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Review Article

Identification of α_{1A}-adrenoceptor selective antagonists for the treatment of benign prostatic hyperplasia

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CONTENTS

Introduction

Benign prostatic hyperplasia (BPH), a urological disorder prevalent in the aging male population, is a manifestation of noncancerous proliferation of glandular and fibromuscular tissue in the transition and periurethral zones of the prostate gland (1, 2). The enlarged prostate radially compresses the urethra thereby impairing urine flow. In addition to this static component, the adrenergic tone of the prostate is elevated in BPH patients, which results in further tightening of urethra (dynamic component). The typical symptoms of prostatism are obstructive (poor urine stream, dribbling, large residual urine volume) and irritative (hesitancy, increased frequency of urination, nocturia) in nature and can significantly compromise the quality of life of patients (3, 4). While surgical procedures or the use of 5α-reductase inhibitors such as finasteride are used to reduce the prostatic mass, α_1-adrenergic receptor antagonists such as terazosin, doxazosin and tamsulosin are administered to treat the dynamic component of BPH (5, 6). These α blockers relax the smooth muscles in the prostate and lower urinary tract and facilitate urine flow by regulating the adrenergic component of the sympathetic nervous system. However, some adverse events such as orthostatic hypotension, tachycardia, syncope and fatigue have been reported with these clinical agents in some patients and a dose titration is usually required (7-9). These cardiovascular side effects are attributed to a nonselective blockade of α_1-adrenoceptors present in vascular smooth muscle in addition to the required blockade of α_1-adrenoceptors in prostatic tissue (10). It has been shown that α_{1A}-subtype is the predominantly expressed α_1-adrenoceptor in human prostate (11). In addition, the binding affinities of a number of antagonists for the recombinant alpha$_{1A}$-adrenoceptor were found to correlate well with the potencies of the same antagonists to block agonist-induced contraction of prostatic smooth muscles (12, 13). Collectively, these observations suggest a possibility that a selective blocker of the α_{1A}-adrenoceptor could alleviate the symptoms associated with BPH with minimal cardiovascular side effects.

A number of antagonists that belong to different structural classes and display varying selectivities for the α_{1A}-adrenoceptor over the α_{1B}- and α_{1D}-adrenoceptors have been reported by several research groups (6, 14, 15). However, the scope of this review is limited to the compounds that were synthesized and studied in the context of the independent and collaborative research efforts from Synaptic Pharmaceutical Corporation and Merck Research Laboratories. This overview will focus on how the research teams used the information regarding structure-activity relationships (SAR), metabolism and pharmacokinetic properties from each structural class of compounds for the design of the subsequent generations of α_{1A}-selective antagonists.

Dihydropyridines

Niguldipine (compound **1**), a dihydropyridine originally used as a calcium channel blocker (K_i = 4.6 nM for rat L-type calcium channel), served as the early lead in the research program at Synaptic due to its high binding affinity (K_i = 0.16 nM) for the recombinant human α_{1A}-adrenoceptor and selectivity (> 300-fold) over α_{1B}- and α_{1D}-adrenoceptors. Judicious alterations of some structural features of niguldipine (*i.e.*, replacement of the ester functionality at C-3 with an amide group and replacement of the 3-nitrophenyl group with a 4-nitrophenyl group at C-6) led to a series of dihydropyridines, that demonstrated high binding affinity (K_i < 1 nM) for the α_{1A}-receptor but were selective (> 300-fold) over the rat L-type calcium channel (Fig. 1). One such compound, SNAP-5089(–) (**2**), possessed high binding affinity (K_i = 0.18 nM) and selectivity (> 1000-fold) for the α_{1A}-receptor over the α_{1B}- and α_{1D}-adrenoceptors, but had significantly lower affinity

