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Synthesis and antiviral evaluation of benzimidazoles, quinoxalines and indoles from dehydroabietic acid

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Abstract—Several heterocycles, such as benzimidazoles, quinoxalines and indoles incorporated into a hydrophenanthrene and naphthalene skeleton, were synthesised from two useful *ortho*-bromonitro precursors derived from dehydroabietic acid: methyl 12-bromo-13-nitro-deisopropyldehydroabietate and methyl 12-bromo-13,14-dinitro-deisopropyldehydroabietate. The new heterocycles were evaluated for their activity in vitro against several RNA and DNA viruses.

1. Introduction

Recent work[1–3] has demonstrated that resin acid derivatives can be a useful tool in the synthesis of drugs active against viruses. The potential of resin acid derivatives,[1–3] and the known antiviral activity of several benzimidazoles,[4] quinoxalines,[5] and indoles[6] as nucleoside analogues or non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs), led us to search for new heterocyclic agents through functionalisation of the aromatic moiety of dehydroabietic acid (**1a**, Scheme 1).

In previous work,[7] we have described the synthesis of imidazoles fused to the aromatic ring **C**, using a deisopropylated nitroarene derived from **1a** as a precursor. In the present study, a different route for the construction of imidazoles, diazines and indoles, fused to ring **C**, is reported. The functionalisation was accomplished through nitro-deisopropylation of the brominated intermediate **2**, from which a new *ortho*-dinitro (**3a**) or a mononitro (**3b**) compound was obtained in one step, depending on the nitric acid concentration (Scheme 1). Subsequent catalytic hydrogenation of **3a** allowed us to prepare two new *ortho*-diamines (**4a** and **4b**) that gave several benzimidazoles (**5a**–**7a**, **5b**–**7b** and **8**) and quinoxalines (**9, 10** and **11**) (Scheme 2) by cyclocondensation. Furthermore, two new indoles (**14** and **15**) were synthesised from **3b** via two different pathways (Scheme 3). All the novel heterocycles described in this work were evaluated for their potential antiviral activity.

2. Results and discussion

2.1. Synthetic approach

The starting material, dehydroabietic acid (**1a**) and the intermediates, methyl dehydroabietate (**1b**) and methyl 12-bromo-dehydroabietate (**2**), were obtained by procedures described before.[8–10] Nitrodeisopropylation of derivatives of **1b**, maintaining the hydrophenanthrene structure, has also been reported.[11–13] Particularly, in previous nitration studies of **2**,[13] methyl 12-bromo-13-nitrodeisopropyl dehydroabietate (**3b**) was obtained; in addition, an uncharacterised dinitro compound was also mentioned, but not isolated, when mixtures of nitric and sulphuric acids with different concentrations were used. The possibility of the two nitro groups being located *ortho* to each other prompted us to further investigate

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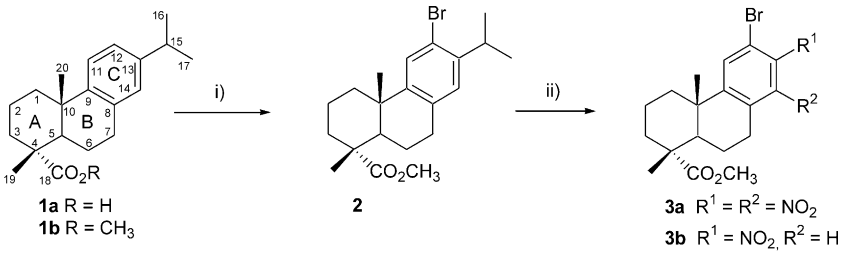
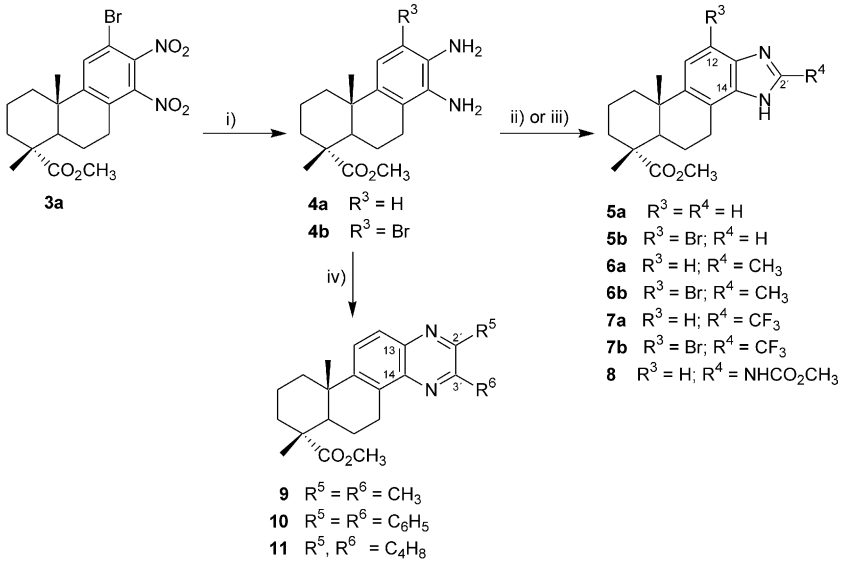
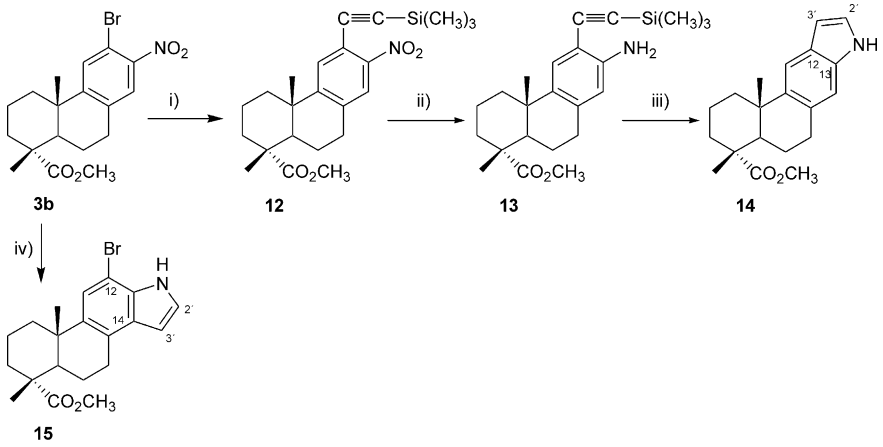


Scheme 1. (i) Br_2, Montmorillonite K10, 0 °C; (ii) HNO_3/H_2SO_4, −18 °C.



Scheme 2. (i) H_2 (100 psi), Pd/C, MeOH, Et_3N (only for **4a**); (ii) R^4CO_2H, Δ; (iii) $CH_3O_2C–NH–C(SCH_3)=N–CO_2CH_3$, CH_3CO_2H, Δ; (iv) diketone, CH_3CO_2H, Δ.



Scheme 3. (i) $HC{\equiv}CSi(CH_3)_3$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, Δ (ii) $Fe/FeSO_4{\cdot}.7H_2O$, HCl (0.1 M), C_6H_6, MeOH, Δ (iii) CuI, DMF, 100 °C; (iv) $CH_2{=}CHMgBr$, THF, −78 °C.

this reaction, since this type of compound can easily be reduced to produce *ortho*-diamines. It is well known from the literature[14–16] that *ortho*-phenylenediamines are useful reagents for the synthesis of 2-substituted benzimidazoles and quinoxalines by simple cyclo-condensations with carboxylic acids and *vic*-diketones, respectively.

In our studies, nitration of **2** with nitric acid (88%, d = 1.47) and concentrated sulphuric acid (95–97%) yielded **3b** while the desired, but unexpected, methyl 12-bromo-13,14-dinitrodehydroabietate (**3a**) was obtained when fuming nitric acid (100%, d = 1.52) was used instead (Scheme 1). These observations stimulated the study described in this paper. The IR, MS, ^1H and ^{13}C NMR spectral data (chemical shifts and multiplicities, 2D HETCOR in combination with DEPT for ^{13}C NMR, and COLOC for long-range ^1H–^{13}C NMR correlation experiments) allowed us to assign all the protons and carbons. Moreover, the *ortho* disposition of

the nitro groups in **3a**, was confirmed from the observed three- and two-bond correlations between H-11 (s, 7.73 ppm) and C-8 (129.3 ppm), C-10 (38.0 ppm), C-13 (141.6 ppm) and C-12 (111.9 ppm). In these reactions, hydrolysis of the ester group of **2** was prevented by keeping the temperature below 0 °C during its addition to the acid mixture.

