found 418.2351.

*5.3.6. Methyl 8-methyl-aureanindol-16-ene-21-oate (**13**)*

Yield, 34%; $[\alpha]_D^{22}$-34.6 (*c* 0.28, $CHCl_3$); IR (film, cm^{-1}): 3408, 2951, 2872, 1699, 1448, 1379, 1255, 1115, 735; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (1H, s, N–H), 7.49 (1H, d, J = 7.4 Hz), 7.04 (1H, dd, J = 8.0, 7.4 Hz), 6.97 (1H, d, J = 8.0 Hz), 6.96 (1H, s), 5.27 (1H, br s), 3.72 (3H, s), 3.08 (1H, m), 3.07 (1H, d, J = 14.1 Hz), 3.03 (1H, d, J = 14.1 Hz), 2.49 (3H, s, $Me_{C\text{-}8}$), 2.40–1.25 (9H, m), 1.19 (3H, s), 0.89 (3H, s), 0.84 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2, 141.5, 135.4, 129.1, 123.1, 122.1, 120.1, 119.4, 117.5, 114.2, 114.1, 52.1, 45.5, 44.7, 38.9, 37.8, 35.4, 31.9, 28.7, 23.7, 23.0, 22.9, 18.8, 16.8, 16.3 ($Me_{C\text{-}8}$); HRMS calcd for $C_{25}H_{34}NO_2$ (M^+ + H) 380.2584, found 380.2590.

*5.3.7. Methyl 8-bromo-aureanindol-16-ene-21-oate (**14**)*

Yield 34%; $[\alpha]_D^{22}$-37.9 (*c* 0.39, $CHCl_3$); IR (film, cm^{-1}): 3372, 2949, 2872, 1716, 1435, 1379, 1336, 1259, 1196, 1113, 733; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16 (1H, br s, N–H), 7.55 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 7.2 Hz), 7.00 (1H, s), 6.98 (1H, dd, J = 8.0, 7.2 Hz), 5.21 (1H, br s), 3.71 (3H, s), 3.08 (1H, d, J = 14.2 Hz), 3.03 (1H, m), 2.91 (1H, d, J = 14.2 Hz), 2.30–1.25 (9H, m), 1.18 (3H, s), 0.90 (3H, s), 0.84 (3H, d, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2, 141.1, 134.5, 130.8, 124.0, 123.9, 120.5, 120.4, 119.0, 114.9, 104.8, 52.1, 45.4, 44.7, 38.8, 38.2, 35.3, 31.8, 28.6, 23.5, 23.0, 22.9, 19.0, 16.3; HRMS calcd for $C_{24}H_{30}NO_2NaBr$ (M^+ + Na) 466.1352, found 466.1365.

*5.3.8. Methyl 8-chloro-aureanindol-16-ene-21-oate (**15**)*

Yield: 27%: mp: 134–136 °C; $[\alpha]_D^{22}$-37.7 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}): 3373, 2951, 2872, 1716, 1436, 1259, 1198, 1113, 733; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (1H, br s, N–H), 7.51 (1H, d, J = 8.0 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.00 (1H, s), 5.22 (1H, br s), 3.72 (3H, s), 3.09 (1H, d, J = 14.2 Hz),3.03 (1H, m), 2.91 (1H, d, J = 14.2 Hz), 2.30–1.25 (9H, m), 1.18 (3H, s), 0.85 (3H, s), 0.83 (3H, d, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2, 141.1, 133.1, 131.1, 124.1, 120.9, 120.5, 119.9, 118.4, 116.6, 114.8, 52.1, 45.5, 44.6, 38.8, 38.2, 35.2, 31.8, 28.7, 23.5, 23.0, 22.9, 19.0, 16.3; HRMS calcd for $C_{24}H_{30}NO_2NaCl$ (M^+ + Na) 422.1857, found 422.1849.

*5.3.9. Methyl 2,6-dimethyl-aureanindol-16-ene-21-oate (**18**)*

Yield: 78%; $[\alpha]_D^{22}$-40.3 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}): 3397, 2922, 2872, 1713, 1449, 1437, 1254, 1238, 1113, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, br s, N–H), 7.37 (1H, s), 7.11 (1H, d, J = 8.1 Hz), 6.89 (1H, d, J = 8.1 Hz), 5.21 (1H, br s), 3.74 (3H, s), 3.15 (1H, m), 2.99 (1H, d, J = 14.4 Hz), 2.83 (1H, d, J = 14.4 Hz), 2.43 (3H, s, $Me_{C\text{-}6}$), 2.32 (3H, s, $Me_{C\text{-}2}$), 1.91–1.31 (9H, m), 1.18 (3H, s), 0.87 (3H, s), 0.82 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 141.2, 133.3, 132.7, 130.8, 127.7, 121.9, 119.6, 119.1, 109.8, 109.4, 51.8, 45.3, 44.9, 38.9, 38.7, 35.0, 31.8, 28.4, 23.4, 22.5, 22.3, 21.5 ($Me_{C\text{-}6}$), 17.6, 16.3, 12.9 ($Me_{C\text{-}2}$); HRMS calcd for $C_{26}H_{36}NO_2$ (M^+ + H) 394.2741, found 394.2740.

*5.3.10. Methyl 6-bromo-2-methyl-aureanindol-16-ene-21-oate (**19**)*

Yield: 95% calculated from conversion; $[\alpha]_D^{22}$-27.5 (*c* 0.40, $CHCl_3$); IR (film, cm^{-1}): 3397, 2949, 2926, 2872, 1709, 1449, 1379, 1250, 1113; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (1H, br s, N–H), 7.62 (1H, d, J = 1.6 Hz), 7.13 (1H, dd, J = 8.2, 1.6 Hz), 7.06 (1H, d, J = 8.2 Hz), 5.17 (1H, br s), 3.75 (3H, s), 3.12 (1H, m, H-15), 2.99 (1H, d, J = 14.6 Hz), 2.74 (1H, d, J = 14.6 Hz), 2.31 (3H, s, $Me_{C\text{-}2}$), 2.10–1.20 (9H, m), 1.17 (3H, s), 0.83 (3H, d, J = 7.0 Hz), 0.82 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.4, 141.0, 134.4, 133.9, 132.5, 123.4, 122.1, 120.3, 112.3, 111.5, 110.4, 52.2, 45.6, 45.0, 39.3, 39.0, 35.2, 32.2, 28.5, 23.6, 22.7, 22.4, 17.9, 16.6, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{25}H_{32}NO_2NaBr$ (M^+ + Na) 480.1509, found 480.1510.

*5.3.11. Methyl 6-chloro-2-methyl-aureanindol-16-ene-21-oate (**20**)*

Yield 94% calculated from transformed reagent; $[\alpha]_D^{22}$-39.4 (*c* 0.57, $CHCl_3$); IR (film, cm^{-1}): 3372, 2953, 2872, 1719, 1449, 1263, 1113, 737; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (1H, br s, N–H), 7.47 (1H, d, J = 2.0 Hz), 7.09 (1H, d, J = 8.4 Hz), 6.99 (1H, dd, J = 8.4, 2.0 Hz), 5.17 (1H, br s), 3.76 (3H, s), 3.14 (1H, m), 2.99 (1H, d, J = 14.4 Hz), 2.75 (1H, d, J = 14.4 Hz), 2.30 (3H, s, $Me_{C\text{-}2}$), 2.10–1.20 (9H, m), 1.19 (3H, s), 0.83 (3H, s), 0.82 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.4, 141.1, 134.7, 133.7, 131.9, 124.6, 120.7, 120.3, 119.0, 111.0, 110.4, 52.2, 45.6, 45.0, 39.2, 39.0, 35.2, 32.1, 28.5, 23.5, 22.7, 22.5, 17.9, 16.5, 13.1 ($Me_{C\text{-}2}$); HRMS calcd for $C_{25}H_{32}NO_2NaCl$ (M^+ + Na) 436.2014, found 436.1995.