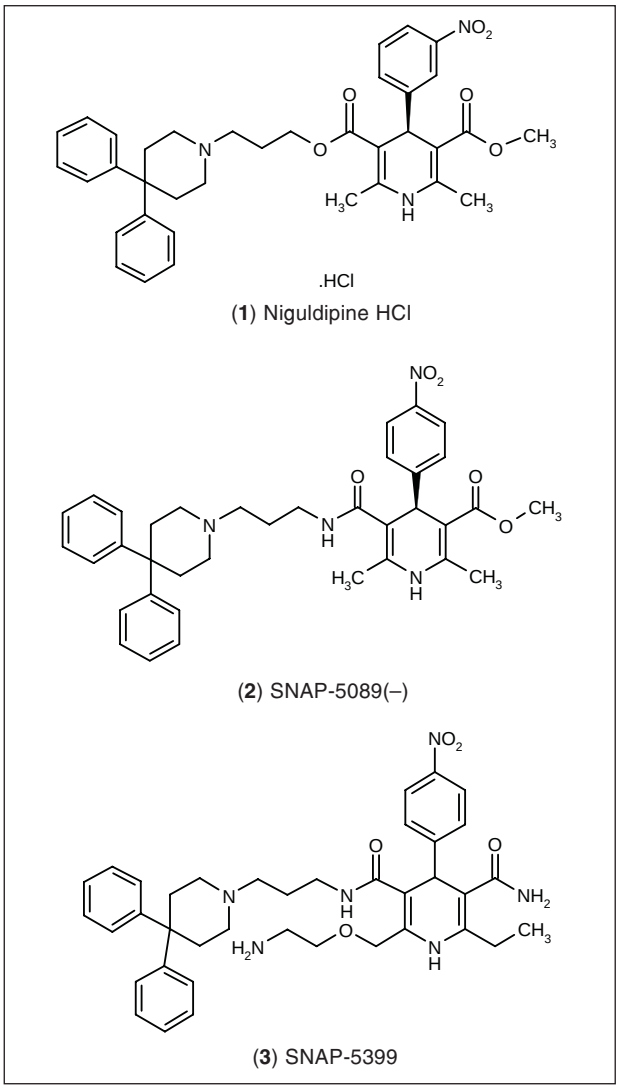

Fig. 1. Dihydropyridines.

(K_i = 670 nM) for the rat L-type calcium channel (16). However, SNAP-5089(–) was difficult to handle, possessed low oral bioavailability and was less potent in the functional assay (17). Some of these issues could be related to the highly lipophilic nature of the compound. The synthesis and SAR in the dihydropyridine series of compounds have been the subject of several publications (18-22). Compounds such as SNAP-5399 (compound **3**), which display good correlation between the binding affinity (K_i = 1.4 nM) and the potency to inhibit the phenylephrine-induced contraction of dog prostate (K_b = 1.4-1.5 nM), were reported (22). However, many dihydropyridines were found to have suboptimal pharmacokinetic properties. The propensity of the 1,4-dihydropyridine nucleus towards metabolic oxidation was suspected to be a possible reason for the short plasma half-life and low oral bioavailability of the compounds. A search was undertaken to replace the dihydropyridine nucleus with other heterocycles with the hope that the new compounds would maintain the desirable binding (K_i < 10 nM) and selectivity (> 100-fold) profile for the α_{1A}-adrenoceptor and have improved pharmacokinetic properties. Initially, dihydropyrimidinones and dihydropyrimidines, which contain a nitrogen atom at the 3-position of the heterocycle, were considered as potential replacements (23, 24). These templates have previously been used as a replacement for the dihydropyridine nucleus in another research program (25).

Dihydropyrimidinones

A number of reports that describe the synthesis and SAR in the dihydropyrimidinone series of compounds as well as some information on the metabolism and functional potency in animals for the selected compounds have been published (23, 26-34). The general structure of a typical dihydropyrimidinone is represented as compound **4** in Figure 2. Some general trends for the dihydropyrimidinone series of compounds with respect to the substitutions on the dihydropyrimidinone core unit, the linker and the side chain heterocycle (piperidine in most cases) are summarized below.

The nitrophenyl group at the 4 position of the dihydropyrimidinone (a remnant from the SNAP-5089-like compounds) was considered to have potential toxicity issues. For this reason, a search was undertaken to identify isosteric replacements for the 4-nitrophenyl group.

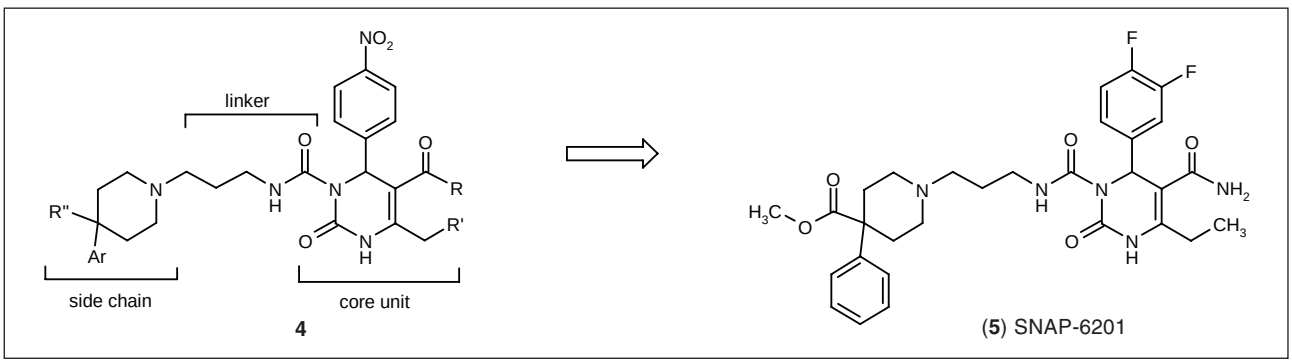

Fig. 2. Dihydropyrimidinones.