Catalytic hydrogenation of **3a** produced the *ortho*-diamine intermediates **4a** or **4b** (Scheme 2), depending on the reaction conditions used. The reactions were best conducted under pressure (100 psi), with palladium as the catalyst, either in the presence or absence of triethylamine.[13] The presence of triethylamine was clearly essential to produce the dehalogenated diamine (**4a**).

The *ortho* coupling (J ca. 8 Hz) observed for the two aromatic protons in **4a** afforded additional confirmation that the nitro groups in the precursor **3a** were vicinal.

Similar examples of dehalogenation under catalytic hydrogenation conditions can be found in the literature.[17,18]

2.1.1. Benzimidazoles and quinoxalines. Ready formation of benzimidazoles (**5a–7a**, **5b–7b** and **8**) and quinoxalines (**9–11**) through reaction of the *ortho*-diamines **4a** or **4b** with carboxylic acids, an iminocarbamate or *vic*-diketones, respectively, further confirmed the *ortho* relationship of the amino groups in both diamines, and consequently of the nitro groups in the parent compound (**3a**). Benzimidazoles **5a–7a** and **5b–7b** were obtained in moderate to good yields (53–72%) by condensation of the intermediate diamines **4a** and **4b** with formic, acetic or trifluoracetic acids under Phillips' conditions.[16,19] Benzimidazole **8**, an analogue of the broad spectrum fungicide Carbendazim®,[20] was synthesised in a similar manner, by reaction of **4a** with an iminocarbamate, [methyl (methoxycarbonylamino)(methylthiomethylene)-carbamate].[20–22] Three different quinoxalines (**9–11**) were prepared by mild acid catalysed condensation of the free diamine **4a** with 2,3-butanedione, benzil and 1,2-cyclohexanedione, under reflux.[23–25] These new quinoxalines were obtained in moderate to good yields (61, 70 and 42%, respectively).

The structural assignments of the new benzimidazoles (**5a–7a**, **5b–7b** and **8**) and quinoxalines (**9–11**) were based on IR, MS, ^{1}H and ^{13}C NMR spectral data, which were fully consistent with the proposed structures. The ^{1}H NMR spectra of the non-brominated benzimidazoles (**5a–7a** and **8**) and quinoxalines (**9–11**) had similar features, showing two aromatic doublets (ca. 7.61–7.73 and 7.76–7.96 ppm) downfield from the corresponding resonances of the diamine precursor (**4a**), due to the deshielding effect caused by formation of the heterocyclic aromatic moiety. The coupling constant values (ca. 8–9 Hz) further substantiated the *ortho* disposition of the two protons in the aromatic ring **C**.[26] The ^{1}H NMR spectra of the brominated benzimidazoles (**5b–7b**) showed the presence of a singlet at ca. 7.3–7.5 ppm as the signal for the only proton in the aromatic ring **C**.

2.1.2. Indoles. The synthesis of methyl 12-bromo-13-nitro-deisopropyldehydroabietate (**3b**) allowed the preparation of two indoles.

Thus, coupling of **3b** with trimethylsilylacetylene catalysed by a complex of palladium in the presence of cuprous iodide[27] to yield **12** (Scheme 3), followed by reduction of the nitro group of **12** to an amine, with Fe/HCl (0.1 M),[28] gave the *ortho*-alkynylaniline **13** in good yield (83%). Cyclisation of **13** with cuprous iodide in dimethylformamide at 100 °C[29] gave the indole **14** in moderate yield (60%).

The synthetic versatility of the *ortho*-bromonitro compound **3b** was further probed by the efficient one-step synthesis of the brominated indole **15**, which was obtained in good yield (70%) by reaction with vinyl magnesium bromide under Bartoli's conditions.[30]

IR, MS, ^{1}H and ^{13}C NMR spectral data were fully consistent with those expected for the assigned structures (**12–15**). The chemoselectivity of the palladium coupling reaction was inferred from the MS spectrum of **12**, which lacked isotopomeric peaks ascribable to the presence of bromine. The presence of the characteristic band of the triple bond (C≡C) at ca. 2150 cm^{-1} was also noteworthy in the IR spectra of both **12** and **13**. The formation of indole **14** was easily confirmed by its ^{1}H NMR spectrum, due to the presence of resonances corresponding to four aromatic protons (δ 6.44–7.52 ppm), in addition to a broad one-proton singlet at δ 7.91 ppm corresponding to the indole N<u>H</u>. The MS spectrum of the second indole (**15**) displayed isotopomeric fragments consistent with the presence of bromine in the aromatic ring **C**. Furthermore, formation of the heterocyclic ring of **15** was confirmed by analysis of its ^{1}H NMR spectrum, which displayed resonances at δ 6.54 ppm (dd), δ 7.21 (t) and δ 8.25 (brs), associated with the three protons of the five-membered ring (H2, H3, and H1, respectively), in addition to a singlet at δ 7.27 ppm corresponding to the only proton of the aromatic ring (C).

2.2. Biological activity tests

The biological activity of the newly synthesised compounds was assessed against herpes simplex virus (HSV-1 and HSV-2), vaccinia virus and vesicular stomatitis virus in human skin-muscle fibroblasts (E_6SM); against Coxsackie B4 and respiratory syncytial virus (RSV) in HeLa cell cultures; against parainfluenza-3, reo-1, Sindbis, and Punta Toro in Vero cell cultures; and against human immunodeficiency virus (HIV-1 and HIV-2) in MT-4 cells. No specific activity against any of these viruses could be discerned with any of the compounds tested (**5–8**, **10**, **11**, **14** and **15**), up to the highest concentration (400 pg/mL) used in the experiments. However, some of the compounds (**7a**, **5b**, **11** and **15**) were found to inhibit both varicella-zoster virus (VZV) and cytomegalovirus (CMV) replication at a concentration ca. 5- to 10-fold lower than the cytotoxic concentration (MCC or CC_{50}), when tested in human embryonic lung (HEL) cells (see Table 1). These compounds can there-

Table 1. Activity of compounds **5–11**, **14** and **15** against human cytomegalovirus (CMV) and varicella-zoster virus (VZV) in HEL cells

Compd	Antiviral potency IC_{50} (μg/mL)[a]		Cytotoxicity	
	CMV	VZV	Cell morphology MCC (μg/mL)[b]	Cell growth CC_{50} (μg/mL)[c]
5a	>0.2	0.2–0.5	≥0.5	5.1
6a	>5	2.1–4.6	20	15.1
7a	1.0–1.2	0.8–1.4	5	10.8
5b	1.1–3.2	0.6–2.8	20	3.9
6b	2–4	0.8–1.4	20	2.9
7b	1.0	>2	5	0.7
8	>2	>2	5	4.5
9	ND	ND	ND	ND
10	>5–15	>20	≥20	>50
11	0.9–1.1	0.3–0.9	≥5	13
14	5	1.5–2.6	20	16
15	1.5–1.6	0.7–2	≥5	12.5
Acyclovir	—	0.3–3.0	>50	>200
Ganciclovir	0.9–1.5	—	>50	200

[a] Inhibitory concentration required to reduce virus plaque formation by 50%. CMV input was 100 plaque forming units (PFU), VZV input was 20 PFU. Data represent range of values for two CMV strains (AD-169, Davis) and four VZV strains (YS, OKA, 07/1 and YS/R).
[b] Minimum cytotoxic concentration causing a microscopically detectable alteration of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.

fore be accredited with some specificity in their anti-VZV and anti-CMV action. The potencies of **5a**, **7a**, **5b**, **6b**, **11**, **14** and **15** as anti-VZV agents were comparable to that of acyclovir;[31] the potencies of **5a**, **7a**, **5b**, **11** and **15** as anti-CMV agents were comparable to that of ganciclovir.[32]

3. Conclusions

We have explored the ability of dehydroabietic acid derivatives to act as synthetic precursors of heteroaromatic compounds with potential biological activities. We describe here the synthesis of several new heterocycles, such as benzimidazoles (**5–8**), quinoxalines (**9**, **10, 11**), and indoles (**14**, **15**), obtained from methyl dehydroabietate (**1b**). These fused heterocyclic-diterpenic compounds were prepared through several synthetic routes, involving in some instances an interesting *ortho*-dinitration step, followed by a catalytic hydrogenation process. Preliminary biological evaluation showed that some of the new heterocycles possess activity against human cytomegalovirus (CMV) and varicella-zoster virus (VZV), suggesting that these benzimidazole, quinoxaline and indole types fused to diterpenic structures may become useful as antiviral agents. The possible improvement of the antiviral properties of these basic structures, through modulation of the ring substituents and/or further functionalisation, warrants further investigation.

