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Synthesis and in vitro structure–activity relationship of 13-*tert*-butyl-ergoline derivatives as 5-HT_{1A} receptor ligands

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Summary — A series of novel 13-*tert*-butyl-ergoline derivatives was prepared and evaluated for affinity to adrenergic, dopaminergic and serotonergic receptor sites. Selectivity for 5-HT_{1A} receptors versus α_1, α_2, D_1, D_2, and 5-HT_2 appears to be influenced by the presence of the *tert*-butyl moiety at position 13 of the ergoline skeleton. Some compounds within this series display nanomolar 5-HT_{1A} affinity and hundred-fold selectivity versus the other receptors considered.

ergoline derivative / 13-*tert*-butyl-ergoline / 5-HT_{1A} affinity / selectivity

Introduction

Ergoline derivatives exhibit marked central and peripheral pharmacological effects [1]. The generally non-selective interaction with the adrenaline, dopamine and serotonin receptors accounts for their wide spectrum of pharmacological actions [2]. The dopamine agonist components D_1, D_2 which have many important clinical applications in the treatment of Parkinsonism [3] and the agonist/antagonist serotonergic components 5-HT_{1A}, 5-HT_{1C} and 5-HT_{2C} with their documented connection with psychiatric disorders such as depression and anxiety [4] have fostered the interest on this class of compounds. From the work in this field, some ergoline derivatives depicted in figure 1 have become valuable drugs. For example the D_2/D_3 agonists pergolide (Permax®) [5] and cabergoline (Dostinex®) [6] are effectively used for the management of hyperprolactinemic states and Parkinson's disease. On the other hand, the 5-HT_{1A} agonist/5-HT_{2C} antagonists metergoline (Lyserdol®) [7] and the selective 5-HT_{2C} antagonist amesergide [8] have been exploited as agents for the symptomatic relief of migraine.

The 5-HT_{1A} receptor subtype is a novel target for putative antidepressants and anxiolytics. Interest in this area was fuelled by the discovery that the anxiolytic agent buspirone (Buspar®) displays high affinity for 5-HT_{1A} receptors [9]. In spite of the identification of several 5-HT_{1A} ligands, there is still demand for new compounds with potent effect at central 5-HT_{1A} receptors with an improved pharmacodynamic profile [10]. The 5-HT_{1A} component is shared by nearly all ergoline derivatives. However this component is not selective. The objective of this work was to identify novel ergoline derivatives endowed with high and selective 5-HT_{1A} affinity. The compounds reported in this study were motivated by considerations of the structural requirement for dopaminergic activity based on the hypothetical model of the DA receptor developed by Mc Dermod et al [11].

Modelling suggests that the receptor model is intolerant to steric hindrance present in the phenyl ring of the ergoline skeleton. Following this assumption, the design strategy was based on the introduction of the bulky and metabolically stable *tert*-butyl group on the phenyl ring at position 13 of the ergoline skeleton, with the expectation to prevent in such a way the access to the hypothesised primary binding sites on the DA receptor. The synthesis of a novel series of 13-*tert*-butyl-ergoline derivatives (**5**, **7–26**) and their affinity for α_1, α_2, D_1, D_2, 5-HT_{1A} and 5-HT_2 are described in this paper [12].

Chemistry

An efficient synthetic method toward 13-*tert*-butyl-ergolines was developed using easily accessible (5 R, 8 R, 10 S) dihydrolysergic acid, obtained by hydro-

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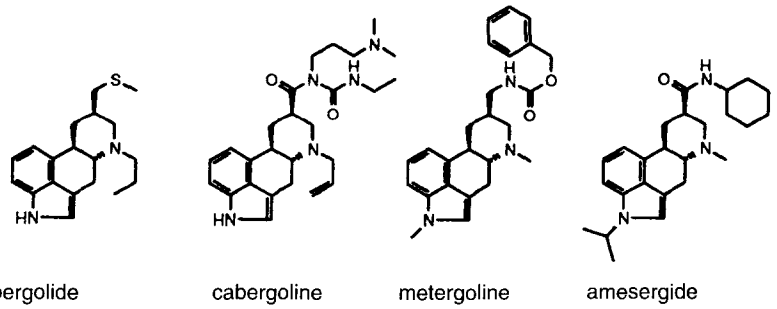


Fig 1. Dopaminergic and serotonergic ergolines.

genation of the natural occurring (5 R, 8 R) lysergic acid. The key step involved the regiospecific introduction of the *tert*-butyl group on the phenyl ring. Removable protection of the more electrophilic position 2 seemed a way of directing *tert*-butylation to the phenyl ring. The thiomethyl group was expected to fulfil this requirement. It can be readily removed by Raney nickel or nickelborohydride [13] and furthermore it has been shown that this group can facilitate electrophilic aromatic substitution at position 13. For instance, the action of bromine with 2-methylthio-dihydrolysergic acid methyl ester **2** in glacial acetic acid almost quantitatively afforded the 13-bromo derivative [14]. The 2-methylthio-dihydrolysergic acid methyl ester **2** was synthesised by direct thiomethylation of dihydrolysergic acid methyl ester **1** [15] with methylsulphenyl chloride that was prepared by reaction of sulphuryl chloride with dimethyl-disulphide at low temperature. On exposure to *tert*-butylacetate/trifluoroacetic acid, **2** underwent a smooth aromatic *tert*-butylation to provide **3** in 70% yield. Subsequent removal of the thiomethyl group with Raney nickel allowed the preparation of the key intermediate **4**, depicted in figure 2. Reduction of the ester **4** to the alcohol analogue **5** and subsequent Mitsunobu reaction [16] provided the amine **7**, via the phthalimido derivative **6**, which served as intermediate for the synthesis of the amides **12–24**, **28–30**, carbamates **25**, **26**, urea derivative **27** and sulphonamide **31**.

The amides **12–24** stemmed from the reaction of **7** with either acyl halide in pyridine at low temperature or by condensation with mixed anhydride in dioxane. The 2-substituted amides **29**, **30** were prepared by reaction of **12** either with *N*-bromosuccinimide [17] or with methylsulphenyl chloride. The amide **30** was prepared by methylation of **12** with methyl iodide in dimethylsulphoxide in the presence of potassium hydroxide (see tables I and II).

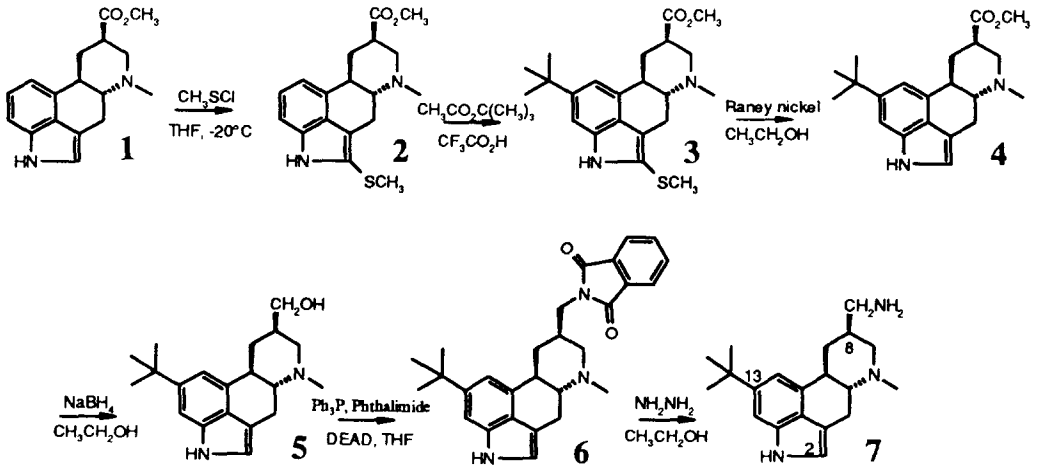
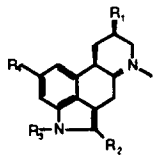
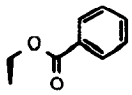
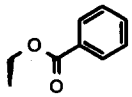
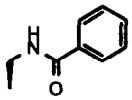
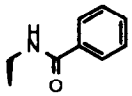
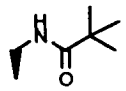
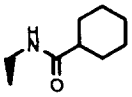
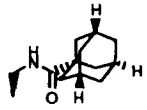
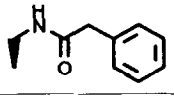


Fig 2. Synthesis of the key intermediates **5**, **7**.