*5.3.12. Methyl 6-fluoro-2-methyl-aureanindol-16-ene-21-oate (**21**)*

Yield: 63% calculated from transformed reagent; $[\alpha]_D^{22}$-44.5 (*c* 0.40, $CHCl_3$); IR (film, cm^{-1}): 3377, 2951, 2932, 2872, 1709, 1487, 1450, 1252, 1115, 910, 735; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.87 (1H, br s, N–H), 7.17 (1H, d, J = 8.8 Hz), 7.10 (1H, d, J = 8.8 Hz), 6.80 (1H, dt, J = 8.8, 2.2 Hz), 5.22 (1H, br s), 3.75 (3H, s), 3.11 (1H, m), 2.94 (1H, d, J = 14.6 Hz), 2.83 (1H, d, J = 14.6 Hz), 2.32 (3H, s, $Me_{C\text{-}2}$), 2.10–1.20 (9H, m), 1.18 (3H, s), 0.84 (3H, s), 0.82 (3H, d, J = 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.4, 157.5 (d, J = 115.0 Hz, C6-F) 141.5, 135.0, 131.8, 131.1, 120.0, 110.9, 110.4 (d, J = 10.0 Hz, C-8), 108.7 (d, J = 25.0 Hz, C-7), 104.7 (d, J = 25.0 Hz, C-5), 52.2, 45.6, 45.2, 39.0, 38.8, 35.2, 32.0, 28.6, 23.5, 22.8, 22.6, 18.1, 16.5, 13.3 ($Me_{C\text{-}2}$); HRMS calcd for $C_{25}H_{32}NO_2NaF$ (M^+ + Na) 420.2309, found 420.2313.

*5.3.13. Methyl 2-methyl-6-methoxy-aureanindol-16-ene-21-oate (**22**)*

Yield: 47% calculated from transformed reagent; $[\alpha]_D^{22}$-53.4 (*c* 0.35, $CHCl_3$); IR (film, cm^{-1}): 3401, 2949, 2872, 1713, 1485, 1452, 1254, 1215, 1113, 733; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (1H, s, N–H), 7.12 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 2.0 Hz), 6.74 (1H, dd, J = 8.4, 2.0 Hz), 5.28 (1H, br s), 3.86 (3H, s, –O<u>Me</u>), 3.73 (3H, s, –COO<u>Me</u>), 3.10 (1H, m), 2.93 (1H, d, J = 14.4 Hz), 2.86 (1H, d, J = 14.4 Hz), 2.32 (3H, s, $Me_{C\text{-}2}$), 2.15–1.20 (9H, m), 1.18 (3H, s), 0.87 (3H, s), 0.80 (3H, d, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3, 153.9, 142.0, 134.0, 131.3, 130.5, 119.6, 110.6, 110.4, 110.2, 102.5, 56.3, 52.1, 45.5, 45.4, 39.1, 38.3, 35.3, 32.0, 28.8, 23.7, 22.8, 22.6, 18.2, 16.5, 13.4 ($Me_{C\text{-}2}$); HRMS calcd for $C_{26}H_{35}NO_3Na$ (M^+ + Na) 432.2509, found 432.2516.

*5.3.14. Methyl 2,8-dimethyl-aureanindol-16-ene-21-oate (**24**)*

Yield: 62% calculated from transformed reagent; $[\alpha]_D^{22}$-28.4 (*c* 0.62, $CHCl_3$); IR (film, cm^{-1}): 3393, 2926, 2872, 1701, 1431, 1379, 1248, 1113, 1103; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (1H, br s, N–H), 7.40 (1H, d, J = 7.4 Hz), 6.99 (1H, d, J = 7.0 Hz), 6.91 (1H, dd, J = 7.4, 7.0 Hz), 5.25 (1H, br s), 3.74 (3H, s), 3.17 (1H, m), 2.95 (2H, br s), 2.46 (3H, s, $Me_{C\text{-}8}$), 2.37 (3H, s, $Me_{C\text{-}2}$), 2.15–1.20 (9H, m), 1.19 (3H, s), 0.87 (3H, s), 0.82 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.4, 141.8, 134.8, 132.6, 130.4, 121.5, 119.7, 119.2, 119.1, 117.5, 111.0, 52.1, 45.6, 45.2, 39.1, 38.6, 35.4, 32.1, 28.7, 23.6, 22.8, 22.6, 18.1, 16.8

($Me_{C\text{-}8}$), 16.5, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{26}H_{35}NO_2Na$ ($M^+ + Na$) 416.2560, found 416.2566.

5.3.15. Methyl 8-bromo-2-methyl-aureanindol-16-ene-21-oate (**25**)

Yield: 87% calculated from transformed reagent; $[\alpha]_D^{22}$-41.2 (*c* 0.33, $CHCl_3$); IR (film, cm^{-1}): 3367, 2949, 2872, 1716, 1446, 1247, 1112, 908, 738; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98 (1H, s, N–H), 7.45 (1H, d, $J = 7.8$ Hz), 7.22 (1H, d, $J = 7.8$ Hz), 6.91 (1H, t, $J = 7.8$ Hz), 5.20 (1H, br s), 3.74 (3H, s), 3.11 (1H, m), 2.98 (1H, d, $J = 14.8$ Hz), 2.86 (1H, d, $J = 14.8$ Hz), 2.37 (3H, s, $Me_{C\text{-}2}$), 2.30–1.20 (9H, m), 1.18 (3H, s), 0.84 (3H, s), 0.82 (3H, d, $J = 7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3, 141.4, 133.9, 133.8, 132.0, 123.1, 120.1, 120.0, 118.9, 111.9, 103.8, 52.1, 45.5, 45.1, 39.0, 38.9, 35.4, 32.1, 28.6, 23.5, 22.8, 22.5, 18.1, 16.5, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{25}H_{32}NO_2NaBr$ ($M^+ + Na$) 480.1509, found 480.1510.

5.3.16. Methyl 8-chloro-2-methyl-aureanindol-16-ene-21-oate (**26**)

Yield: 95% calculated from transformed reagent; $[\alpha]_D^{22}$-44.0 (*c* 0.47, $CHCl_3$); IR (film, cm^{-1}): 3368, 2949, 2922, 1717, 1449, 1250, 1200, 1113, 908, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 8.05 (1H, br s, N–H), 7.41 (1H, d, $J = 7.4$ Hz), 7.07 (1H, d, $J = 7.4$ Hz), 6.97 (1H, t, $J = 7.4$ Hz), 5.20 (1H, br s), 3.75 (3H, s), 3.12 (1H, t, $J = 7.8$ Hz), 2.98 (1H, d, $J = 14.4$ Hz), 2.86 (1H, d, $J = 14.4$ Hz), 2.37 (3H, s, $Me_{C\text{-}2}$), 2.10–1.20 (9H, m), 1.18 (3H, s), 0.85 (3H, s), 0.82 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3, 141.4, 133.9, 132.5, 132.3, 120.1, 120.0, 119.7, 118.3, 115.6, 111.9, 52.2, 45.5, 45.1, 39.0, 38.8, 35.3, 32.1, 28.6, 23.5, 22.8, 22.6, 18.1, 16.5, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{25}H_{32}NO_2NaCl$ ($M^+ + Na$) 436.2014, found 436.1999.

5.4. General procedure for cyclisation reactions

To a 0.02 M solution of the indole derivative in C_6H_6, 1 eq. of HI 57% was added. The mixture was heated up to 85 °C for 1 h. It was cooled down to r.t. and diluted with EtOAc. The organic layer was washed with 10% $NaHSO_3$, 6% $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the solvents affords the corresponding pentacyclic derivatives.