4. Experimental

4.1. Materials

All reagents were of analytical grade, dried and purified when necessary. Dehydroabietic acid **1a** was obtained from commercially disproportionated rosin and purified by repeated crystallisation of the ethanolamine salt.[8] Methyl dehydroabietate **1b**[9] was prepared by methylation of **1a** with diazomethane. Methyl 12-bromodehydroabietate **2** was prepared by bromination of methyl dehydroabietate **1b** using the system Br_2/Montmorillonite K10 as described previously.[10] Light petroleum ether refers to the bp 40–60 °C fraction and ether refers to diethyl ether. Silica gel used for column chromatography was 230–400 mesh.

Melting points were determined in a Reichert Thermovar apparatus and were not corrected. Spectra were obtained as follows: FTIR spectra were recorded on a Perkin-Elmer 1725 spectrometer; ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR at 75.5 MHz, on a Varian Gemini 300 instrument; mass spectra were recorded on a VG micromass 7070E instrument under electron impact at 70 eV. Microanalyses were performed on a Carlo Erba model 1106 CHN analyser.

4.1.1. Methyl 12-bromo-13,14-dinitro-deisopropyldehydroabietate (3a). Methyl 12-bromo-dehydroabietate **2** (3.38 g, 8.62 mmol) was added with vigorous stirring, during 40 min, to a previously prepared mixture of fuming nitric acid (100%) (18.4 mL) and concentrated sulphuric acid (95–97%) (1.4 mL) maintained in an ice-NaCl bath (−18 °C). The resulting mixture was quenched in ice-water, the solution was made basic by addition of saturated aqueous sodium carbonate and was then extracted with ether. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The gum obtained (3.64 g) was purified by silica column chromatography with ether-light petroleum ether (1:1) as the eluent. Upon recrystallisation, white crystals of the dinitro compound **3a** (2.10 g, 4.77 mmol, 58%) were obtained, mp 171–172.8 °C (from ether); IR (Nujol) ν_{max} 1720, 1544, 1354, 1252, 1188, 1136, 1119 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, s, 10-C$\underline{H}_3$), 1.29 (3H, s, 4-C$\underline{H}_3$), 1.51–1.59 (2H, m, 1-Hα and 6-Hβ), 1.71–1.87 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.19 (1H, dd, J = 12.6 and 2.4 Hz,

5-Hα), 2.30 (1H, brd, $J = 12.9$ Hz, 1-Hβ), 2.82–2.90 (2H, m, 7-H_2), 3.70 (3H, s, $CO_2C\underline{H}_3$), 7.72 (1H, s, 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-$C\underline{H}_3$), 18.2 (C-2), 20.0 (C-6), 24.7 (10-$C\underline{H}_3$), 25.0 (C-7), 36.3 (C-3), 38.0 (C-10), 38.5 (C-1), 43.4 (C-5), 47.2 (C-4), 52.0 ($CO_2C\underline{H}_3$), 111.9 (C-12), 129.3 (C-8), 132.3 (C-11), 141.6 (C-13), 144.5 (C-14), 156.4 (C-9), 177.8 ($\underline{C}O_2CH_3$) ppm; MS *m/z* 442 (3%), 440 M^+ (3%), 425 (42%), 423 (43%), 367 (39%), 365 (70%), 301 (97%), 299 (100%). Anal. calcd for $C_{18}H_{21}BrN_2O_6$: C 48.99, H 4.80, N 6.35; found: C 49.08, H 4.81, N 6.34%.

4.1.2. Methyl 12-bromo-13-nitro-deisopropyldehydroabietate (3b). The procedure was identical to that described above, starting from methyl 12-bromo-dehydroabietate **2** (3.64 g, 9.29 mmol), but using a mixture of nitric acid (88%, d = 1.47) (21 mL) and concentrated sulphuric acid (95-97%) (0.99 mL). The gum obtained (3.40 g) was purified by silica column chromatography with ether-light petroleum ether (1:1) as the eluent. Upon recrystallisation, yellow crystals of the mononitro compound **3b** (2.00 g, 5.1 mmol, 53%) were obtained, mp 133–134 °C (from ether/methanol) (lit:[13] 132 °C); IR (KBr) ν_{max} 1728, 1561, 1524, 1430, 1334, 1246, 1175, 1132, 1110, 1085, 967, 911, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, s, 10-C$\underline{H}_3$), 1.28 (3H, s, 4-C$\underline{H}_3$), 1.41–1.58 (2H, m, 1-Hα and 6-Hβ), 1.66–1.80 (4H, m, 2-H_2 and 3-H_2), 1.80–1.90 (1H, m, 6-Hα), 2.17 (1H, dd, $J = 12.3$ and 1.8 Hz, 5-Hα), 2.28 (1H, brd, $J = 12.9$ Hz, 1-Hβ), 2.82–2.97 (2H, m, 7-H_2), 3.69 (3H, s, $CO_2C\underline{H}_3$), 7.56 (1H, s, 11-H or 14-H), 7.58 (1H, s, 14-H or 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-$C\underline{H}_3$), 18.2 (C-2), 20.9 (C-6), 24.8 (10-$C\underline{H}_3$), 29.2 (C-7), 36.4 (C-3), 37.6 (C-1), 37.7 (C-10), 43.9 (C-5), 47.4 (C-4), 52.1 ($CO_2C\underline{H}_3$), 111.2 (C-12), 126.3 (C-14), 131.2 (C-11), 136.2 (C-8), 146.8 (C-13), 155.9 (C-9), 178.5 ($\underline{C}O_2CH_3$) ppm; MS *m/z* 397 (9%), 395 M^+ (9%), 380 (49%), 378 (44%), 322 (83%), 320 (100%). Anal. calcd for $C_{18}H_{22}BrNO_4$: C 54.56, H 5.60, N 3.53; found: C 54.49; H 5.57, N 3.48%.

4.1.3. Methyl 13,14-diaminodeisopropyldehydroabietate (4a). A mixture of methyl 12-bromo-13,14-dinitrodeisopropyldehydroabietate **3a** (709 mg, 1.61 mmol), 5% Pd/C (160 mg), ethanol (19 mL) and triethylamine (2 mL) was hydrogenated (H_2, 100 psi) in a pressure reactor at rt. After the reaction was completed (19 h), the reaction mixture was filtered over Celite, washed with dichloromethane and the solution evaporated to dryness. The extract was dissolved in ether, washed with water, dried over anhydrous magnesium sulphate and then filtered. Evaporation of the solvent gave a white foam (414 mg) that was purified by silica column chromatography with dichloromethane-methanol (9.5:0.5) as eluent. Upon recrystallisation, white crystals of the diamine **4a** (362 mg, 1.19 mmol, 74%) were obtained, mp 143–144 °C (from ethanol); IR (film) ν_{max} 3351, 1722, 1620, 1491, 1447, 1300, 1245, 1174 and 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, s, 10-C$\underline{H}_3$), 1.27 (3H, s, 4-C$\underline{H}_3$), 1.41–1.55 (2H, m, 1-Hα and 6-Hβ), 1.61–1.92 (5H, m, 2-H_2 and 3-H_2, 6-Hα), 2.20 (1H, dd, $J = 12.8$ and 2.4 Hz, 5-Hα), 2.26 (1H, d, $J = 10.2$ Hz, 1-Hβ), 2.54–2.64 (2H, m, 7-H_2), 3.06 (4H, brs, 2×N$\underline{H}_2$, exchangeable with D_2O), 3.65 (3H, s, $CO_2C\underline{H}_3$), 6.60 (1H, d, $J = 8.1$ Hz, 12-H), 6.65 (1H, d, $J = 8.4$ Hz, 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.4 (4-$C\underline{H}_3$), 18.6 (C-2), 21.2 (C-6), 25.1 (10-$C\underline{H}_3$), 25.3 (C-7), 36.6 (C-10), 36.7 (C-3), 38.4 (C-1), 44.3 (C-5), 47.6 (C-4), 51.8 ($CO_2C\underline{H}_3$), 114.8 (C-12), 115.5 (C-11), 120.7 (C-8), 130.8 (C-13 or C-14), 133.0 (C-14 or C-13), 142.9 (C-9), 179.4 ($\underline{C}O_2CH_3$) ppm; MS *m/z*: 302 M^+ (40%), 287 (25%), 227 (100%). Anal. calcd for $C_{18}H_{26}N_2O_2$ C 71.49, H 8.66, N 9.26; found: C 71.26, H 8.63, N 9.21%.

