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Synthesis and antihypertensive activity of 2,4-dioxoimidazolidin-1-yl and perhydro-2,4-dioxopyrimidin-1-yl ergoline derivatives

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Abstract

The synthesis and antihypertensive activity of a series of 2,4-dioxoimidazolidin-1-yl and perhydro-2,4-dioxopyrimidin-1-yl ergoline derivatives are reported. The oral antihypertensive activity was studied in spontaneously hypertensive rats (SHRs) by measuring systolic blood pressure by an indirect tail-cuff method at different times after treatment. The prolactin lowering activity (indirectly measured by the nidation test) in rats and the oral acute toxicity in mice were also studied. The results of this study revealed potent antihypertensive ergoline derivatives devoid of side-effects related to the dopaminergic stimulation and the importance of the $\Delta^{9,10}$ double bond for conferring high potency within these compounds.

Keywords: Ergolines; Antihypertensive activity; Nidation inhibitory activity

1. Introduction

Ergot alkaloids and their derivatives have long been recognized for their potent pharmacological activities of which the effects upon the endocrine and the central nervous system (CNS) have been the most extensively studied [1]. A number of ergot derivatives are currently in clinical use for the treatment of CNS and endocrine disorders, such as nicergoline [2], used in the treatment of senile mental impairment, and the dopamine agonists pergolide [3] and cabergoline [4], developed as effective agents in the management of hyperprolactinemic states and Parkinson's disease (Fig. 1).

An increasing body of experimental data supports the concept that dopamine plays an important role in the control of blood pressure [5]. Dopaminergic ergoline derivatives such as bromocriptine [6], lergotrile [7] and pergolide [8] have been shown to lower blood pressure when administered to experimental animals or humans. It has therefore been suggested that they exert their hypotensive effect by stimulating dopamine receptors. However, while dopamine agonists proved to be antihypertensive agents, their effects upon prolactin secretion and nausea are serious side-effects, which limit their use for an antihypertensive indication. It is well known that ergoline derivatives, besides stimulating DA receptor sites, can exert complex pharmacological effects involving simultaneous interaction with the different monoaminergic (adrenergic α_1 and α_2, and serotonergic 5-HT_1 and 5-HT_2) recognition sites [9]. A useful approach in developing antihypertensive agents from this chemical class has been suggested which takes advantage of ergoline's multitarget activity such as a combination of the inhibition of sympathetic tone via α_1 adrenoceptor blockade and antagonism of 5-HT_2 receptors that moreover facilitate the action of the α_1 adrenoceptor antagonist [10]. In addition, the potential antihypertensive activity related to the agonistic 5-HT_1 component, commonly present in this class of compounds in different amounts, might contribute to the antihypertensive effect [11]. On the other hand, the antihypertensive activity of the various classes of ergoline derivatives has received no systematic attention and very little is known about the structural requirements of the molecule to be selectively endowed with this activity. In the identification of antihypertensive ergolines, we have observed compounds **1** (FCE 22716) and **13** (FCE 22715) to be promising antihypertensive agents [12]. These compounds have notable antihypertensive activity, the former being more potent than the latter, and are almost devoid of unwanted side-effects such as depression of the central nervous system, present in a high number of anti-

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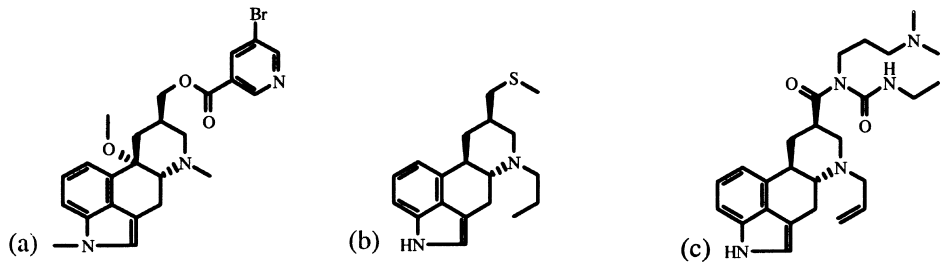


Fig. 1. (a) Nicergoline; (b) pergolide; (c) cabergoline.

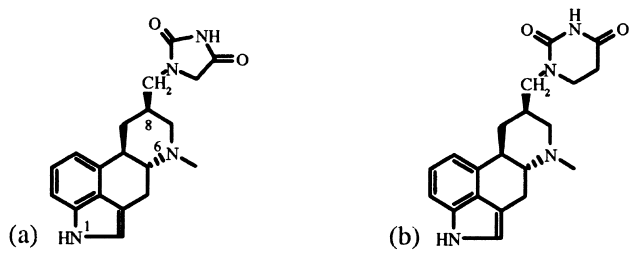


Fig. 2. (a) Compound **1** (FCE 22716); (b) **13** (FCE 22715).

hypertensive compounds, as well as decreasing prolactin secretion and nausea mainly connected to central DA stimulation (Fig. 2).

As far as the mechanism of action is concerned, preliminary findings indicated that **1** induced α_1 adrenoceptor and serotonin 5-HT_2 blockade (a potent antagonistic activity against 5-HT_2 receptors in rabbit aorta was observed), accompanied by weak stimulation of dopamine receptors [13]. The identification of these antihypertensive ergoline derivatives with minimal side-effects which we wished to avoid, prompted the synthesis of analogues of **1** and **13** in the search for more potent compounds with potential for human hypertension therapy to enable us to gain more insight on the structure–activity relationship within this series. The most significant structural modifications carried out on **1** and **13** can be summarized as follows:

(a) replacement of a carbonyl either by a thiocarbonyl or a sulfonyl group in the 2,4-dioxoimidazolidin-1-yl or in the perhydro-2,4-dioxopyrimidin-1-yl ring system;

(b) investigation of the role of the imidic proton by substitution with a linear or branched alkyl group;

(c) investigation of the role of the distance of the heterocyclic ring from the ergoline nucleus either by shortening or lengthening the chain in position 8;

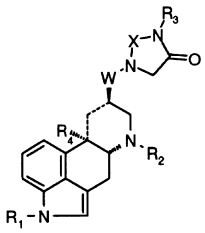
(d) modifications in positions 1, 6, 8, 9, 10 of the ergoline skeleton.

The compounds synthesized were evaluated by screening the arterial blood pressure in spontaneously hypertensive rats (SHRs). Compounds showing interesting activities were also tested for effects upon prolactin secretion. As a measure of lethality, the dose which produced death in 50% of mice treated (LD_{50}) was also determined for the selected compounds. Some of these compounds markedly reduced blood pressure in SHRs and are endowed with modest antiprolactin activity and toxicity. The affinities towards the α_1, α_2, D_1, D_2, 5-HT_1 and 5-HT_2 receptor sites were evaluated for the most interesting compounds **1**, **10**, **13** and **21**, as an indication of the mechanism of action. Among them, the $\Delta^{9,10}$-unsaturated compounds **10** and **21** emerged as very potent antihypertensive agents with a highly favourable selectivity ratio when the blood pressure lowering potency, measured as ED_{25} (dose lowering mean blood pressure (MPB) by 25 mmHg), was compared with the prolactin inhibitory effect and toxicity. Structure–activity relationships within the new classes of compounds are discussed.