Table I. Chemical data for compounds **5**, **7–18**.

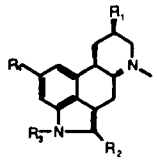


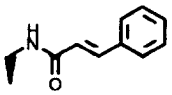
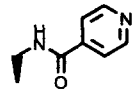
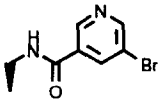
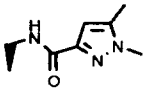
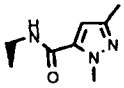
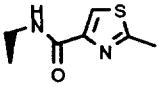
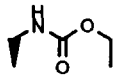
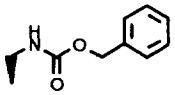
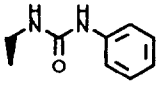
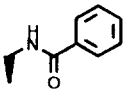
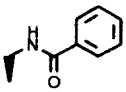
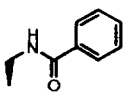
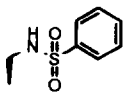
Compound	R_1	R_2	R_3	R_4	*Formula*	*Mp (°C)*
5	CH_2OH	H	H	$(CH_3)_3C$	$C_{20}H_{28}N_2O$	240–243
7	NH_2	H	H	$(CH_3)_3C$	$C_{20}H_{29}N_3$	230–232
8	CH_2OH	H	H	H	$C_{16}H_{20}N_2O$	285–288
9	NH_2	H	H	H	$C_{16}H_{21}N_3$	228–229
10		H	H	$(CH_3)_3C$	$C_{27}H_{32}N_2O_2$	238–241
11		H	H	H	$C_{23}H_{24}N_2O_2$	210–214
12		H	H	$(CH_3)_3C$	$C_{27}H_{33}N_3O$	190–193
13		H	H	H	$C_{27}H_{25}N_3O$	247–251
14		H	H	$(CH_3)_3C$	$C_{22}H_{31}N_3O$	196–198
15		H	H	$(CH_3)_3C$	$C_{25}H_{38}N_3O$	238–240
16		H	H	$(CH_3)_3C$	$C_{27}H_{40}N_3O$	151–154
17		H	H	$(CH_3)_3C$	$C_{31}H_{43}N_3O$	240–243
18		H	H	$(CH_3)_3C$	$C_{28}H_{35}N_3O$	165–167

Pharmacology

The α_1, α_2, D_1, D_2, 5-HT_{1A} and 5-HT_2 receptor binding affinities of the synthesised compounds **5**, **7–31** was determined by measurement of displacement of [^{3}H]-prazosin binding in rat frontal cortex [18], [^{3}H]-yohimbine binding in rat frontal cortex [19], [^{3}H]-SCH-23390 binding in rat striatum [20], [^{3}H]-spiroperidol binding in rat striatum [21], [^{3}H]-8-OH-DPAT binding in rat hippocampus [22] and [^{3}H]-ketanserin binding in rat pre-frontal cortex [23] respectively.

Table II. Chemical data of the ergoline derivatives **19–31**.



Compound	R_1	R_2	R_3	R_4	*Formula*	*Mp (°C)*
19		H	H	$(CH_3)_3C$	$C_{29}H_{35}N_3O$	190–192
20		H	H	$(CH_3)_3C$	$C_{26}H_{32}N_4O$	241–243
21		H	H	$(CH_3)_3C$	$C_{26}H_{31}BrN_4O$	285–287
22		H	H	$(CH_3)_3C$	$C_{26}H_{35}N_5O$	263–266
23		H	H	$(CH_3)_3C$	$C_{26}H_{35}N_5O$	206–209
24		H	H	$(CH_3)_3C$	$C_{25}H_{32}N_4OS$	265–268
25		H	H	$(CH_3)_3C$	$C_{23}H_{33}N_3O_2$	235–238
26		H	H	$(CH_3)_3C$	$C_{28}H_{35}N_3O_2$	139–142
27		H	H	$(CH_3)_3C$	$C_{27}H_{34}N_4O$	238–240
28		H	Br	$(CH_3)_3C$	$C_{27}H_{32}BrN_3O$	151–155
29		H	CH_3S	$(CH_3)_3C$	$C_{28}H_{35}N_3OS$	183–186
30		CH_3	H	$(CH_3)_3C$	$C_{28}H_{35}N_3O$	126–129
31		H	H	$(CH_3)_3C$	$C_{26}H_{33}N_3O_2S$	289–291

Results and discussion

The results of the binding assays for **5**, **7–31** are illustrated in table III. Affinity expressed as IC_{50} in μM, standard errors are ±10% of the mean reported values. Compounds **5** and **7** show a marked decrease in adrenergic, dopaminergic components compared to their unsubstituted analogues **8** and **9**, respectively. The affinity to the 5-HT_{1A} receptor sites was marginally affected. These early results seem to suggest that the 13-*tert*-butyl group hinders sterically the binding to the adrenergic and dopaminergic receptors enhancing the serotonergic selectivity, particularly for the 5-HT_{1A} site. The same tendency was observed for **10** and **12** compared to **11** and **13**, respectively. These compounds also showed a remarkable decrease in 5-HT_2 affinity. The satisfactory 5-HT_{1A} affinity and selectivity of **12** prompted the synthesis of amino derivatives **14–31**. Considering the influence of the acyl moiety in **14–19**, it is difficult to draw general conclusions from this pattern of substitution. Although the 5-HT_{1A} component appeared as somewhat enhanced, the 5-HT_{1A} versus α_2 and 5-HT_2 selectivity was reduced in comparison with **12**.

The compounds **20–24**, encompassing an heteroaryl residue, displayed a slightly but consistently greater affinity to 5-HT_{1A} receptor sites, with **24** being the most potent compound of the series. It is of interest to note the pronounced difference in the 5-HT_2 component shown by the regioisomers **22** and **23**. The carba-

Table III. Binding profile for compounds **5**, **7–31** (affinity expressed as IC_{50} in μM).

Compound	α_1	α_2	D_1	D_2	*5-HT$_{1A}$*	*5-HT$_2$*
5	> 10	0.13	> 10	4.32	0.10	0.86
7	7.73	0.79	> 10	> 10	0.125	> 10
8	4.34	0.68	5.56	0.25	0.26	1.6
9	3.45	1.23	3.68	0.72	0.48	2.68
10	4.68	5.17	> 10	7.72	0.122	1.94
11	1.56	0.17	7.85	0.13	0.15	0.34
12	6.5	> 10	3.4	5.2	0.025	6.7
13	1.32	0.48	4.15	0.075	0.014	0.43
14	> 10	0.37	> 10	> 10	0.027	0.18
15	> 10	1.39	> 10	4.43	0.018	0.97
16	> 10	0.47	> 10	1.92	0.013	0.83
17	> 10	1.95	> 10	3.57	0.061	2.48
18	6.11	0.83	> 10	2.77	0.012	1.86
19	1.48	0.87	> 10	3.07	0.055	3.64
20	4.96	0.19	> 10	3.33	0.012	0.71
21	6.68	0.67	> 10	1.13	0.011	3.27
22	4.28	0.46	> 10	2.12	0.013	3.27
23	4.16	0.74	> 10	1.32	0.005	0.21
24	3.22	0.56	> 10	1.89	0.003	1.16
25	5.9	0.19	> 10	4.98	0.012	1.17
26	7.41	2.17	> 10	1.25	0.018	0.52
27	> 10	2.62	> 10	2.86	0.097	1.92
28	0.56	0.66	> 10	1.78	0.018	1.62
29	7.98	0.82	> 10	2.36	1.15	1.28
30	2.93	0.65	> 10	1.72	0.012	0.25
31	5.8	0.066	> 10	0.64	0.02	0.15