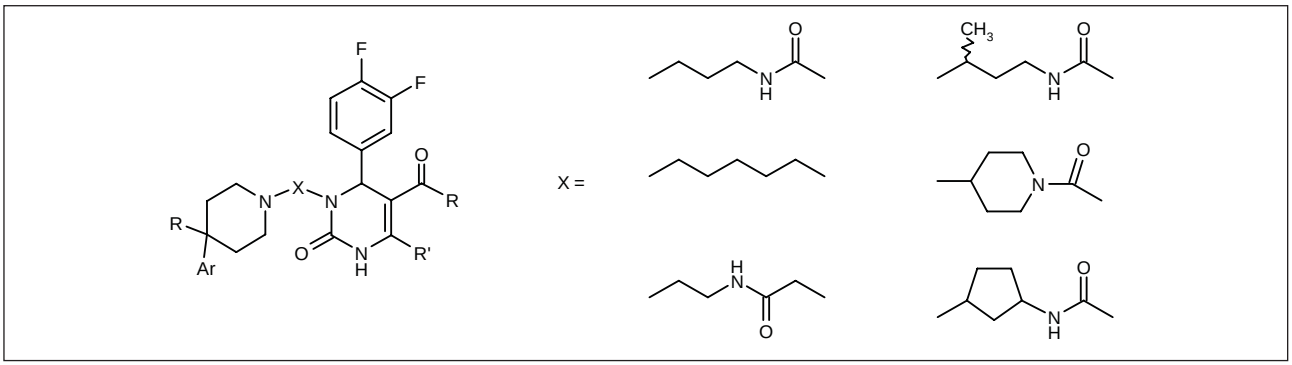

Fig. 3. Modifications in the linker.

Compounds possessing a di- or trifluorophenyl group at the C-4 position of the dihydropyrimidinone ring showed binding affinities and selectivities for the α_{1A}-receptor that were comparable to those of the corresponding nitrophenyl compounds. The 3,4-difluorophenyl group was the most widely used moiety among the published structures of dihydropyrimidinones. However, compounds with other C-4 substituents such as 3,4-benzofurazanyl, 2,4- or 3,5-difluorophenyl and 3,4,5-trifluorophenyl also show comparable binding affinity and selectivity for the α_{1A}-receptor (23). In general, the (+)-enantiomer (*S* configuration at the C-4 stereogenic center) of the dihydropyrimidinone led to the more active compound compared to the (–)-enantiomer and the racemate. The structure of one of the most thoroughly studied dihydropyrimidinones is shown in Figure 2 as compound **5** (SNAP-6201).

A number of modifications at the C-5 (esters, acid, amides, ketones) and C-6 (methyl, ethyl, methoxymethyl, *etc.*) positions of the dihydropyrimidinone ring are tolerated to yield compounds with subnanomolar binding affinity for the α_{1A}-receptor. Similarly, different linkers such as $–CONH(CH_2)_3–$, $–CH_2CONH(CH_2)_2–$ and $–(CH_2)_5–$ (Fig. 3) were found to be well-tolerated (25). The length of the linker between the nitrogen at the 3 position of the dihydropyrimidinone moiety and the nitrogen of the piperidine ring were crucial and a distance of 5 atoms was found to be optimal. Incorporation of other heterocycles (piperidines) or carbocycles (1,3-diaminocyclopentanes) in the linker portion was tolerated in some cases (26, 27).

Some data on the *in vivo* and *in vitro* metabolism of dihydropyrimidinones have been published and are summarized in Figure 4. The major metabolite in most cases was found to be the piperidine (or piperazine) via *N*-dealkylation (27). Some compounds containing modified linker chain that could potentially slow down the *N*-dealkylation (and thereby improve the plasma half-lives of

