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Ergoline derivatives: receptor affinity and selectivity

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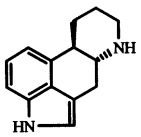
Abstract

Ergot comprises a group of indole alkaloids which are predominantly found in various species of the ascomycete *Claviceps*. In pharmacopoeias, the sclerotia of *Claviceps purpurea* (Fr.) Tulasne parasitizing on rye, *Secale cereale* L., are designed as ergot or *Secale cornutum*. Now, the term ergot is used in a broader sense to describe the sclerotia of various *Claviceps* species growing on different host plants or their saprophytic mycelia. Due to their many fascinating features, there is a continuing and extensive interest in these secondary metabolites. Thus, the chemistry of ergot alkaloids and derivatives has presented many challenges to organic chemists. The ergot alkaloids and derivatives have attracted great interest for their broad spectrum of pharmacological action that includes central, neurohumoral and peripheral effects. These are mainly responses mediated by noradrenaline, serotonin, or dopamine receptors. No other group of natural products exhibits such a wide spectrum of biological action. For this reason, ergot has been termed a 'veritable treasure house of pharmacological constituents'. Moreover, ergot alkaloids have been an important stimulus in the development of new drugs by providing structural prototypes of molecules with pronounced pharmacological activities. This concise review, moving from the experience of our group in Pharmacia & Upjohn, will briefly mention the most representative ergoline derivatives featured in the literature. Our work in this field originated compounds with quite different pharmacological activities. In fact, by continuous modification of the same main template structure, the ergoline skeleton, it ultimately led to the development of new dopaminergic agents and to the identification of new series of serotonergic agents.

Keywords: Ergoline derivatives; Dopaminergic agents; Serotonergic agents

Up to the present day, more than 40 ergot alkaloids have been isolated from natural sources. The ergot alkaloids can all be considered derivatives of the tetracyclic ergoline skeleton [1].



On the basis of their structural differences, the ergot alkaloids (Scheme 1) may be divided into two main groups. One group includes all lysergic acid derivatives of the acid amide types, such as amine alkaloids (e.g. ergonovine) and the structural more complex ergopeptines (e.g. ergotamine, ergocristine) which bear a bulky cyclitol moiety. The other group containing either a methyl or a hydroxymethyl group at position 8 is the so-called 'clavine alkaloids' and consists principally of both 9-ergolenes (e.g. lysergol) and 8-ergolenes (e.g. elymoclavine, agroclavine). Optical isomerism is due to the presence of two asymmetrical carbon atoms (positions 5 and 8) in the lysergic portion of the molecule. Generally, derivatives of L-lysergic acid (the epimer at position 5) and D-isolysergic acid (the epimer at position 8) display a relatively little biological activity.

The ergot alkaloids and their derivatives display such a diversity of biological activity that they cannot be regarded as a single pharmacological or therapeutic entity. There is no evidence to suggest that the diversity of biological properties exhibited by ergot compounds is attributable to a common underlying mechanism at the cellular or molecular level. Indeed, it is more likely that their wide range of biological activities may be best explained by assuming:

1. that ergot compounds interact with more than one receptor site;