5.4.1. (2R,3R,17R)-2,3-dihydro-2,17-cyclo-aureanindol-15-ene (**31**)

Yield: 81%; $[\alpha]_D^{22}$+137.1 (*c* 0.28, MeOH); IR (film, cm^{-1}): 3359, 2920, 2868, 1310, 1481, 1458, 1382, 1245, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, br s, N–H), 7.08 (1H, d, $J = 7.2$ Hz), 7.00 (1H, dt, $J = 7.6$, 7.2 Hz), 6.71 (1H, t, $J = 7.2$), 6.67 (1H, d, $J = 7.6$ Hz), 3.76 (1H, dd, $J = 6.0$, 4.8 Hz), 3.11 (1H, m), 2.66 (1H, m), 2.10–1.10 (10H, m), 1.04 (3H, s), 1.01 (3H, s), 1.00 (3H, s), 0.84 (3H, d, $J = 6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 137.6, 135.8, 131.4, 127.0, 123.1, 118.7, 110.1, 67.0, 41.7, 40.3, 38.5, 37.8, 37.4, 34.7, 33.5, 28.3, 27.7, 27.2, 25.6, 24.3, 18.2, 16.3; HRMS calcd for $C_{23}H_{32}N$ ($M^+ + H$) 322.2529, found 322.2407.

5.4.2. Methyl (2R,3R,17R)-2,3-dihydro-2,17-cyclo-aureanindol-15-en-21-oate (**33**)

Yield: 97%; $[\alpha]_D^{22}$+49.2 (*c* 0.17, $CHCl_3$); IR (film, cm^{-1}): 3367, 2924, 2873, 1724, 1610, 1456, 1379, 1251, 1132, 910, 736; ^1H NMR (200 MHz, $CDCl_3$) δ 7.08 (1H, d, $J = 7.4$ Hz), 7.02 (1H, dd, $J = 7.8$, 7.4 Hz), 6.71 (1H, t, $J = 7.4$ Hz), 6.67 (1H, d, $J = 7.8$ Hz), 3.80 (1H, dd, $J = 6.0$, 4.8 Hz), 3.67 (3H, s), 3.14 (1H, dt, $J = 12.0$, 6.0 Hz), 2.69 (1H, m), 2.30–1.25 (11H, m), 1.30 (3H, s), 1.02 (3H, s), 0.85 (3H, d, $J = 6.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.0, 150.2, 136.0, 135.0, 132.5, 127.3, 123.4, 119.0, 110.5, 66.9, 52.1, 47.6, 41.6, 40.2, 38.9, 38.2, 33.3 (x2), 27.3, 26.7, 24.1, 23.7, 18.5, 16.4; HRMS calcd for $C_{24}H_{32}NO_2$ ($M^+ + H$) 366.2428, found 366.2416.

5.4.3. Methyl (2R,3R,17R)-6-methyl-2,3-dihydro-2,17-ciclo-aureanindol-15-ene-21-oate (**34**)

Yield: 99%; $[\alpha]_D^{22}$+63.1 (*c* 0.20, $CHCl_3$); IR (film, cm^{-1}): 3365, 2922, 2872, 1726, 1491, 1431, 1379, 1250, 1130, 735; ^1H NMR (200 MHz, $CDCl_3$) δ 6.91 (1H, s), 6.83 (1H, d, $J = 7.8$ Hz), 6.60 (1H, d, $J = 7.8$ Hz), 3.77 (1H, dd, $J = 5.8$, 4.8 Hz), 3.67 (3H, s), 3.09 (1H, dt, $J = 12.2$, 5.8 Hz), 2.67 (1H, m), 2.00–1.25 (11H, m), 2.26 (3H, s, $Me_{C\text{-}6}$), 1.29 (3H, s), 1.09 (3H, s), 0.84 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.0, 147.7, 136.6, 135.0, 132.5, 128.6, 127.7, 124.2, 110.7, 67.1, 52.1, 47.6, 41.7, 40.2, 39.0, 38.3, 33.4 (x2), 27.2, 26.7, 24.1, 23.7, 21.1 ($Me_{C\text{-}6}$), 18.6, 16.4; HRMS calcd for $C_{25}H_{34}NO_2$ ($M^+ + H$) 380.2584, found 380.2602.

5.4.4. Methyl (2R,3R,17R)-6-bromo-2,3-dihydro-2,17-cyclo-aureanindol-15-en-21-oate (35)

Yield: 92%; $[\alpha]_D^{22}$+93.1 (*c* 0.15, $CHCl_3$); IR (film, cm^{-1}): 3368, 2924, 2873, 1718, 1451, 1379, 1254, 1379, 1254, 808, 737; ^1H NMR (200 MHz, $CDCl_3$) δ 7.16 (1H, d, $J = 2.0$ Hz), 7.09 (1H, dd, $J = 8.2$, 2.0 Hz), 6.52 (1H, d, $J = 8.2$ Hz), 3.79 (1H, dd, $J = 6.0$, 4.6 Hz), 3.67 (3H, s), 3.11 (1H, dt, $J = 12.2$, 6.0 Hz), 2.66 (1H, m), 2.30–1.25 (11H, m), 1.29 (3H, s), 1.00 (3H, s), 0.84 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 149.2, 138.3, 134.6, 132.8, 129.9, 126.5, 111.8, 110.6, 67.0, 52.1, 47.5, 41.4, 40.2, 38.9, 38.2, 33.3, 33.2, 27.2, 26.7, 24.0, 23.7, 18.6, 16.4; HRMS calcd for $C_{24}H_{31}NO_2Br$ ($M^+ + H$) 444.1533, found 444.1528.

5.4.5. Methyl (2R,3R,17R)-6-chloro-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-oate (**36**)

Yield: 91%; $[\alpha]_D^{22}$+54.9 (*c* 0.32, $CHCl_3$); IR (film, cm^{-1}): 3368, 2926, 2873, 1719, 1477, 1431, 1254, 908, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 7.01 (1H, d, $J = 2.2$ Hz), 6.95 (1H, dd, $J = 8.2$, 2.2 Hz), 6.65 (1H,d, $J = 8.2$ Hz), 3.80 (1H, dd, $J = 5.8$, 4.6 Hz), 3.67 (3H, s), 3.11 (1H, dt, $J = 12.0$, 5.8 Hz), 2.30–1.25 (11H, m), 1.29 (3H, s), 1.00 (3H, s), 0.84 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 148.8, 137.8, 134.6, 132.7, 127.0, 123.7, 123.4, 111.2, 67.1, 52.1, 47.5, 41.4, 40.2, 39.0, 38.2, 33.3, 33.2, 27.2, 26.7, 24.1, 23.7, 18.5, 16.4; HRMS calcd for $C_{24}H_{31}NO_2Cl$ ($M^+ + H$) 400.2038, found 400.2023.

5.4.6. Methyl (2R,3R,17R)-6-fluoro-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-oate (**37**)

Yield: 93%; $[\alpha]_D^{22}$+40.8 (*c* 0.26, $CHCl_3$); IR (film, cm^{-1}): 3366, 2926, 2873, 1719, 1485, 1379, 1253, 1219, 1123, 808, 737; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (1H, dd, $J = 8.2$, 2.4 Hz), 6.69 (1H, dt, $J = 8.2$, 2.4 Hz), 6.58 (1H, dd, $J = 8.2$, 4.3 Hz), 3.80 (1H, t, $J = 5.3$ Hz), 3.67 (3H, s), 3.11 (1H, dt, $J = 12.0$, 4.0Hz), 2.67 (1H, m), 2.30–1.25 (9H, m), 1.76–1.71 (2H, dd, $J = 13.3$, 5.7 Hz), 1.29 (3H, s), 1.01 (3H, s), 0.84 (3H, d, $J = 5.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 156.9 (d, $J = 135.0$ Hz, C-6), 145.6, 137.7 (d, $J = 5.0$ Hz, C-4), 134.5, 132.5, 112.9 (d, $J = 10.0$ Hz, C-7), 110.8 (d, $J = 5.0$ Hz, C-5), 110.5, 67.0, 51.8, 47.3, 41.0, 39.9, 39.1, 38.0, 33.4, 33.0, 26.9, 26.4, 23.8, 23.4, 18.4, 16.1; HRMS calcd for $C_{24}H_{31}NO_2F$ ($M^+ + H$) 384.2333, found 384.2337.