4.1.4. Methyl 12-bromo-13,14-diaminodeisopropyldehydroabietate (4b). A mixture of methyl 12-bromo-13,14-dinitrodeisopropyldehydroabietate **3a** (402 mg, 0.91 mmol), 5% Pd/C (41 mg) and ethanol (15 mL) was hydrogenated (H_2, 100 psi) in a pressure reactor at room temperature. After the reaction was completed (4 h 45 min), the reaction mixture was filtered over Celite, washed with dichloromethane, and the solution was evaporated to dryness. The resulting oil was purified by silica column chromatography with dichloromethane–methanol (9.6:0.4). The bromodiamine **4b** was obtained as a yellow foam (180 mg, 0.47 mmol, 50%); IR (film) ν_{max} 3423, 1722, 1621, 1470, 1428, 1247, 1176, 1128, 1043, 730, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, s, 10-C$\underline{H}_3$), 1.26 (3H, s, 4-C$\underline{H}_3$), 1.39–1.55 (2H, m, 1-Hα and 6-Hβ), 1.61–1.80 (5H, m, 2-H_2 and 3-H_2, 6-Hα), 2.16 (1H, dd, $J = 12.6$ and 2.4 Hz, 5-Hα), 2.20 (1H, d, $J = 13.2$ Hz, 1-Hβ), 2.48–2.56 (2H, m, 7-H_2), 3.28 (4H, brs, 2×N$\underline{H}_2$, exchangeable with D_2O), 3.66 (3H, s, $CO_2C\underline{H}_3$), 6.90 (1H, s, 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-$C\underline{H}_3$), 18.5 (C-2), 21.1 (C-6), 25.2 (10-$C\underline{H}_3$), 25.2 (C-7), 36.6 (C-3), 36.8 (C-10), 38.4 (C-1), 44.2 (C-5), 47.5 (C-4), 51.9 ($CO_2C\underline{H}_3$), 110.1 (C-12), 118.1 (C-11), 119.7 (C-8), 129.2 (C-13), 133.7 (C-14), 143.5 (C-9), 179.1 ($\underline{C}O_2CH_3$) ppm; MS *m/z*: 382 (61%), 380 M^+ (54%), 367 (29%), 365 (27%), 307 (100%), 305 (97%). Anal. calcd for $C_{18}H_{25}BrN_2O_2$: C 56.70, H 6.61, N 7.35; found: C 56.65, H 6.57, N 7.09%; HRMS: calcd for $C_{18}H_{25}{}^{79}BrN_2O_2$: 380.10995; found: 380.10974.

4.1.5. Methyl 13,14-imidazolyl-deisopropyldehydroabietate (5a). A mixture of methyl 13,14-diaminodeisopropyldehydroabietate **4a** (70 mg, 0.23 mmol) and formic acid (98–100%; 2.5 mL) was heated under reflux for 4 h. The solution was then neutralized with aqueous sodium hydroxide (20%) and extracted with ether. The organic phase was washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness. The residue (66 mg) was purified by preparative thin layer chromatography on silica gel, with dichloromethane-methanol (9.7:0.3) as eluent. The imidazole **5a** was obtained as a white foam (41 mg, 0.13 mmol, 55%), IR (film) ν_{max} 3415, 1724, 1589, 1254, 1115, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, s, 10-C$\underline{H}_3$), 1.31 (3H, s, 4-C$\underline{H}_3$), 1.42–1.58 (2H, m, 1-Hα and 6-Hβ), 1.66–1.95 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.34 (1H, d, $J = 12.9$ Hz, 5-Hα), 2.41 (1H, brs, 1-Hβ), 3.04–3.22 (2H, m, 7-H_2), 3.68 (3H, s, $CO_2C\underline{H}_3$), 7.24 (1H, d, $J = 8.7$ Hz, 11-H or 12-H), 7.46 (1H, d, $J = 8.4$ Hz, 12-H or 11-H), 8.06 (1H, brs, 2′-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-$C\underline{H}_3$), 18.6 (C-2), 21.1 (C-6), 25.2 (10-$C\underline{H}_3$), 25.6 (C-7), 36.7 (C-3), 37.4 (C-10), 38.4 (C-1), 45.2 (C-5), 47.8 (C-4), 52.0

($CO_2\underline{C}H_3$), 113.4 (C-12), 120.0 (C-11), 122.1 (C-8), 135.1 (C-13 or C-14), 135.6 (C-14 or C-13), 140.0 (C-2′), 144.4 (C-9), 179.2 ($\underline{C}O_2CH_3$) ppm; MS *m*/*z*: 312 M^+ (16%), 297 (20%), 237 (100%); HRMS: calcd for $C_{19}H_{24}N_2O_2$: 312.18378, found: 312.18396.

4.1.6. Methyl 2′-methyl-13,14-imidazolyl-deisopropyldehydroabietate (6a). Diamine **4a** (67 mg, 0.22 mmol), glacial acetic acid (4 mL), and 4 M hydrochloric acid (1 mL) were heated under reflux for 1 h 30 min. The residue (64 mg) was purified by preparative thin layer chromatography on silica gel, with dichloromethane–methanol (9.5:0.5) as eluent. The imidazole **6a** was obtained as a white foam (50 mg, 0.15 mmol, 67%), IR (film) ν_{max} 2937, 1725, 1539, 1252, 1114, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (3H, s, 10-C$\underline{H}_3$), 1.30 (3H, s, 4-C$\underline{H}_3$), 1.48–1.56 (2H, m, 1-Hα and 6-Hβ), 1.66–1.92 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2,32 (1H, dd, *J* = 12,6 and 1,9 Hz, 5-Hα), 2,39 (1H, brs, 1-Hβ), 2,56 (3H, s, 2′-C$\underline{H}_3$), 3.00–3.13 (2H, m, 7-H_2), 3.67 (3H, s, $CO_2C\underline{H}_3$), 7.15 (1H, d, *J* = 8.6 Hz, 11-H or 12-H), 7.32 (1H, d, *J* = 8,7 Hz, 12-H or 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.2 (2′-$\underline{C}H_3$), 16.5 (4-$\underline{C}H_3$), 18.6 (C-2), 21.1 (C-6), 25.3 (C-7), 25.5 (10-$\underline{C}H_3$), 36.7 (C-3), 37.3 (C-10), 38.4 (C-1), 45.2 (C-5), 47.7 (C-4), 52.0 ($CO_2\underline{C}H_3$), 112.3 (C-12), 119.3 (C-11), 121.2 (C-8), 135.1 (C-13 or C-14), 135.8 (C-14 or C-13), 143.9 (C-9), 150.4 (C-2′), 179.3 ($\underline{C}O_2CH_3$) ppm; MS *m*/*z*: 326 M^+ (18%), 311 (23%), 251 (100%); HRMS: calcd for $C_{20}H_{26}N_2O_2$: 326.19943, found: 326.19931.

4.1.7. Methyl 2′-trifluoromethyl-13,14-imidazolyl-deisopropyldehydroabietate (7a). Diamine **4a** (79 mg, 0.26 mmol), trifluoroacetic acid (0.4 mL), and 4 M hydrochloric acid (0.6 mL) were heated under reflux for 3 h. The residue (83 mg) was purified by preparative thin layer chromatography on silica gel with dichloromethane–methanol (9.5:0.5) as eluent. The imidazole **7a** was obtained as a white solid (70 mg, 0.18 mmol, 70%), mp 236–238 °C; IR (film) ν_{max} 2941, 1727, 1540, 1254, 1147 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, s, 10-C$\underline{H}_3$), 1.33 (3H, s, 4-C$\underline{H}_3$), 1.48–1.56 (2H, m, 1-Hα and 6-Hβ), 1.73–1.98 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.35 (1H, d, *J* = 12.6 Hz, 5-Hα), 2.41 (1H, brs, 1-Hβ), 3.01 (2H, m, 7-H_2), 3.71 (3H, s, $CO_2C\underline{H}_3$), 7.31 (1H, d, *J* = 7.8 Hz, 11-H or 12-H), 7.63 (1H, d, *J* = 8.4 Hz, 12-H or 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.4 (4-$\underline{C}H_3$), 18.5 (C-2), 21.0 (C-6), 25.1 (C-7), 25.5 (10-$\underline{C}H_3$), 36.8 (C-3), 37.5 (C-10), 38.2 (C-1), 45.1 (C-5), 47.8 (C-4), 52.2 ($CO_2\underline{C}H_3$), 117.2 (CF_3, *J* = 271 Hz), 118.5 (C-11 or C-12), 120.9 (C-12 or C-11), 124.4 (C-8), 132.6 (C-13 and C-14), 139.9 (C-2′, *J* = 40.1 Hz), 146.6 (C-9), 179.8 ($\underline{C}O_2CH_3$) ppm; MS *m*/*z* 380 M^+ (10%), 365 (12%), 305 (100%). Anal. calcd for $C_{20}H_{23}F_3N_2O_2$: C 63.15, H 6.09, N 7.36; found: C 63.07, H 6.14, N 7.33%.