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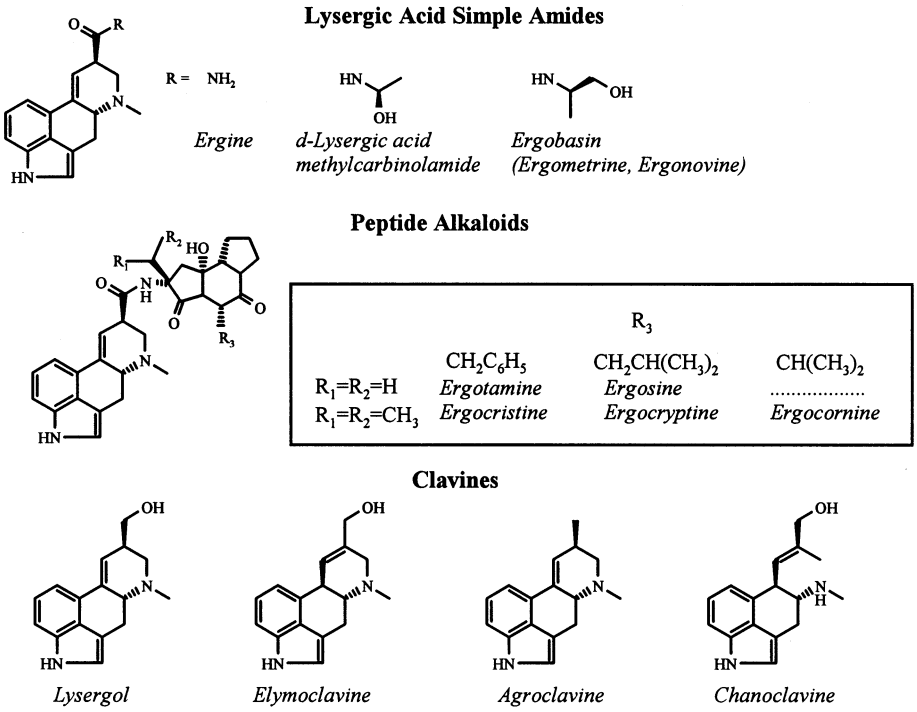
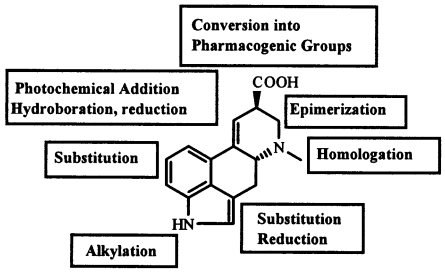


Scheme 1.

2. that the population of receptor sites to which they have access varies from organ to organ;
3. that affinity for receptor sites and intrinsic activity (efficacy) vary from compound to compound.

The biogenic amines, norepinephrine, dopamine, and serotonin, may be viewed as structural elements of the ergoline ring system, which is shared by all the ergot alkaloids [2] (Scheme 2).

However, there are also structural differences between the ergot compounds and the biogenic amines, which may explain why the ergoline derivatives may not only act as agonists or antagonists at the receptor sites of the above-mentioned biogenic amines, but may also assume the dual role of partial-agonists and antagonists. In keeping with their wide spectrum of pharmacological activities, the ergolines find application in the treatment of a variety of clinical conditions. Probably the more important of their many indications are postpartum hemorrhage, migraine and other vascular headaches, orthostatic hypotension, senile cerebral insufficiency, conditions associated with hyperprolactinemia and Parkinson's disease [3]. Hundreds of chemical modifications and synthetic variations of ergot derivatives have been prepared in our and other laboratories. These efforts were aimed at finding compounds with a narrower range of activity with more selective, more specific effect. The basic hypothesis of our work was the assumption that it should have been possible by synthesis to unravel simple ergoline derivatives having an appropriate substituent in position 8 and, in that case, bearing a modified ergoline skeleton, displaying some of the pharmacological activities of the more structurally complex ergot alkaloids. The core of the investigation was the unlimited supply of lysergic acid obtainable by submerged fermentation, which already contains the full ergoline skeleton and a very handy substituent from which a wide array of derivatives could be prepared.



In recent years, our goals were mainly set on the identification of potential drugs of the following type:

- Antiprolactin/dopaminergic

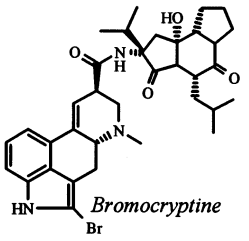
Scheme 2.

- Antidopaminergic
- Serotonergic
- Antiserotonergic

Even more important, but more difficult to achieve in this field, was the quest of highly selective agents, since ergot derivatives normally interfere with a number of different receptor sites: in such a situation is not surprising that the drugs developed (as well as the natural alkaloids) displayed a number of side-effects.