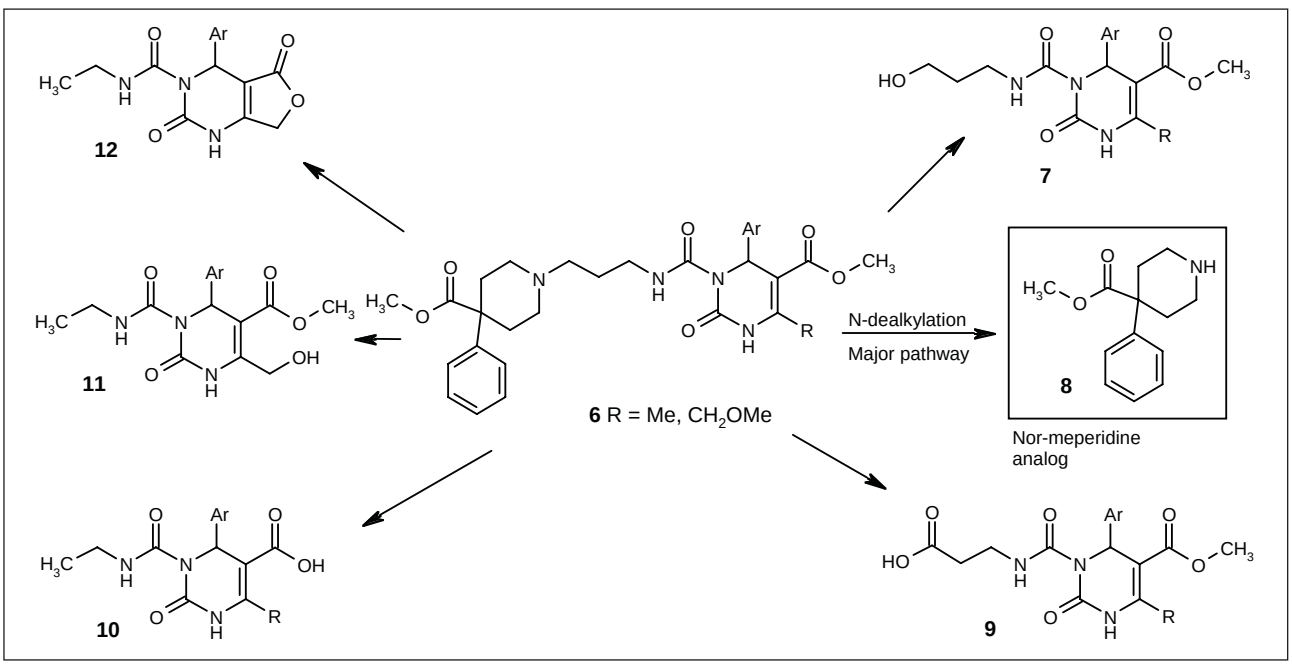

Fig. 4. General metabolic pathways for dihydropyrimidinones.

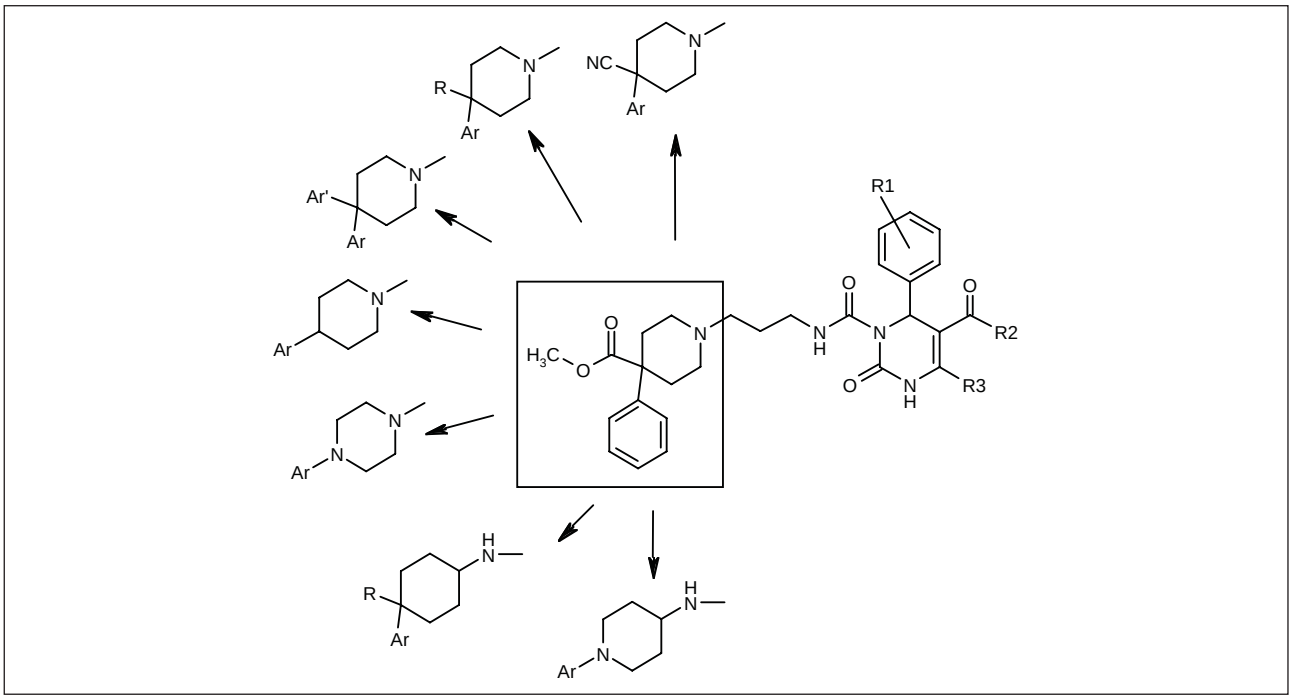

Fig. 5. Replacements for 4-carbomethoxy-4-phenylpiperidine.

the compounds) were synthesized. However, those analogs failed to show significant improvement in the plasma half-lives. Other metabolites formed by hydrolysis of the C-5 ester group, hydroxylation of the C-6 methyl group, demethylation of a methoxymethyl group at the C-6 position and cyclization to furo[3,4-*d*]pyrimidinone (28) were also observed. The major metabolite in some of the earlier compounds such as SNAP-6201, was 4-methoxycarbonyl-4-phenyl-piperidine, which was found to be an agonist for the μ-opioid receptor (IC_{50} = 3 μM) and had a long plasma half-life (> 12 h). This metabolite bears a close structural resemblance to a known opioid agonist, meperidine (IC_{50} = 1.1 μM). Meperidine is commonly used as a sedative but has a potential for substance abuse. The concerns regarding potential side effects due to agonism of the opioid receptors prompted us to subsequently replace the 4-methoxycarbonyl-4-phenyl-piperidine moiety with 4-aryl-piperidines (27), 4-aryl-piperazines (29), 4-arylcyclohexylamines (30, 31) and 4-amino-*N*-arylpiperidines (32) as shown in Figure 5. The structures of few selected dihydropyrimidinones (compounds **13-16**) are shown in Figure 6. Compound **16** differs from the compounds **13-15** in terms of the linker (and the side chain) being attached through C-5 carbonyl group instead of the more commonly used N-3 position of the dihydropyrimidinones (33). In this series of compounds, (*R*)-(–)-enantiomer rather than the (*S*)-(+)-enantiomer exhibited greater affinity for the α_{1A}-adrenoceptor.