mates **25** and **26** still maintain 5-HT_{1A} affinity, whereas a marked decrease was observed for the urea derivative **27**. Substitution at position 2 of the ergoline skeleton exerted a deleterious effect as far as 5-HT_{1A} affinity and selectivity are concerned. In fact, the introduction of a bromine as in **28** led to the reapperance of the α_1 component. The 5-HT_{1A} affinity was nonetheless maintaincd. Conversely, the introduction of a thiomethyl group as in **29** dramatically reduced receptor affinity and selectivity. A significant increase in α_2 and 5-HT_2 component was encountered in the 1-methyl derivative **30** in comparison with its unsubstituted analogue **12**. The behaviour displayed by **28–30** seems to indicate that substitution at position 1 and 2 are uncompatible with 5-HT_{1A} affinity and selectivity. The 5-HT_{1A} selectivity was lost in the sulphonamide **31** when compared to the amide **12**. In conclusion, this novel series of 13-*tert*-butyl-ergoline derivatives led to the characterization of several potent and selective 5-HT_{1A} ligands. Selectivity for 5-HT_{1A} versus α_1, α_2, D_1, D_2 and 5-HT_2 binding sites appears to be influenced by the presence of a *tert*-butyl group at position 13. Some compounds of this class, in particular **22–24**, display nM affinity for 5-HT_{1A} receptor sites accompanied by at least a hundred-fold selectivity over other receptors. The compounds of this series provide further evidence of the delicate balance between structure and biological activity for ergoline derivatives and underline the pharmacological potential of this class.

Experimental protocols

Chemistry

Analytical and spectroscopic data were consistent with the structure of the corresponding compounds. IR spectra were recorded on a Bruker IF 548 infrared spectrometer. ^{1}H-NMR spectra were recorded on a Bruker AC 200 spectrometer at 200 MHz. Chemical shifts are reported as δ values in part per million (ppm) relative to tetramethylsilane (δ 0.00) used as internal standard. Microanalyses were performed on a Carlo Erba autoanalyser and were within 0.4% of the calculated values.

2-Methylthio-6-methyl-8β-methoxycarbonyl-ergoline **2**
A solution of sulphurylchloride (28.7 g, 210 mmol) in dichloromethane (250 mL) was slowly added dropwise to a stirred solution of dimethyldisulphide (25.1 g, 270 mmol) in dichloromethane (1250 mL) at –20 °C. The yellow solution was set aside at room temperature for 1 h, and was then added dropwise to a stirred solution of 6-methyl-8β-methoxycarbonyl-ergoline **1** (75 g, 260 mmol) in dichloromethane (700 mL) at –35 °C. After being kept for 1 h at this temperature, the solution was slowly warmed to room temperature and partitioned with 0.1 M ammonium hydroxide. The organic phase was washed with brine and then dried. After removal of the solvent, the residue was crystallised from ethylacetate to give **2** (77 g, 86% yield), mp 187–191 °C. IR (KBr, cm^{-1}): 1740 (ν CO); 1440–1415 (ν CH_3S); 1320 (ν CH_3N). ^{1}H-NMR ($CDCl_3$) δ 1.5–1.7 (m, 1H, H-9ax); 2.15 (ddd, 1 H, J = 4.3, 9.2, 11.0 Hz, H-5); 2.33 (dd, 1 H, J = 11.4, 11.4, Hz, H-7ax); 2.38 (s, 3 H, CH_3S); 2.52 (s, CH_3N); 2.5–2.7 (m, 1 H, H-4ax); 2.8–3.0 (m, 3 H, H-8, H-9, H-10); 3.41 (dd, 1 H, J = 4.3, 15.0 Hz, H-4eq); 3.73 (s, 3 H, CO_2CH_3); 6.9–7.2 (m, 3 H, H-12, H-13, H-14); 7.89 (bs, 1 H, NH-1). MS *m/z* 330 (100 [M]$^{+\cdot}$); 315 (39); 299 (8); 255 (17); 213 (12); 200 (21); 167 (12); 154 (30); 127 (21); 59 (14). Anal $C_{18}H_{22}N_3O_3S$ (C, H, N).

*2-Methylthio-6-methyl-8β-methoxycarbonyl-13-*tert*-butyl-ergoline* **3**
tert-Butylacetate (24.5 mL, 235 mmol) was added dropwise to a stirred solution of **2** (23 g, 70 mmol) in trifluoroacetic acid (230 mL). After heating at 40 °C for 5 h, the solvent was removed and the resulting dark residue was taken up in ethyl acetate and partitioned with 0.1 M of ammonium hydroxide. The organic phase was washed with brine, dried and treated with charcoal. The solvent was evaporated off and the residue was dissolved in the minimum amount of boiling methanol. By cooling, 18.7 g of **3** (71% yield) were obtained, mp 259–261 °C. IR (KBr, cm^{-1}): 1740 (ν CO); 1440–1415 (ν CH_3S); 1320 (ν CH_3N); 945 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 9 H, $(CH_3)_3C$); 1.5–1.7 (m, 1 H, H-9ax); 2.16 (m, 1 H, H-5); 2.34 (s, 3 H, CH_3S); 2.34 (dd, 1 H, J = 11.3, 11.3 Hz, H-7ax); 2.51 (s, 3 H, CH_3N); 2.58 (dd, 1 H, J = 15.1, 11.1 Hz, H-4eq); 2.8–3.0 (m, 3 H, H-8, H-9eq, H-10); 3.24 (m, 1 H, H-7ax); 3.39 (dd, 1 H, J = 15.0, 4.3 Hz, H-4eq); 3.14 (s, 3 H, CO_2CH_3); 7.01 (s, 1 H, H-12), 7.13 (s, 1 H, H-12); 7.79 (bs, 1 H, NH-1). MS *m/z* 386 (100 [M]$^{+\cdot}$); 371 (24); 355 (6); 311 (6); 269 (3); 256 (6); 246 (3); 226 (5); 210 (3); 193 (6); 57 (8). Anal $C_{22}H_{30}N_2O_2S$ (C, H, N).

*6-Methyl-8β-methoxycarbonyl-13-*tert*-butyl-ergoline* **4**
Raney nickel (10 g) was added portionwise to a stirred solution of **3** (11.5 g, 30 mmol) in methanol (200 mL) under nitrogen. After refluxing for 25 min, the suspension was filtered, and the Raney nickel was thoroughly washed with methanol. The solvent was removed and the residue was crystallised from ethylacetate to give 8.9 g of **4** (88% yield), mp 175–177 °C. IR (KBr, cm^{-1}): 1735 (ν CO); 1320 (ν CH_3N); 950 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.36 (s, 9 H, $(CH_3)_3C$); 1.5–1.7 (m, 1 H, H-9ax); 2.18 (ddd, 1 H, J = 11.1, 9.2, 4.3 Hz, H-5); 2.35 (dd, 1 H, J = 11.4, 11.4 Hz, H-5); 2.48 (s, 3 H, CH_3N); 2.64 (ddd, 1 H, 14.7, 11.9, 1.7 Hz, H-4ax); 2.8–3.1 (m, 3 H, H-8, H-9eq, H-10); 3.2–3.3 (m, 1 H, H-7eq); 3.337 (dd, 1 H, J = 14.7, 4.3 Hz, H-4eq); 6.82 (dd, 1 H, J = 1.7, 1.7 Hz, H-2); 7.02 (s, 1 H, H-12); 7.20 (s, 1 H, H-14); 7.82 (bs, 1 H, NH-1). MS *m/z* 340 (100 [M]$^{+\cdot}$); 325 (8); 309 (5); 284 (6); 281 (4); 223 (8); 210 (6); 200 (8); 154 (8); 94 (5); 56 (5). Anal $C_{21}H_{28}N_2O_2$ (C, H, N).

