Search for New Lead Compounds: The Example of the Chemical and Pharmacological Dissection of Aminopyridazines

Camille-Georges Wermuth

Faculté de Pharmacie, 74, Route du Rhin, 67401 Illkirch-Cedex, France

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In the last years, molecular biology, automated bioassays and the rapid developments in combinatorial chemistry have merged to form high throughput screening programs as the latest approach to new drug lead discovery. Thanks to automated high throughput methodologies, the major pharmaceutical companies became able to screen on various biological targets 100,000 to 1,000,000 molecules per year. Huge numbers of compounds can be screened in a short time for activity against a large and growing variety of molecular targets. However, after an initial craze for these approaches, people become less enthusiastic and discover the "embarrassement of riches":

1 - Effectively, if one considers the fairly typical situation of a screening program consisting of sixteen assays and a library of 150,000 compounds to be completed in one year, and if a hit rate of only 0.01% seems reasonable, then 120 active leads per year can be expected. In practice, only a very small number of them can be pursued toward development.

2 - On the other hand the costs of these massive testing strategies can grow very rapidly and become a limiting factor. Thus for a set of 200,000 compounds tested on 40 different targets and assuming a mean price of $10 per test, the investment will be $80,000,000!

3 - Finally, many available libraries are made by assembling thousands and thousands of diverse chemicals, often originating from catalogues or in-house collections, alternatively they can originate from combinatorial chemistry. As these compounds stem essentially from arbitrarly chosen libraries, the risk exists of selecting many "low quality" hits for which no information about their bioavailability and their toxicity in man is available.

Taken together, all these drawbacks justify the use of alternative approaches. In this context, we suggest the pharmacological and chemical dissection of a well-known and established drug molecule. For such a molecule bioavailability and toxicity studies have already been performed and the usefulness in human therapy has been proven. The rationale behind this approach lies in the fact that, in addition to their main activity, almost all drugs used in human therapy are able to exert interactions with some other biological targets. The task for the medicinal chemist is then, using traditional optimization procedures, to raise one of the observed "side activities" and to abolish the original main activity. As a result, potent, selective and patentable molecules can be expected, presenting a high probability of success in human therapy.

Applied to the antidepressant aminopyridazine minaprine, this approach has led to interesting dopaminergic, serotoninergic, cholinergic, and γ-aminobutyric acid-ergic (GABA-ergic) ligands as well as to monoamine oxidase and acetylcholinesterase inhibitors. Even more, progressive isosteric modifications have led to highly potent antagonists of the neuropeptide corticotropin releasing hormone (Figure 1).

Aminopyridazines as Monoamine Oxidase Inhibitors.

Further to the pharmacological works on minaprine, a large series of analogues were synthesized and structure-activity relationship studies were undertaken in order both to find new, more potent antidepressant drugs of the minaprine type and to try to dissociate the various behavioral activities of minaprine [1]. Detailing these studies and their results would be too long and we will only present the results obtained with the 4-cyano derivative, 3-(2-morpholinoethylamino)-4-cyano-6-phenylpyridazine (compound **2**: SR 95191), which proved to be a potential antidepressant drug with monoamine oxidase inhibiting properties [2,3]. Compound **2** antagonized reserpine-induced ptosis in both mice and rats, was weakly active in the despair test but did not potentiate yohimbine. On the other hand, compound **2** strongly potentiated the effects of 5-hydroxytryptophan, but hardly modified those of phenylethylamine; this suggested that compound **2** could inhibit type A, but not type B monoamine oxidase activity. In addition, **2** (1-10 mg/kg i.p.) also antagonized rat muricidal behavior.

Given our knowledge on minaprine, a potential dopaminomimetic effect of **2** was also studied. Like minaprine, compound **2** antagonized haloperidol-induced catalepsy, induced stereotyped behavior in rats, and induced contralateral rotations in 6-hydroxydopamine lesioned mice. These effects were sensitive to α-methyltyrosine treatment. Finally, like minaprine, **2** did not induce sedative, stimulant or anticholinergic side-effects.

In terms of mechanism of action, *in vitro* and *ex vivo* studies have shown that **2** specifically and reversibly inhibited type A monoamine oxidase activity (Table 1).

This was confirmed by analysis of brain monoamine levels which were increased, and brain metabolite levels which were decreased. However, compound **2** did not inhibit monoamine uptake, neither *in vitro* nor *in vivo*, nor did exhibit any affinity for the main brain receptors. Thus, it could be assumed that the antidepressant properties of **2** ascribe to its reversible monoamine oxidase inhibiting properties, whereas its dopaminomimetic activity remains unexplained.