2. Chemistry

The most widely used method for preparing the compounds described in this paper (see Tables 1 and 2) was based on the nucleophilic reaction of the corresponding ergolinyl or ergolenylamine with methyl acrylate or ethyl bromoacetate. The alkylation of the amines with ethyl bromoacetate in dimethylformamide in the presence of an acid scavenger such as potassium carbonate or triethylamine at room temperature afforded the corresponding glycine ethyl ester derivatives in good yields [14]. These intermediates were subsequently converted into the 2,4-dioxoimidazolidin-1-yl derivatives **1**–**12** by treatment with cyanic or thiocyanic acid, generated by the action of hydrochloric acid on potassium cyanate or potassium thiocyanate, or by reaction with the appropriate alkyl isocyanate [15]. When the ring closure of the α-ureido- or thioureidoethyl acetate derivative did not spontaneously occur, the intermediates were heated in vacuo for some minutes. Condensation of the amines with methyl acrylate in refluxing 1,4-dioxane afforded, through a Michael 1,4-addition, the β-alanine methyl ester derivatives [16]. These, in turn, were converted into the perhydro-2,4-dioxopyrimidin-1-yl derivatives **13**–**23** by means of the same treatment mentioned above [17]. In the case of the sulfonyl analogues **6**, **18**, the *N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester and the *N*-[(6-methylergolin-8β-yl)methyl]-β-alanine methyl ester were melted with neat sulfonamide. The 6-nor derivative **2** was obtained by action of the 2,2,2-trichloroethyl chloroformate on **1** to give the *N*-[(6-trichloroethyloxycarbonylergolin-8β-yl)methyl]glycine ethyl ester, which was subsequently reduced to the 6-nor derivative by reaction with Zn dust in acetic acid [18]. The 2,3-dihydro derivative **3** was obtained in an acceptable yield by reduction of **1** using

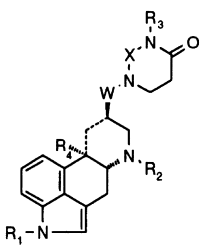
Table 1
2,4-Dioxoimidazolidin-1-yl ergolines **1**–**12**



Comp.	W	X	R_1	R_2	R_3	R_4	$\Delta^{8,9}$, $\Delta^{9,10}$	Formula	M.p. (°C)
1	CH_2	CO	H	CH_3	H	H		$C_{19}H_{22}N_4O_2$	>300
2	CH_2	CO	H	H	H	H		$C_{18}H_{20}N_4O_2$	240–242
3	CH_2	CO	H	CH_3	HH	H		$C_{19}H_{24}N_4O_2$	160–165
4	CH_2	CO	H	CH_3	n-C_3H_7	H		$C_{22}H_{28}N_4O_2$	188–189
5	CH_2	CO	H	CH_3	i-C_3H_7	H		$C_{22}H_{28}N_4O_2$	210–212
6	CH_2	SO_2	H	CH_3	H	H		$C_{18}H_{22}N_4O_3$	>300
7		CO	H	CH_3	H	H		$C_{18}H_{20}N_4O_2$	295–297
8	C_2H_4	CO	H	CH_3	H	H		$C_{20}H_{24}N_4O_2$	242–244
9	CH_2	CO	CH_3	CH_3	H	H		$C_{20}H_{24}N_4O_2$	292–294
10	CH_2	CO	H	CH_3	H		9,10	$C_{19}H_{20}N_4O_2$	282–284
11	CH_2	CO	H	CH_3	NH_2	H		$C_{19}H_{23}N_5O_2$	191–193
12	CH_2	CO	H	CH_3	H	OCH_3		$C_{20}H_{24}N_4O_3$	234–236

Compound **3** (2,3-dihydro derivative).

Table 2
Perhydro-2,4-dioxopyrimidin-1-yl ergolines **13**–**23**



Comp.	W	X	R_1	R_2	R_3	R_4	$\Delta^{8,9}$, $\Delta^{9,10}$	Formula	M.p. (°C)
13	CH_2	CO	H	CH_3	H	H		$C_{20}H_{24}N_4O_2$	>300
14	CH_2	CO	H	CH_3	CH_3	H		$C_{21}H_{26}N_4O_2$	117–119
15	CH_2	CO	H	CH_3	n-C_3H_7	H		$C_{23}H_{30}N_4O_2$	201–203
16	CH_2	CO	H	CH_3	i-C_3H_7	H		$C_{23}H_{30}N_4O_2$	175–177
17	CH_2	CS	H	CH_3	H	H		$C_{20}H_{24}N_4OS$	>300
18	CH_2	SO_2	H	CH_3	H	H		$C_{19}H_{24}N_4O_3S$	>300
19		CO	H	CH_3	H	H		$C_{18}H_{22}N_4O_2$	>300
20	C_2H_4	CO	H	CH_3	H	H		$C_{21}H_{26}N_4O_2$	140–142
21	CH_2	CO	H	CH_3	H		9,10	$C_{20}H_{22}N_4O_2$	290–292
22	CH_2	CO	H	CH_3	H	H	8,9	$C_{20}H_{22}N_4O_2$	190–193
23	CH_2	CO	CH_3	CH_3	H	H		$C_{21}H_{26}N_4O_2$	>300

$NaCNBH_3$ in acetic acid [19]. Reaction of *N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester with *p*-nitrophenyl chloroformate in pyridine afforded in almost quantitative yield the *N*-(*p*-nitrophenyloxycarbonyl)-*N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester, which was converted into **11** in reasonable yield by the action of hydrazine (Fig. 3).

The amines required for preparing the compounds listed in Tables 1 and 2 were prepared as follows: 6-methylergoline-8β-methanamine **24**, 6-methylergoline-8β-methanamine-10α-methoxy **25** and 1,6-dimethylergoline-8β-methanamine **26** were obtained by reduction of the corresponding primary carboxamide by lithium aluminium hydride. 1,6-Dimethylergoline-8β-carboxamide, necessary for the preparation of the