The compounds that had high binding affinity (< 5 nM) for the recombinant human α_{1A}-receptor and significant selectivity (> 100-fold) over the α_{1B}- and α_{1D}-receptors in the binding assays were screened in a number of *in vitro* and *in vivo* assays. The results for some representative compounds are summarized in Table I. Most of the dihydropyrimidinones displayed comparable binding affinities and selectivities for the recombinant rat or dog α_{1A}-receptors. A few compounds were screened for cross-reactivity against more than 30 G-protein coupled receptors such as α_2-adrenergic, serotonin and opioid receptors and showed excellent selectivity (> 300-fold) for the α_{1A}-receptor.

Functional antagonism of the α_{1A}-adrenergic receptor was determined as the K_b for inhibition of contraction of isolated rat or human prostate tissue in response to the α_{1A}-selective agonist, to A-61603 (34). In most cases, the compounds were found to be more potent (K_b = 0.1-3.3 nM) than terazosin (K_b = 25 nM), and a good correlation between the K_i and K_b of the compounds was observed. On the other hand, K_b for the inhibition of the contraction of rat aorta (which predominantly expresses the α_{1D}-subtype) in response to a norepinephrine challenge was used as a screen to assess the selectivity of the compounds for the α_{1A}-receptor in the functional assay. The dihydropyrimidinones, unlike terazosin, displayed a clear separation between their abilities to antagonize functional responses in the prostatic and aortic tissue preparations, respectively. The functional potency (AD_{50}) of the compounds in anesthetized rats was determined as the dose required to inhibit the phenylephrine-induced contractile response by 50% in the *in situ* rat prostate. A typical AD_{50} for the dihydropyrimidinones in the *in situ* prostate assay was about 20 μg/kg compared to

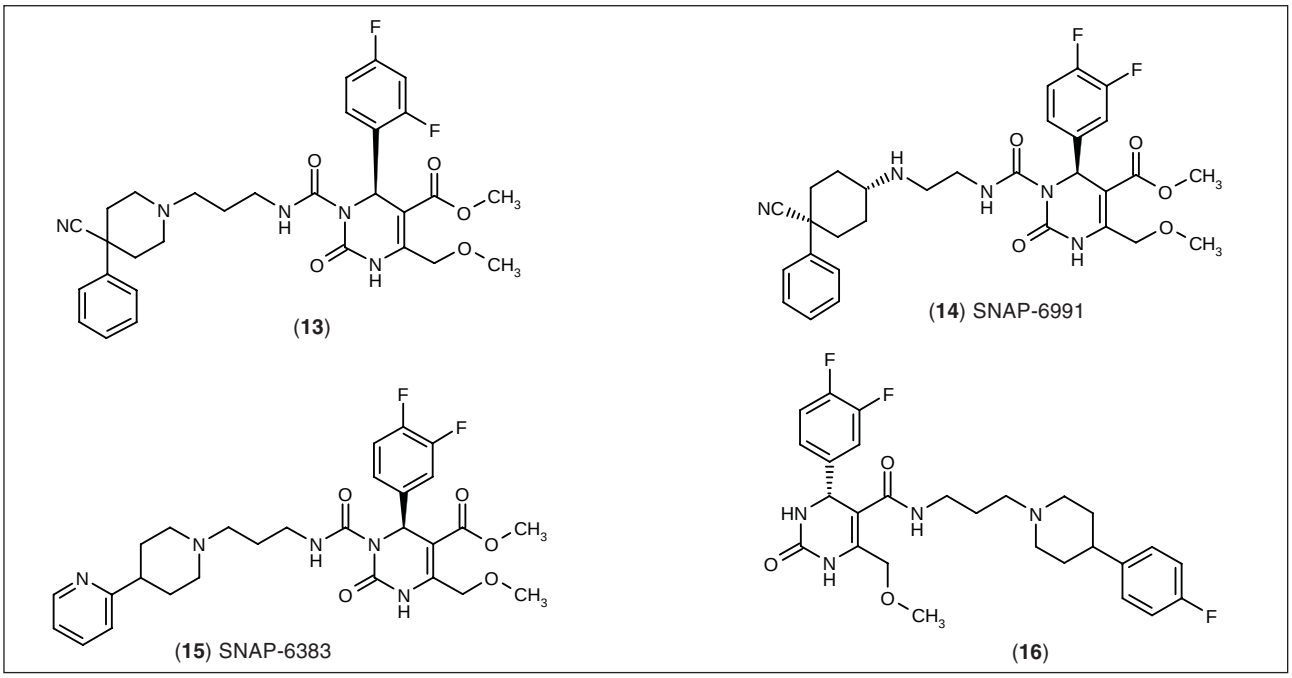

Fig. 6. Selected modified dihydropyrimidinones.