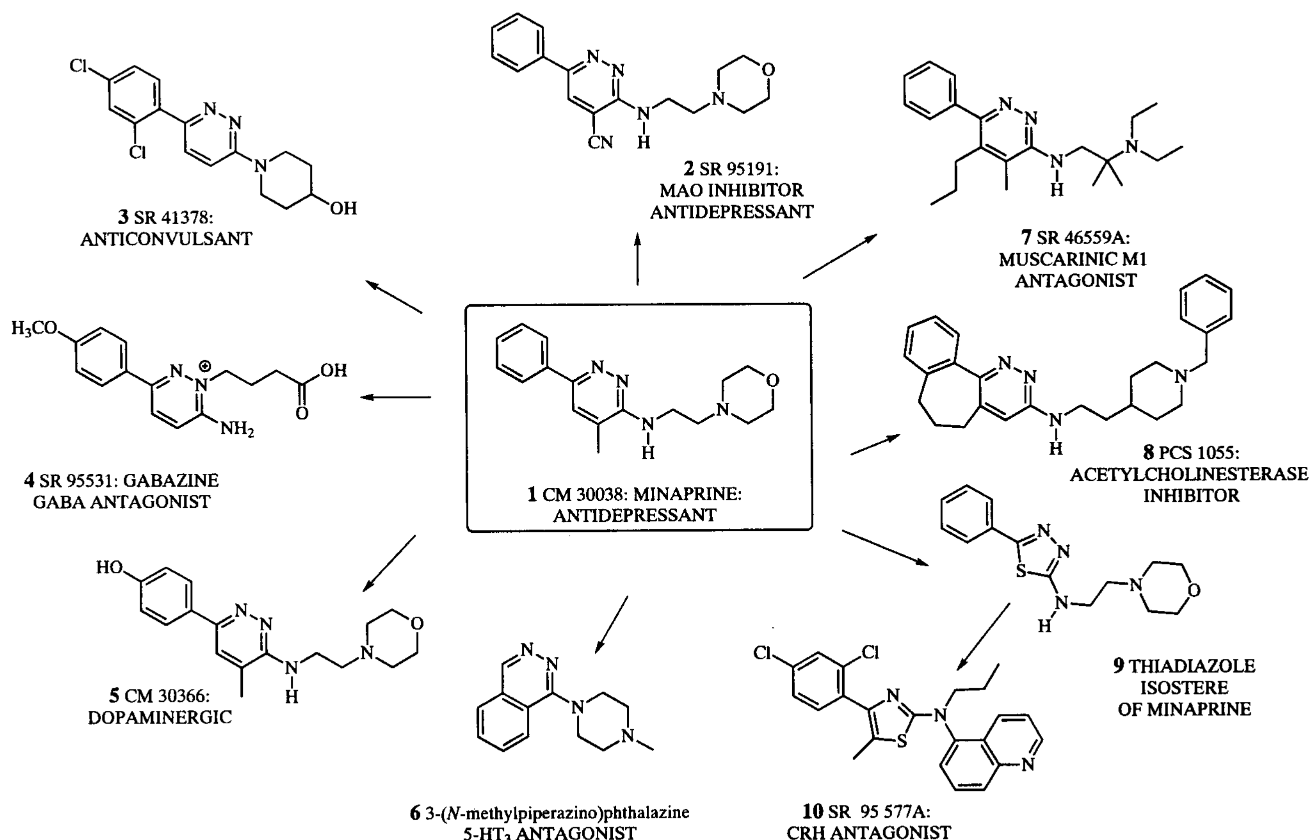


Figure 1. Minaprine-derived structures with various biological activities.

Table 1
Summary of Neurochemical Effects of Compound **2**

In vitro

1) Enzyme Inhibition

Inhibition of MAO-A: IC_{50} = 7 μM

Inhibition of MAO-B: IC_{50} = 600 μM

2) Effects on uptake and receptors (up to 100 μM on):

* Uptake: 5-HT, NA, DA: No effect

* Receptors: 5-HT, NA, DA, ACh, GABA, BZD

Ex vivo

1) Enzyme Inhibition

* Inhibition of MAO-A: ID_{50} = 5-15 mg/kg p.o.

* Inhibition of MAO-B: ID_{50} = >300 mg/kg p.o.

* 1/2 life: brain 8 hours, liver 16 hours

* Reversible (Antagonism of clorgyline)

2) Effects on neurotransimitters and their metabolites (At 10-300 mg/kg p.o.):

* Striatum: ↑ 5-HT; ↓ 5-HIAA
* Striatum: ↑ DA; ↓ 8-MT; ↓ DOPAC
* Hypothalamus: ↑ NA; ↓ MHPG

3) Uptake Inhibition

No inhibition of monoamine uptake up to 100mg/kg i.p.

In summary, 2 appears slightly more potent than minaprine as an antidepressant drug, much more potent than minaprine as a monoamine oxidase inhibitor, and about equipotent as a dopamine (DA) stimulant drug. Finally, it must be noted that 2 has lost the cholinomimetic activity of minaprine.

Piperidinylpyridazines as Anticonvulsant Drugs.

During investigations on putative metabolites of minaprine such as the hydroxyethyl derivative, 3-hydroxyethylamino-4-methyl-6-phenylpyridazine (**11**, CM 30094, Figure 2), it turned out that this compound possessed some anticonvulsant properties. Compound **11** and its homologue **12** blocked seizures induced by bicuculline and strychnine in mice [4].