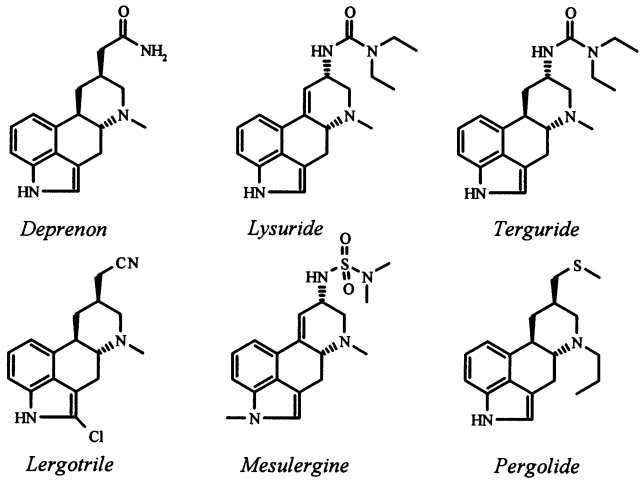
1. Antiprolactin/dopaminergic

In addition to the 'classical' vascular, muscular and CNS effects of ergot alkaloids, Shelesnyak found that ergotoxine (a 1:1:1 mixture of ergocornine, ergocristine and ergocryptine) inhibited the deciduoma reaction that was involved in ovum implantation in rat uterus. Since this action of ergotoxin could be reversed by injecting progesterone, it was concluded that the drug acted via the hypothalamus and pituitary to inhibit prolactin secretion. The ability of ergot alkaloids to inhibit prolactin release from the pituitary assumes an additional significance with the role played by prolactin in the development and growth of certain mammary tumors in animals and its possible significance in human breast cancer. Ergotoxin had a wide range of actions, so Sandoz researchers initiated a search for a selective inhibitor of prolactin secretion. This culminated with the discovery of bromocryptine (2-bromo-ergocryptine) that became the first clinically useful prolactin inhibitor in the ergoline series, used to treat prolactin-related disorders, such as galactorrhoea, prolactin-dependent mammary carcinoma, amenorrhoea, acromegaly [4].



Bromocryptine

Parkinson's disease is a prototype neurodegenerative disorder in which the pathogenic process affects only a small portion of neurons within the mammalian CNS with a high degree of selectivity. Parkinson's disease is characterized behaviorally by movement disorders such as akinesia, rigidity, tremors and flexed posture, and most of the motor symptoms of Parkinsonian patients can be ascribed to forebrain dopamine (DA) depletion. These motor impairments can be corrected by supplying exogenously the immediate DA precursor L-DOPA. A major limitation of the DA replenishment approach with L-DOPA, however, is its relatively short-lived efficacy. The discovery that bromocryptine had dopamine-like activity, due to its interaction with the dopaminergic receptor sites, and moreover its oral efficacy when given to Parkinsonian patients, promoted the search of more potent dopaminergic ergot derivatives [5]. A number of ergolines have been described as dopamine agonists with selectivity for D_2 receptors, and some of them have been evaluated in the treatment of prolactin-related disorders and as replacement for L-DOPA therapy in PD [6] (Scheme 3).



Scheme 3.

Among these ergolines, lisuride, its dihydro analog terguride and particularly pergolide showed potent dopaminergic activity and have been launched on the market as antiprolactin and antiParkinson agents. On the contrary, lergotrile, and mesulergine, very interesting for its biphasic effects on the dopaminergic system, progressed no further for serious toxicological problems [7]. There has been a considerable interest in the identification of the dopamine pharmacophore of the ergolines. Some groups claim (from stereochemical and partial structure considerations) that it is the pyrroleethylamine moiety that confers dopaminergic properties to this class of compounds, while others (from partial structures only) assert that it is the phenylethylamine or rather indoleethylamine partial structure that is the important one.

2. Cabergoline

In Pharmacia & Upjohn, as part of a program to discover new and possibly more selective central dopaminergic agents, a series of ergolinyl-8β-acylurea were synthesized. The design of this class stemmed from the serendipitous observation that a by-product formed from the reaction of dihydrolysergic acid and DCC was endowed with a significant prolactin secretion inhibitory activity. Cabergoline, for its outstanding phar-

Table 1

Comp.[a]	α_1	α_2	D_1	D_2	5-HT	5-HT_2
Cabergoline	3200	290	560	3	170	1000
Bromocryptine	180	360	2000	6	360	280
Pergolide	400	1600	600	20	100	140

[a] Affinity expressed as IC_{50} (nM/l).

macological and pharmacodynamic properties, was selected from this group of dihydrolysergylureas which were obtained by treatment of dihydrolysergic acid with an appropriate carbodiimide or, regioselectively, by reaction of a dihydrolysergamide with a large excess of an alkyl isocyanate [8] (Scheme 7).