*6-Methyl-8β-hydroxymethyl-13-*tert*-butyl-ergoline* **5**
A solution of **4** (4.5 g, 130 mmol) in methanol (25 mL) was added dropwise to a stirred solution of sodiumborohydride (4.7 g, 130 mmol) in methanol (50 mL). The resulting suspension was heated at 60 °C for 1 h, then diluted with water (200 mL). The precipitate was filtered off, washed with water and subsequently crystallised from ethanol to afford 3.5 g of **5** (85% yield). IR (KBr, cm^{-1}): 3100–300 (ν H bond); 1085–1050 (ν C–O); 1325 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$); 1.3–1.5 (m, 1 H, H-9ax); 2.07 (dd, 1 H, J = 11.2, 11.2 Hz, H-7ax); 2.2–2.3 (m, 1 H, H-9); 2.42 (s, 3 H, CH_3N); 2.3–2.5 (m, 1 H, H-8); 2.83 (ddd, 1 H, J = 14.8, 11.0, 1.7 Hz, H-4ax); 3.05 (m, 1 H, H-9eq); 3.17 (m, 1 H, H-10); 3.36 (m, 1 H, H-7eq); 3.49 (dd, 1 H, J = 14.8,

4.4 Hz, H-4eq); 3.7–3.9 (m, 2H, CH_2OH); 6.25 (bs, 1 H, OH); 7.18 (dd, 1 H, J = 1.7, 1.7 Hz, H-2), 7.28 (dd, 1 H, J = 1.3, 1.3 Hz, H-14); 7.42 (s, 1 H, H-12); 11.33 (bs, 1 H, NH-1). MS *m/z* 312 (100 $[M]^{+\cdot}$); 297 (7); 223 (6); 210 (7); 200 (11); 194 (7); 180 (6); 168 (5); 154 (6); 57 (5). Anal $C_{20}H_{28}N_2O$ (C, H, N).

*6-Methyl-8β-phtalimidomethyl-13-*tert*-butyl-ergoline* **6**
A solution of diethylazodicarboxylate (2.5 g, 14.3 mmol) in tetrahydrofuran (10 mL) was added dropwise to a stirred solution containing **5** (3 g, 9.6 mmol), triphenylphosphine (3 g, 11.5 mmol) and phtalimide (2 g, 13.6 mmol) in tetrahydrofuran (25 mL). After stirring for 2 h at room temperature, the solution was diluted with 0.1 M methanesulphonic acid (100 mL) and thoroughly extracted with ethylacetate. The aqueous phase was basified with 0.1 M ammonium hydroxide and extracted with ethylacetate, washed with brine and dried. Concentration of the solution provided 3.8 g of **6** (90% yield), mp 132–137 °C. IR (KBr, cm^{-1}): 1780 (ν CO); 1710 (ν CO); 1320 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.1–1.3 (m, 1 H, H-9ax); 1.37 (s, 9 H, $(CH_3)_3C$); 2.0–2.2 (m, 2 H, H-5, H-7ax); 2.41 (s, 3 H, CH_3N); 2.3–2.5 (m, 1 H, H-8); 2.60 (m, 1 H, H-9eq); 2.9–3.0 (m, 2 H, H-7eq, H-10); 3.35 (dd, 1 H, J = 14.8, 4.3 Hz, H-4eq); 3.6–3.8 (m, 2 H, $CH_2C_8H_4NO_2$); 6.80 (dd, 1 H, J = 1.7, 1.7 Hz, H-2); 7.0 (s, 1 H, H-14); 7.19 (s, 1 H, H-12); 7.7–7.9 (m, 4 H, (H-2, H-3, H-4, H-5)phtaloyl). MS *m/z* 441 (100 $[M]^{+\cdot}$); 293 (13); 279 (15); 223 (20); 210 (16); 200 (49); 180 (16); 154 (31); 104 (32); 94 (48); 57 (47). Anal $C_{28}H_{31}N_3O_2$ (C, H, N).

*6-Methyl-8β-aminomethyl-13-*tert*-butyl-ergoline* **7**
A solution of **6** (15 g, 340 mmol) and hydrazine hydrate (30 mL) in ethanol (300 mL) was stirred at 50 °C for 2 h. The suspension was filtered off and the solvent was removed. The residue was taken up in ethylacetate and washed with 0.1 N sodium hydroxide. The organic phase was washed with brine and dried. Concentration of the solution afforded 8.7 g of **7** (82% yield). IR (KBr, cm^{-1}): 3250–3200 (ν NH_2); 1330 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR (Py–d_5) δ 1.21 (m, 1 H, H-9ax); 1.40 (s, 9-H, $(CH_3)_3C$); 1.82 (dd, 1 H, J = 10.9, 10.9 Hz, H-7ax); 2.00 (m, 1 H, H-8); 2.16 (m, 1 H, H-5); 2.39 (s, 3 H, CH_3N); 2.69 (m, 2 H, CH_2NH_2); 2.85 (m, 1 H, H-4ax); 2.88–3.08 (m, 2 H, H-7eq, H-10); 3.48 (dd, 1 H, J = 14.6, 4.3 Hz, H-4eq); 5.00 (bm, 2 H, CH_2NH_2); 7.30 (s, 1 H, H-12); 7.42 (m, 1 H, H-14); 11.3 (bs, 1 H, NH-1). MS *m/z* 311 (100, $[M]^{+\cdot}$); 293 (31); 281 (21); 279 (18); 237 (11); 223 (31); 281 (21); 279 (18); 237 (11); 223 (53); 210 (27); 200 (42); 180 (15); 139 (31); 154 (18); 139 (31); 57 (33). Anal $C_{20}H_{29}N_3$ (C, H, N).

*6-Methyl-8β-benzoyloxymethyl-13-*tert*-butyl-ergoline* **10**
To a stirred solution of **5** (1.2 g, 4 mmol) in pyridine (30 mL) was added benzoyl chloride (0.6 g, 4.3 mmol) at room temperature. After stirring for 2 h, the solution was diluted with ethylacetate and thoroughly washed with 0.05 M sodium hydroxide, brine and dried. Removal of the solvent and crystallisation from diethylether furnished 1.2 g of **10** (73% yield). IR (KBr, cm^{-1}): 1720 (ν CO); 940 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.35 (m, 1 H, H-9ax); 1.36 (s, 9-H, $(CH_3)_3C$); 2.13 (dd, 1 H, J = 11.2, 11.2 Hz, H-7ax); 2.22 (m, 1 H, H-5); 2.48 (s, 3 H, CH_3N); 2.45 (m, 1 H, H-8); 2.59–2.81 (m, 2 H, H-4ax, H-9eq); 3.02 (m, 1 H, H-10); 3.18 (m, 1 H, H-7eq); 3.39 (dd, 1 H, J = 14.6, 4.3 Hz, H-4eq); 4.22 (dd, 1 H, J = 11.0, 7.3 Hz, C(*H*)HOH); 4.41 (dd, 1 H, J = 11.0, 4.7 Hz, C(*H*)HOH); 6.82 (t, 1 H, J = 1.74 Hz, H-14); 7.02 (s, 1 H, H-12); 7.39–7.59 (m, 3 H, (H-3, H-4, H-5)phenyl); 7.80 (bs, 1 H, NH-1); 8.05 (m, 2 H, (H-2, H-6)phenyl). MS *m/z* (100 $[M]^{+\cdot}$); 311 (4); 293 (11); 279 (11); 210 (16); 200 (21); 154 (20); 139 (51); 105 (75); 77 (63); 57 (28). Anal $C_{27}H_{32}N_2O_2$ (C, H, N).