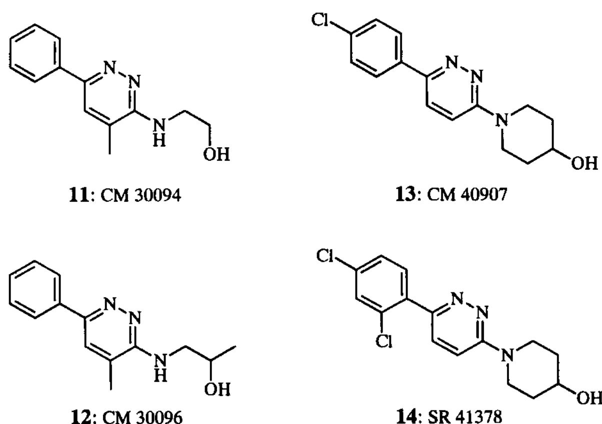


Figure 2. Anticonvulsant Aminopyridazines.

Further investigations, by Hallot and coworkers at Sanofi Research led to the synthesis of a series of 3-(4-hydroxypiperidinyl)pyridazine derivatives. Two of them, compounds **13** and **14**, (Table 2) proved to be potent, wide-spectrum anticonvulsants [5-7]. These compounds are potent antagonists of electroshock, bicuculline and pentatraazole-induced seizures. They antagonize also photogenic epilepsy in *Papio papio* baboons and kindled amygdaloid seizures in the rat, after oral administrations.

The molecular mechanism of action of this drug remains unknown, but there are some indications that the Cl-ionophore may be involved. Although compounds such as **13** and **14** do not displace [^{3}H]-*tert*-butylbicyclo[2.2.2]phosphorothionate ([^{3}H]-TBPS), the corresponding acetic or carbamic esters are potent displacers, with IC_{50} values in the nanomolar range (Heaulme, Sanofi Research, Personal communication).

Table 2

Anticonvulsant Aminopyridazines Bearing Hydroxylated Side Chains

Compound	Maximal Electroshock Seizures ED_{50}, mg/kg, p.o., mice	Bicuculline Seizures ED_{50}, mg/kg, p.o., mice
11	107	286
12	209	175
13	10	38
14	10	8.5

Pyridazinyl-γ-aminobutyric Acid Derivatives as γ-Aminobutyric Acid$_A$ Antagonists.

With the objective of designing γ-aminobutyric acid-mimetic drugs able to penetrate the CNS, we incorporated the γ-aminobutyric acid moiety in an aminopyridazine structure. This was achieved by N(2) alkylation of a 3-amino-6-phenylpyridazine (Scheme 1). Surprisingly these pyridazinyl-γ-aminobutyric acid derivatives turned out to be potent and selective *antagonists* of the γ-aminobutyric acid$_A$ receptor subtype [8-12]. The compounds **15**, **16** and **17** for example (Scheme 1) displaced [^{3}H]-γ-aminobutyric acid from binding sites in brain, and are much more potent than the classical antagonist bicuculline (Table 2).

The compounds also antagonized, *in vitro*, the γ-aminobutyric acid-elicited enhancement of [^{3}H]-diazepam binding, with a still greater potency than bicuculline. This observation was the first evidence indicating that the compounds were antagonists rather than agonists at the γ-aminobutyric acid$_A$ receptor sites (Table 2).

The antagonistic profile of the pyridazinyl-γ-aminobutyric acid derivatives has been confirmed in electrophysiological experiments. *In vitro*, using the dorsal root ganglion preparation, Feltz *et al.* have shown that compound **15** was able to antagonize the γ-aminobutyric acid induced depolarization in a concentration-dependent manner [9]. Similarly, *in vivo*, using microiontophoretic applications in the cuneate nucleus of the anesthetized rat, it has been shown by Michaud *et al.* that these drugs selectively reversed the inhibition of firing induced by γ-aminobutyric acid, but not that induced by glycine [11].

Finally, when injected intravenously, these antagonists induced clonic seizures which could be blocked by the γ-aminobutyric acid agonist muscimol. However, in this respect, the Sanofi Recherche drugs were far less potent than bicuculline, suggesting a poor penetration into the brain. Compound **17** has been tritiated and shown to specifically label γ-aminobutyric acid$_A$ receptors with a high affinity. This ligand, called Gabazine, is now available for further research [13,14].