Table I: A summary and comparison of the in vitro *and* in vivo *properties of* **5**, **13**, **14** with terazosin.

Assay	Agonist/Antagonist	**5**	**13**	**14**	Terazosin
K_i, α_{1A} nM	[^{3}H]-Prazosin	0.2	0.7	0.1	6.9
$\alpha_{1B,1D}/\alpha_{1A}$	[^{3}H]-Prazosin	>1000	>900	>150	< 1.0
$\alpha_{2A,2B,2C}/\alpha_{1A}$	[^{3}H]-Rauwolscine	>1000	>1000	>1000	< 10.0
K_b Rat prostate (nM)	Phenylephrine	0.5	2.2	3.3	25
K_b Rat aorta (nM)	Norepinephrine	>1000	>1000	>3000	19
K_b human prostate (nM)	A-61603	0.1	ND	0.1	25
AD_{50} (rat prostate) μg/kg	Phenylephrine	20	18	28	52
Duration of action (rat) h	A-61603	>4	1.5	>4	3
DBP[a]-K_b/IUP[b]-K_b (dog)	Phenylephrine	>30	>20	>30	1
K_b (IUP[a], dog) μg/kg	Phenylephrine	4.2	14.2	6.4	16.4
K_b (DBP[b], dog) μg/kg	Phenylephrine	187	>300	116	15.7
μ K_i (μM)	—	4	51	>30	—
Rat: F, half-life (h)	—	15%, 2.0	8%, 0.4	23%, 2.4	49%, 7.5
Dog: F, half-life (h)	—	26%, 2.5	19%, 2.3	43%, 6.7	—

[a]Diastolic blood pressure, [b]Intra-urethral pressure

50 μg/kg for terazosin. The functional uroselectivity of the alpha$_1$-antagonists was determined in anaesthetized dogs by comparing the doses required to inhibit the phenylephrine-induced increase in intraurethral pressure (IUP) *versus* the dose required to inhibit the drop in diastolic blood pressure (DBP) elicited by phenylephrine. If the ratio of K_b(DBP) over K_b(IUP) for a compound was higher, the compound is expected to exhibit selectivity for relieving the urethral pressure *versus* causing undesired cardiovascular effects. For the nonselective antagonist, terazosin, K_b(DBP)/K_b(IUP) was about 1 whereas for the α_{1A}-selective dihydropyrimidinones the ratio was typically more than 15. However, the pharmacokinetic properties of many dihydropyrimidinones were inferior to terazosin with plasma half-lives of about 4 h and oral bioavailability around 20-30% in rats and dogs. Interestingly, some dihydropyrimidinones displayed much longer duration of action (> 4 h) in the *in situ* prostate assay in rats compared to the plasma half-lives obtained from the pharmacokinetic studies.

One of the α_{1A}-selective antagonists, compound **15** (SNAP-6383) was selected for a double-blind, comparator-controlled clinical trial to test the safety and efficacy of the compound in humans. The compound binds to the recombinant human α_{1A}-adrenergic receptor with K_i of 0.36 nM and was greater than 1000-fold selective over the other subtypes (35). SNAP-6383 showed selectivity in binding to human or dog prostate (K_i = 0.13 and 0.49 nM,

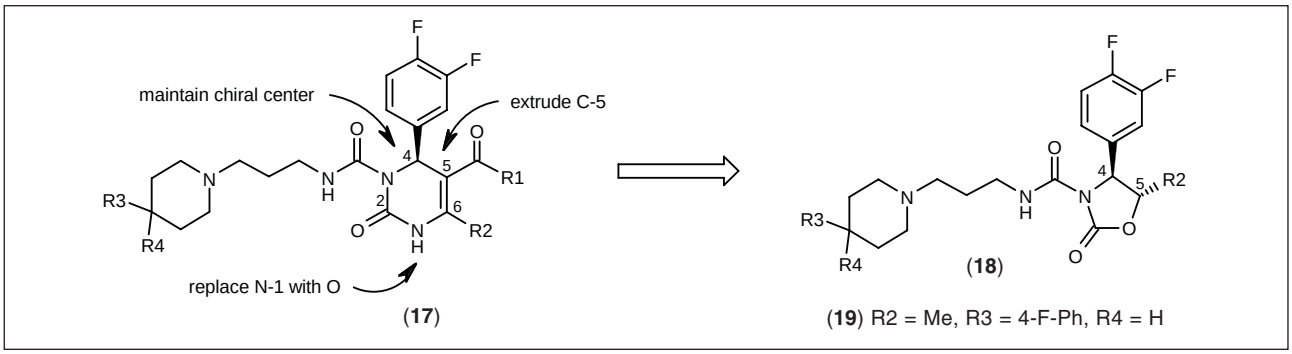

Fig. 7. Oxazolidinones.