*6-Methyl-8β-benzoylaminomethyl-13-*tert*-butyl-ergoline* **12**
Compound **12** was synthesised from compound **7** (75% yield) using benzoyl chloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1640 (ν CO); 1570–1515 (ν NH bending); 1330 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR (Py–d_5) δ 1.25 (m, 1 H, H-9ax); 1.38 (s, 9-H, $(CH_3)_3C$); 2.03 (dd, 1 H, J = 11.1, 11.1 Hz, H-7ax); 2.17–2.36 (m, 2 H, H-5, H-8); 2.50 (s, 3 H, CH_3N); 2.64–2.78 (m, 2 H, H-4ax, H-9eq); 2.92–3.22 (m, 2 H, H-7eq, H-10); 3.40 (dd, 1 H, J = 14.4, 4.2 Hz, H-4eq); 3.52 (m, 1 H, CH_2NHCO); 6.37 (m 1 H, CH_2NHCO); 6.84 (s, 1 H, H-2), 7.02 (s, 1 H, H-14); 7.22 (s, 1 H, H-12); 7.49 (m, 3 H, (H-3, H-4, H-5)phenyl); 7.85 (m, 2 H, (H-2, H-5)phenyl); 7.94 (bs, 1 H, NH-1). MS *m/z* 415 (100 $[M^{+\cdot}]$); 293 (7); 281 (11); 237 (6); 223 (9); 200 (20); 154 (9); 105 (60); 77 (48); 57 (36). Anal $C_{27}H_{33}N_3O$ (C, H, N).

*6-Methyl-8β-acetylaminomethyl-13-*tert*-butyl-ergoline* **14**
Compound **14** was synthesised from compound **7** (85% yield) using acetyl chloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1630 (ν CO); 1340 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR (Py–d_5) δ 1.28 (m, 1 H, H-9ax); 1.39 (s, 9-H, $(CH_3)_3C$); 1.94 (dd, 1 H, J = 11.2, 11.2 Hz, H-7ax); 2.10 (s, 3 H, CH_3CO); 2.35 (m, 1 H, H-5); 2.35 (s, 3 H, CH_3N); 2.40 (m, 1 H, H-8); 2.70; 3.21 (m, 4 H, H-4ax, H-7eq, H-9eq, H-10); 3.40–3.53 (m, 3 H, $CH_2NHCOCH_3$, H-4eq); 7.16 (s, 1 H, H-2); 7.41 (s, 1 H, H-14), 8.68 (m, 1 H, $CH_2NHCOCH_3$); (bs, 1 H, NH-1). MS *m/z* 353 (100 $[M^{+\cdot}]$); 293 (15); 279 (17); 237 (15); 223 (31); 210 (26); 200 (64); 154 (19); 139 (25); 57 (65); 43 (88). Anal $C_{22}H_{31}N_3O$ (C, H, N).

*6-Methyl-8β-(β-dimethylpropionyl)aminomethyl-13-*tert*-butyl-ergoline* **15**
Compound **15** was synthesised from compound **7** (70% yield) using β-dimethylpropionyl chloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1640 (ν CO); 1330 (ν CH_3N); 945 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.19 (m, 1H, H-9ax); 1.24 (s, 9 H, $(CH_3)_3CCO$); 1.34 (s, 9-H, $(CH_3)_3C$); 2.00 (dd, 1 H, J = 11.2, 11.2 Hz, H-7ax); 2.11 (m, 1 H, H-8); 2.16 (m, 1 H, H-5); 2.47 (s, 3 H, CH_3N); 2.62–2.69 (m, 2 H, H-4ax, H-9eq); 2.94–3.03 (m, 2 H, H-7eq, H-10); 3.31 (m, 2 H, CH_2NHCO); 3.40 (dd, 1 H, J = 4.3, 14.3 Hz, H-4eq), 5.74 (t, 1 H, J = 5.7 Hz, CH_2NHCO); 6.83 (t, 1 H, J = 1.7 Hz, H-2); 7.00 (s, 1 H, H-14); 7.21 (s, 1 H, H-12); 7.83 (bs, 1 H, NH-1). MS *m/z* 395 (100 $[M^{+\cdot}]$); 293 (11); 281 (12); 279 (9); 223 (13); 210 (7); 200 (15); 194 (14); 154 (11); 57 (35). Anal $C_{25}H_{37}N_3O$ (C, H, N).

*6-Methyl-8β-cyclohexylcarbonyaminomethyl-13-*tert*-butyl-ergoline* **16**
Compound **16** was synthesised from compound **7** (55% yield) using cyclohexylcarbonyl chloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1650 (ν CO); 1335 (ν CH_3N); 945 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.38 (m, 1 H, H-9ax); 1.0–2.0 (m, 12 H, H-7ax, H-9eq, 5(CH_2)cyclohex); 2.0–2.2 (m, 3 H, H-5, H-8, $CH_2NHCOCH$); 2.47 (s, 3 H, CH_3N); 2.6–2.8 (m, 2 H, H-4ax, H-9eq), 2.9–3.1 (m, 2 H, H-7eq, H-10); 3.2–3.5 (m, 3 H, H-4eq, CH_2NHCO); 5.94 (t, 1 H, J = 5.8 Hz, CH_2NHCO); 6.83 (dd, 1 H, J = 1.7, 1.7 Hz, H-2), 7.00 (dd, 1 H, J = 1.0, 1.3 Hz, H-14); 7.21 (dd, 1H, J = 1.0, 1.0 Hz, H-14); 7.83 (bs, 1H, NH-1). MS *m/z* 421 (100 $[M^{+\cdot}]$); 293 (9); 281 (12); 279 (9); 237 (12); 223 (12); 210 (8); 200 (15); 167 (8); 82 (12). Anal $C_{27}H_{39}N_3O$ (C, H, N).

6-Methyl-8β-(1-adamantyl)carbonylaminomethyl-13-tert-*butyl-ergoline* ***17***

Compound **17** was synthesised from compound **7** (65% yield) using 1-adamantylcarbonyl chloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1645 (ν CO); 1334 (ν CH_3N); 945–930 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.1–1.3 (m, 1 H, H-9ax); 1.38 (m, 1 H, H-9ax); 1.7–1.89 (m, 12 H, 6(CH_2)-adamantyl); 1.99 (dd, 1 H, *J* = 11.1, 11.1 Hz, H-7ax); 2.0–2.1 (m, 4 H, H-8, 3(CH)adamantyl); 2.12 (m, 1H, H-5); 2.48 (s, 3 H, CH_3N); 2.6–2.7 (m, 2 H, H-4ax, H-9eq); 2.9–3.1 (m, 2 H, H-7eq, H-10); 3.2–3.4 (m, 2 H, CH_2NHCO); 3.39 (dd, 1 H, *J* = 4.2, 14.4 Hz, H-4eq); 5.70, (t, 1 H, *J* = 6.0 Hz, CH_2NHCO); 6.83 (s, 1 H, H-2); 7.00 (dd, 1 H, *J* = 1.2, 1.2 Hz, H-14); 7.21 (s, 1 H, H-12); 7.83 (bs, 1 H, NH-1). MS *m/z* 473 (100 $[M]^{+\cdot}$); 293 (6); 281 (7); 279 (7); 223 (11); 210 (6); 200 (7); 180 (5); 154 (5); 135 (37). Anal $C_{31}H_{43}N_3O$ (C, H, N).