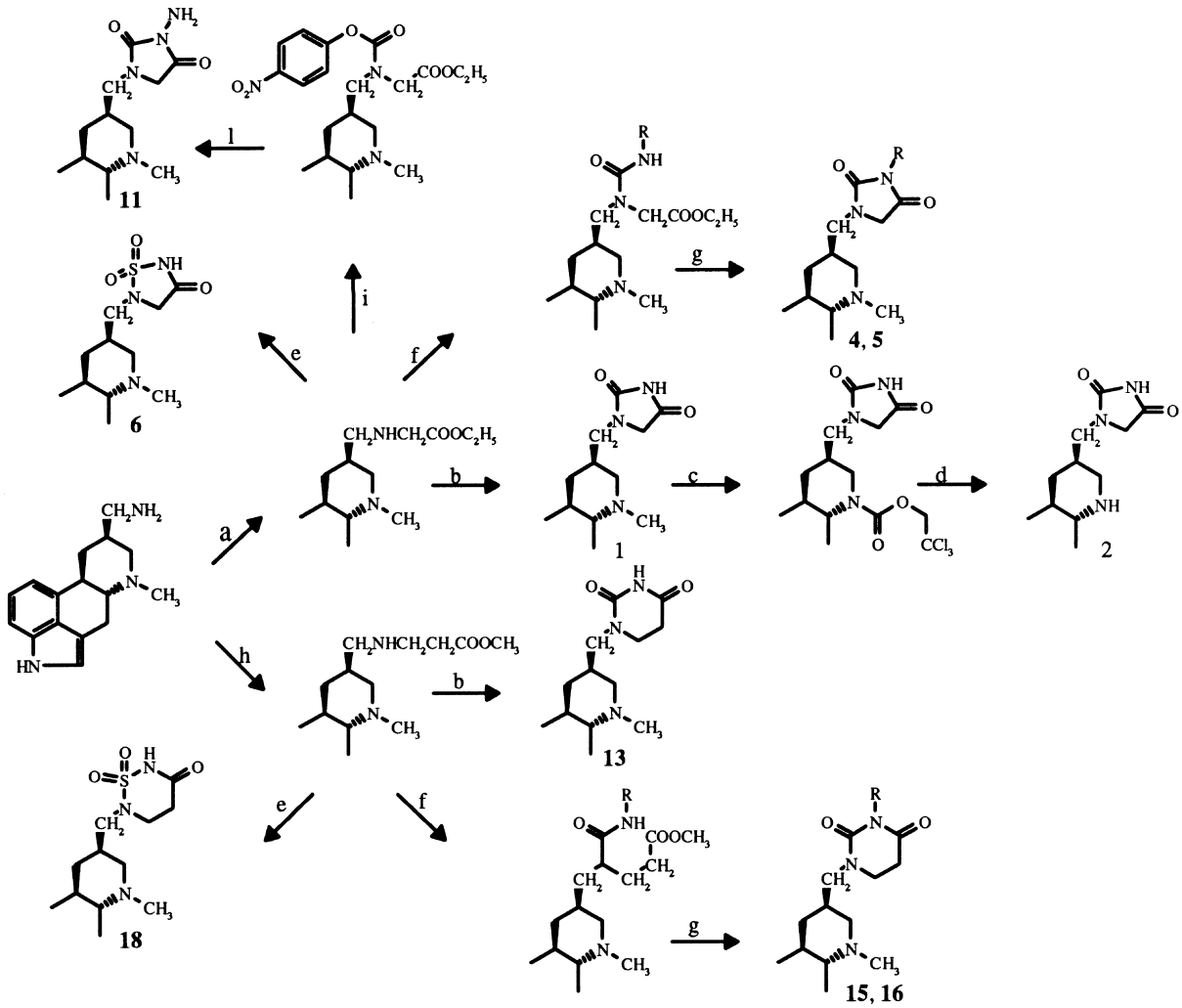


Fig. 3. (a) $BrCH_2COOC_2H_5$, K_2CO_3, DMF, r.t.; (b) KOCN, 1 N HCl, 90°C; (c) CCl_3CH_2OCOCl, $KHCO_3$, toluene, reflux; (d) powder Zn, AcOH, 35°C; (e) $NH_2SO_2NH_2$, 150°C; (f) RNCO, dioxane, reflux; (g) 170°C, vacuum; (h) CH_2=$CHCOOCH_3$, dioxane, reflux; (i) *p*-nitrophenyl chlorocarbonate, pyridine, r.t.; (l) NH_2NH_2, pyridine, reflux.

last compound, was prepared by methylation of the indole nitrogen of the 6-methylergoline-8β-carboxamide with potassium amide and methyl iodide in liquid ammonia [20]. 6-Methyl-$\Delta^{8,9}$-didehydroergoline-8-methanamine **28** and 6-methyl-$\Delta^{9,10}$-didehydroergoline-8β-methanamine **27** were prepared from elymoclavine and lysergol, after conversion into the corresponding azide, followed by reduction with tin chloride [21]; 6-methylergoline-8β-amine **29** was prepared through a Curtius degradation carried out on the hydrazide of dihydrolysergic acid [22]; 6-methylergoline-8β-ethylamine **30** was provided by reduction of 6-methylergoline-8β-acetonitrile [23] (Fig. 4).

3. Results and discussion

*3.1. 2,4-Dioxoimidazolidin-1-yl ergoline derivatives **1–12***

The prototype **1** significantly lowered MBP in a dose dependent way. Furthermore, **1** lacked inhibitory activity on egg nidation up to 32 mg/kg p.o. and showed low toxicity (Table 3). The ED_{25} was found to be 1.9 (1.3–2.4) mg/kg p.o. and lasted 6–8 h. The 6-desmethyl analogue **2** showed weaker antihypertensive activity in comparison with **1**. The 2,3-dihydro derivative **3** displayed a short-lasting activity that disappeared 5 h after treatment. The disubstituted derivatives **4**, **5** revealed interesting antihypertensive activity but had a greater toxicity than **1**. The sulfonyl derivative **6** showed a substantial decrease of activity. Shortening the side-chain at C-8 led to **7**, which was less active than **1**. Increasing the distance of the 2,4-dioxoimidazolidin-1-yl ring from the ergoline skeleton by a methylene unit gave **8**. Compound **8** showed modest antihypertensive activity and an enhanced toxicity and nidation inhibitory effect. Substitution at position 1, as in **9**, markedly reduced activity and increased toxicity. The introduction of a double bond in position 9,10 of the ergoline nucleus afforded **10**, displaying a very high antihypertensive activity at 1 mg/kg p.o. and lacking nidation inhibitory activity up to 32 mg/kg p.o. The safety ratio of **10** was very favourable, with an LD_{50} exceeding 800 mg/kg p.o.

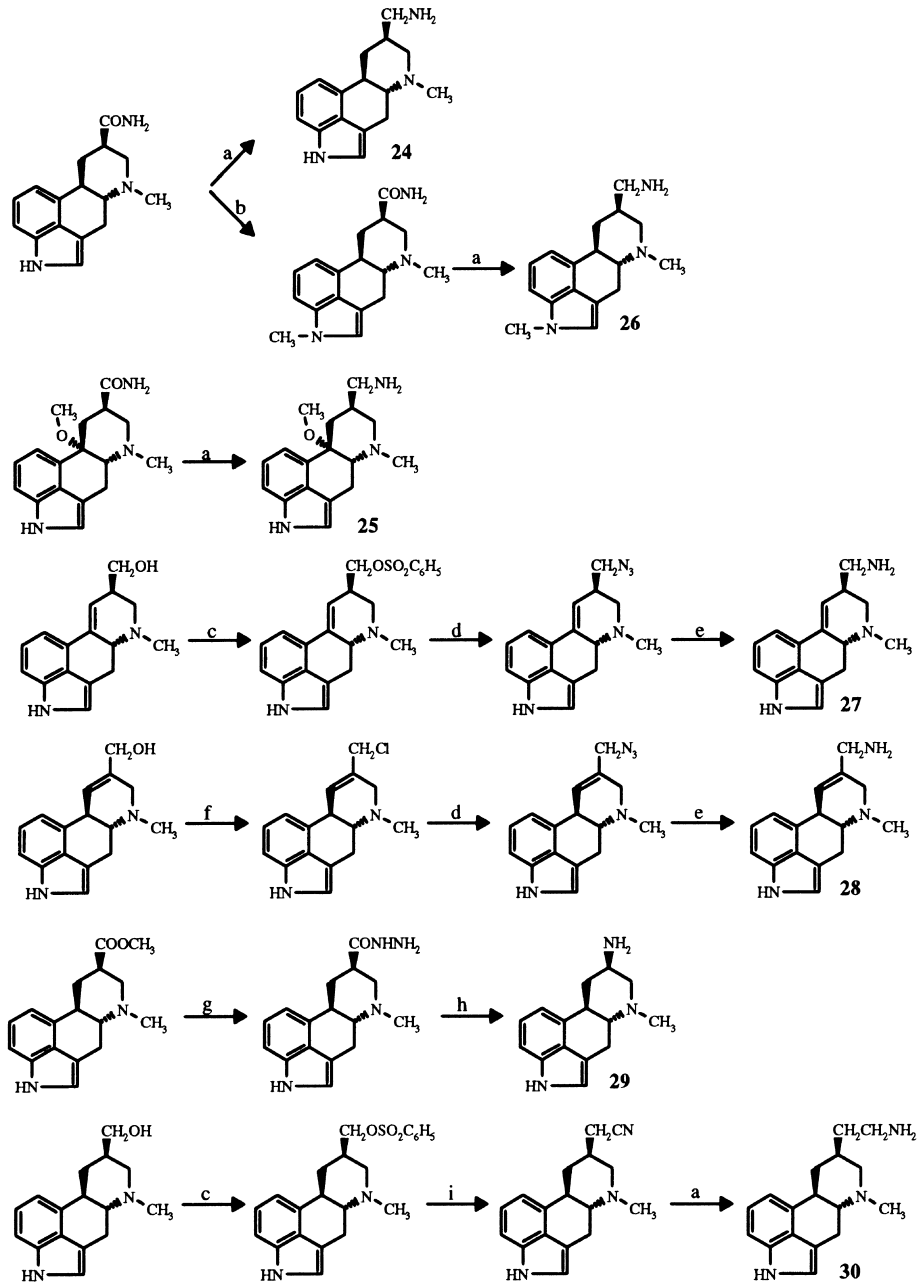


Fig. 4. (a) $LiAlH_4$, THF, reflux; (b) K, liq. NH_3, CH_3I; (c) $C_6H_5SO_2Cl$, pyridine, 0°C; (d) NaN_3, HMPA, 45°C; (e) $SnCl_2$, 2 N NaOH, 0°C; (f) ClCOCOCl, DMF/CH_3CN, −70°C; (g) NH_2NH_2, EtOH, reflux; (h) $NaNO_2$, 1 N HCl, 0°C/150°C; (i) KCN, DMSO, 50°C.