*Table II: Profiles for **19** and terazosin in in vitro and in vivo functional assays.*

Assay	Agonist	**19**	Terazosin
K_b human prostate (nM)	A-61603	0.1 ± 0.035	25 ± 2.7
K_b dog prostate (nM)	Phenylephrine	0.33 ± 0.05	130 ± 33
K_b rat prostate (nM)	A-61603	0.26 ± 0.13	25 ± 3
K_b rat aorta (nM)	Norepinephrine	>1000	19 ± 2.4
AD_{50} rat (μg/kg)	Phenylephrine	12 ± 1.8	52 ± 15
K_b (IUP),[a] dog (μg/kg)	Phenylephrine	3.0	16
DBP_{15},[b] dog (μg/kg)	Phenylpehrine	>300	72
Rat: F, half-life (h)	—	25%, 6.0 ± 1.2	49%[c], 7.5
Dog: F, half-life (h)	—	74 ± 17% >12	—

[a]Intra-urethral pressure; [b]DBP_{15} is the dose of a compound required to cause a drop of 15 mmHg in diastolic blood pressure; [c]No S.D. available.

respectively) compared to human or dog aorta (K_i = 410 and 340 nM, respectively). Pharmacokinetic and *in vivo* functional data on this compound have not been reported to date. The clinical trials on this compound revealed that the compound was well tolerated at 5 and 20 mg doses in BPH patients. An increase in peak urine flow was observed that was significant compared to placebo and slightly inferior compared to tamsulosin (36). These results support the hypothesis that α_{1a}-antagonists play an important role in alleviating the obstructive symptoms of BPH, although the contribution of other subtypes cannot be ruled out. Extensive data on the metabolism of the SNAP-6383 showed that the compound was primarily metabolized by the cytochrome P-450 3A4 (CYP3A4) isozyme which might be the cause for drug-drug interactions (37).

Oxazolidinones

In an effort to improve the pharmacokinetic profiles of the α_{1A}-antagonists, we considered the possibility of replacing the dihydropyrimidinone moiety with another heterocycle. The SAR in the dihydropyrimidinone series (discussed in the previous section) was utilized in the design of new heterocycles. Replacement of the dihydropyrimidinone (**17**) with an oxazolidinone moiety **18** was proposed, where the chiral center from **17** was maintained, the C-5 carbon atom was extruded and the nitrogen at the 1-position was replaced with an oxygen. One of the oxazolidinones, compound **19** (SNAP-7915), displayed desirable binding and selectivity properties and has been studied in some detail (38) (Fig. 7). Three routes for the synthesis of the (*S*,*S*)-(+)-4-(3,4-difluorophenyl)-5-methyloxazolidin-2-one core unit as well as the spectroscopic evidence that validates the assigned absolute and relative configuration at the stereogenic centers, have been published (39). Among the 4 possible diastereomers, the one with (*S*,*S*) absolute configuration, showed the highest binding affinity (K_i = 0.17 nM) for recombinant human α_{1A}-adrenoceptor. This binding affinity is comparable to that of the dihydropyrimidinones discussed previously. SNAP-7915 did not show significant affinity for more than 30 other G-protein coupled receptors including α_{1B}- and α_{1D}-adrenergic receptors.

Compound **19** was found to be potent and selective in *in vitro* prostatic functional assays (Table II) and showed higher functional potency (AD_{50} = 12 μg/kg) for inhibition of the phenylephrine-induced contractile response of the *in situ* rat prostate as compared to terazosin (AD_{50} = 52 μg/kg). Compound **19** did not show hypotensive effects even at a high dose and failed to show a dose-dependent decrease in the diastolic blood pressure, which was observed with both terazosin and prazosin in anesthetized male dogs (Fig. 8). Also in anesthetized dogs, SNAP-7915 displayed excellent uroselectivity (the ratio of the dose required to drop the diastolic blood pressure by

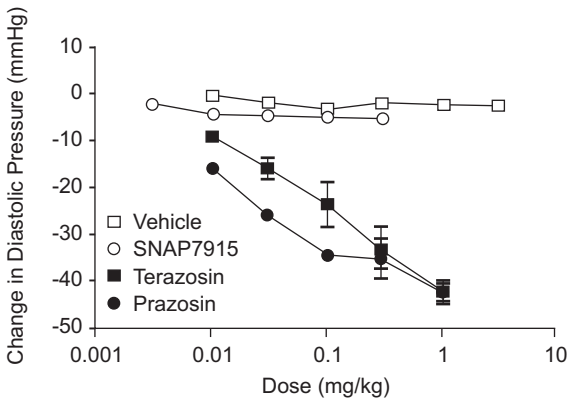

Fig. 8. Effect of α_1-antagonists on baseline diastolic blood pressure in anesthetized male dogs (10 min post i.v. administeration). Data shown as the mean ± SEM. The error bars are not shown when smaller than the size of the symbols used.