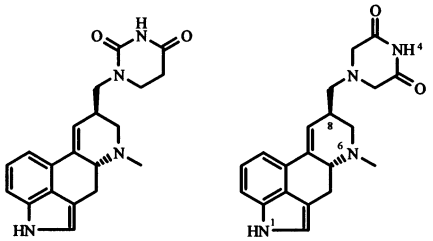
Cabergoline is a potent and selective D_2 receptor agonist, at least 200-fold more potent than bromocryptine in the prevention of fertilized egg implantation in rats (ED_{50} 0.025 versus 5.7 mg/kg), and devoid of hypotensive activity and emesis present in almost all the compounds of this therapeutical class (Table 1).

Moreover, its very long half-life, providing a continuous dopaminergic stimulation, makes this drug a welcome advance among the dopaminomimetics. In prolactin-related disorders, this drug compares very favorably with other prolactin-lowered drugs when efficacy, safety compliance and postwithdrawal data are considered [9]. Clinical studies in Parkinsonians indicates that cabergoline can alleviate Parkinsonian symptoms and reduce motor complication related to L-DOPA therapy, such as dyskinesias and 'on–off' fluctuations with few side-effects [10].

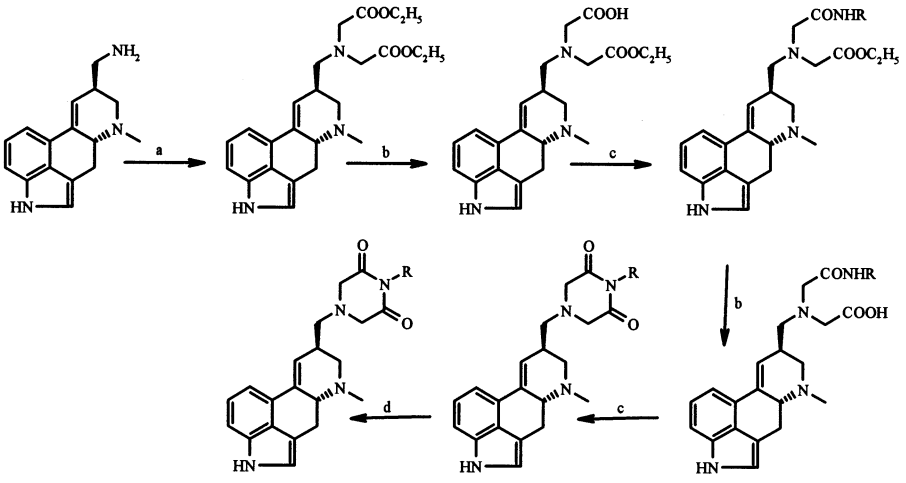
Cabergoline (Cabaser®, Dostinex®) has been launched in different European countries and in USA.

3. Antidopaminergic

Compounds defined as antidopaminergic could find use as antiemetics and in the management of schizophrenia. Potential antidopaminergic ergolines have been sorted out by the climbing behavior test in which pretreatment of mice with a potential antidopaminergic agent counteracts the apomorphine-induced climbing behavior. A positive test indicates that the substance is a potential neuroleptic, being either an antagonist of dopamine at postsynaptic level or a dopamine agonist at presynaptic level. This picture is made more complex in some cases by a biphasic behavior, showing antidopaminergic activity in the above-mentioned test and yet being active in the nidation or turning behavior test predictive for dopaminergic activity. Metabolism may also play a role since ergoline metabolites are often biologically active and the profile can be similar or opposite as in the case of mesulergine. In identifying antihypertensive ergolines, we have observed that PNU 160425 had a very promising antihypertensive activity. This prompted us to synthesize analogs to discover more potent and selective compounds. Replacement of the perhydro-2,4-dioxopyrimidin-1-yl by the isomer 3,5-dioxo-piperazin-1-yl moiety led to PNU 160260. Thus, it was found that the latter was devoid of antihypertensive activity but showed a unique central pharmacological profile.

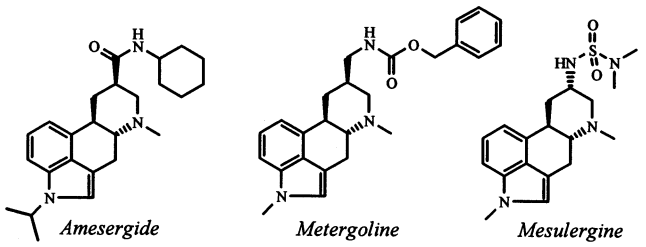


PNU 160425 *PNU 160260*



a) $BrCH_2COOC_2H_5$, K_2CO_3, DMF, rt b) 0.1 M KOH, EtOH, rt c) RNH_2, DIC, Dioxane, reflux
d) 3 atm H_2, Pd/C, CH_3COOH, rt

Scheme 4.