When MPB was measured directly in chronically cannulated SHRs, the strong antihypertensive effect observed during the screening was confirmed (Fig. 5). The ED_{25} of **10** was determined and was found to be 142.0 (96.0–190.0) μg/kg p.o. The antihypertensive effect had a prompt onset and was long lasting. Increases of heart rate (HR) (Fig. 6) after administration of **10** were modest even at the highest dose (250 μg/kg p.o.) The *N*-amino derivative **11** was revealed to be a potent antihypertensive but with a short duration of action. Introduction of a methoxy group at position 10α led to **12** which was totally inactive.

*3.2. Perhydro-2,4-dioxopyrimidin-1-yl ergoline derivatives **13–23***

The prototype compound **13** lacking substitution on the heterocyclic ring was a very potent and selective antihypertensive agent. This compound had no effect on prolactin secretion, even when it was administered at very high doses (Table 4). The substituted compounds **14–16** showed that the replacement of the imidic hydrogen by a linear or branched alkyl group led to a similar antihypertensive activity. However, this was accompanied by increased toxicity.

Table 3
Antihypertensive activity of 2,4-dioxoimidazolidin-1-yl ergolines **1**–**12**

Comp.	Dose (mg/kg p.o.)	Antihypertensive activity: SBP [b] after treatment, Δ (mmHg)		Nidation inhibition in rats: ED_{50} (mg/kg p.o.)	Approximate toxicity in rats: LD_{50} (mg/kg p.o.)
		1 h	5 h		
Vehicle [a]		+3.7±2.4	+3.5±2.3		
1	20	−60.0±12.4**	−72.5±2.5	>32	>800
	1	−16.5±8.3	−37.5±7.7**		
2	20	−43.7±8.7**	−35.0±6.1**		>800
3	20	−40.6±6.7*	−8.7±8.2		>800
4	1	−43.7±2.3**	−41.2±1.2**	>8	400–800
5	7.5	−37.5±14.0	−26.2±8.9	>8	200–400
6	3.75	−35.0±10.2*	−26.2±11.9*	>8	100–200
	1	−11.0*±12.3	−13.7±13.9		
7	20	−17.5±10.3	−13.7±8.9		>800
8	15	−50.0±15.0*	−55.0±5.0**	>8	400–800
	5	−6.2±6.5	−7.5±8.3		
9	20	−55.0±5.4**	−52.0±4.3**	4–8	400–800
	1	−28.7±7.7	−28.7±6.5*		
10	7.5	−55.0±15.7*	−63.7±8.0**	>32	>800
11	1	−40.0±4.5*	−58.7±4.2**	>32	>800
12	20	−17.5±8.7	−25.0±10.6		

[a] Methocel 0.5% wt./vol., 2 ml/kg; *$p<0.05$; **$p<0.01$ from corresponding control values by Dunnet's test.
[b] SBP, systolic blood pressure.

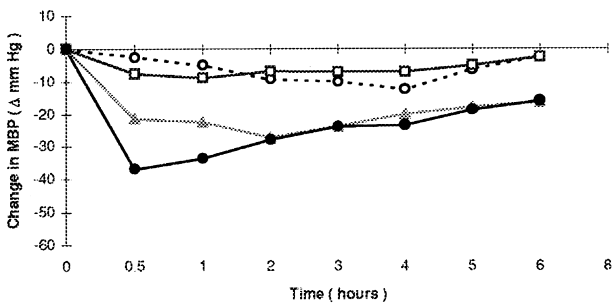


Fig. 5. Time course of effects on mean blood pressure (MPB) produced by compound **10** in chronically cannulated SHRs. The results represent mean changes ± from pretreatment values ($n=6$–20/group). Solid symbols represent statistically ($p<0.01$) significant changes from pre-drug status (Dunnet's test); ○, control vehicle; □, 62; ▲, 125; ●, 250 μg/kg p.o.

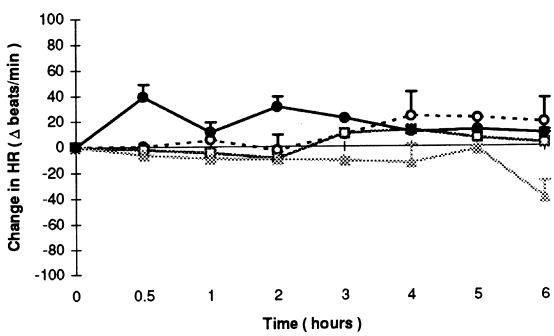


Fig. 6. Time course of effects on heart rate (HR) produced by compound **10** in chronically cannulated SHRs. The results represent mean changes ± from pretreatment values ($n=6$–20/group). Solid symbols represent statistically ($p<0.01$) significant changes from pre-drug status (Dunnet's test); ○, control vehicle; □, 62; ▲, 125; ●, 250 μg/kg p.o.

17, which possesses a perhydro-2-thioxo-4-oxopyrimidin-1-yl moiety, exhibited potency similar to **13**, although with an increased nidation inhibitory effect and toxicity. By analogy with the former series, a relevant decrease in activity was observed by the sulfonyl analogue **18**. In correlating the activity with the distance of the dihydrouracyl to the ergoline nucleus, it was shown that direct linking of the perhydro-2,4-dioxopyrimidin-1-yl moiety to the ergoline skeleton led to decreased potency, as shown by **19**. Lengthening of one methylene unit, as in the case of **20**, resulted in a slight decrease of activity and increase of toxicity. Similarly to **10**, the antihypertensive activity was remarkably enhanced by the presence of a $\Delta^{9,10}$ double bond as in **21**. Shifting the double bond from position 9,10 to position 8,9 gave **22**. This compound was still active, although a dose related correlation was not found. Alkylation in position 1, as in the case of **23**, reduced the antihypertensive activity and dramatically increased toxicity. The extremely marked effect of the unsaturated compound **21** in the screening test prompted us to investigate further its antihypertensive activity by direct measurement of MPB in chronically cannulated SHRs. As shown from the data in Fig. 7, this compound is endowed with a marked activity at very low doses (31.2–50.0) μg/kg p.o. The ED_{25} was 24.3 (6.2–44.0) μg/kg p.o. Similarly to **10**, the antihypertensive effect had a prompt onset and was long lasting, reaching a peak 4–6 h after treatment at all dosages. Heart rate was not significantly affected for animals treated with **21** compared with controls (Fig. 8). Interestingly, the ED_{25} (24.3 μg/kg p.o.) was about 100 times lower than that affecting prolactin secretion (2.4 mg/kg p.o.).

Table 4
Antihypertensive activity of perhydro-2,4-dioxopyrimidin-1-yl ergolines **13**–**23**

Comp.	Dose (mg/kg p.o.)	Antihypertensive activity: SBP [b] after treatment, Δ (mmHg)		Nidation inhibition in rats: ED_{50} (mg/kg p.o.)	Approximate toxicity in rats: LD_{50} (mg/kg p.o.)
		1 h	5 h		
Vehicle [a]		+3.6±2.4	+3.7±2.4		
13	20	−85.0±3.5**	−65.0±3.5	>32	>800
	1	−20.0±7.3	−38.7±2.4**		
14	7.5	−55.0±7.6**	−56.2±5.9**		200–400
15	7.5	−51.8±8.0**	−65.3±3.5**		
	1	−31.2±8.6	−35.8±8.8**		
16	1	−23.7±9.4	−25.0±9.7		400–800
17	20	−62.5±4.8**	−66.2±4.7**	4	400–800
	5	−38.7±13.9**	−66.7±15.9**		
18	20	−26.2±13.0	−12.5±3.3		>800
19	20	−50.0±3.5	−18.7±2.3	>8	>800
20	20	−51.6±24.5**	−55.0±5.0**	16	400–800
	1	−20.0±4.5**	−28.7±7.1*		
21	20	−115.0±0**	−126.2±4.3**	2.4	>800
22	20	−60.0±13.2	−66.2±9.4**	8	>800
	5	−32.5±9.2	−48.7±3.1**		
23	1	−18.7±4.3	−11.2±1.2		50–100

[a] Methocel 0.5% wt./vol., 2 ml/kg; *$p<0.05$; **$p<0.01$ from corresponding control values by Dunnet's test.
[b] SBP, systolic blood pressure.