On the chemical side (Scheme 1), the main difficulty consists in the synthesis of suitable 3-aminopyridazines; effectively the direct amination of 3-chloropyridazines

Scheme 1

Synthesis of Pyridazinyl-γ-aminobutyric Acid Derivatives and Chemical Structures of the Pyridazinyl-γ-aminobutyric Acid Derivatives Examined in this Study

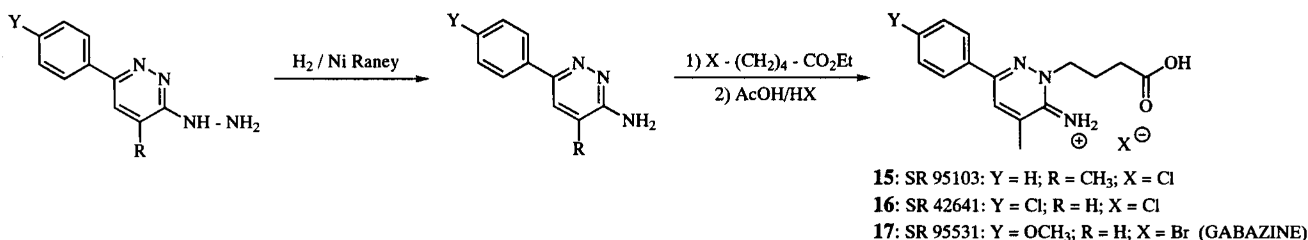


Table 3

Pyridazinyl-γ-aminobutyric Acid Derivatives: Summary of *in vitro* and *in vivo* Activities

Drugs	Displacement of [^{3}H]-GABA (IC_{50}, μ*M*)	Antagonism of GABA-induced rise of [^{3}H]-FNZ binding (IC_{50}, μ*M*)	Induction of Convulsions (*M*) CD_{50} (mg/iv)
15	2.2	11	139
16	0.28	0.25	15
17 (Gabazine)	0.15	0.44	10
Bicuculline	38	13	0.6

IC_{50} = 50 per cent inhibitory concentration (*in vitro*); CD_{50} = 50 per cent convulsant dose (*in vivo*).

with ammonia takes place with low and/or erratic yields. Therefore, an indirect preparation, based on a catalytic hydrogenolysis of the 3-hydrazinopyridazines was finally preferred [15].

The chemical reactivity of the delocalized *exo-endo* amidinic system in 3-aminopyridazines entails that *alkylating* reagents lead selectively to N(2) *endo*-alkylations, whereas *acylating* reagents readily and selectively act on the *exo* amino group. We took advantage of this particular behavior in preparing the *exo*-alkylated isomer **21** of the Sanofi Recherche γ-aminobutyric acid antagonists as illustrated in Scheme 2 [4]. This compound was found to be totally inactive in [^{3}H]-γ-aminobutyric acid displacement experiments. On the other hand, it is noteworthy to mention that in the N(2) *endo*-alkylated compounds, such as **15-17**, the γ-aminobutyric side-chain can be replaced by other γ-aminobutyric acid-mimetic structures such as muscimol, thiomuscimol [16], or homotaurine (Wermuth and Bourguignon, unpublished results) again yielding potent γ-aminobutyric acid antagonists.

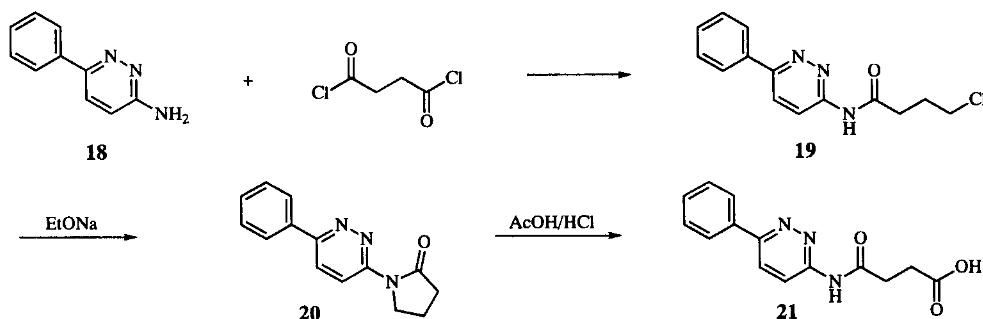
Structure-activity relationship studies demonstrated that besides the mimetic character due to the γ-aminobutyric acid moiety, the nature of the substituents on the phenyl ring were of prime importance [4,12,16]. Computer graphics modeling of the pyridazinyl-γ-aminobutyric acid derivatives, with regard to other known γ-aminobutyric acid antagonists, allowed us to propose a common pharmacophore and to elucidate the reasons for which apparently active compounds are actually inactive [17].

Dopaminergic Properties of Aminopyridazines.

In *in vivo* experiments minaprine clearly demonstrates dopamine-like activities. Particularly it antagonizes potently prochlorperazine-induced catalepsy in rats and potentiates amphetamine-induced stereotyped behavior [18]. The main first pass metabolite of minaprine is the corresponding *para*-hydroxy derivative [3-(2-morpholinoethylamino)-4-methyl-6-(4-hydroxyphenyl)pyridazine] **5b** [19]. The corresponding dihydrobromide, compound, 3-(2-morpholinoethylamino)-4-methyl-6-(4-hydroxyphenyl)pyridazine hydrobromide (CM 30366, **5a**) was extensively studied by Worms *et al.* [20]. These authors observed the high dopaminomimetic activity of this compound, suggesting that the dopaminomimetic activity observed for minaprine *in vivo* may be due to its metabolic hydroxylation at the *para* position. The rational explanation of the dopaminergic profile becomes clear if we consider the following analogies (Figure 3).