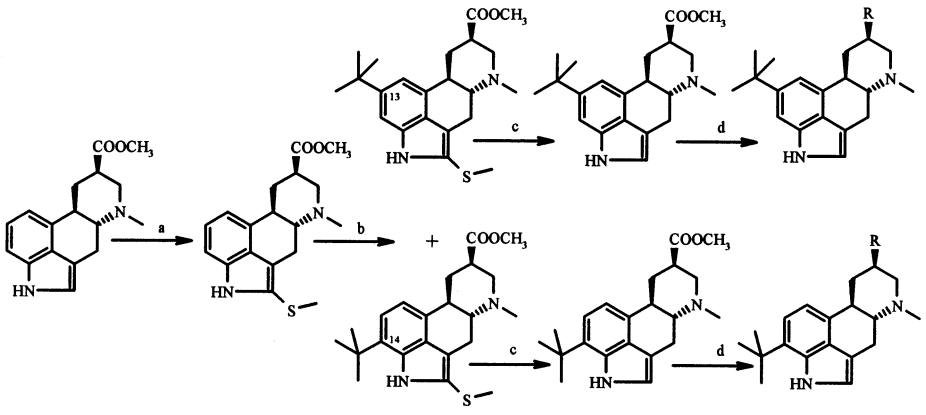
Scheme 5.

This compound behaves as a full dopamine antagonist in normal animals, but shows full agonist properties in denervated models in the same dose range. The compound antagonizes apomorphine-induced climbing behavior in mice, yawning in rats, emesis in dogs and amphetamine-induced toxicity in grouped mice. However, after severely depleting central dopamine experimentally, PNU 160260 behaves as a powerful dopamine D_1 receptor agonist. This compound induces contralateral turning behavior in 6-hydroxydopamine-lesioned rats and reverses 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced akinesia in monkeys and reserpine-induced hypokinesia in mice. Consequently PNU 160260 acts as a D_2 receptor antagonist under normal physiological conditions, but is able to stimulate the D_1 receptors preferentially when endogenous dopamine is no longer available. These results indicate that the antagonist or agonist activity of the compound is substrate-dependent and mostly related to the presence or absence of DA. Mixed agonist/antagonist activity on brain dopamine receptors has been reported for other ergot derivatives with different pharmacological profile, but to our knowledge none of these changes from antagonist to agonist depend on the functional state of the substrate. This leads to the apparently paradoxical suggestion that PNU 160260 could be useful both in psychotic states and extrapyramidal diseases, i.e. in clinical conditions characterized by either excessive or impaired Daergic neurotransmission [11]. In order to gain more insight into such an uncommon pharmacological profile, a series of analogs were synthesized according to Scheme 4.

The structure–activity relationship showed that the dopamine antagonistic/agonistic activity can be strongly affected by the choice of the substituent in position 1 or 2 of the ergoline skeleton leading to in vivo potent dopamine antagonists/agonists, or by the 3,5-dioxopiperazin-4′-nitrogen substituent that mainly afforded in vivo potent D_2 agonists.

4. Serotonergic/antiserotonergic

Serotonin (5-HT, 5-hydroxytryptamine) is an important neurotransmitter that mediates many central and peripheral physiological functions including food intake, sleep, sexual behavior, memory and blood pressure. 5-HT attains such a variety of functions by acting on distinct receptor types. The most recent classification of 5-HT receptor subtypes is based upon the amino acid sequence, gene structure, coupling to the second messenger and pharmacological profile. Of these, 5-HT_{1A} and 5-HT_2 receptor sites have been the most studied as it is generally accepted that they are involved in psychiatric disorders such as depression, schizophrenia and anxiety [12]. Several classes of agents such as arylpiperazines, phenylalkylamines, indolylalkylamines and ergoline derivatives bind at these receptor sites. Notwithstanding the receptorial non-selectivity of most ergolines, compounds such as 5-HT_{2A} antagonist amesergide, 5-HT_{1A} agonist/5-$HT_{2A/2C}$ antagonist metergoline, or 5-$HT_{2A/2C}$ antagonist mesulergine (Scheme



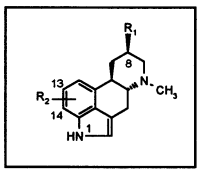
Scheme 6.