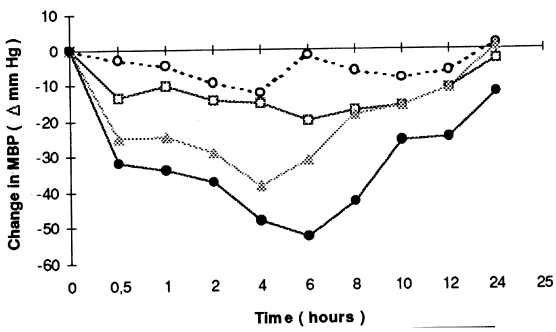


Fig. 7. Time course of effects on mean blood pressure (MPB) produced by compound **21** in chronically cannulated SHRs. The results represent mean changes ± from pretreatment values ($n=6$–20/group). Solid symbols represent statistically ($p<0.01$) significant changes from pre-drug status (Dunnet's test); ○, control vehicle; □, 31.2; ▲, 125; ●, 500 μg/kg p.o.

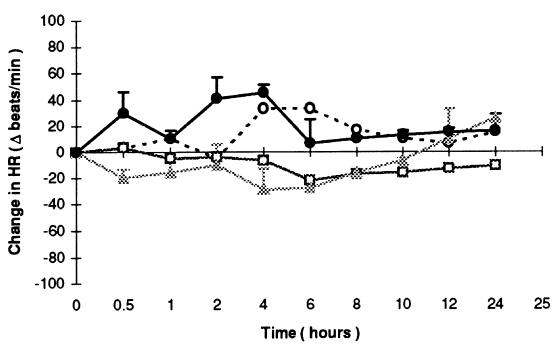
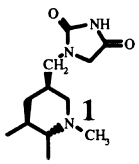
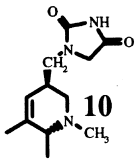
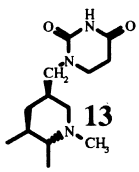
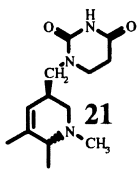


Fig. 8. Time course of effects on heart rate (HR) produced by compound **21** in chronically cannulated SHRs. The results represent mean changes ± from pretreatment values ($n=6$–20/group). Solid symbols represent statistically ($p<0.01$) significant changes from pre-drug status (Dunnet's test); ○, control vehicle; □, 31.2; ▲, 125; ●, 500 μg/kg p.o.

According to the binding results in Table 5, some structure–affinity relationship can be drawn for the most interesting compounds **1**, **10** and **13**, **21**. The adrenergic α_1, α_2 components were higher in the 2,4-dioxoimidazolidin-1-yl than in the perhydro-2,4-dioxopyrimidin-1-yl series. The dopaminergic D_1, D_2 components were negligible in the two series. The low D_2 component was in accordance with the in vivo nidation inhibiting activity data. This correlation was further demonstrated by **21**. Compound **21** has the highest D_2 affinity among the compounds considered. This affinity was accompanied by the highest activity in the nidation test. The introduction of the $\Delta^{9,10}$ double bond remarkably affected the serotonergic 5-HT_1, 5-HT_2 components. A noticeable increase in affinity was observed when **1** and **13** were compared with **10** and **21**. Such enhancement was more pronounced for the perhydro-2,4-dioxopyrimidin-1-yl series, where the increase in 5-HT_1 was more than thirtyfold and in 5-HT_2 more than tenfold.

In conclusion, our results showed that either the perhydro-2,4-dioxopyrimidin-1-yl or 2,4-dioxoimidazolidin-1-yl moieties, introduced by way of a C–N bond, can be useful substituting groups in the search for novel ergoline derivatives endowed with antihypertensive effect. With respect to compounds **1** and **13**, the antihypertensive activity is not substantially affected by the substituent present in position 3 of the 2,4-dioxoimidazolidin-1-yl and perhydro-2,4-dioxopyrimidin-1-yl rings, whereas toxicity is increased. Decreased activity was observed by shortening the chain in position 8. On the contrary, the antihypertensive activity was not affected by lengthening the side-chain. The replacement of the carbonyl by a thiocarbonyl group did not affect the antihyper-

Table 5
Binding profile for the ergoline derivatives **1**, **10**, **13**, **21**

Structure	α_1	α_2	D_1	D_2	5-HT_1	5-HT_2
	0.13	0.17	2.21	1.05	0.21	0.27
	0.21	0.18	1.52	1.20	0.01	0.11
	1.02	0.33	1.13	1.12	3.50	1.10
	0.79	0.32	1.03	0.45	0.05	0.04

Affinities are expressed as IC_{50} in μM; standard errors are ±10% of the mean reported values.

tensive activity, whilst the replacement by a sulfonyl group led to a marked decrease in potency. A remarkable increase in antihypertensive activity was achieved by introduction of a double bond between positions 9 and 10 of the ergoline nucleus in both series. Our results showed that the introduction of a methyl group in position 1 or a methoxy in position 10α of the ergoline nucleus almost abolished the antihypertensive activity and increased the toxicity. Compounds **10** and **21** have been selected for further preclinical evaluation on the basis of their in vitro profile implying a potential serotonergic mechanism of action and their high antihypertensive activity accompanied by very low toxicity.

4. Experimental

4.1. Pharmacological methods

4.1.1. Antihypertensive activity

Indirect measurements of systolic blood pressure were carried out in groups of 4–5 spontaneously hypertensive male rats, age 8–10 weeks (SHR, Kyoto, Japan; C. River, Italy). On the day of the experiment, the animals were maintained in an environment of 36°C for 15 min. Systolic blood pressure was measured by an indirect tail- cuff method using a W + W/BP Recorder, model 8005. Each determination was averaged from at least four readings. Blood pressure measurements were carried out before treatment, and at 1 and 5 h after dosing. Control animals received the vehicle methocel 0.5% wt./vol., 2 ml/kg b.w. The results were evaluated by means of two-way analyses of variance. The significance of the differences between means was evaluated by Dunnett's multiple comparison test. This compared the blood pressure changes (Δ mmHg) at different times after treatment with the corresponding values of the control group. Intra-arterial measurement of mean blood pressure was performed through catheters implanted in the right carotid artery of 6–20 rats/group under halothane anesthesia. Twenty-four hours following surgery, the animals were placed in a Ballman cage and the arterial cannula was connected through a Statham P23 Db pressure transducer to a Beckmann Dynograph for continuous recording of mean blood pressure and heart rate. Recordings were made under basal conditions and up to 24 h after drug or vehicle was orally administered.

4.1.2. Prolactin inhibitory activity

The prolactin secretion inhibitory activity was evaluated indirectly using the nidation inhibition test in rats. Adult Sprague-Dawley female rats (C. River, Italy) were caged with fertile male rats in the evening of the day of proestrus. Only rats with spermatozoa in vaginal smears on the following day (1 day of pregnancy) were included in the protocol. They were treated orally on the morning of day 5 of pregnancy with a suspension of the test compounds in methocel (0.5% wt./vol.) orally. On day 14, the animals were anesthetized and the uteri were examined for the presence of implantation sites [24]. Compounds were tested at different doses (6–8 animals per group) and the dose inhibiting nidation in 50% of the animals (ED_{50}) was determined.