4.1.8. Methyl 2′-methoxycarbonylamino-13,14-imidazolyl-deisopropyldehydroabietate (8) (a) Preparation of [$CH_3O_2CNHC(SCH_3)$=NCO_2CH_3]. *N,O* - Bis(trimethylsilyl)acetamide (2.1 mL, 8.62 mmol) was added to a solution of *S*-methylisothiourea (500 mg, 3.60 mmol) in dry and recently distilled dichloromethane (5 mL), with vigorous stirring, under N_2 at rt. After 1 h 10 min, methyl chloroformate (0.66 mL, 8.62 mmol) in dry and freshly distilled dichloromethane (5 mL) was added to the reaction mixture in an ice bath. After 2 h, a buffer solution of 0.1 M KH_2PO_4/Na_2HPO_4 (pH = 7) was added to the reaction mixture in an ice bath, followed by extraction with diethyl ether. The organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and evaporated to dryness, affording $CH_3O_2CNH–C(SCH_3)$=N–CO_2CH_3 as white crystals (322 mg, 1.56 mmol, 44%), mp 98–100 °C (lit:[22] 100 °C); IR (film) ν_{max} 3583, 1753, 1657, 1594, 1438, 1403, 1281, 1215, 1062, 808, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (3H, s), 3.82 (6H, s), and 11.86 (1H, s); *m*/*z* 206 M^+ (41%), 174 (74%), 83 (47%), 71 (54%), 59 (100%), 47 (34%). Anal. calcd for $C_6H_{10}N_2O_4$:S C 34.95, H 4.89, N 13.58; found: C 35.16, H 4.88, N 13.64%.

(b) Cyclisation. Diamine **4a** (68 mg, 0.23 mmol), glacial acetic acid (4 mL), and $CH_3O_2CNHC(SCH_3)$=NCO_2CH_3 (49 mg, 0.24 mmol) were heated under reflux for 3 h 30 min. The residue (105 mg) was purified by preparative thin layer chromatography on silica gel with dichloromethane–methanol (9.7:0.3) as eluent. The imidazole **8** was obtained as a white solid (31 mg, 0.08 mmol, 35%), mp 276–278 °C; IR (film) ν_{max} 3409, 2949, 1723, 1646, 1605, 1264, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, s, 10-C$\underline{H}_3$), 1.32 (3H, s, 4-C$\underline{H}_3$), 1.55–1.59 (2H, m, 1-Hα and 6-Hβ), 1.66–1.97 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.34 (1H, dd, *J* = 12.6 and 1.8 Hz, 5-Hα), 2.41 (1H, brs, 1-Hβ), 2.97–3.02 (2H, m, 7-H_2), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.92 (3H, s, $NHCO_2C\underline{H}_3$), 7.16 (1H, d, *J* = 8.7 Hz, 11-H or 12-H), 7.33 (1H, d, *J* = 9 Hz, 12-H or 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-$\underline{C}H_3$), 18.7 (C-2), 21.0 (C-6), 25.2 (10-$\underline{C}H_3$), 25.4 (C-7), 36.7 (C-3), 37.3 (C-10), 38.5 (C-1), 45.1 (C-5), 47.8 (C-4), 52.0 ($CO_2\underline{C}H_3$), 52.7 ($CO_2\underline{C}H_3$), 112.7 (C-8), 118.8 (C-11 and C-12), 131.0 (C-13 or C-14), 133.9 (C-14 or C-13), 143.5 (C-9), 149.2 (C-2′), 157.3 ($NH\underline{C}O_2CH_3$), 179.2 ($\underline{C}O_2CH_3$) ppm; MS *m*/*z* 385 M^+ (9%), 370 (7%), 353 (23%), 310 (24%), 278 (100%), 44 (42%). Anal. calcd for $C_{21}H_{27}N_3O_4$: C 65.44, H 7.06, N 10.90; found: C 65.43, H 7.06, N 10.87%.

4.1.9. Methyl 12-bromo-13,14-imidazolyl-deisopropyldehydroabietate (5b). Diamine **4b** (47 mg, 0.12 mmol) and formic acid (3 mL) were heated under reflux for 2 h. The residue (40 mg) was purified by preparative thin layer chromatography on silica gel with dichloromethane–methanol (9.5:0.5) as eluent. The imidazole **5b** was obtained as an amorphous white solid (27 mg, 0.07 mmol, 59%); IR (Nujol) ν_{max} 3082, 2949, 1721, 1259, 1125, 1104, 1033, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (3H, s, 10-C$\underline{H}_3$), 1.30 (3H, s, 4-C$\underline{H}_3$), 1.43–1.57 (2H, m, 1-Hα and 6-Hβ), 1.67–1.94 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.30 (1H, dd, *J* = 13 and 2.1 Hz, 5-Hα), 2.37 (1H, brs, 1-Hβ), 2.91–3.18 (2H, m, 7-H_2), 3.68 (3H, s, $CO_2C\underline{H}_3$), 7.38 (1H, s, 11-H), 8.06 (1H, s, 2′-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-$\underline{C}H_3$), 18.6 (C-2), 20.9 (C-6), 25.2 (10-$\underline{C}H_3$), 25.4 (C-7), 36.7 (C-3), 37.5 (C-10), 38.4 (C-1), 45.1 (C-5), 47.7 (C-4), 52.1 ($CO_2\underline{C}H_3$), 106.1

(C-12), 121.7 (C-8), 122.6 (C-11), 135.0 (C-13 or C-14), 136.8 (C-14 or C-13), 140.4 (C-2′), 145.8 (C-9), 179.2 (C$O_2$$CH_3$) ppm; MS *m*/*z* 392 (15%), 390 M^+ (17%), 377 (11%), 375 (12%), 317 (100%), and 315 (93%). Anal. calcd for $C_{19}H_{23}BrN_2O_2$: C 58.32, H 5.92, N 7.16; found: C 57.69, H 6.09, N 6.82%; HRMS: calcd for $C_{19}H_{23}{}^{79}BrN_2O_2$ 390.09430, found 390.09431.

4.1.10. Methyl 2′-methyl-12-bromo-13,14-imidazolyl-deisopropyldehydroabietate (6b). Diamine **4b** (73 mg, 0.19 mmol), glacial acetic acid (4 mL) and 4 M hydrochloric acid (1 mL) were heated under reflux for 1 h 20 min. The residue (85 mg) was purified by preparative thin layer chromatography on silica gel with dichloromethane–methanol (9.6:0.4). Upon recrystallisation, white crystals of the imidazole **6b** (56 mg, 0.14 mmol, 72%) were obtained, mp 168–170 °C (from ether); IR (film) ν_{max} 1725, 1251, 1128, 1036, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3H, s, 10-CH_3), 1.29 (3H, s, 4-CH_3), 1.48–1.57 (2H, m, 1-Hα and 6-Hβ), 1.63–1.95 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.30 (1H, d, *J* = 11.4 Hz, 5-Hα), 2.35 (1H, brs, 1-Hβ), 2.52 (3H, s, 2′-CH_3), 2.88–3.12 (2H, m, 7-H_2), 3.67 (3H, s, CO_2CH_3), 7.30 (1H, s, 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.8 (2′-CH_3), 16.4 (4-CH_3), 18.5 (C-2), 21.0 (C-6), 25.3 (C-7), 25.4 (10-CH_3), 36.6 (C-3), 37.4 (C-10), 38.4 (C-1), 45.0 (C-5), 47.7 (C-4), 52.0 (CO_2CH_3), 105.4 (C-12), 120.4 (C-8), 121.6 (C-11), 135.9 (C-13 or C-14), 137.1 (C-14 or C-13), 145.1 (C-9), 151.1 (C-2′), 179.2 (C$O_2$$CH_3$) ppm; MS *m*/*z* 406 (15%), 404 $[M]^+$ (16%), 391 (13%), 389 (14%), 331 (100%), 329 (91%). Anal. calcd for $C_{20}H_{25}BrN_2O_2$: C 59.26, H 6.22, N 6.91; found: C 59.66, H 6.22%, N 6.86%; HRMS: calcd for $C_{20}H_{25}{}^{79}BrN_2O_2$: 404.10992, found: 404.10904.