5.4.7. Methyl (2R,3R,17R)-6-methoxy-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-oate (**38**)

Yield: 90%; $[\alpha]_D^{22}$+71.2 (*c* 0.16, $CHCl_3$); IR (film, cm^{-1}): 3360, 2934, 1719, 1491, 1225, 733; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, d, $J = 2.3$ Hz), 6.34 (1H, d, $J = 8.3$ Hz), 6.58 (1H, dd, $J = 8.3$, 2.3 Hz), 3.77 (1H, m), 3.74 (3H, s, MeO–), 3.67 (3H, s, –COOMe), 3.10 (1H, dt, $J = 12.0$, 6.0 Hz), 2.68 (1H, m), 2.30–1.30 (11H, m), 1.28 (3H, s), 1.01 (3H, s), 0.84 (3H, d, $J = 6.1$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.0, 153.9, 143.8, 138.3, 134.9, 132.6, 112.0, 111.6, 110.5, 67.3, 56.1 (MeO–), 52.1 (–COOMe), 47.6, 41.5, 40.2, 39.6, 38.3, 33.4, 33.3, 27.2, 26.7, 24.1, 23.7, 18.6, 16.4; HRMS calcd for $C_{25}H_{34}NO_3$ ($M^+ + H$) 396.2533, found 396.2538.

*5.4.8. Methyl (2R,3R,17R)-6-trifluoromethyl-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-oate (**39**)*

Yield: 87%; $[\alpha]_D^{22}$+1.9 (*c* 0.26, $CHCl_3$); IR (film, cm^{-1}): 3368, 2926, 1717, 1618, 1466, 1327, 1265, 1157, 1109; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (1H, s), 7.25 (1H, s), 6.63 (1H, d, J = 8.8 Hz), 3.87 (1H, dd, J = 6.2, 4.8 Hz), 3.67 (3H, s), 3.18 (1H, dt, J = 12.0, 6.2 Hz), 2.69 (1H, m), 2.40–1.30 (11H, m), 1.29 (3H, s), 1.01 (3H, s), 0.85 (3H, d, J = 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 153.1, 143.0, 135.8, 132.9, 132.4, 126.3, 125.2, 120.6, 66.9, 52.1, 47.0, 41.3, 40.1, 38.3, 38.2, 33.0 (x2), 27.2, 26.7, 24.0, 23.6, 18.5, 16.4; HRMS calcd for $C_{25}H_{31}NO_2F_3$ (M^+ + H) 434.2301, found 434.2297.

*5.4.9. Methyl (2R,3R,17R)-8-methyl-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-oate (**45**)*

Yield: 93%; $[\alpha]_D^{22}$+11.5 (*c* 0.27, $CHCl_3$); IR (film, cm^{-1}): 3366, 2924, 2872, 1719, 1449, 1232, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 6.95 (1H, d, J = 7.0 Hz), 6.87 (1H, d, J = 7.4 Hz), 6.66 (1H, dd, J = 7.4, 7.0 Hz), 3.81 (1H, dd, J = 6.0, 4.8 Hz), 3.67 (3H, s), 3.16 (1H, dt, J = 12.0, 6.0 Hz), 2.70 (1H, m), 2.40–2.20 (2H, m), 2.15 (3H, s, $Me_{C\text{-}8}$), 2.00–1.40 (8H, m), 1.80–1.71 (2H, dd, J = 13.3, 5.5 Hz), 1.30 (3H, s), 1.02 (3H, s), 0.85 (3H, d, J = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 148.5, 135.1, 135.0, 132.4, 128.1, 121.0, 119.9, 118.8, 66.3, 51.7, 47.3, 41.4, 39.8, 38.8, 37.9, 33.3, 33.2, 27.0, 26.4, 23.9, 23.5, 18.3, 16.8 ($Me_{C\text{-}8}$), 16.1 (C-24); HRMS calcd for $C_{25}H_{34}NO_2$ (M^+ + H) 380.2584, found 380.2584.

*5.4.10. Methyl (2R,3R,17R)-8-bromo-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-oate (**46**)*

Yield: 99%; $[\alpha]_D^{22}$-91.2 (*c* 0.08, $CHCl_3$); IR (film, cm^{-1}): 3385, 2924, 1717, 1452, 1234, 1103, 737; ^1H NMR (200 MHz, $CDCl_3$) δ 7.14 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 6.8 Hz), 6.56 (1H, dd, J = 8.0, 6.8 Hz), 3.85 (1H, t, J = 5.5 Hz), 3.68 (3H, s), 3.25 (1H, dt, J = 12.2, 6.0 Hz), 2.68 (1H, m), 2.30–1.30 (11H, m), 1.29 (3H, s), 1.01 (3H, s), 0.85 (3H, d, J = 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 148.8, 137.0, 134.5, 132.8, 129.9, 122.2, 120.0, 104.1, 66.2, 52.1, 47.5, 41.3, 40.1, 39.9, 38.1, 33.4, 33.2, 27.2, 26.7, 24.0, 23.8, 18.6, 16.4; HRMS calcd for $C_{24}H_{31}NO_2Br$ (M^+ + H) 444.1533, found 444.1520.

*5.4.11. Methyl (2R,3R,17R)-8-chloro-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-oate (**47**)*

Yield: 99%; $[\alpha]_D^{22}$-10.7 (*c* 0.80, $CHCl_3$); IR (film, cm^{-1}): 3356, 2924, 1726, 1611, 1458, 1236, 1105, 735; ^1H NMR (200 MHz, $CDCl_3$) δ 7.01 (1H, dd, J = 7.8, 1.0 Hz), 6.95 (1H, dd, J = 7.8, 1.0 Hz), 6.62 (1H, t, J = 7.8 Hz), 3.84 (1H, dd, J = 6.0, 4.8 Hz), 3.68 (3H, s), 3.22 (1H, dt, J = 12.0, 6.0 Hz), 2.68 (1H, m), 2.30–1.30 (11H, m), 1.30 (3H, s), 1.01 (3H, s), 0.85 (3H, d, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 147.3, 137.2, 134.5, 132.8, 127.1, 121.7, 119.6, 115.6, 66.6, 52.1, 47.5, 41.3, 40.1, 39.7, 38.2, 33.4, 33.2, 27.2, 26.7, 24.0, 23.8, 18.6, 16.4; HRMS calcd for $C_{24}H_{31}NO_2Cl$ (M^+ + H) 400.2038, found 400.2030.

*5.4.12. (2R,3R,17R)-2,3-dihydro-2,17-cyclo-aureanindol-15-ene-21-yl acetate (**53**)*

Yield: 98%; $[\alpha]_D^{22}$+51.3 (*c* 0.52, $CHCl_3$); IR (film, cm^{-1}): 3368, 2929, 1739, 1610, 1464, 1371, 1242, 1036, 738, 667; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, d, J = 7.4 Hz), 7.01 (1H, t, J = 7.4 Hz), 6.70 (1H, t, J = 7.4 Hz), 6.64 (1H, d, J = 7.4 Hz), 4.08 (1H, d, J = 10.8 Hz), 3.99 (1H, d, J = 10.8 Hz), 3.77 (1H, dd, J = 6.0, 4.6 Hz), 3.11 (1H, dt, J = 12.2, 6.0 Hz), 2.71–2.64 (1H, m), 2.03 (3H, s), 2.15–1.18 (11H, m), 1.03 (3H, s), 1.02 (3H, s), 0.84 (3H, d, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.4, 149.9, 135.7, 135.3, 133.3, 127.1, 123.1, 118.7, 110.0, 70.0, 66.6, 41.8, 40.2, 38.5 (x2), 38.0, 33.6, 31.7, 27.0, 25.7, 23.5, 23.0, 21.0 (–OOC<u>Me</u>), 18.1, 16.2; HRMS calcd for $C_{25}H_{34}NO_2$ (M^+ + H) 380.2584, found 380.2574.