4.1.3. Acute toxicity

The acute oral toxicity was evaluated in male Swiss mice (C. River, Italy). Each compound was suspended in methocel (0.5% wt./vol.) and administered at various dose levels (three animals per dose). The dose causing the death of 50% of the animals (LD_{50}) within 7 days following treatment was determined.

4.1.4. Binding profile

The compounds described in this study were evaluated for their α_1, α_2, D_1, D_2, 5-HT_1 and 5-HT_2 receptor binding affinities assessed by measuring the displacement of [^{3}H]-prazosin binding in rat frontal cortex [25], [^{3}H]-yohimbine binding in rat frontal cortex [26], [^{3}H]-SCH-23390 binding in rat striatum [27], [^{3}H]-spiroperidol binding in rat striatum [28], [^{3}H]-5-HT binding in rat hippocampus [29] and [^{3}H]-ketanserin binding in rat prefrontal cortex [30], respectively.

4.2. Chemical methods

Melting points were determined using a Büchi melting point apparatus and are uncorrected. IR spectra were recorded

on a Perkin- Elmer 125 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-200 spectrometer in $CDCl_3$ or DMSO-d_6 solutions. Chemical shifts are expressed in δ (ppm from zero tetramethylsilane (TMS)). Assignments were supported by suitable decoupling experiments. The chemical shifts are reported only for protons with clear attribution. EI were recorded at 70 eV on a Varian MAT 311-A spectrometer. All compounds had IR, ^{1}H NMR and mass spectra that were fully consistent with their structure. The results of the elemental analyses (C, H, N) were within $\pm$0.4% of the theoretical values. The examples presented below are representative of all synthetic procedures.

4.2.1. N-[(6-Methylergolin-8β-yl)methyl]glycine ethyl ester

A solution of 14.4 g (0.086 mol) of ethyl bromoacetate in 50 ml of dimethylformamide at room temperature was slowly added dropwise to a stirred solution of 20 g (0.078 mol) of **24** and 10.8 g (0.080 mol) of potassium carbonate in 250 ml of dimethylformamide. After stirring for 5 h, the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and brine. The organic layer was dried (Na_2SO_4), then evaporated to dryness. The crude reaction mixture was chromatographed on silica gel eluting with chloroform. The first fractions provided 2.3 g of *N*-[(6-methylergoline-8β)methyl]iminodiacetic acid ethyl ester as a white foam. *Anal.* ($C_{24}H_{33}N_3O_4$) C, H, N. IR (KBr): 3400 (ν N–H); 1745 (ν C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05 (ddd, *J* = 12.1, 12.1, 12.0 Hz, *1H*, H-9ax); 1.26 (t, *J* = 7.1 Hz, *6H*, $COOCH_2CH_3$); 1.90 (dd, *J* = 11.2, 11.2 Hz, *1H*, H-7ax); 2.15 (m, *2H*, H-5ax, H-8ax); 2.48 (s, *3H*, CH_3N); 2.56 (dd, *J* = 8.6, 12.7 Hz, *1H*, C*H*(H)-8); 2.7 (m, *2H*, H-4ax, H-9e); 3.41 (dd, *J* = 4.2, 14.8 Hz, *1H*, H-4e); 3.59 (m, *4H*, CH_2NCH_2); 4.16 (q, *J* = 7.1 Hz, *4H*, $COOCH_2CH_3$); 6.8–7.2 (m, *4H*, aromatic protons); 7.92 (b s, *1H*, NH-1). MS (EI) *m*/*z* 427 (14, M^{+-}); 354 (8); 340 (6); 238 (31), 237 (31); 223 (23); 167 (100); 154 (33); 130 (48); 127 (11). Continuing the elution with a mixture of chloroform/ethanol (98:2), 23 g (86% yield) of *N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester were recovered after crystallization from ethyl acetate, m.p. 174–176°C. *Anal.* ($C_{20}H_{27}N_3O_2$) C, H, N. IR (KBr): 3300 (ν N–H); 1725 (ν C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.97 (ddd, *J* = 12.3, 12.3, 12.3 Hz, *1H*, H7-ax); 1.20 (t, *J* = 7.0 Hz, *3H*, $COOCH_2CH_3$); 2.0 (m, *2H*, H-8ax, H-8ax); 2.23 (ddd, *J* = 4.3, 9.5, 11.5 Hz, *1H*, H-5ax); 2.46 (s, *3H*, CH_3N); 2.40–2.7 (m, *4H*, H-9e, H-4ax, CH_2-8); 2.88 (ddd, *J* = 3.5, 9.5, 12.3 Hz, *1H*, H-10ax); 3.14 (b d, *J* = 7.3 Hz, *1H*, H-7e); 4.16 (q, *J* = 7.1 Hz, *2H*, $COOCH_2CH_3$); 6.79 (d, *J* = 8 Hz, *1H*, H-12); 6.98 (s, *1H*, H-2); 7.0 (t, *J* = 8.0 Hz, *1H*, H-13); 7.12 (d, *J* = 8.0 Hz, *1H*, H-14); 10.68 (b s, *1H*, NH-1). MS (EI) *m*/*z* 341 (76, M^{+-}); 268 (14); 238 (62), 225 (26); 223 (40); 183 (18); 167 (100); 154 (65); 144 (30); 127 (19).

*4.2.2. 1-[(6-Methylergoline-8β)methyl]-2,4-dioxoimidazolidine **1***

A solution of 9.4 g (0.116 mol) of potassium cyanate in 100 ml of water was slowly added dropwise to a stirred solution of 20 g (0.058 mol) of *N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester in 116 ml of 1 N hydrochloric acid. After stirring for 2 h at room temperature, the solution was heated at 75°C for 5 h then set aside overnight. The precipitate was filtered off, washed with water then twice crystallized from methanol, furnishing 18.5 g (94%) of **1**. *Anal.* ($C_{19}H_{22}N_4O_2$) C, H, N. IR (KBr): 3400 (ν N–H amide); 1750 (ν C=O); 1705 (ν C=O); 1465 (ν N–H amide) cm^{-1}. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.94 (ddd, *J* = 12.3, 12.3, 12.3 Hz, *1H*, H9-ax); 1.79 (dd, *J* = 11.4, 11.4 Hz, *1H*, H-7ax); 1.93 (dd, *J* = 4.3, 9.2 Hz, *1H*, H-8ax); 2.10 (m, *1H*, H-9ax); 2.23 (ddd, *J* = 4.3, 9.5, 11.5 Hz, *1H*, H-5ax); 2.32 (s, *3H*, CH_3N); 2.3–2.36 (m, *2H*, H-4ax, H-9e); 2.75 (ddd, *J* = 3.5, 9.5, 12.3 Hz, *1H*, H-10ax); 2.88 (b d, *J* = 11.4, *1H*, H-7e); 3.16 (m, *2H*, CH_2-8); 3.28 (dd, *J* = 4.3, 14.6 Hz, *1H*, H-4e); 3.99 (s, *2H*, NCH_2CO); 6.77 (d, *J* = 8.0 Hz, *1H*, H-12); 6.99 (t, *J* = 8.0 Hz, *1H*, H-13); 7.10 (d, *J* = 8.0 Hz, *1H*, H-14); 10.59 (b s, *1H*, NH-1); 10.74 (b s, *1H*, CONHCO). MS (EI) *m*/*z* 338 (88, M^{+-}); 237 (12); 225 (22), 223 (27); 197 (19); 180 (23); 167 (27); 154 (61); 144 (100); 127 (22).