4.1.11. Methyl 2′-trifluoromethyl-12-bromo-13,14-imidazolyl-deisopropyldehydroabietate (7b). Diamine **4b** (64 mg, 0.17 mmol), trifluoroacetic acid (0.4 mL) and 4 M hydrochloric acid (0.6 mL) were heated under reflux for 2 h. The residue (61 mg) was purified by preparative thin layer chromatography on silica gel with dichloromethane–methanol (9.7:0.3). Upon recrystallisation, white crystals of the imidazole **7b** (42 mg, 0.09 mmol, 53%) were obtained, mp 151–153 °C (dichloromethane–hexane); IR (Nujol) ν_{max} 2949, 1726, 1582, 1254, 1145, 1035, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, s, 10-CH_3), 1.31 (3H, s, 4- CH_3), 1.42-1.57 (2H, m, 1-Hα and 6-Hβ), 1.73–1.98 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.30 (1H, d, *J* = 12.3 Hz, 5-Hα), 2.37 (1H, brs, 1-Hβ), 3.02–3.08 (2H, m, 7-H_2), 3.70 (3H, s, CO_2CH_3), 7.48 (1H, s, 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.3 (4-CH_3), 18.4 (C-2), 20.8 (C-6), 25.1 (10-CH_3), 25.3 (C-7), 36.7 (C-3), 37.6 (C-10), 38.2 (C-1), 45.0 (C-5), 47.7 (C-4), 52.1 (CO_2CH_3),102.7 (C-12), 116.9 (CF_3, *J* = 270.5 Hz) 124.4 (C-8 and C-11), 134.7 (C-13 or C-14), 136.7 (C-14 or C-13), 140.8 (C-2′, *J* = 40.7 Hz), 147.4 (C-9), 179.6 (C$O_2$$CH_3$) ppm; MS *m*/*z* 460 (15%), 458 M^+ (16%), 445 (8%), 443 (9%), 385 (96%), 383 (100%), 305 (57%). Anal. calcd for $C_{20}H_{22}BrF_3N_2O_2$: C 52.30, H 4.83, N 6.10; found: C 52.80, H 5.15, N 5.63%; HRMS: calcd for $C_{20}H_{22}BrF_3N_2O_2$: 458.08167, found: 458.08076.

4.1.12. Methyl 2′,3′-dimethyl-13,14-pyrazinyldeisopropyldehydroabietate (9). A mixture of **4a** (102 mg, 0.34 mmol), butane-2,3-dione (0.3 mL, 0.34 mmol) and glacial acetic acid (2 mL) was heated under reflux and N_2 for 40 min. The solvent was evaporated under reduced pressure after cooling down the reaction mixture to rt. The residue (133 mg) was purified by preparative thin layer chromatography on silica gel with dichloromethane–methanol (9.9:0.1). The quinoxaline **9** (113 mg, 0.32 mmol, 61%) was obtained as a white foam; IR (film) ν_{max} 2946, 1727, 1451, 1338, 1247, 1173, 1116, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3H, s, 10-CH_3), 1.32 (3H, s, 4-CH_3), 1.50–1.68 (2H, m, 1-Hα and 6-Hβ), 1.72–1.97 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.33 (1H, dd, *J* = 12.6 and 2.1 Hz, 5-Hα), 2.41 (1H, brs, 1-Hβ), 2.70 (6H, s, 2′-CH_3 and 3′-CH_3), 3.15–3.28 (1H, m, 7-Hα or 7-Hβ), 3.55–3.66 (1H, m, 7-Hβ or 7-Hα), 3.68 (3H, s, CO_2CH_3), 7.61 (1H, d, *J* = 8.9 Hz, 12-H), 7.76 (1H, d, *J* = 8.9 Hz, 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-CH_3), 18.6 (C-2), 21.3 (C-6), 22.9 (2′- or 3′-CH_3), 23.2 (2′- or 3′-CH_3), 24.6 (10-CH_3), 25.7 (C-7), 36.5 (C-3), 37.7 (C-10), 38.0 (C-1), 45.2 (C-5), 47.7 (C-4), 51.9 (CO_2CH_3), 125.8 (C-11), 126.0 (C-12), 132.4 (C-8), 139.2 (C-13), 140.0 (C-14), 149.0 (C-9), 151.9 (C-2′ or C-3′), 152.0 (C-3′ or C-2′), 179.0 (C$O_2$$CH_3$) ppm; MS *m*/*z* 352 M^+ (93%), 337 (17%), 293 (18%), 277 (100%), 223 (24%). Anal. calcd for $C_{22}H_{28}N_2O_2$: C 74.97, H 8.01, N 7.95; found: C 74.64, H 8.19, N 7.86%.

4.1.13. Methyl 2′,3′-diphenyl-13,14-pyrazinyl-deisopropyldehydroabietate (10). A mixture of **4a** (90 mg, 0.30 mmol), benzil (65 mg, 0.30 mmol) and glacial acetic acid (3 mL) was heated under reflux and N_2 for 2 h. After cooling down to room temperature, the reaction mixture was quenched in ice-water (50 mL), and a white precipitate was formed. The solid was filtered and washed with water. Upon recrystallisation, the quinoxaline **10** (113 mg, 0.24 mmol, 79%) was obtained as white crystals, mp 138–140 °C (from ether–methanol); IR (Nujol) ν_{max} 1723, 1462, 1378, 1350, 1246, 1173, 1116, 766, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (3H, s, 10-CH_3), 1.34 (3H, s, 4-CH_3), 1.55–1.70 (2H, m, 1-Hα and 6-Hβ), 1.79–2.00 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.38 (1H, dd, *J* = 12.3 and 1.8 Hz, 5-Hα), 2.45 (1H, d, *J* = 11.4 Hz, 1-Hβ), 3.27–3.40 (1H, m, 7-Hα or 7-Hβ), 3.66–3.75 (1H, m, 7-Hβ or 7-Hα), 3.68 (3H, s, CO_2CH_3), 7.30–7.36 (6H, m, 6×H-Ar), 7.49-7.55 (4H, m, 4×H–Ar), 7.73 (1H, d, *J* = 9.3 Hz, 11-H), 7.96 (1H, d, *J* = 9.3 Hz, 12-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-CH_3), 18.6 (C-2), 21.3 (C-6), 24.5 (10-CH_3), 25.7 (C-7), 36.5 (C-3), 37.8 (C-10), 37.9 (C-1), 45.2 (C-5), 47.8 (C-4), 52.0 (CO_2CH_3), 126.6 (C-12), 127.5 (C-11), 128.1 (2×CH–Ar), 128.3 (2×CH–Ar), 128.6 (2×CH–Ar), 129.8 (2×CH–Ar), 130.2 (2×CH–Ar), 133.3 (C-8), 139.3 (C-13), 139.6 (2×C–Ar), 140.0 (C-14), 150.2 (C-9), 151.7 (C-2′ or C-3′), 152.3 (C-3′ or C-2′), 179.0 (C$O_2$$CH_3$); MS *m*/*z* 476 M^+ (100%), 461 (16%), 417 (15%), 401 (54%), 347 (21%). Anal. calcd for $C_{32}H_{32}N_2O_2$: C 80.64; H 6.77, N 5.88; found: C 80.34, H 6.74, N 5.84%.

4.1.14. Methyl 2′,3′-cyclohexyl-13,14-pyrazinyl-deisopropyldehydroabietate (11). A mixture of the diamine **4a** (100 mg, 0.33 mmol), cyclohexane-1,2-dione (37 mg, 0.33 mmol), sodium acetate (52 mg, 0.63 mmol) and glacial acetic acid (2 mL) was heated under reflux and

N_2 for 1 h 30 min. The reaction mixture was quenched with water (40 mL). The pH was then made alkaline by addition of 1 N sodium hydroxide, and the product was extracted with ether. The organic phase was washed with water, dried with anhydrous magnesium sulphate, filtered and evaporated to dryness under reduced pressure. The residue (99 mg) was purified by preparative thin layer chromatography on silica gel with dichloromethane–methanol (9.9:0.1) as eluent. The quinoxaline **11** (52 mg, 0.14 mmol, 42%) was obtained as a white foam, IR (film) ν_{max} 2941, 1727, 1488, 1446, 1429, 1340, 1246, 1184, 1172, 1115, and 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3H, s, 10-C$\underline{H}_3$), 1.32 (3H, s, 4-C$\underline{H}_3$), 1.50–1.68 (2H, m, 1-Hα and 6-Hβ), 1.74–1.94 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 1.97–2.03 (4H, m, 2×CH_2-cyclohexyl), 2.33 (1H, dd, J = 12.3 and 2.1 Hz, 5-Hα), 2.41 (1H, d, J = 11.7 Hz, 1-Hβ), 3.12 (4H, s, 2×C$\underline{H}_2$-cyclohexyl), 3.17–3.27 (1H, m, 7-Hα or 7-Hβ), 3.53–3.62 (1H, m, 7-Hβ or 7-Hα), 3.68 (3H, s, $CO_2C\underline{H}_3$), 7.61 (1H, d, J 9 Hz, 12-H), 7.76 (1H, d, J = 9 Hz, 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.5 (4-$\underline{C}H_3$), 18.6 (C-2), 21.3 (C-6), 23.0 (2×$\underline{C}H_2$-cyclohexyl), 24.5 (10-$\underline{C}H_3$), 25.8 (C-7), 32.9 ($\underline{C}H_2$-cyclohexyl), 33.4 ($\underline{C}H_2$-cyclohexyl), 36.5 (C-3), 37.7 (C-10), 37.9 (C-1), 45.2 (C-5), 47.7 (C-4), 51.9 ($CO_2\underline{C}H_3$), 125.8 (C-11), 126.3 (C-12), 132.4 (C-8), 139.3 (C-13), 140.2 (C-14), 149.0 (C-9), 152.6 (C-2′ or C-3′), 152.7 (C-3′ or C-2′), 179.0 ($\underline{C}O_2CH_3$) ppm; MS m/z 378 M^+ (90%), 363 (17%), 319 (20%), 303 (100%), 249 (35%). Anal. calcd for $C_{24}H_{30}N_2O_2$: C 76.16, H 7.99, N 7.40; found: C 75.99, H 7.99, N 7.38%.