Scheme 2

Synthesis of the *exo*-Alkylated Pyridazinyl-γ-aminobutyric Acids



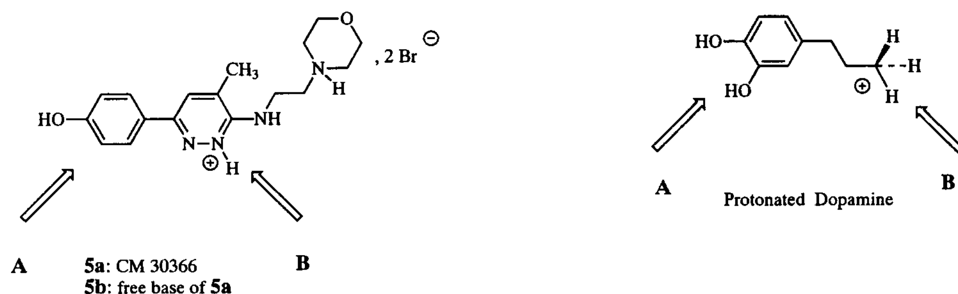


Figure 3. Comparison of the minaprine metabolite CM 30366 **5a** and dopamine. **A** = Presence of a planar phenyl ring bearing at least one phenolic hydroxy group; **B** = Presence of a positive charge located at a distance of two carbon atoms from the aromatic ring.

It was effectively shown that the protonation of substituted aminopyridazines takes place at the *endo* nitrogen of the *endo-exo* amidinic function [21-23]. Logically it can be speculated that the side chain-truncated analogue **22** of **5a** (Figure 4) will maintain the dopaminomimetic profile. On the contrary, the removal of the *p*-hydroxyphenyl group, yielding the diprotonated desphenylminaprine **23**, would probably inactivate the molecule in terms of dopaminomimetic activity.

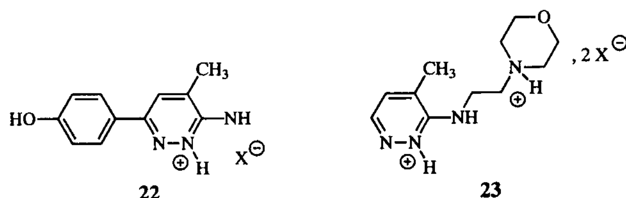


Figure 4. Truncated analogues of compound **5a**.

Serotoninergic Properties of Aminopyridazines.

As many antidepressants, minaprine exhibits serotoninomimetic activities as illustrated in rats by its ability to potentiate 5-hydroxytryptophane-induced tremors and head twitches (ED_{50} = 24 mg/kg i.p.) and its antagonism of the muricide behavior in aggressive rats at 10 mg/kg i.p. [24]. After consideration of the X-ray structure of minaprine and some analogues [21], a model was proposed to account for the serotonin-like properties [24]. In this model the methyl group in the four position and the exocyclic sp^2 atom of minaprine ensure the correct orientation of the morpholinoethyl side chain and the coplanarity of its first methylene group with the pyridazine nucleus (Figure 5). This latter can be overlayed with the phenyl ring of serotonin and the lone pair of the N1 nitrogen can each play the role of the lone pairs of the 5-OH oxygen of serotonin.