5.5. General procedure for oxidation reactions

A 0.01 M solution of the pentacyclic hexahydro derivative with NMO (3 eq.) and TPAP (2 mg), molecular sieves (500 mg/mmol) in DCM was stirred at r.t. and under Ar atmosphere for 5–7 min. The crude was filtered through a silica and celite column, using EtOAc as eluent. After removing the solvent, the crude was purified through column chromatography to afford the corresponding tetrahydro carbazole derivatives.

*5.5.1. (17R)-2,17-cyclo-aureanindol-15-ene (**32**)*

Yield: 63%; $[\alpha]_D^{22}$-53.1 (*c* 0.04, $CHCl_3$); IR (film, cm^{-1}): 3412, 2962, 2927, 1460, 1384, 1093, 739; ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (1H, br s, N–H), 7.44 (1H, d, J = 7.0 Hz), 7.30 (1H, d, J = 7.0 Hz), 7.15–7.02 (2H, m), 2.66 (2H, br s), 1.04 (3H, s), 0.99 (6H, s), 0.98 (3H, d, J = 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.1, 136.8, 136.4, 131.7, 128.2, 121.1, 119.3, 118.1, 110.6, 108.8, 39.3, 38.6, 38.1, 36.4, 34.9, 34.1, 29.0, 27.3, 26.7, 26.0, 23.0, 21.8, 16.1; HRMS calcd for $C_{23}H_{30}N$ (M^+ + H) 320.2373, found 320.2391.

*5.5.2. Methyl (17R)-2,17-cyclo-aureanindol-15-ene-21-oate (**40**)*

Yield: 36%; $[\alpha]_D^{22}$-189.0 (*c* 0.12, $CHCl_3$); IR (film, cm^{-1}): 3393, 2932, 1699, 1450, 739; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, br s, N–H), 7.45 (1H, d, J = 7.6 Hz), 7.30 (1H, d, J = 7.6 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.09 (1H, t, J = 7.6 Hz), 3.57 (3H, s), 3.47 (1H, m), 2.76 (1H, d, J = 15.2 Hz), 2.67 (1H, d, J = 15.2 Hz), 2.30–1.35 (9H, m), 1.33 (3H, s), 1.03 (3H, d, J = 6.8 Hz), 1.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 136.2, 136.0, 135.1, 131.1, 127.9, 121.0, 119.1, 117.8, 110.4, 108.8, 51.9, 46.9, 38.6, 38.1, 36.0, 35.1, 33.5, 26.8, 26.1, 25.2, 24.5, 21.7, 15.7; HRMS calcd for $C_{24}H_{30}NO_2$ (M^+ + H).364.2271, found 364.2256.

*5.5.3. Methyl 17R-6-methyl-2,17-cyclo-aureanindol-15-ene-21-oate (**41**)*

Yield: 66%; $[\alpha]_D^{22}$-136.7 (*c* 0.90, $CHCl_3$); IR (film, cm^{-1}): 3397, 2930, 1713, 1452, 1240, 1204, 733; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, br s, N–H), 7.24 (1H, d, J = 1.6 Hz), 7.18 (1H, d, J = 8.2 Hz), 6.94 (1H, dd, J = 8.2, 1.6 Hz), 3.57 (3H, s), 2.74 (1H, dd, J = 15.0, 1.8 Hz), 2.62 (1H, d, J = 15.0 Hz), 2.44 (3H, s, $Me_{C\text{-}6}$), 2.30–1.35 (9H, m), 1.33 (3H, s), 1.03 (3H, d, J = 5.6 Hz), 1.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 136.4, 135.4, 134.8, 131.2, 128.6, 128.4, 122.6, 117.9, 110.4, 108.6, 52.1, 47.2, 38.8, 38.3, 36.3, 35.4, 33.8, 27.1, 26.3, 25.5, 24.7, 22.0, 21.7 ($Me_{C\text{-}6}$), 16.0; HRMS calcd for $C_{2.5}H_{31}NO_2Na$ (M^+ + Na) 400.2247, found 400.2248.

*5.5.4. Methyl 17R-6-bromo-2,17-cyclo-aureanindol-15-en-21-oate (**42**)*

Yield: 50%; $[\alpha]_D^{22}$-91.2 (*c* 0.08, $CHCl_3$); IR (film, cm^{-1}): 3372, 2928, 1719, 1431, 1204, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (1H, br s, N–H), 7.56 (1H, s), 7.17 (2H, s), 3.58 (3H, s), 3.48 (1H, m), 2.66 (1H, d, J = 16.4 Hz), 2.60 (1H, d, J = 16.4 Hz), 2.20–1.40 (8H, m), 1.33 (3H, s), 1.02 (3H, d, J = 7.2 Hz), 1.00 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.5, 137.7, 135.1, 134.9, 131.7, 130.0, 123.9, 120.8, 112.8, 112.6, 108.9, 52.2, 47.2, 38.8, 38.3, 36.1, 35.3, 33.5, 27.0 26.3, 25.4, 24.7, 21.9, 16.0.

*5.5.5. Methyl 17R-6-fluoro-2,17-cyclo-aureanindol-15-ene-21-oate (**43**)*

Yield: 59%; $[\alpha]_D^{22}$-110.8 (*c* 0.043, $CHCl_3$); IR (film, cm^{-1}): 3379, 2931, 1699, 1450, 735; ^1H NMR (200 MHz, $CDCl_3$) δ 7.71 (1H, s, N–H), 7.18 (1H, dd, J = 8.8, 4.4 Hz), 7.08 (1H, dd, J = 9.4, 2.6 Hz), 6.84 (1H, dt, J = 9.2, 2.6 Hz), 3.58 (3H, s), 2.73 (1H, dd, J = 15.0, 1.8 Hz), 2.60 (1H, d, J = 15.0 Hz), 2.30–1.35 (9H, m), 1.33 (3H, s), 1.03 (3H, d, J = 6.2 Hz), 1.01 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.5, 158.9 (d, J = 140.0 Hz, C-6), 144.9, 138.3, 135.0, 132.9, 128.6 (d, J = 5.0 Hz, C-4) 125.2, 111.1 (d, J = 10.0 Hz, C-7), 109.1 (d, J = 30.0 Hz, C-8), 103.3 (d,

J = 15.0 Hz, C-5), 52.2, 46.9, 38.8, 38.3, 36.2, 35.3, 33.8, 27.0, 26.3, 25.5, 24.7, 22.0, 16.0; HRMS calcd for $C_{24}H_{28}NO_2FNa$ (M^+ + Na) 404.1996, found 404.1978.

*5.5.6. Methyl 17R-6-methoxy-2,17-cyclo-aureanindol-15-ene-21-oate (**44**)*

Yield 79%; $[\alpha]_D^{22}$-105.5 (*c* 0.10, $CHCl_3$); IR (film, cm^{-1}): 3393, 2936, 1726, 1711, 1458, 1217; ^1H NMR (200 MHz, $CDCl_3$) δ 7.59 (1H, br s, N–H), 7.19 (1H, d, J = 8.8 Hz), 6.92 (1H, d, J = 2.6 Hz), 6.77 (1H, dd, J = 8.8, 2.6 Hz), 3.85 (3H, s, MeO–), 3.57 (H, s, –COOMe), 2.74 (1H, d, J = 14.2 Hz), 2.60 (1H, d, J = 14.2 Hz), 2.30–1.35 (9H, m), 1.33 (3H, s), 1.03 (3H, d, J = 6.6 Hz), 1.02 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.6, 154.1, 137.3, 135.3, 131.6, 131.3, 128.5, 111.3, 110.9, 109.0, 100.6, 56.2 (MeO–), 52.2 (–COOMe), 47.2, 38.9, 38.3, 36.3, 35.4, 33.9, 27.0, 26.3, 25.5, 24.7, 22.0, 16.0; HRMS calcd for $C_{25}H_{32}NO_3$ (M^+ + H) 394.2377, found 394.2377.