6-Methyl-8β-phenylacetylaminomethyl-13-tert-*butyl-ergoline* ***18***

Compound **18** was synthesised from compound **7** (53% yield) using phenylacetyl chloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1640 (ν CO); 1334 (ν CH_3N); 945–930 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.0–1.3 (m, 1 H, H-9ax); 1.38 (m, 9 H, $(CH_3)_3C$); 1.89 (dd, 1 H, *J* = 11.3, 11.3 Hz; H-7ax); 1.9–2.2 (m, 2 H, H-5, H-8); 2.43 (s, 3 H, CH_3N); 2.5–2.7 (m, 2 H, H-4ax, H-9eq); 2.8–3.0 (m, 2 H, H-7eq, H-10); 3.1–3.4 (m, 3 H, H-4eq, CH_2NHCO); 3.63 (s, 2 H, $C_6H_5CH_2$CO); 5.45 (m, 1 H, CH_2NHCO); 6.82 (d, 1 H, *J* = 1.3 Hz, H-2); 6.93 (dd, 1 H, *J* = 1.3, 1.3 Hz, H-14); 7.20 (s, 1 H, H-12); 7.2–7.4 (m, 5 H, $C_6H_5CH_2$); 7.80 (bs, 1 H, NH-1). MS *m/z* 429 (100 $[M^{+\cdot}]$); 293 (12); 281 (13); 279 (13); 223 (24); 210 (20); 200 (53); 194 (24), 154 (20); 139 (16); 91 (62); 57 (35). Anal $C_{28}H_{35}N_3O$ (C, H, N).

6-Methyl-8β-(3-phenyl-acriloyl)aminomethyl-13-tert-*butyl-ergoline* ***19***

Compound **19** was synthesised from compound **7** (77% yield) using 3-phenylacriloyl chloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1650–1635 (ν CO); 1345 (ν CH_3N); 945–930 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.23 (m, 1 H, H-9ax); 1.39 (m, 9 H, $(CH_3)_3C$); 2.03 (dd, 1 H, *J* = 11.1, 11.1 Hz; H-7ax); 2.03 (m, 2 H, H-5, H-8); 2.10–2.25 (m, 2 H, H-5, H-8); 2.48 (s, 3 H, CH_3N); 2.60–2.77 (m, 2 H, H-4ax, H-9eq); 3.13 (m, 2 H, H-7eq, H-10); 3.35–3.50 (m, 2 H, H-4eq, CH_2NHCO); 5.73 (t, 1 H, *J* = 5.5 Hz, CH_2NHCO); 6.45 (d, 1 H, *J* = 15.5 Hz, C_6H_5CH=*CH*CO); 6.83 (s, 1 H, H-2); 7.02 (s, 1 H, H-14); 7.21 (s, 1 H, H-12); 7.39–7.51 (m, 5 H, C_6H_5CH=CHCO); 7.67 (d, 1 H, *J* = 15, 5 Hz, C_6H_5CH=CHCO); 7.86 (bs, 1 H, NH-1). MS *m/z* 441 (100 $[M^{+\cdot}]$); 293 (25); 281 (38); 279 (26); 237 (16); 223 (29); 200 (38); 147 (52); 131 (36); 103 (34); 77 (25). Anal $C_{29}H_{35}N_3O$ (C, H, N).

6-Methyl-8β-isonicotinoylaminomethyl-13-tert-*butyl-ergoline* ***20***

Compound **20** was synthesised from compound **7** (45% yield) using isonicotinoyl chloride hydrochloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1685 (ν CO); 1330 (ν CH_3N); 945 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.26 (m, 1 H, H-9ax); 1.41 (m, 9 H, $(CH_3)_3C$); 2.03 (dd, 1 H, *J* = 11.1, 11.1 Hz; H-7ax); 2.17 (m, 1 H, H-5); 2.28 (m, 1 H, H-8); 2.46 (s, 3 H, CH_3N); 2.61 (dd, 1 H, *J* = 1.6, 14.6 Hz, H-4ax); 2.70 (m, 1 H, H-9eq); 2.96 (m, 1 H, H-10); 3.08 (m, 1 H, H-7eq); 3.38 (dd, 1 H, *J* = 4.4, 14.6 Hz, H-4eq), 3.51 (m, 2 H, CH_2NHCO); 6.36 (t, 1 H, *J* = 5.9 Hz, CH_2NHCO); 6.82 (m, 1 H, H-2); 7.19 (s, 1 H, H-14); 7.19 (s, 1 H, H-12); 7.60 (d, 2 H, *J* = 6.0, (H-2, H-6)pyridine); 7.86 (bs, 1 H, NH-1); 8.74 (d, 2 H, *J* = 6.0, (H-3, H-5)pyridine). MS *m/z* 416 (100 $[M^{+\cdot}]$); 312 (47); 281 (14); 279 (16); 237 (12); 223 (20); 210 (14); 200 (35); 154 (15); 72 (59). Anal $C_{26}H_{32}N_4O$ (C, H, N).

6-Methyl-8β-(5-bromo-nicotinoyl)aminomethyl-13-tert-*butyl-ergoline* ***21***

Compound **21** was synthesised from compound **7** (68% yield) using 5-bromonicotinoyl chloride hydrochloride following the procedure reported for **10**. IR (KBr, cm^{-1}): 1680 (ν CO); 1335 (ν CH_3N); 940 (ν $(CH_3)_3C$), 750 (ν ar meta sust). ^{1}H-NMR (DMSO-d_6) δ 1.0–1.2 (m, 1 H, H-9ax); 1.41 (m, 9 H, $(CH_3)_3C$); 1.8–2.0 (m, 2 H, H-5, H-7ax), 2.21 (m, 1 H, H-8); 2.33 (s, 3 H, CH_3N); 2.4–2.5 (m, 1 H, H-4ax); 2.6–2.8 (m, 2 H, H-9eq, H-10); 2.98 (m, 1 H, H-7eq); 3.2–3.4 (m, 3 H, H-4eq, CH_2NHCO); 6.89 (s, 2 H, H-2, H-14); 7.07 (s, 1 H, H-12); 8.46 (dd, 1 H, *J* = 2.0, 2.2 Hz, (H-4)pyridine); 8.86 (d, 1 H, *J* = 2.2 Hz, (H-6)pyridine); 9.00 (d, 1 H, *J* = 2.0 Hz, (H-2)pyridine); 10.43 (d, 1 H, *J* = 1.3 Hz, NH-1). MS *m/z* 494 (100 $[M^{+\cdot}]$); 293 (19); 281 (20); 279 (27); 237 (19); 223 (31); 210 (22); 200 (36); 184 (16); 154 (17); 57 (19). Anal $C_{26}H_{31}BrN_4O$ (C, H, N).

6-Methyl-8β-(1,5-dimethyl-1-H-3-pyrazoyl)aminomethyl-13-tert-*butyl-ergoline* ***22***

A solution of ethylchlorocarbonate (2.43 g, 25 mmol) in tetrahydrofuran (15 mL) was added dropwise to a stirred solution of 1,5-dimethyl-1-*H*-pyrazol-3-carboxylic acid (4.4 g, 31 mmol) and triethylamine (4.69 g, 46.5 mmol) in dimethylformamide (10 mL) at −5 °C. After stirring for 10 min, a solution of **7** (7.7 g, 25 mmol) in dioxane (50 mL) was slowly added and the stirring was continued for 1 h at 0 °C, then overnight at room temperature. After removal of the solvent, the residue was taken up in chloroform and washed with 0.05 M sodium hydroxide, then with brine and dried. The solvent was evaporated off and the residue was filtered on a small pad of silica gel eluting with ethylacetate to afford after crystallisation from acetone, 8.9 g of **22** (82% yield). IR (KBr, cm^{-1}): 1675 (ν CO); 1335 (ν CH_3N); 925 (ν $(CH_3)_3C$). ^{1}H-NMR (DMSO-d_6) δ 1.0 (m, 1 H, H-9ax); 1.41 (m, 9 H, $(CH_3)_3C$); 1.8–2.0 (m, 2 H, H-5, H-7ax); 2.15 (s, 3 H, (CH_3-5)pyrazole); 2.21 (m, 1 H, H-8); 2.43 (s, 3 H, CH_3N); 2.5 (m, 1 H, H-4ax); 2.6–2.75 (m, 2 H, H-9eq, H-10); 3.05 (m, 1 H, H-7eq); 3.3–3.5 (m, 3 H, H-4eq, CH_2NHCO); 3.85 (s, 3 H, (CH_3-1)pyrazole); 6.5 (s, 1 H, (H-4)pyrazole); 6.95 (s, 2 H, H-2, H-14); 7.09 (s, 1 H, H-12); 9.85 (bs, 1 H, NH-1). MS *m/z* 433 (100 $[M]^{+\cdot}$); 293 (20); 281 (17); 279 (13); 237 (87); 223 (13); 200 (22); 180 (15); 123 (38); 94 (14); 57 (10). Anal $C_{26}H_{35}N_5O$ (C, H, N).