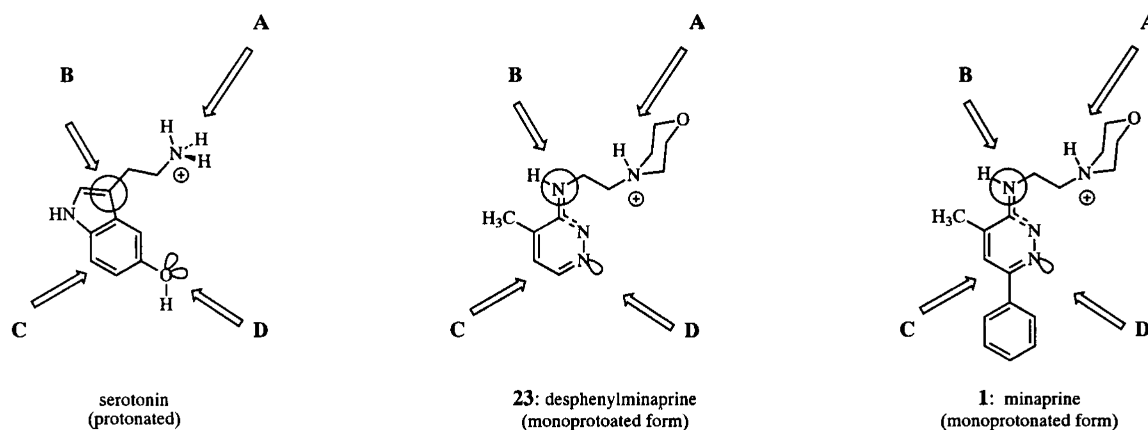
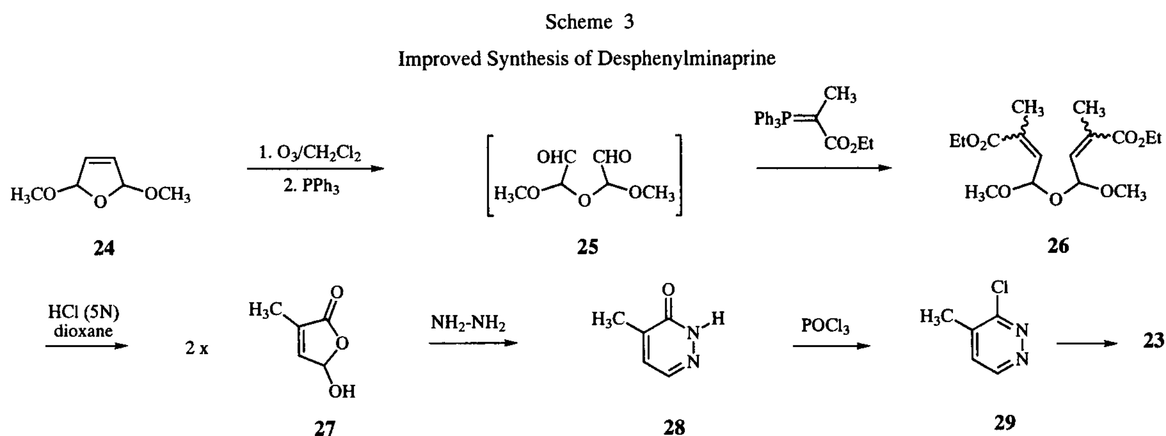


Figure 5. Bioisosterism between minaprine, desphenylminaprine and serotonin. **A** = protonated nitrogen; **B** = *sp*[2] carbon or nitrogen; **C** = aromatic plane; **D** = oxygen or nitrogen lone pairs.

According to this model the phenyl ring in position 6 of minaprine does not appear essential and desphenylminaprine should conserve the serotoninomimetic profile. However it should no longer possess dopaminergic activity. This was effectively observed in some preliminary studies [24]. With the objective of reinvestigating the profile of desphenylminaprine on the different subtypes of serotonin and dopamine receptors, Leisner and Mann developed in our laboratory an original route to this molecule. The synthesis is based on the use of 5-hydroxy-3-methyl-2(5*H*)-furanone **27** which was prepared according to Fell and Harbridge [25] (Scheme 3).

Scheme 3

Improved Synthesis of Desphenylminaprine



Later on, molecular modeling studies performed on 3-aminopyridazine-derived muscarinic M_1 agonists (see below) showed some striking similarities between the muscarinic M_1 agonist and the 5-hydroxytryptamine receptor (5-HT_3) antagonist pharmacophore models. This analogy prompted us to use the 3-aminopyridazine core also for the design of 5-HT_3 receptor antagonists [26]. The most active compound turned out to be the phthalazine analogue *endo-N*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1*H*-indazole-3-carboxamide hydrochloride (**29**) ([^{3}H]-BRL 43694 displacement: IC_{50} = 10 n*M*; Figure 6).

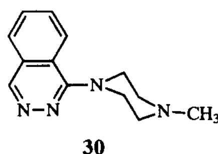


Figure 6. Structure of an aminopyridazine-derived 5-HT_3 antagonist.

Aminopyridazines as Muscarinic Agents.

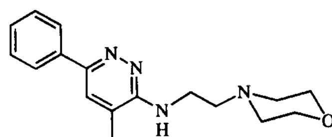
Besides its original antidepressant properties, minaprine exhibits some cholinomimetic activities in rodents [27]. It was also found beneficial in senile dementia [28]. In biochemical experiments, minaprine has a weak, but highly selective, affinity for hippocampal M_1 receptors (IC_{50} = 17 *μM*) and behaves as a partial agonist. Along with the excellent tolerance of minaprine in humans, these results prompted us to design in this series new non-toxic, selective and potent agonists at the M_1 muscarinic receptors [29-31]. Thanks to classical structure-activity relationship studies we were able to improve the affinity of the partial agonist minaprine for hippocampic M_1 receptors by a factor of 5660. Critical improvements resulted from a shift of the 4-methyl to the 5-methyl position (**1** → **31**), replacement of morpholine by a more lipophilic amine (**31** → **32**) and introduction of a phenolic hydroxyl group in the *ortho* position of the 6-phenyl ring (**32** → **33**; Figure 7).