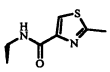
5) do show relative serotonergic selectivity. Thus, the ergolines may be considered a valuable template in the design of serotonergic agents for their conformationally constrained serotonin framework encompassed in the tetracyclic ergoline skeleton.

Our work has been addressed to identify novel ergoline derivatives displaying high and selective affinity either for 5-HT_{1A} or 5-HT_2 receptor sites. Consideration of the general requirements for DA receptor binding, based on the hypothetical model of the DA receptor developed by McDermed et al. suggested that the interaction of ergoline derivatives with DA receptors might be prevented by a bulky group on the phenyl ring of the ergoline skeleton [13]. Following this assumption, the design strategy was based on the introduction of the bulky and metabolically stable *tert*-butyl group on the phenyl ring of the ergoline skeleton, with the expectation to prevent in such a way access to the hypothesized primary binding sites on DA receptors. The key step of the chosen synthetic approach involved the 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 fulfill this requirement. It can be readily removed by action of Raney nickel or nickelborohydride and, furthermore, it has been shown that the 2-thiomethyl group can facilitate aromatic substitution on the phenyl ring of the ergolines [14] (Scheme 6).

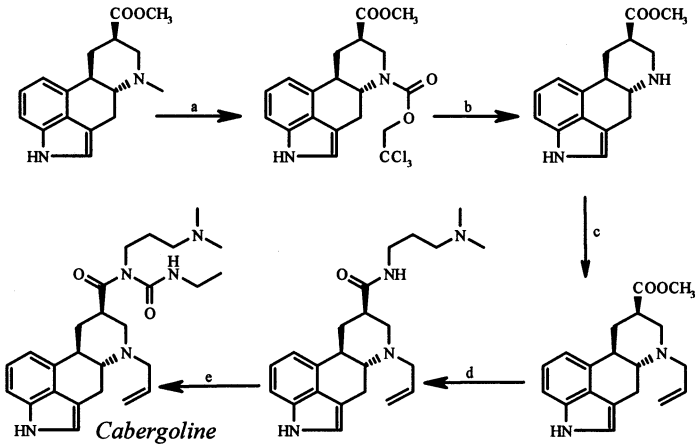
The ester moiety of 13- and 14-*tert*-butyl-methyldihydrolysergate was subsequently converted into a different pharmacogenic group observed to impart central

Table 2



Comp.	R_1	R_2	α_1	α_2	D_1	D_2	5-HT_{1A}	5-HT_2
1		H	0.73	0.41	0.19	0.17	0.82	0.26
2		13-$(CH_3)_3C$	5.23	1.82	>10	1.12	0.12	0.43
3		14-$(CH_3)_3C$	1.11	0.81	>10	1.26	0.58	0.002
4		H	0.35	0.51	0.57	0.22	0.69	0.52
5		13-$(CH_3)_3C$	6.57	0.83	3.81	2.62	0.34	1.22
6		14-$(CH_3)_3C$	1.55	0.87	7.22	0.96	0.57	0.003
7		H	1.32	0.48	4.15	0.075	0.014	0.43
8		13-$(CH_3)_3C$	6.53	>10	3.43	5.17	0.025	6.73
9		14-$(CH_3)_3C$	>10	0.71	>10	2.07	0.031	0.048
10		H	>10	0.08	1.23	0.73	0.24	0.31
11		13-$(CH_3)_3C$	>10	3.57	>10	5.47	0.18	0.61
12		14-$(CH_3)_3C$	0.78	0.45	4.58	1.41	0.93	0.003
13		13-$(CH_3)_3C$	3.22	0.66	>10	1.89	0.003	3.27

Affinity expressed as IC_{50} (nM/l).



a) CCl_3CH_2OCOCl, K_2CO_3, Toluene, reflux B) Zn dust, CH_3COOH, rt c) CH_2=$CHCH_2Br$, K_2CO_3, DMF, rt
d) $(CH_3)_2NCH_2CH_2CH_2NH_2$, cat. CH_3COOH, Toluene, reflux e) CH_3CH_2N=C=O, Toluene, reflux