6-Methyl-8β-(1,3-dimethyl-1-H-5-pyrazoyl)aminomethyl-13-tert-*butyl-ergoline* ***23***

Compound **23** was synthesised from compound **7** (70% yield) using 1,3-dimethyl-1-*H*-pyrazole-5-carboxylic acid following the procedure reported for **22**. IR (KBr, cm^{-1}): 1685 (ν CO); 1335 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR (Py-d_5) δ 0.85 (m, 1 H, H-9ax); 1.51 (m, 9 H, $(CH_3)_3C$); 2.0–2.2 (m, 2 H, H-5, H-7ax); 2.35 (m, 1 H, H-8); 2.43 (s, 3 H, CH_3N); 2.5 (m, 1 H, H-4ax); 2.6–2.75 (m, 2 H, H-9eq, H-10); 2.05 (s, 3 H, (CH_3-3)pyrazole); 3.05 (m, 1 H, H-7eq); 3.3–3.5 (m, 3 H, H-4eq, CH_2NHCO); 3.9 (s, 3 H, (CH_3-1)pyrazole); 6.7 (s, 1 H, (H-4)pyrazole); 6.9 (s, 2 H, H-2, H-14); 7.1 (s, 1 H, H-12); 10.2 (bs, 1 H, NH-1). MS *m/z* 433 (100 $[M]^{+\cdot}$); 293 (8); 281 (11); 279 (10); 223 (14); 210 (8); 200 (23); 180 (7); 123 (18); 94 (9); 57 (15). Anal $C_{26}H_{35}N_5O$ (C, H, N).

6-Methyl-8β-(2-methyl-3-thiazoyl)aminomethyl-13-tert-*butyl-ergoline* ***24***

Compound **24** was synthesised from compound **7** (85% yield) using 2-methyl-thiazole-3-carboxylic acid following the proce-

dure reported for **22**. IR (KBr, cm^{-1}): 1670 (ν CO); 1330 (ν CH_3N); 935 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.2–1.4 (m, 1 H, H-9ax); 1.40 (m, 9 H, $(CH_3)_3C$); 2.04 (dd, 1 H, H-7ax); 2.1–2.4 (m, 2 H, H-5, H-8); 2.48 (s, 3 H, CH_3N); 2.73 (s, 3 H, $(CH_3$-2)thiazole); 2.6–2.9 (m, 2 H, H-4ax, H-9eq); 3.01 (m, 1 H, H-10); 3.12 (m, 1 H, H-eq); 3.40 (dd, 1 H, J = 4.2, 14.6 Hz, H-4eq); 3.50 (dd, 2 H, J = 6.6, 6.2 Hz, CH_2NHCO); 6.84 (s, 1 H, H-2); 7.04 (s, 1 H, H-14); 7.22 (s, 1 H, H-12); 7.48 (t, 1 H, J = 6.2 Hz, CH_2NHCO); 7.93 (bs, 1 H, NH-1); 7.97 (s, 1 H, (H-5)thiazole). MS *m/z* 436 (100 $[M]^{+\cdot}$); 293 (10); 281 (15); 279 (12); 223 (15); 200 (21); 154 (10); 126 (55); 98 (19); 94 (28); 57 (93). Anal $C_{25}H_{32}N_4OS$ (C, H, N).

6-Methyl-8β-ethyloxycarbonylaminomethyl-13-tert-*butyl-ergoline* ***25***

Compound **25** was synthesised from compound **7** (60% yield) using ethyl chloroformate following the procedure reported for **10**. IR (KBr, cm^{-1}): 1710 (ν CO); 1335 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.16 (m, 1 H, H-9ax); 1.27 (t, 3 H, J = 7.1 Hz, CH_3CH_2OCO); 1.38 (m, 9 H, $(CH_3)_3C$); 1.91–2.22 (m, 3 H, H-5, H-7ax, H-8); 2.47 (s, 3 H, CH_3N); 2.59–2.74 (m, 2 H, H-4ax, H-9eq); 3.20 (m, 2 H, CH_2NHCO); 3.39 (dd, 1 H, J = 4.2 Hz, H-4eq); 4.15 (q, 2 H, J = 7.1 Hz, CH_3CH_2OCO); 7.01 (m, 1 H, H-14); 7.21 (s, 1 H, H-12); 7.83 (bs, 1 H, NH-1). MS *m/z* 383 (100 $[M^{+\cdot}]$); 337 (20); 293 (11); 281 (13); 279 (12); 223 (14); 210 (13); 200 (26); 154 (10); 57 (13). Anal $C_{23}H_{33}N_3O_2$ (C, H, N).

6-Methyl-8β-benzyloxycarbonylaminomethyl-13-tert-*butyl-ergoline* ***26***

Compound **26** was synthesised from compound **7** (80% yield) using benzyl chloroformate following the procedure reported for **10**. IR (KBr, cm^{-1}): 1715 (ν CO); 1330 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR (Py–d_5) δ 1.30 (m, 1 H, H-9ax); 1.40 (s, 9 H, $(CH_3)_3C$); 1.96 (m, 1 H, H-7ax); 2.16 (m, 1 H, H-5ax); 2.35 (s, 3 H, CH_3N); 2.40 (m, 1 H, H-8); 2.71–3.23 (m, 4 H, H-4ax, H-7eq, H-9eq, H-10); 3.39–3.50 (m, 3 H, H-4eq, CH_2NHCO); 5.38 (s, 2 H, $C_6H_5CH_2OCO$); 7.17 (s, 1 H, H-2); 7.22 (s, 1 H, H-12); 7.42 (s, 1 H, H-14); 7.22–7.57 (m, 5 H, $C_6H_5CH_2OCO$); 8.38 (t, 1 H, J = 5.8 Hz, CH_2NHCOO); 11.31 (bs, 1 H, NH-1). MS *m/z* 445 (87 $[M^{+\cdot}]$); 354 (3); 337 (18); 293 (17); 279 (20); 223 (13); 210 (9); 200 (20); 154 (12); 139 (7); 91 (100); 57 (9). Anal $C_{28}H_{35}N_3O_2$ (C, H, N).

6-Methyl-8β-phenylaminocarbonylaminomethyl-13-tert-*butyl-ergoline* ***27***

A solution of **7** (2.33 g, 75 mmol) and phenylisocyanate (0.83 g, 82 mmol) in dioxane (35 mL) was refluxed for 3 h. After charcoalisation, the solvent was removed and the residue was twice crystallised from isopropanol to provide 2.75 g of **27** (85% yield). IR (KBr, cm^{-1}): 1630 (ν CO); 1320 (ν CH_3N); 930 (ν $(CH_3)_3C$. ^{1}H-NMR (Py–d_5) δ 1.00 (m, 1 H, H-9ax); 1.31 (s, 9 H, $(CH_3)_3C$); 1.76–2.02 (m, 3 H, H-5, H-7ax, H-8); 2.33 (s, 3 H, CH_3N); 2.38–2.54 (m 1 H, H-4ax); 2.56–2.80 (m, 2 H, H-9eq, H-10); 2.94 (m, 1 H, H-7eq); 3.08 (m, 2 H, CH_2NHCO); 3.31 (m, 1 H, H-4eq); 6.30 (t, 1 H, CH_2NHCO); 6.89 (m, 2 H, H-2, H-14); 7.22–7.40 (m, 5 H, C_6H_5NH); 8.40 (s, 1 H, C_6H_5NHCO); 10.44 (d, 1 H, J = 1.7 Hz, NH-1). MS *m/z* 430 (19 $[M^{+\cdot}]$); 337 (8); 311 (100); 293 (17); 281 (12); 279 (8); 223 (16); 210 (9); 200 (13); 154 (7); 119 (51); 93 (14); 57 (9). Anal $C_{27}H_{34}N_4O$ (C, H, N).