*5.5.7. Methyl 17R-8-methyl-2,17-cyclo-aureanindol-15-ene-21-oate (**48**)*

Yield: 85%; $[\alpha]_D^{22}$-125.6 (*c* 0.09, $CHCl_3$); IR (film, cm^{-1}): 3393, 2965, 2934, 1699, 1452, 1202; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, s, N–H), 7.30 (1H, d, J = 7.4 Hz), 7.00 (1H, t, J = 7.4 Hz), 6.92 (1H, d, J = 7.4 Hz), 3.57 (3H, s), 3.40 (1H, m), 2.77 (1H, dd, J = 15.5, 2.2 Hz), 2.65 (1H, d, J = 15.5 Hz), 2.47 (3H, s, $Me_{C\text{-}8}$), 2.30–1.35 (9H, m), 1.34 (3H, s), 1.03 (3H, d, J = 6.9 Hz), 1.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 135.7, 135.6, 135.2, 131.0, 127.4, 121.7, 119.5, 119.3, 115.6, 109.4, 51.9, 46.9, 38.6, 38.1, 36.1, 35.1, 33.5, 26.8, 26.2, 25.2, 24.5, 21.7, 16.6 ($Me_{C\text{-}8}$), 15.7; HRMS calcd for $C_{25}H_{32}NO_2$ (M^+ + H) 378.2428, found 378.2435.

*5.5.8. Methyl 17R-8-bromo-2,17-cyclo-aureanindol-15-ene-21-oate (**49**)*

Yield: 46%; $[\alpha]_D^{22}$-163.3 (*c* 0.06, $CHCl_3$); IR (film, cm^{-1}): 3356, 2928, 1719, 1452, 1196, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (1H, br s, N–H), 7.38 (1H, d, J = 8.2 Hz), 7.25 (1H, d, J = 6.6 Hz), 6.95 (1H, dd, J = 8.2, 6.6 Hz), 3.58 (3H, s), 2.75 (1H, d, J = 14.4 Hz), 2.63 (1H, d, J = 14.4 Hz), 2.30–1.35 (9H, m), 1.34 (3H, s), 1.03 (3H, d, J = 6.6 Hz), 1.01 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.5, 137.1, 134.9, 134.8, 131.8, 129.4, 123.5, 120.5, 117.3, 110.4, 104.5, 52.2, 47.2, 41.6, 38.8, 36.4, 35.3, 33.8, 27.0, 26.3, 25.4, 24.7, 21.9, 16.0; HRMS calcd for $C_{24}H_{28}NO_2BrNa$ (M^+ + Na) 442.1376, found 442.1363.

*5.5.9. Methyl 17R-8-chloro-2,17-cyclo-aureanindol-15-ene-21-oate (**50**)*

Yield: 47%; $[\alpha]_D^{22}$-186.0 (*c* 0.08, $CHCl_3$); IR (film, cm^{-1}): 3356, 2931, 1719, 1452, 1198, 733; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89 (1H, br s, N–H), 7.34 (1H, d, J = 7.4 Hz), 7.12 (1H, d, J = 7.4), 7.00 (1H, t, J = 7.4 Hz), 3.58 (3H, s), 2.76 (1H, dd, J = 15.4, 2.2 Hz), 2.64 (1H, d, J = 15.4 Hz), 2.30–1.35 (9H, m), 1.34 (3H, s), 1.03 (3H, d, J = 6.4 Hz), 1.01 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.5, 137.1, 134.9, 133.6, 131.7, 129.7, 120.6, 120.1, 116.7, 116.2, 110.3, 52.2, 47.2, 39.0, 38.8, 36.3, 35.3, 33.8, 27.0, 26.3, 25.4, 24.7, 21.9, 16.0; HRMS calcd for $C_{24}H_{28}NO_2ClNa$ (M^+ + Na) 420.1701, found 420.1694.

*5.5.10. 17R-2,17-cyclo-aureanindol-15-ene-21-yl acetate (**54**)*

Yield: 27%; $[\alpha]_D^{22}$-183.0 (*c* 0.03, $CHCl_3$); IR (film, cm^{-1}): 3388, 2925, 1720, 1461, 1384, 1241, 1094, 1034, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, br s, N–H), 7.44 (1H, d, J = 7.6 Hz), 7.28 (1H, d, J = 7.5 Hz), 7.15–7.05 (2H, m), 4.05 (1H, d, J = 11.0 Hz), 3.88 (1H, d, J = 11.0 Hz), 2.95 (1H, d, J = 15.6 Hz), 2.73 (1H, d, J = 15.2 Hz), 2.65 (1H, d, J = 15.6 Hz), 2.60 (1H, d, J = 15.2 Hz), 2.49 (1H, d, J = 15.2 Hz), 2.41 (1H, d, J = 15.2 Hz), 1.93 (3H, s), 1.07 (3H, s), 1.03 (3H, d, J = 6.9 Hz), 0.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.4, 136.2, 135.9, 132.1, 127.8, 120.4, 119.1, 117.8, 110.4, 108.4, 69.1, 39.0, 38.7, 38.0, 36.0, 33.6, 33.0, 27.0, 25.4, 24.4, 23.8, 21.0 (–COOMe), 20.8, 15.9; HRMS calcd for $C_{25}H_{31}NO_2Na$ (M^+ + Na) 400.2247, found 400.2260.

*5.5.11. 21-acetoxy-2,17-cyclo-aureanindol-14,16-diene-18-one (**55**)*

Yield: 5%; $[\alpha]_D^{22}$-180.0 (*c* 0.03, $CHCl_3$); $UV_{\lambda max}$ (nm): 434, 343, 299, 280, 195; IR (film, cm^{-1}): 3398, 2958, 2927, 1735, 1655, 1459, 1384, 1271, 1122, 1074, 1042; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, d, J = 7.2 Hz), 7.38 (1H, d, J = 7.2 Hz), 7.16 (1H, t, J = 7.2 Hz), 7.12 (1H, t, J = 7.2 Hz), 6.21 (1H, dd, J = 6.4, 3.2 Hz), 4.23 (1H, d, J = 11.2 Hz), 4.01 (1H, d, J = 11.2 Hz), 3.08 (1H, d, J = 16.0 Hz), 2.76 (1H, d, J = 16.0 Hz), 2.76 (1H, d, J = 16.0 Hz), 2.50 (1H, d, J = 16.0 Hz), 2.02 (3H, s), 1.16 (3H, s), 1.10 (3H, d, J = 6.8 Hz), 1.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 182.8, 170.1, 152.7, 136.8, 135.9, 132.1, 129.3, 126.3, 121.9, 120.0, 118.2, 111.4, 108.9, 70.6, 46.8, 40.1, 40.1, 37.9, 32.5, 32.3, 24.1, 20.7 (–COOMe), 15.3, 14.9, HRMS calcd for $C_{25}H_{27}NO_3Na$ (M^+ + Na) 412.1883, found 412.1901.

*5.6. 14,15-dinor-ent-halim-1(10)-ene-13,16-diol (**2**)*

To an ice-cooled solution of **1** (630 mg, 2.27 mmol) in EtOH (22 mL), $NaBH_4$ (145 mg, 3.85 mmol) was added and it was stirred for 1 h 30 min at r.t. The solvent vas removed and H_2O and 2 M HCl were added. It was then extracted with EtOAc, washed with brine and dried over anhydrous Na_2SO_4. After filtering and evaporating the solvent compound **2** was obtained. Yield 97%; IR (film, cm^{-1}) 3373, 3043, 2929, 2871, 1456, 1379, 1065; ^1H NMR (200 MHz, $CDCl_3$) δ 5.27 (1H, t, J = 3.4 Hz), 3.57 (2H, m), 3.41–3.30 (1H, m), 2.10–1.00 (16H, m), 0.85 (3H, s), 0.83 (3H, s), 0.80 (3H, s), 0.78 (3H, d, J = 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.7, 120.0, 73.4, 67.1, 43.6, 43.0, 39.2, 35.0, 33.6, 31.6, 29.3, 28.4, 27.9, 26.2, 23.8, 23.3, 22.6, 15.9; HRMS calcd for $C_{18}H_{32}O_2Na$ (M^+ + Na) 303.2295, found 303.2298.