Based on industrial considerations, compounds such as **33-36** (Figure 8) were considered rather than **33**. Finally 6-(*N,N*-diethylamino-2,2-dimethylethylamino)-3-phenyl-4-(*n*-propyl)pyridazine (compound **36**, SR 46559A) has been retained as candidate for preclinical development. Compound **36** is not toxic at doses up to 300 mg/kg (p.o.) and does not produce any of the classical cholinomimetic side effects at such a dose [32]. It antagonizes rotations induced by intrastriatal injection of the M_1 antagonist pirenzepine (ED_{50} = 0.12 mg/kg p.o.) in mice.

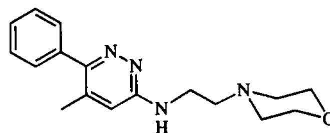
Like muscarinic agonists (oxotremorine and arecoline) compound **36**, already at the dose of 0.1 mg/kg (p.o.) potentiates haloperidol-induced catalepsy in rats. It antagonizes scopolamine- and pirenzepine-induced deficit in passive avoidance learning rats with ED_{50} of 0.25 mg/kg and 0.027 mg/kg (p.o.) respectively. Moreover, using the social memory test with aged mice or ischemic rats, compound **36** improves memory deficits at minimal effective doses of respectively 0.1 mg/kg and 3 mg/kg (p.o.).

Aminopyridazines as Acetylcholineesterase Inhibitors.

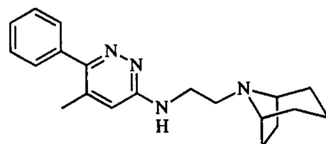
Studies performed by Garattini *et al.* on the mode of action of minaprine suggested already in the early eighties, that this compound may, at least in part, act as an inhibitor of acetylcholineesterase. Thus, an *in vivo* administration of minaprine (30 mg/kg p.o.) to rats, significantly increased the acetylcholine levels in hippocam-



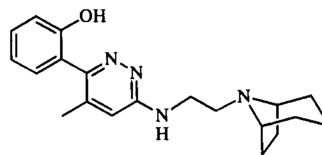
1 IC_{50} = 17 μM



31 IC_{50} = 0.550 μM

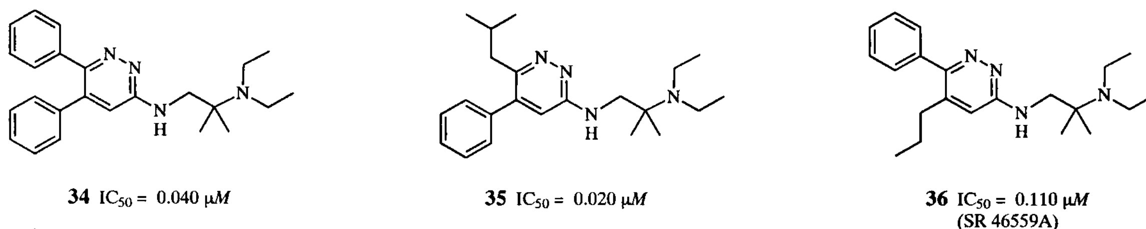


32 IC_{50} = 0.050 μM



33 IC_{50} = 0.003 μM

Figure 7. Progressive increase of the muscarinic M_1 potency of minaprine.



34 IC_{50} = 0.040 μM

35 IC_{50} = 0.020 μM

36 IC_{50} = 0.110 μM (SR 46559A)

Figure 8. Muscarinic M_1 agonists.

pus (38%) and in striatum (60%) [33]. On the other hand, minaprine being recognized by the muscarinic M_1 receptors, we hypothesized that, it should also be recognized by the enzyme acetylcholineesterase, both systems interacting with the same biomolecule, acetylcholine. Minaprine would thus represent an original lead for the development of new acetylcholineesterase inhibitors. Effectively, when we tested minaprine on *in vitro* assays, it showed a weak, competitive and reversible, acetylcholineesterase inhibitive activity (Ki = 85 μM on purified cerebral rat acetylcholineesterase).

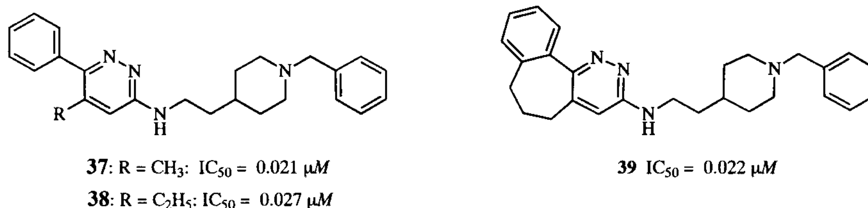
Here again, thanks to a combination of classical structure-activity relationship explorations and of computer-aided design, we were able to strongly improve the acetylcholineesterase inhibition potency. The critical elements that we observed for high acetylcholineesterase inhibiting activity are somewhat different from that necessary for muscarinic affinity [34]. With respect to minaprine, they can be summarized as follows: a) necessity of a more lipophilic cationic head, *N*-benzyl piperidine representing an optimum; b) change from a 2 to a 4-5 carbon units distance between the pyridazinic *exo* nitrogen and the cationic head; c) a torsion angle of about 50° between the pyridazine ring and the phenyl ring. A typical representatives are the compounds **37-39** shown in Figure 9, they exhibit IC_{50} values of about 0.020 μM on electric eel acetylcholineesterase which, in comparison to minaprine represent a 4000-fold gain in potency. The corresponding value for butyrylcholineesterase inhibition is IC_{50} = 0.94 μM and represents butyrylcholineesterase/acetylcholineesterase ratio of 45, which can be considered as satisfying.