*4.2.3. 1-[(6-Methylergoline-8β)methyl]-2,4-dioxo-3-propylimidazolidine **4***

A solution of 3 g (0.01 mol) of *N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester and 1 g (0.011 mol) of n-propyl isocyanate in 75 ml of 1,4-dioxane was refluxed for 2 h. After removal of the solvent, the crude α-ureido ester was heated at 150°C in a vacuum of 10 mmHg for 30 min. The resulting product was filtered over a small pad of silica gel eluting with chloroform. Crystallization from acetone provided 2.7 g of **4** (81%). *Anal.* ($C_{21}H_{26}N_4O_2$) C, H, N. IR (KBr): 1755 (ν C=O); 1705 (ν C=O); 1465 (ν N–H amide) cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.94 (t, *J* = 7.3 Hz, *3H*, $NCH_2CH_2CH_3$); 1.18 (ddd, *J* = 12.2, 12.2, 12.2 Hz, *1H*, H-9ax); 1.67 (m, *2H*, $NCH_2CH_2CH_3$); 2.02 (dd, *J* = 11.2, 11.2 Hz, *1H*, H-7ax); 2.20 (m, *2H*, H-5ax, H-8ax); 2.27 (ddd, *J* = 1.7, 11.4, 14.8 Hz, *1H*, H-4ax); 2.37 (s, *3H*, CH_3N); 2.60 (m, *1H*, H-9e); 2.95 (m, *2H*, H-7e, H-10ax); 3.2–3.6 (m, *5H*, H-4e, $NCH_2CH_2CH_3$, CH_2-8); 3.92 (m, *2H*, NCH_2CO), 6.8–7.2 (m, *4H*, aromatics), 7.99 (b s, *1H*, NH-1). MS (EI) *m*/*z* 366 (100, M^{+-}); 239 (17); 225 (36), 223 (34); 195 (18); 182 (22); 167 (32); 154 (50); 144 (94); 127 (21).

*4.2.4. 1-[(6-Methylergoline-8β)methyl]-2-S,S-dioxide thiodiazolidine-3-one **6***

A finely ground mixture of 5 g (0.014 mol) of *N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester and 5 g (0.052 mol) of sulfamide was slowly heated until melting with continuous stirring and kept at melting point for 10 min.

After cooling, the mixture was extracted with chloroform/methanol (10:2) and the solution was washed with brine and dried. The solvent was removed and the dark residue was chromatographed on silica gel eluting with acetone. The eluted product was crystallized from methanol, affording 2.8 g (53%) of **6**. *Anal*. ($C_{18}H_{22}N_4O_3S$) C, H, N. IR (KBr): 3100–3700 (ν N–H); 1640 (ν C=O); 1280 (ν SO_2 antisym.); 1140 (ν SO_2 sym.) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.31 (ddd, J = 12.0, 12.0,12.0 Hz, *1H*, H-9ax); 2.96 (s, *3H*, CH_3N^+); 3.49 (m, *2H*, NCH_2C=O); 6.8–7.2 (m, *4H*, aromatic protons); 9.71 (b s, *1H*, SO_2NH); 10.5 (b s, *1H*, NH-1). MS (EI) m/z 374 (23, M^{+-}); 310 (4); 269 (10), 255 (16); 237 (35); 223 (68); 167 (81); 154 (100); 144 (54); 127 (58).

4.2.5. N-(6-Methylergolin-8β-yl)glycine ethyl ester

A solution of 3.1 g (0.018 mol) of ethyl bromoacetate in 20 ml of dimethylformamide at room temperature was slowly added dropwise to a stirred solution of 4 g (0.167 mol) of **29** and 2.29 g (0.167 mol) of potassium carbonate in 50 ml of dimethylformamide. After 3 h, the solution was diluted with ethyl acetate and washed several times with brine. Drying and removal of the solvent afforded a residue that was twice crystallized from a small volume of ethanol, affording 3.9 g (75% yield) of *N*-(6-methylergolin-8β-yl)glycine ethyl ester, m.p. 231–233°C. *Anal*. ($C_{19}H_{25}N_3O_2$) C, H, N. IR (KBr): 3340 (ν N–H); 1740 (ν C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29 (ddd, J = 12.2, 12.2, 12.2 Hz, *1H*, H-9ax); 1.30 (t, J = 7.1 Hz, *3H*, $COOCH_2CH_3$); 2.04 (dd, J = 10.5, 10.5 Hz, *1H*, H-7ax); 2.18 (ddd, J = 4.3, 9.6, 11.0 Hz, *1H*, H-5ax); 2.49 (s, 3H, CH_3N); 2.67 (ddd, J = 1.7, 11.0, 14.7 Hz, 1H, H-4ax); 2.8–3.1 (m, 3H, H-8ax, H-9e, H-10ax); 3.17 (ddd, J = 2.1, 4.0, 10.5 Hz, 1H, H-7e); 3.40 (dd, J = 4.3, 14.7 Hz, 1H, H-4e); 3.55 (s, 2H, $NHCH_2COO$); 4.22 (q, J = 7.1 Hz, 2H, $COOCH_2CH_3$); 6.8–7.2 (m, 4H, aromatic protons); 8.08 (b s, 1H, NH-1). MS (EI) m/z 327 (16, M^{+-}); 253 (5); 223 (8), 209 (4); 198 (26); 181 (16); 167 (18); 155 (35); 154 (100); 127 (24).

*4.2.6. 1-(6-Methylergolin-8β-yl)-2,4-dioxoimidazolidine **7***

A solution of 1.5 g (0.018 mol) of potassium cyanate in 10 ml of water was added dropwise to a stirred solution of 3 g (0.009 mol) of *N*-(6-methylergolin-8β-yl)glycine ethyl ester in 18.0 ml of 1 N hydrochloric acid. After stirring for 1 h at room temperature, the solution was heated at 90°C for 3 h. After cooling, the precipitate was filtered off, washed with water and subsequently crystallized twice from ethanol, providing 2.7 g of **7**. *Anal*. ($C_{18}H_{20}N_4O_2$) C, H, N. IR (KBr): 3390 (ν N–H); 1750 (ν C=O); 1700 (ν C=O); 1460 (ν N–H amide) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.50 (ddd, J = 12.2, 12.2, 12.2 Hz, *1H*, H-9ax); 1.98 (ddd, J = 4.3, 9.4, 10.8 Hz, *1H*, H-5ax); 2.21 (dd, J = 11.0, 11.0 Hz, *1H*, H-7ax); 2.35 (s, *3H*, CH_3N); 2.49 (ddd, J = 1.7, 11.0, 14.9 Hz, *1H*, H-4ax); 2.60–3.0 (m, *3H*, H-7e, H-9e, H-10ax); 3.28 (dd, J = 4.3, 14.9 Hz, *1H*, H-4e); 3.98 (m, *2H*, NCH_2CO); 4.30 (m, *1H*, H-8ax); 6.77 (d, J = 7.0 Hz, *1H*, H-12); 6.96 (d, J = 1.7 Hz, *1H*, H-2); 7.0 (m, J = 7.0 Hz, *1H*, H-13); 7.12 (d, J = 7.0, *1H*, H-14); 10.62, 10.80 (two b s, *2H*, NH-1, CONHCO). MS (EI) m/z 324 (31, M^{+-}); 224 (59); 223 (100), 209 (9); 197 (8); 181 (12); 167 (57); 155 (37); 154 (77); 127 (36).