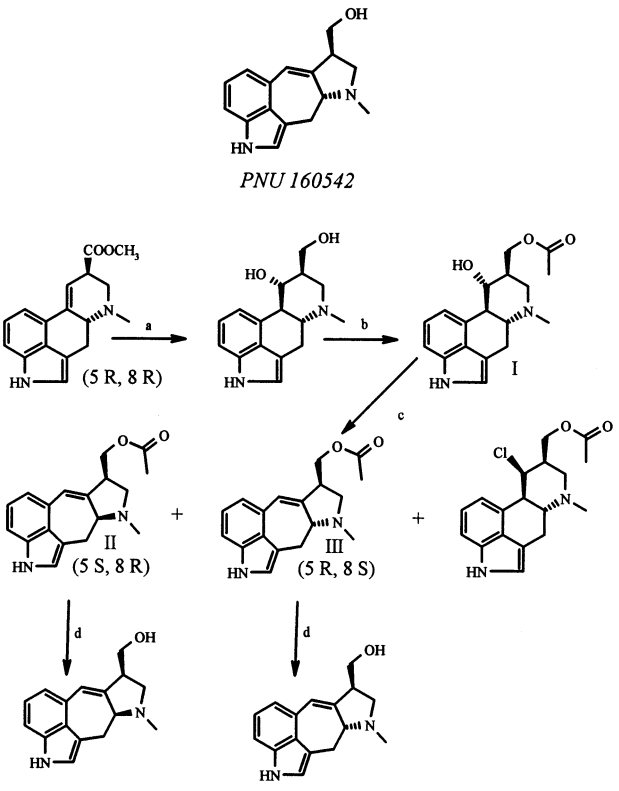
Scheme 7.

activity in the case of the unsubstituted analogs. From the binding data it emerged that the introduction of a *tert*-butyl group either in position 13 or 14 of the ergoline skeleton resulted in a valid strategy for the identification of reasonably potent and selective 5-HT_{1A} or 5-HT_2 ligands. Some general trends can be easily identified. Selectivity for 5-HT_{1A} versus α_1, α_2, D_1, D_2 and 5-HT_2 receptor sites (Table 2) appears to be determined by the presence of a *tert*-butyl group in position 13. The most favorable affinity–selectivity profile is exemplified by **8**, that became the prototype of a series of analogs, some of them, for example **13**, displaying nM affinity for 5-HT_{1A} receptor sites accompanied by at least 100-fold selectivity over other receptors. In vitro (inhibition forskolin-stimulated adenylyl cyclase) and in vivo (5-HT turnover, induction of 5-HT syndrome) data indicated an agonistic activity on the receptor function for these compounds.

In contrast, selectivity for 5-HT_2 versus α_1, α_2, D_1, D_2 and 5-HT_{1A} receptor sites (Table 2) is originated by the presence of a *tert*-butyl group in position 14. Some compounds of this class, for example **3**, **6** and **12**, display nM affinity for the 5-HT_2 receptor accompanied by at least a 100-fold separation in selectivity over the other receptors. Within this set of ergoline derivatives, the adrenergic and dopaminergic binding sites seem to be very sensitive to increases in steric demand in the area of the phenyl ring. Changes in steric demands caused by the aromatic *tert*-butylation have a noteworthy effect on either 5-HT_{1A} selectivity or 5-HT_2 affinity and selectivity. These results provide further evidence of the delicate balance between structure and biological activity for ergot derivatives.

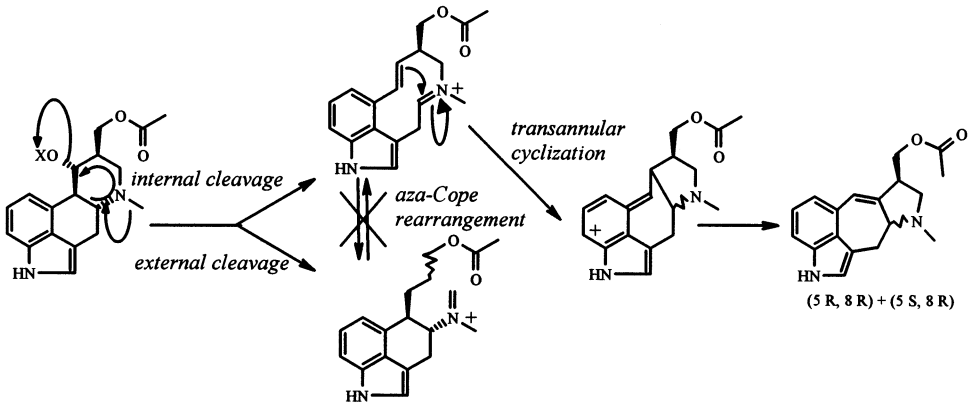
5. Serotonergic abeo-ergoline

In the process of screening different classes of ergolines as novel 5-HT_{1A} ligands, the 5(10→9)*abeo*-ergoline was identified on the basis of its reasonable 5-HT_{1A} affinity and selectivity.