4.1.15. Methyl 12-trimethylsylilethinyl-13-nitro-deisopropyldehydroabietate (12). According to the procedure described in the literature,[27] palladium dichloro bis-triphenylphosphine (32 mg, 0.05 mmol) and copper (I) iodide (34 mg, 0.34 mmol) were added to a mixture of trimethylsylilacetylene (0.3 mL, 2.1 mmol) and methyl 12-bromo-13-nitro-deisopropyldehydroabietate **3b** (513 mg, 1.3 mmol) in triethylamine (17 mL). The reaction proceeded for 18 h at room temperature, under nitrogen and with vigorous stirring. Upon conclusion, the solvent was evaporated to dryness. The residue was dissolved in ether and washed with water. The organic phase was dried with anhydrous magnesium sulphate, filtered and evaporated to dryness. The extract (542 mg) was purified by silica column chromatography, using hexane–ether (6:4) as eluent. Upon recrystallisation, white crystals of methyl 12-trimethylsylilethinyl-13-nitro-deisopropyldehydroabietate **12** (502 mg, 1.21 mmol, 93%) were obtained, mp 166–168 °C (from light petroleum ether); IR (Nujol) ν_{max} 2928, 2154, 1731, 1555, 1519, 1340, 1245, 1185, 1111, 865, 840, 759 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.28 (9H, s, Si(C$\underline{H}_3$)$_3$), 1.21 (3H, s, 10-C$\underline{H}_3$), 1.28 (3H, s, 4-C$\underline{H}_3$), 1.46-1.55 (2H, m, 1-Hα and 6-Hβ), 1.63–1.88 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.17 (1H, dd, J = 12.3 and 2.1 Hz, 5-Hα), 2.34 (1H, d, J = 12.6 Hz, 1-Hβ), 2.93–2.98 (2H, m, 7-H_2), 3.69 (3H, s, $CO_2C\underline{H}_3$), 7.50 (1H, s, 11-H), 7.72 (1H, s, 14-H) ppm; ^{13}C NMR ($CDCl_3$) δ 0.0 (Si($\underline{C}H_3$)$_3$), 16.8 (4-$\underline{C}H_3$), 18.6 (C-2), 21.3 (C-6), 25.0 (10-$\underline{C}H_3$), 30.0 (C-7), 36.8 (C-3), 37.9 (C-10), 38.0 (C-1), 44.4 (C-5), 47.8 (C-4), 52.4 ($CO_2\underline{C}H_3$), 100.6 (C≡C), 101.8 (C≡C), 115.9 (C-12), 125.5 (C-14), 131.8 (C-11), 137.7 (C-8), 147.8 (C-13), 155.4 (C-9), 178.9 ($\underline{C}O_2CH_3$) ppm; MS m/z 413 $[M]^+$ (4%), 398 (8%), 338 (11%), 310 (23%), 73 (100%). Anal. calcd for $C_{23}H_{31}NO_4Si$: C 66.79, H 7.55, N 3.39; found: C 67.09, H 7.64, N 3.61%.

4.1.16. Methyl 12-trimethylsylilethinyl-13-amino-deisopropyldehydroabietate (13). According to the procedure described in the literature,[28] iron (515 mg, 0.01 mmol) and iron (II) sulphate heptahydrate (175 mg, 0.62 mmol) were added to a mixture of methyl 12-trimethylsylilethinyl-13-nitro-deisopropyldehydroabietate **12** (98 mg, 0.24 mmol), benzene (2 mL), methanol (0.5 mL) and 0.1 M hydrochloric acid (5.5 mL) with vigorous stirring. The mixture was refluxed during 8 h. Upon conclusion, the reaction mixture was cooled to room temperature, extracted with ether and washed with water. The organic phase was dried with anhydrous magnesium sulphate, filtered and evaporated to dryness. The extract (85 mg) was purified by silica column chromatography, using hexane–ether (1:1) as eluent. Compound **13** was obtained as a colorless oil (75 mg, 0.20 mmol, 83%), IR (film) ν_{max} 3483, 3384, 2927, 2141, 1731, 1621, 1462, 1249, 1133, 863, 840, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 (9H, s, Si(C$\underline{H}_3$)$_3$), 1.15 (3H, s, 10-C$\underline{H}_3$), 1.25 (3H, s, 4-C$\underline{H}_3$), 1.33–1.49 (2H, m, 1-Hα and 6-Hβ), 1.61–1.82 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.14 (1H, dd, J = 12.6 and 2.1 Hz, 5-Hα), 2.24 (1H, d, J = 13.2 Hz, 1-Hβ), 2.75–2.80 (2H, m, 7-H_2), 3.66 (3H, s, $CO_2C\underline{H}_3$), 4.02 (2H, brs, N$\underline{H}_2$, exchangeable with D_2O), 6.36 (1H, s, 11-H or 14-H), 7.16 (1H, s, 14-H or 11-H) ppm; ^{13}C NMR ($CDCl_3$) δ 0.15 (Si($\underline{C}H_3$)$_3$), 16.4 (4-$\underline{C}H_3$), 18.5 (C-2), 21.5 (C-6), 25.0 (10-$\underline{C}H_3$), 30.0 (C-7), 36.5 (C-3), 36.6 (C-10), 38.1 (C-1), 45.0 (C-5), 47.5 (C-4), 51.8 ($CO_2\underline{C}H_3$), 98.4 (C≡C), 102.5 (C≡C), 106.1 (C-12), 114.1 (C-14), 128.2 (C-11), 137.6 (C-8), 140.0 (C-13), 145.6 (C-9), 179.1 ($\underline{C}O_2CH_3$) ppm; MS m/z 383 M^+ (40%), 368 (38%), 324 (5%), 308 (100%), 73 (42%); HRMS: calcd for $C_{23}H_{33}NO_2Si$: 383.22809; found: 383.22836.

4.1.17. Methyl 12,13d-pyrrolyldeisopropyldehydroabietate (14). According to the procedure described in the literature,[29] a mixture of methyl 12-trimethylsylilethinyl-13-amino-deisopropyl-dehydroabietate **13** (49 mg, 0.13 mmol) and copper(I) iodide (28 mg, 0.15 mmol) in dimethylformamide (3 mL) was heated to 100 °C, under N_2, during 1 h 10 min. The reaction mixture was filtered through a layer of Celite and washed with ether, after being cooled to room temperature. The organic solution was washed with a concentrated solution of brine, dried with anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The extract (43 mg) was purified by silica column chromatography using hexane–ether (4:6) as eluent. The indole **14** (23 mg, 0.074 mmol, 60%) was obtained as a colourless oil, IR (film) ν_{max} 3394, 2927, 1727, 1463, 1246, 1107, 1132, 833, 723, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (3H, s, 10-C$\underline{H}_3$), 1.31 (3H, s, 4-C$\underline{H}_3$), 1.38–1.58 (2H, m, 1-Hα and 6-Hβ), 1.58–1.97 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.30 (1H, dd, J = 12.3 and 2.7 Hz, 5-Hα), 2.44 (1H, d, J = 11.8 Hz, 1-Hβ), 3.02–3.07 (2H, m, 7-H_2), 3.66 (3H, s, $CO_2C\underline{H}_3$), 6.44–6.46 (1H, m, 3′-H), 7.04 (1H, s, 11-H), 7.09 (1H, t, J = 2.8 Hz, 2′-H), 7.52 (1H, s, 14-H), 7.91

(1H, brs, NH, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$) δ 16.6 (4-$\underline{C}H_3$), 18.8 (C-2), 22.0 (C-6), 25.6 (10-$\underline{C}H_3$), 30.3 (C-7), 36.8 (C-3), 37.4 (C-10), 38.8 (C-1), 45.2 (C-5), 47.8 (C-4), 51.9 ($CO_2\underline{C}H_3$), 102.4 (3′-CH), 110.3 (C-14), 115.6 (C-11), 124.0 (2′-CH), 126.6 (C-12), 129.8 (C-8), 134.7 (C-13), 142.6 (C-9), 179.4 ($\underline{C}O_2CH_3$) ppm; MS *m*/*z* 311 $[M]^+$ (28%), 296 (13.7%), 252 (3%), 236 (100%); HRMS: calcd for $C_{20}H_{25}NO_2$ 311.18854; found 311.18850.