*4.2.7. 1-[(6-Methylergolin-8β-yl)methyl]-2,4-dioxo-3-aminoimidazolidine **11***

A solution of 2.4 g (0.012 mol) of *p*-nitrophenyl chloroformate dissolved in 25 ml of tetrahydrofuran was added dropwise to a stirred solution of 3 g (0.008 mol) of *N*-[(6-methylergolin-8β-yl)methyl]glycine ethyl ester in 30 ml of pyridine. After stirring for 2 h at room temperature, 5 ml of hydrazine hydrate were added and the solution was refluxed for 1 h. The solvent was removed then the residue was taken up in ethyl acetate and washed several times with a 10% solution of potassium carbonate. After drying and removal of the solvent, the crude product was chromatographed over silica gel eluting with chloroform. Crystallization from ethanol gave 1.9 g (61% yield) of **11**. *Anal*. ($C_{19}H_{23}N_5O_2$) C, H, N. IR (KBr): 3390 (ν N–H); 1770 (ν C=O); 1710 (ν C=O); 1465 (ν N–H amide) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ 0.94 (ddd, J = 12.2, 12.2, 12.2 Hz, *1H*, H-9ax); 1.81 (dd, J = 11.1, 11.1 Hz, *1H*, H-7ax); 1.94 (ddd, J = 4.2, 9.4, 10.7 Hz, *1H*, H-5ax); 2.13 (m, *1H*, H-8ax); 2.30 (s, 3H, CH_3N); 2.4–2.6 (m, *2H*, H-4ax, H-9e); 2.76 (m, *1H*, H-10ax); 2.82 (m, *1H*, H-7e); 3.1–3.3 (m, *3H*, CH_2-8H, H-4e); 3.97 (s, *2H*, NCH_2CO); 4.75 (s, *2H*, NNH_2); 6.67 (d, J = 7.0 Hz, *1H*, H-13); 6.95 (s, *1H*, H-2); 6.99 (t, J = 7 Hz, *1H*, H-13); 7.10 (d, J = 7.0 Hz, *1H*, H-14); 10.60 (b s, *1H*, NH-1). MS (EI) m/z 353 (100, M^{+-}); 237 (14); 225 (20), 223 (23); 197 (13); 182 (11); 167 (20); 154 (46); 144 (59); 127 (18).

4.2.8. N-[(6-Methylergolen-$\Delta^{9,10}$-8β-yl)methyl]-β-alanine methyl ester

A solution of 10 g (0.04 mol) of **27** and 3.75 g (0.043 mol) of methyl acrylate in 150 ml of 1,4-dioxane was refluxed for 5 h. After removal of the solvent, the residue was filtered through a pad of silica gel eluting with acetone. The first fractions afforded, after evaporation of the solvent and crystallization from diethyl ether, 0.7 g of *N*-(β-methoxycarbonylethyl)-*N*-[(6-methylergolen-$\Delta^{9,10}$-8β-yl)methyl]-β-alanine methyl ester, m.p. 157–159°C. *Anal*. ($C_{24}H_{31}N_3O_4$) C, H, N. IR (KBr): 3430 (ν N–H); 1725 (ν C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.12 (dd, J = 10.2 Hz, *1H*, H-7ax); 2.1-2.5 (m, *6H*, CH_2-8, 2 CH_2COO); 2.56 (s, *3H*, CH_3N); 2.68 (ddd, J = 1.7, 11.3, 14.4 Hz, *1H*, H-4ax); 2.70 (m, *1H*, H-8); 2.89 (m, *4H*, NCH_2_CH_2); 3.02 (dd, J = 5.0, 10.2 Hz, *1H*, H-7e); 3.12 (m, *1H*, H-5ax); 3.52 (dd, J = 5.4, 14.4Hz, *1H*, H-4e); 3.67 (s, *6H*, $COOCH_3$); 6.36 (b s, *1H*, H-9); 6.89 (dd, J = 1.7, 1.7 Hz, *1H*, H-2); 7.18 (s, *3H*, H-12, H-13, H-14); 7.92 (b s, *1H*, NH-1). MS (EI) m/z 425 (3.5, M^{+-}); 352 (4); 221 (11); 203 (11), 202 (100); 192

(4); 189 (3); 167 (3); 154 (4). Continuing the elution with the same solvent, 11.4 g (85%) of *N*-[(6-methylergolen-$\Delta^{9,10}$-8β-yl)methyl]-β-alanine methyl ester were recovered after crystallization from acetone, m.p. 187–190°C. *Anal.* ($C_{20}H_{25}N_3O_2$) C, H, N. IR (KBr): 3520 (ν N–H); 1735 (ν C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.24 (dd, $J=10.2$ Hz, *1H*, H-7ax); 2.5–2.8 (m, *5H*, H-4ax, CH_2-8, CH_2COO); 2.57 (s, *3H*, CH_3N); 2.68 (ddd, $J=1.7$, 11.3, 14.4 Hz, *1H*, H-4ax); 2.84 (m, *1H*, H-8); 2.95 (m, *2H*, NCH_2-CH_2); 3.10 (m, *2H*, H-7e, H-5ax); 3.51 (dd, $J=5.4$, 14.4 Hz, *1H*, H-4e); 3.70 (s, *3H*, $COOCH_3$); 6.38 (b s, *1H*, H-9); 6.88 (dd, $J=1.9$, 1.9 Hz, *1H*, H-2); 7.18 (m, *3H*, H-12, H-13, H-14); 8.07 (b s, *1H*, NH-1). MS (EI) *m/z* 339 (61, M^{+-}); 236 (21); 224 (100); 221 (46), 193 (59); 192 (55); 180 (15); 167 (20); 154 (20).

4.2.9. Perhydro-1-[(6-methylergolin-8β-yl)methyl]-2-thioxo-4-oxopyrimidine ***17***

Potassium isothiocyanate 2.25 g (0.023 mol) was added portionwise to a stirred solution of 5 g (0.015 mol) of *N*-[(6-methylergolin-8β-yl)methyl]-β-alanine methyl ester in 75 ml of glacial acetic acid. The resulting red solution was heated for 2 h at 90°C. The solvent was removed, then the crude mixture was partitioned between chloroform and a solution of 1 M of potassium carbonate. The organic phase was dried and evaporated to dryness. The residue was chromatographed on silica gel eluting with chloroform. The fractions containing the compound were pooled and concentrated to a small volume, affording 3.7 g (67%) of **17**. *Anal.* ($C_{20}H_{24}N_4OS$) C, H, N. IR (KBr): 3440 (ν N–H amide); 1710 (ν C=O); 1545 (ν C–N thioamide) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.08 (ddd, $J=12.0$, 12.0, 12.0 Hz, *1H*, H-9ax); 2.35 (s, *3H*, CH_3N); 2.67 (m, *2H*, CH_2CONH); 3.73 (m, *2H*, NCH_2CH_2); 2.95 (m, *2H*, NCH_2-CH_2); 6.8–7.1 (m, *4H*, aromatic protons); 10.61, 10.94 (two b s, *2H*, NH-1, CSNHCO). MS (EI) *m/z* 368 (69, M^{+-}); 335 (100); 237 (46); 223 (33), 194 (17); 167 (49); 155 (28); 154 (68); 144 (29); 127 (28).

4.2.10. Perhydro-1-[(6-methylergolen-$\Delta^{9,10}$-8β-yl)methyl]-2,4-pyrimidinedione ***21***

A solution of 3.75 g (0.046 mol) of potassium cyanate in 20 ml of water was added dropwise to a stirred solution of 7.5 g (0.023 mol) of *N*-[(6-methylergolen-$\Delta^{9,10}$-8β-yl)methyl]-β-alanine methyl ester in 46 ml of 1M hydrochloric acid at room temperature. The solution was heated at 80°C for 3 h, then, after cooling, the precipitate was filtered off, washed thoroughly with water and subsequently crystallized from methanol yielding 6.8 g (84%) of pure compound **9** as shiny crystals. *Anal.* ($C_{20}H_{22}N_4O_2$) C, H, N. IR (KBr): 3440 (ν N–H amide); 1710, 1685 (ν C=O); 1490 (ν C–N amide) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ 2.10 (dd, $J=12.1$, 12.1, 12.0 Hz, *1H*, H-7ax); 2.42 (m, *1H*, H-4ax); 2.43 (s, *3H*, CH_3N); 2.56 (m, *2H*, CH_2CO); 2.80–3.0 (m, *3H*, H-5x, H-7e, H-8); 3.2–3.5 (m, *5H*, H-4e, CH_2-8, NCH_2-CH_2); 6.22 (b s, *1H*, H-9); 7.02–7.2 (m, *3H*, H-12, H-13, H-14); 10.11, 10.67 (two b s, *2H*, NHCO, NH-1). MS (EI) *m/z* 350 (100, M^{+-}); 292 (9); 235 (32); 223 (64), 221 (59); 205 (25); 192 (71); 180 (64); 167 (24); 154 (38).

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