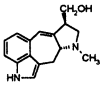
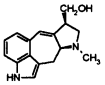
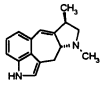
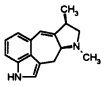
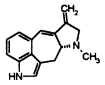
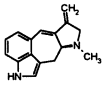
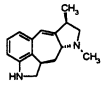
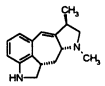
a) $NaBH_4$, $BF_3.Et_2O$, THF, -30°C, then H_2O_2, KOH, THF, 40-50°C, then CH_3OH, reflux
b) CH_3COCl, Py, -10°C C) $POCl_3$, Py.HCl, Py, 40-50°C d) 0.1 M KOH, CH_3OH rt

Scheme 8.



Scheme 9.

Table 3

Comp.	Structure	α_1	α_2	D_1	D_2	5-HT_{1A}	5-HT_2
14		>10	0.23	2.14	1.02	0.02	0.19
15		>10	>10	>10	>10	>10	>10
16		2.33	0.09	1.85	0.94	0.006	0.11
17		7.46	0.78	>10	2.68	0.033	1.63
18		4.39	0.16	6.556	0.52	0.02	0.08
19		4.09	0.21	5.81	0.49	0.015	0.14
20		7.46	0.78	>10	2.68	0.033	1.63
21		>10	1.36	>10	>10	0.003	>10

Affinity expressed as IC_{50} (nM/l).

The (5*R*,8*R*)- and (5*S*,8*R*)-*abeo*-ergoline skeletons were unexpectedly obtained by treatment of the monoacethyl derivative **I** with phosphoryl chloride in pyridine in the presence of pyridine hydrochloride, in an attempt to replace the 9α-hydroxy by a chlorine atom (Scheme 8).

A Wagner–Meerwein rearrangement favored by the antiperiplanarity of the 5–10 and C9–OH bonds was initially proposed as a mechanism of the transposition reaction leading to the 5(10→9)*abeo*-ergoline skeleton (Scheme 9).

Such a mechanism did not account for the formation of **II** having an opposite chirality at C-5 with respect to **I**. Experiments pointed out that a Grob fragmentation, via an internal cleavage through an azecine intermediate, followed by an aza-Cope rearrangement complies better with the formation of the two diastereoisomers [15]. The identification of PNU 160542 prompted the preparation and evaluation of a new series of analogs with a view to identifying compounds with a higher affinity and selectivity for 5-HT_{1A} receptors. The structure–affinity relationship (SAFIR) study revealed sev-

eral 5(10→9)*abeo*-ergoline derivatives with high 5-HT_{1A} affinity and selectivity over α_1, α_2, D_1, 5-HT_2 receptor sites (Table 3).

Within this class of compounds, the receptor binding profile indicated that 5-HT_{1A} affinity was generally enhanced by conversion of the 8β-hydroxymethyl group into a methyl group, for example **14** versus **16**. On the other hand, the highest affinity was associated with 2,3-double bond reduction. In fact, indoline **21** displayed an astounding 5-HT_{1A} selectivity for a compound of this class, being the most potent and selective 5-HT_{1A} ergoline derivative so far reported. PNU 160542 and **21** potently induced 5-HT syndrome in mice, and were highly active in the rat pups-ultrasound vocalization and in the counteraction of stress-induced hyperthermia assays, predictive for a potential anxiolytic activity. It is interesting to note that the diastereoisomer (5*S*,8*R*) **15** was devoid of receptor affinity. Conversely, deoxy **17** and, particularly, diene analog **15**, showed an appreciable 5-HT_{1A} affinity.

These data illustrate the subtle structure–affinity relationship class of the ergoline derivatives, and highlight the richness of this class as a source of potential therapeutic agents.

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