*5.7. 14,15,16-trinor-ent-halim-1(10)-en-13-al (**3**)*

To a mixture of **2** (648 mg, 2.31 mmol) in C_6H_6 (21 mL), $Pb(AcO)_4$ (2.55 g, 5.76 mmol) was added and the resultant mixture was stirred at r.t. for 20 min. The bulk reaction was then filtered through a pad of celite, using EtOAc as solvent. The organic layer was washed with 6% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and filtered to afford **3**. Yield 95%; $[\alpha]_D^{22}$+73.5 (*c* 2.1, $CHCl_3$); IR (film, cm^{-1}): 2926, 2872, 2703, 1726, 1465, 1380; ^1H NMR (200 MHz, $CDCl_3$) δ 9.69 (1H, br s, –CHO), 5.30 (1H, br s), 2.30–1.00 (14H, m), 0.83 (3H, s), 0.81 (3H, s), 0.78 (3H, d, J = 7.0 Hz), 0.77 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.4, 141.0, 121.0, 43.5, 42.7, 39.8, 39.3, 33.6, 31.6, 30.7, 29.2, 28.4, 25.9, 23.6, 23.3, 22.6, 16.0.

*5.8. Methyl 6-chloro-2-formyl-aureanindol-16-ene-21-oate (**27**)*

To a solution of **17** (212 mg, 0.515 mmol) in C_6H_6 (2.9 mL), Na_2CrO_4 (94 mg, 0.572 mmol), fused AcONa (85.5 mg, 1.03 mmol), Ac_2O (1.16 mL, 12.9 mmol) and AcOH (0.53 mL, 10.3 mmol) were added and the mixture was heated up to 55 °C for 30 min. It was quenched with crushed ice and extracted with EtOAc. The organic phase was washed with 6% $NaHCO_3$, H_2O and brine, it was dried over anhydrous Na_2SO_4 and filtered and the solvent was removed. The crude was purified by column chromatography (Hex/EtOAc 98:2) to afford **27**. Yield: 30%; IR (film, cm^{-1}): 3314, 2951, 2872, 1724, 1647, 1450, 1381, 1246, 1113, 739; ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (1H, s, –CHO), 9.18 (1H, br s, N–H), 7.68 (1H, s), 7.31 (1H, d, J = 8.8 Hz), 7.28 (1H, dd, J = 8.8, 1.7 Hz), 5.06 (1H, br s), 3.75 (3H, s), 3.42 (1H, d, J = 14.1 Hz), 3.03 (1H, d, J = 14.1 Hz), 3.02 (1H, m), 2.10–1.20 (9H, m), 1.17 (3H, s), 0.90 (3H, d, J = 6.9 Hz), 0.71 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.8 (–CHO), 178.7, 138.9, 135.4, 134.4, 130.2, 127.5, 126.0, 125.8, 122.0, 121.5, 113.3, 51.9, 45.2, 44.1, 40.0,

38.5, 33.9, 31.7, 27.8, 23.2, 22.4, 22.0, 17.7, 16.5; HRMS calcd for $C_{25}H_{30}NO_3ClNa$ (M^+ + Na) 450.1806; found 450.1800.

5.9. Methyl 2-(2-nitro-vinyl)-aureanindol-16-ene-21-oate (**28**)

To a solution of aldehyde **27** (16 mg, 0.041 mmol) in nitromethane (0.5 mL), excess of NH_4OAc was added and the mixture was heated up to 100 °C for 3 h. It was cooled down to r.t., diluted H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtering and removing of the solvent, **28** was obtained. Yield: 66%; $[\alpha]_D^{22}$-13.8 (*c* 0.04, $CHCl_3$); IR (film, cm^{-1}): 3356, 2651, 2926, 1719, 1701, 1609, 1448, 1317, 966, 739; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, br s, N—H), 8.00 (1H, d, J = 13.4 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.51 (1H, d, J = 13.4 Hz), 7.31 (2H, m), 7.09 (1H, t, J = 7.8 Hz), 5.16 (1H, br s), 3.77 (3H, s), 3.10 (1H, d, J = 14.2 Hz), 3.07 (1H, m), 3.03 (1H, d, J = 14.2 Hz), 2.10—1.20 (9H, m), 1.18 (3H, s), 0.82 (3H, d, J = 6.9 Hz), 0.74 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3, 140.5, 138.6, 132.9, 130.1, 128.4, 128.0, 127.6, 126.8, 122.1, 121.1, 120.6, 111.5, 53.3, 45.6, 44.5, 39.1, 39.0, 35.1, 31.7, 28.5, 23.9, 22.8, 22.4, 18.3, 16.5; HRMS calcd for $C_{26}H_{32}N_2O_4Na$ (M^+ + Na) 459.2254, found 459.2271.

5.10. Methyl 6-chloro-N-diphenylmethyl-2-methyl-aureanindol-16-ene-21-oate (**29**)

A solution of **20** (80 mg, 0.194 mmol) in DMF (0.7 mL) was added, under Ar atmosphere, over an ice-cooled mixture of NaH (60% in mineral oil, 16 mg, 0.41 mmol) in DMF (0.1 mL) and the resulting mixture was stirred for 30 min. After that time, a solution of bromodiphenylmethane (109 mg, 0.44 mmol) in DMF (0.5 mL) was added, and the mixture was stirred at r.t. for 1 h 15 min. It was cooled down again to 0 °C and quenched by carefully addition of H_2O. It was extracted with Et_2O and the organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, filtered and the solvent was removed. The residue was purified by column chromatography (Hex/EtOAc 99:1) to yield **29**. Starting material was also recovered. Yield: 38%; $[\alpha]_D^{22}$-42.4 (*c* 0.82, $CHCl_3$); IR (film, cm^{-1}): 2949, 2872, 1719, 1449, 1248, 1111, 908, 733, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47 (1H, d, J = 2.0 Hz), 7.31 (6H, m, —Ph), (4H, m, —Ph), 6.89 (1H, s, $Ph_2C\underline{H}$—), 6.76 (1H, dd, J = 8.8, 2.0 Hz), 6.51 (1H, d, J = 8.8 Hz), 5.10 (1H, br s), 3.71 (3H, s), 3.09 (1H, d, J = 14.6 Hz), 2.77 (1H, d, J = 14.6 Hz), 2.17 (3H, s, $Me_{C\text{-}2}$), 2.00—1.20 (10H, m), 0.84 (3H, d, J = 6.6 Hz), 0.81 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2, 140.7, 139.4 and 139.3 (—Ph), 137.0, 134.9, 131.7, [128.8, 128.5, 128.4 and 128.0 (—Ph)], 124.6, 120.5, 120.4, 119.0, 112.3, 111.2, 62.7 ($Ph_2\underline{C}H$—), 52.1, 45.5, 44.9, 39.8, 39.1, 35.3, 32.0, 28.4, 23.6, 22.7, 22.3, 17.7, 16.7, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{38}H_{42}NO_2NaCl$ (M^+ + Na) 602.2796, found 602.2798.