4.1.18. Methyl 12-bromo-13,14b-pyrrolyl-deisopropyldehydroabietate (15). Vinyl magnesium bromide (1.8 mL) was added dropwise[30] to a solution of methyl 12-bromo-13-nitro-deisopropyldehydroabietate **3b** (209 mg, 0.53 mmol) in dry and freshly distilled tetrahydrofuran (2.5 mL) at −78 °C and under N_2, with vigorous stirring. The reaction proceeded at −78 °C for 3 h. After quenching by addition of a concentrated ammonium chloride solution, the mixture was extracted with ether. A concentrated ammonium chloride solution was added to the reaction mixture, followed by extraction with ether. The organic phase was then dried with anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue (232 mg) was purified by silica column chromatography using hexane–ether (1:1) as eluent. The bromo-indole **15** was obtained as a yellow precipitate (143 mg, 0.37 mmol, 70%), mp 171–173 °C; IR (film) ν_{max} 3354, 2932, 1708, 1485, 1435, 1328, 1260, 1174, 1131, 1114, 1095, 725, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (3H, s, 10-C$\underline{H}_3$), 1.30 (3H, s, 4-C$\underline{H}_3$), 1.48–1.56 (2H, m, 1-Hα and 6-Hβ), 1.61–1.99 (5H, m, 2-H_2, 3-H_2 and 6-Hα), 2.32 (1H, dd, J = 12.6 and 2.1 Hz, 5-Hα), 2.33 (1H, d, J = 12.6 Hz, 1-Hβ), 2.91-3.06 (2H, m, 7-H_2), 3.68 (3H, s, $CO_2C\underline{H}_3$), 6.54 (1H, dd, J = 2.2 and 3.2 Hz, 3′-H), 7.21 (1H, t, J = 2.8 Hz, 2′-H), 7.27 (1H, s, 11-H), 8.25 (1H, brs, N$\underline{H}$, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$) δ 16.4 (4-$\underline{C}H_3$), 18.6 (C-2), 21.2 (C-6), 25.3 (10-$\underline{C}H_3$), 27.1 (C-7), 36.6 (C-3), 37.3 (C-10), 38.6 (C-1), 45.3 (C-5), 47.8 (C-4), 51.9 ($CO_2\underline{C}H_3$), 102.1 (3′-CH), 120.9 (C-12), 121.4 (C-11), 124.2 (2′-CH), 126.2 (C-8), 128.3 (C-14), 132.2 (C-13), 142.4 (C-9), 179.2 ($\underline{C}O_2CH_3$) ppm; MS *m*/*z* 391 (26%), 389 $[M]^+$ (28%), 376 (15%), 374 (15%), 316 (91%), 314 (100%). Anal. calcd for $C_{20}H_{24}BrNO_2$: C 61.54, H 6.20, N 3.59; found: C 61.69, H 6.24, N 3.32%.

4.2. In vitro antiviral assays

Evaluations of antiviral activity of the reported compounds against different viruses, in particular cytomegalovirus (CMV) and varicella-zoster virus (VZV) in human embryonic lung (HEL) cells, were performed as previously described.[33]

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References and notes

1. Tagat, J. R.; Nazareno, D. V.; Puar, M. H.; McCombie, S. W.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1101.
2. Mauldin, S.C.; Monroe, J. E., US Patent 6,180,815 B1, 2001, and references therein.
3. Gigante, B.; Santos, C.; Silva, A. M.; Curto, M. J. M.; Nascimento, M. S. J.; Pinto, E.; Pedro, M.; Cerqueira, F.; Pinto, M. M.; Duarte, M. P.; Laires, A.; Rueff, J.; Gonçalves, J.; Pegado, M. I. and Valdeira, M. L. *Bioorg. Med. Chem.* **2003**, *11*, 1631.
4. Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W.; Michejda, C. J. *J. Med. Chem.* **1997**, *49*, 4199. Migawa, M. T.; Girardet, J. L.; Walker, J. A.; Koszalka, G. W.; Chamberlain, S. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1242. Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1252. Garuti, L.; Roberti, M.; Cermelli, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2525. Zou, R. M.; Kawashima, E.; Freeman, G. A.; Kolszalka, G. W.; Drach, J. C.; Townsend, L. B. *Nucleos. Nucleot. Nucl.* **2000**, *19*, 125.
5. Balzarini, J.; De Clercq, E.; Carbonez, A.; Burt, V.; Kleim, J. P. *AIDS Res. Hum. Retroviruses* **2000**, *16*, 517. Catarzi, D.; Colotta, V.; Varano, F.; Cecchi, L.; Filacchioni, G.; Galli, A.; Costagli, C.; Carlà, V. *J. Med. Chem.* **2000**, *43*, 3824.
6. Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743. Hayashi, H.; Ohmoto, S.; Somei, M. *Heterocycles* **1997**, *45*, 1647.
7. Fonseca, T.; Gigante, B.; Gilchrist, T. L. *Tetrahedron* **2001**, *57*, 1793.
8. Halbrook, N. J.; Lawrence, R. V. *J. Org. Chem.* **1966**, *31*, 4246.
9. Zinkel, D. F.; Han, J. S. *Naval Stores Rev.* **1986**, *96*, 11.
10. Esteves, M. A.; Narender, N.; Gigante, B.; Curto, M. J. M.; Alvarez, M. F. *Synth. Commun.* **1999**, *29*, 275.
11. Cambie, R. C.; Franich, R. A. *J. Chem. Soc., Chem. Commun* **1970**, 845.
12. Tahara, A.; Akita, H.; Ohtsuka, Y. *Chem. Pharm. Bull.* **1974**, *22*, 1555, and references therein.
13. Yamamoto, J.; Uchikawa, A.; Kawato, A.; Shibata, A.; Muzitani, T. and Nakashima, R. *J. Chem. Soc. Jpn, Chem. Ind. Chem. (Nippon Kagaku Kaishi)* **1992**, 874.
14. Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed; Addison Wesley Longman: Harlow, 1997; p 284.
15. Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Thieme Organic Chemistry Monograph Series; Thieme: Stuttgart, New York, 1995, p 174, 433.
16. Grimmet, M. R. *Imidazole and Benzimidazole Synthesis*; Academic: London, 1997.
17. March, J. *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: New York, 1992; p 510.
18. Hudlicky, M. *Reductions in Organic Chemistry*; John Wiley & Sons: New York, 1984; p 26, 67.
19. Phillips, M. A. *J. Chem. Soc* **1931**, 1143.
20. Matolcsy, G.; Nádasy, M.; Andriska, V. *Pesticide Chemistry*; Elsevier: Amsterdam, 1988; p 388.
21. Raucher, S.; Jones, D. S. *Synth. Commun.* **1985**, *15*, 1025.
22. Girandon, R. US Patent 3,812,173, 1974; *Chem. Abstr.* **1974**, *81*, 25412.
23. Leonard, N. J.; Bayer, J. H. *J. Am. Chem. Soc.* **1950**, *72*, 2980.
24. Bost, R. W.; Towel, E. E. *J. Am. Chem. Soc.* **1948**, *70*, 903.
25. Morley, J. S. *J. Chem. Soc* **1952**, 4008.
26. Lopyrev, V. A.; Larina, L. I.; Vakul'skaya, T. I.; Larin,

M. F.; Nefedova, O. B.; Shibanova, E. F.; Voronkov, M. G. *Org. Magn. Res.* **1981**, *15*, 219.
27. Takashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihava, N. *Synthesis* **1980**, 627.
28. Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305.
29. Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Perez, M.; Garcia-Martin, M. A.; Gonzalez, J. M. *J. Org. Chem.* **1996**, *61*, 5804.
30. Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129.
31. Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Nat. Acad. Sci. U.S.A.* **1977**, *74*, 5716.
32. Smith, K. O.; Galloway, K. S.; Kennell, W. L.; Ogilvie, K. K.; Radatus, B. K. *Antimicrob. Agents Chemother.* **1982**, *22*, 55.
33. De Clercq, E. In *In Vivo and Ex Vivo Test Systems to Rationalize Drug Design and Delivery*; Crommelin, D., Couvreur, P., Duchêne, D., Eds.; Editions de Santé: Paris, France, 1994; p 108.