An additional interest in these compounds resides in the fact that they possess simultaneously the capacity to directly activate the muscarinic M_1 receptors, apparently as partial agonists and to stimulate the acetylcholine release, apparently in blocking the presynaptic M_2 receptors. The values we found for compound **39** were respectively IC_{50} = 141 nM (M_1 affinity, [^{3}H]-pirenzepine displacement in rat cerebral cortex), IC_{50} = 250 nM (M_2 affinity, [^{3}H]-methoctramine displacement in rat heart tissue). This triple profile renders the compounds particularly attractive, compared to conventional acetylcholine esterase inhibitors.

Aminopyridazines as Leads for Corticotropin Releasing Hormone Antagonists.

In the early phases of development of the antidepressant minaprine, we considered the possibilities of replacement of the central pyridazine ring by various isosteric heterocycles such as pyridine, pyrimidine, pyrazine, triazines thiadiazoles and thiazoles [35]. Starting from the thiadiazole analog **9** (Figure 1) the Sanofi scientists switched progressively to thiazole analogs. These compounds were less active than minaprine in terms of antidepressant properties, but, some years later, in a broad screening program, they turned out to exhibit antagonistic properties toward the receptors of corticotropin releasing hormone.

Corticotropin releasing hormone is a 41-amino acid peptidic hormone released by corticotropin releasing hormone neurons of the endocrine hypothalamus. Its physiological role is to trigger the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary and thus to induce the secretion of glucocorticoids such as



37: R = CH_3: IC_{50} = 0.021 μM

38: R = C_2H_5: IC_{50} = 0.027 μM

39 IC_{50} = 0.022 μM

Figure 9. Minaprine-derived acetylcholineesterase inhibitors.

cortisol from the adrenal cortex (Figure 10). Antagonists of the corticotropin releasing hormone may be useful for the treatment of stress-induced syndromes or of depressive states.

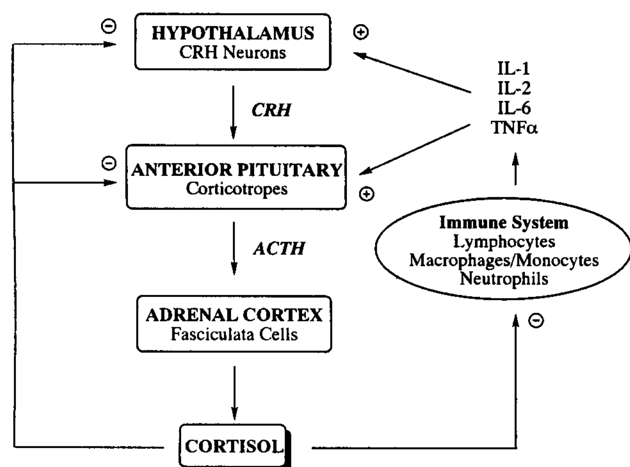


Figure 10. Overview of the hypothalamic-pituitary-adrenal (HPA) axis and its bi-directional communication with the immune system (after Schimmer and Parker, [36]).

Within this series of compounds again we were able, in collaboration with Gully and Roger from the Sanofi company, to increase the selectivity and the potency to subnanomolar ranges [37]. A representative example in these series is the compound **10** (Figure 1) which is able to displace [^{3}H]-corticotropin releasing hormone with an IC_{50} value of 80 n*M* and which functionally inhibits corticotropin releasing hormone-induced adrenocorticotropic hormone release.

Conclusion.

The results presented in this review aim first to demonstrate the interest of aminopyridazines in medicinal chemistry. Starting from one given bioactive aminopyridazine, we were able to open eight new and different avenues in important therapeutic areas. Other posssibilities can certainly be explored in the future, particularly taking into account that the *exo-endo* amidine function present in the 3-aminopyridazines can act as bioisostere of peptide or ester functions. The protonated amidino group may also be used as guanidino surrogate.

However, another lesson we learned is that identifying the multiple activity facets of an already well-known drug is a fertile lead source for new drug candidates. Of course, some of the researched potentialities are only present in a weak manner in the parent molecule and have to be scaled up. Moreover the different unwanted activities have to be abolished. Surprisingly, the systematic application of conventional chemical modifications and structure-activity explorations achieve these two goals in a reasonable time span and more easily than one would expect *a priori*. For all these reasons the approach we propose constitutes an interesting alternative to the various high throughput methodologies and should therefore be maintained in the practice of medicinal chemistry.

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