5.11. 6-chloro-N-diphenylmethyl-2-methyl-aureanindol-16-ene-21-oic acid (**30**)

A solution of **29** (30 mg, 0.052 mmol) in ^{t}BuOK/^{t}BuOH (1.0 M, 2 mL) was heated up to 90 °C for 16 h. It was let to cool down to r.t and 3 M HCl was added (pH = 1). A solution of 3 M NaOH was added drop wise to pH = 7. It was extracted with EtOAc and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent afforded **30**. Yield: 95%; $[\alpha]_D^{22}$-27.3 (*c* 0.37, $CHCl_3$); IR (film, cm^{-1}): 3500—2750 (br), 2926, 2872, 1701, 1449, 908, 735, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46 (1H, d, J = 2.0 Hz), 7.31 (6H, m, —Ph), 7.07 (4H, m, —Ph), 6.87 (1H, br s, $Ph_2C\underline{H}$—), 6.75 (1H, dd, J = 8.8, 2.0 Hz), 6.50 (1H, d, J = 8.8 Hz), 5.10 (1H,s), 3.09 (1H, d, J = 14.4 Hz), 2.77 (1H, d, J = 14.4 Hz), 2.16 (3H, s, $Me_{C\text{-}2}$), 2.10—1.30 (10H, m), 1.17 (3H, s), 0.84 (3H, d, J = 7.0 Hz), 0.81 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.4, 140.6, 139.4 and 139.3 (—Ph), 137.0, 134.9, 131.7, [128.8, 128.5, 128.3 and 127.9 (—Ph)], 124.6, 120.5, 120.5, 119.0, 112.3, 111.1, 62.7 ($Ph_2\underline{C}H$—), 45.3, 45.0, 39.7, 38.8, 35.2, 32.0, 28.3, 23.6, 22.6, 22.3, 17.6, 16.7, 13.2 ($Me_{C\text{-}2}$); HRMS calcd for $C_{37}H_{40}NO_2NaCl$ (M^+ + Na) 588.2940, found 588.2645.

5.12. Aureanindol-16-ene-21-ol (**51**)

To an ice-cooled solution of **6** (316 mg, 0.87 mmol) in Et_2O (9 mL), LAH (33 mg, 0.87 mmol) was added, and the mixture was stirred at r.t for 45 min. It was cooled down again to 0 °C and the excess of LAH was quenched by slow addition of wet Et_2O. It was dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent afforded **51**. Yield: 97%; $[\alpha]_D^{22}$-4.7 (*c* 0.94, $CHCl_3$); IR (film, cm^{-1}): 3415, 3052, 2925, 1457, 1378, 1040, 908, 737, 665; ^1H NMR (200 MHz, $CDCl_3$) δ 7.99 (1H, br s, N—H), 7.61 (1H, dd, J = 6.8, 1.6 Hz), 7.33 (1H, dd, J = 6.8, 1.6 Hz), 7.15 (1H, dt, J = 6.8, 1.6 Hz), 7.06 (1H, dt, J = 6.8, 1.6 Hz), 6.95 (1H, d, J = 2.2), 5.27 (1H, dd, J = 4.0, 3.0 Hz), 3.47 (1H, d, J = 10.8 Hz), 3.31 (1H, d, J = 10.8 Hz), 3.17 (1H, d, J = 14.6 Hz), 2.86 (1H, d, J = 14.6 Hz), 2.36—1.02 (10H, m), 0.93 (3H, s), 0.86 (3H, s), 0.84 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.0, 135.8, 129.4, 123.1, 121.5, 120.5, 119.6, 119.2, 113.5, 111.1, 70.1, 44.9, 38.4, 37.5, 36.9, 34.9, 29.6, 29.5, 23.9, 23.2, 22.7, 20.3, 16.2; HRMS calcd for $C_{23}H_{31}NONa$ (M^+ + Na) 360.2298, found 360.2296.

5.13. Aureanindol-16-en-21-yl acetate (**52**)

To a solution of **51** (890 mg, 2.64 mmol) in pyridine (3.3 mL) Ac_2O (3.3 mL) was added and the mixture was stirred at r.t for 1 h and 30 min. It was then quenched with crushed ice and extracted with EtOAc. The organic layer was washed with 2 M HCl, 6% $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed. It was purified by column chromatography (Hex/EtOAc 9/1) to yield **11**. Yield: 95%; $[\alpha]_D^{22}$: −15.2 (*c* 0.97, $CHCl_3$); IR (film, cm^{-1}): 3409, 3052, 2926, 1740, 1458, 1376, 1242, 1035, 739, 666; ^1H NMR (200 MHz, $CDCl_3$) δ 8.10 (1H, br s, N—H), 7.59 (1H, dd, J = 7.0, 1.6 Hz), 7.30 (1H, dd, J = 7.0, 1.6 Hz), 7.14 (1H, dt, J = 7.0, 1.6 Hz), 7.08 (1H, dt, J = 7.0, 1.6 Hz), 6.89 (1H, d, J = 2.2), 5.29 (1H, dd, J = 3.8, 2.6 Hz), 3.93 (1H, d, J = 10.6 Hz), 3.78 (1H, d, J = 10.6 Hz), 3.12 (1H, d, J = 14.8 Hz), 2.89 (1H, d, J = 14.8 Hz), 1.97 (3H, s), 2.33—1.01 (10H, m), 0.92 (3H, s), 0.89 (3H, s), 0.82 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 141.8, 135.9, 129.4, 122.9, 121.6, 120.4, 119.5, 119.2, 113.4, 111.1, 71.3, 44.8, 38.4, 38.1, 35.4, 34.9, 29.6, 29.2, 23.7, 23.2, 22.6, 21.1 (—OOC$\underline{Me}$), 20.7, 16.1; HRMS calcd for $C_{25}H_{33}NO_2Na$ (M^+ + Na) 402.2404, found 402.2403.

5.14. Biology

All starting materials were commercially available research-grade chemicals and used without further purification. RPMI 1640 medium was purchased from Flow Laboratories (Irvine, UK), foetal calf serum (FCS) was from Gibco (Grand Island, NY), trichloroacetic acid (TCA) and glutamine were from Merck (Darmstadt, Germany), penicillin G, streptomycin, DMSO and sulforhodamine B (SRB) were from Sigma (St Louis, MO), and Mueller Hinton broth was from Becton Dickinson (USA).

5.14.1. Microbiology

The Gram-negative bacterial strains *E. coli* (ATCC35218), *Klebsiella pneumonia* (ATCC700603), and *P. aeruginosa* (ATCC27853), and the Gram-positive *E. faecalis* (ATCC29212), and *S. aureus* (ATCC29213) were used in this study. Bacteria were grown on nutrient agar plates at 35—37 °C. After 24 h of incubation, cells were suspended in normal saline at a concentration of approximately 5.0×10^5 cfu mL^{-1} by matching with 0.5 McFarlands standards. Whole cell antimicrobial activity of compounds was determined in

96-well microtiter plates by a broth microdilution procedure using Mueller Hinton broth. Proper growth and sterile screening controls were included. Pure compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration, that is, 100 μM. Each compound was tested in duplicates at eight different 10-fold serial dilutions ranging from 100 to 0.05 μM. The microtiter plates were incubated at 35–37 °C in a moist dark chamber. After incubation, plates were shaken and the optical density values were recorded spectrophotometrically. Plates were read at 630 nm after 24 h of incubation. The minimum inhibitory concentration (MIC) was established as the concentration of compound that inhibited visible growth of the microorganism.

5.14.2. Tumour cell lines

The human solid tumour cell lines A549, HBL-100, HeLa, SW1573, T-47D and WiDr were used in this study. These cell lines were a kind gift from Prof. G. J. Peters (VU Medical Center, Amsterdam, The Netherlands). Cells were maintained in 25 cm^2 culture flasks in RPMI 1640 supplemented with 5% heat inactivated foetal calf serum and 2 mM L-glutamine in a 37 °C, 5% CO_2, 95% humidified air incubator. Exponentially growing cells were trypsinized and re-suspended in antibiotic containing medium (100 units penicillin G and 0.1 mg of streptomycin per mL). Single cell suspensions displaying >97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 μL per well at densities of 10,000 (A549, HBL-100, HeLa and SW1573), 15,000 (T-47D), and 20,000 (WiDr) cells per well, based on their doubling times.

5.14.3. Chemosensitivity testing

Compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (0.25% v/v, negative control). Each agent was tested in triplicate at different dilutions in the range of 1–100 μM. The drug treatment was started on day 1 after plating. Drug incubation times were 48 h, after which time cells were precipitated with 25 μL ice-cold TCA (50% w/v) and fixed for 60 min at 4 °C. Then the SRB assay was performed [14]. The optical density (OD) of each well was measured at 492 nm, using BioTek's PowerWave XS Absorbance Microplate Reader. Values were corrected for background OD from wells only containing medium.

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