2-Bromo-6-methyl-8β-benzoylaminomethyl-13-tert-*butyl-ergoline* ***28***

N-bromosuccinimide (1.15 g, 6.75 mmol) was added portionwise to a stirred solution of **10** (2.5 g, 6.5 mmol) in dioxane (50 mL) at 40 °C. After stirring for 2 h, the solution was diluted with ethylacetate and washed with 0.05 M $NaHSO_3$, then with brine and dried. The solvent was removed and the residue was columned over silica gel eluting with ethylacetate/cyclohexane, 1:3, to give after crystallisation from acetone 1.7 g of **28** (53% yield). IR (KBr, cm^{-1}): 1635 (ν CO); 1560–1525 (ν NH bending); 1330 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR (Py–d_5) δ 1.38 (s, 9 H, $(CH_3)_3C$); 1.3–1.5 (m, 1 H, H-9ax); 2.59 (s, 3 H, CH_3N); 2.3–2.7 (m, 2 H, H-5, H-7ax); 2.7–3.0 (m, 2 H, H-8, H-9eq); 3.08 (m, 1 H, H-4ax); 3.3–3.6 (m, 3 H, H-4eq, H-7eq, H-10); 3.6–3.8 (m, 2 H, CH_2NHCO); 7.17 (s, 1 H, H-12); 7.3–7.9 (m, 4 H, H-14, (H-3, H-4, H-5)phenyl); 8.2–8.3 (m, 2 H, (H-2, H-6)phenyl); 9.39 (t, 1 H, J = 5.8 Hz, CH_2NHCO); 12.59 (bs, 1 H, NH-1). MS *m/z* 493 (62 $[M]^{+\cdot}$); 415 (20); 371 (7); 359 (18); 293 (11); 278 (15); 134 (16); 105 (100); 77 (70); 57(39). Anal $C_{27}H_{32}BrN_3O$ (C, H, N).

2-Methylthio-6-methyl-8β-benzoylaminomethyl-13-tert-*butyl-ergoline* ***29***

Compound **29** was synthesised from compound **10** (45% yield) following the procedure reported for **2**. IR (KBr, cm^{-1}): 1640 (ν CO); 1560 (ν NH bending); 1450 (ν CH_3S); 1330 (ν CH_3N); 940 (ν $(CH_3)_3C$). ^{1}H-NMR (Py–d_5) δ 1.48 (s, 9 H, $(CH_3)_3C$); 1.3–1.5 (m, 1 H, H-9ax); 2.6 (s, 3 H, CH_3N); 2.3–2.7 (m, 2 H, H-5, H-7ax); 2.50 (s, 3 H, CH_3S); 2.8–3.1 (m, 2 H, H-8, H-9eq); 3.1 (m, 1 H, H-4ax); 3.2–3.56 (m, 3 H, H-4eq, H-7eq, H-10); 3.6–3.8 (m, 2 H, CH_2NHCO); 7.17 (s, 1 H, H-12); 7.3–7.9 (m, 4 H, H-14, (H-3, H-4, H-5)phenyl); 8.25–8.35 (m, 2 H, (H-2, H-6)phenyl); 9.4 (t, 1 H, J = 5.8 Hz, CH_2NHCO); 12.7 (bs, 1 H, NH-1). MS *m/z* 461 (74 $[M]^{+\cdot}$); 414 (21); 363 (34); 327 (9); 293 (11); 278 (7); 223 (31); 210 (5); 77 (42); 57 (43). Anal $C_{28}H_{35}N_3Os$ (C, H, N).

1,6-Dimethyl-8β-benzoylaminomethyl-13-tert-*butyl-ergoline* ***30***

Methyl iodide (1.25 g, 8.5 mmol) was added at room temperature to a stirred solution of **10** (3.5 g, 7.5 mmol) and potassium hydroxide (0.85 g, 15 mmol) in dimethylsulphoxide (35 mL). After stirring for 30 min, the solution was diluted with brine and partitioned with ethylacetate, then the extract was washed with brine and dried. The solvent was evaporated off and the residue was chromatographed on silica gel eluting with ethylacetate/cyclohexane, 1:4, to afford after crystallisation from isopropanol 1.3 g of **30** (32% yield). IR (KBr, cm^{-1}): 1635 (ν CO); 1580 (ν NH bending); 1330 (ν CH_3N); 945 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.27 (m, 1 H, H-9ax); 1.42 (s, 9 H, $(CH_3)_3C$); 2.08 (dd, 1 H, J = 11.1, 11.1 Hz, H-7ax); 2.1–2.4 (m, 2 H, H-5, H-8); 2.48 (s, 3 H, CH_3N); 2.6–2.8 (m, 2 H, H-4ax, H-9eq); 3.00 (m, 1 H, H-10); 3.13 (m, 1 H, H-7eq), 3.38 (dd, 1 H, J = 4.2, 14.9 Hz, H-4eq); 3.5–3.6 (m, 2 H, CH_2NHCO); 3.76 (s, 3 H, CH_3N-1); 6.29 (t, 1 H, J = 5.9 Hz, CH_2NHCO); 6.69 (d, 1 H, J = 1.4 Hz, H-2); 7.01 (s, 1 H, H-12); 7.12 (s, 1 H, H-14); 7.4–7.6 (m, 3 H, (H-3, H-4, H-5)phenyl); 7.81 (m, 2 H, (H-2, H-6)phenyl). MS *m/z* 429 (100 $[M]^{+\cdot}$); 307 (7); 295 (8); 293 (8); 237 (15); 224 (10); 214 (15); 134 (5); 105 (45); 77 (28); 57 (15). Anal $C_{28}H_{35}N_3O$ (C, H, N).

6-Methyl-8β-phenylsulphonylaminomethyl-13-tert-*butyl-ergoline* ***31***

Compound **31** was synthesised from compound **7** (75% yield) using phenylsulphonyl chloride following the procedure reported for **2**. IR (KBr, cm^{-1}): 3260–3270 (ν NH); 1130–1120 (ν SO_2N); 1320 (ν CH_3N); 930 (ν $(CH_3)_3C$). ^{1}H-NMR ($CDCl_3$) δ 1.05 (m, 1 H, H-9ax); 1.35 (s, 9 H, $(CH_3)_3C$); 1.87 (dd, 1 H, J = 11.1, 11.1 Hz, H-7ax); 1.9–2.2 (m, 2 H, H-5, H-8); 2.41 (s, 3 H, CH_3N); 2.5–2.7 (m, 2 H, H-4ax, H-9eq); 2.8–3.1 (m, 4 H,

H-7eq, H-10, CH_2NHSO_2); 3.34 (dd, 1 H, J = 4.3, 14.8 Hz, H-4eq); 4.47 (t, 1 H, J = 6.3, CH_2NHSO_2); 6.80 (s, 1 H, H-2); 6.92 (s, 1 H, H-14); 7.18 (s, 1 H, H-12); 7.78 (s, 1 H, NH-1); 7.5–7.9 (m, 5 H, (H-2, H-3, H-4, H-5, H-6)phenyl). MS *m/z* 451 (80 $[M]^{+\cdot}$); 310 (5); 281 (32); 279 (13); 223 (15); 210 (12); 200 (23); 180 (11); 154 (19); 141 (14); 94 (23); 77 (100); 57 (36). Anal $C_{26}H_{33}N_3O_2S$ (C, H, N).

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