15 mmHg compared to the K_b for intraurethral pressure) compared to terazosin. In addition, Compound **19** displayed vastly superior oral bioavailability and long plasma half-life in rats (25% and 6 h) and dogs (74% and > 12 h) compared to the pharmacokinetic profile observed for dihydropyrimidinones. The development status of this compound has not been disclosed. Although the SAR in the oxazolidinone series of compounds has not been published, some other oxazolidinones have been shown to avidly bind to the α_{1A}-receptor (40-43).

Other templates

The common pharmacophore design, *i.e.*, a heterocycle attached to a 4-arylpiperidine moiety *via* a spacer (typically an alkyl linker), has been utilized for the synthesis

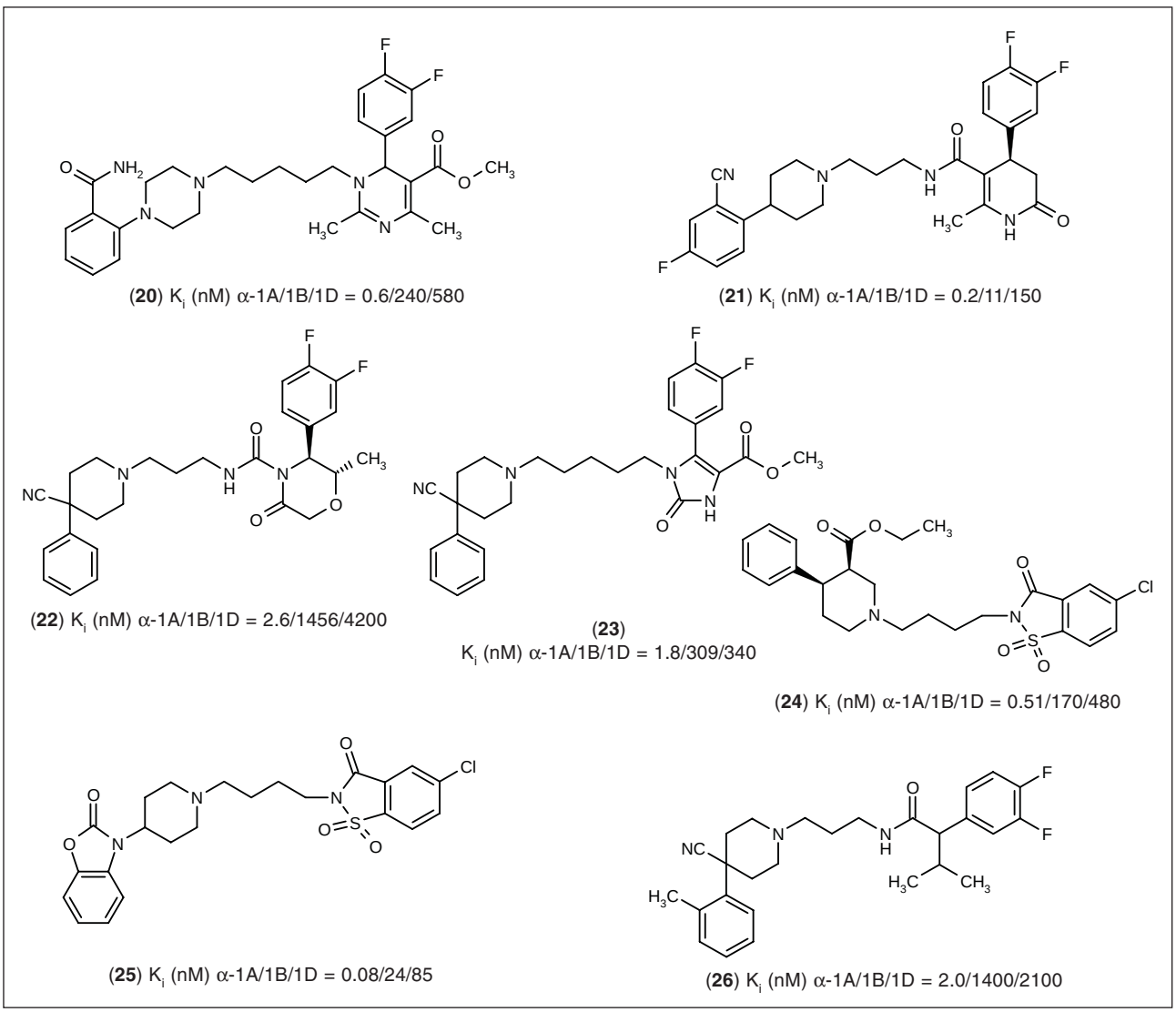

Fig. 9.

of many α_{1A}-selective antagonists. Compounds containing different heterocycles in place of the dihydropyrimidinone nucleus such as dihydropyrimidine (24), morpholinone (44), 4-aryl-3,4-dihydropyridin-2-one (45), 1,3-dihydroimidazol-2-one (46) and saccharin (47, 48) have been reported from either collaborative or independent efforts from Synaptic and Merck (Fig. 9). Phenylacetamides that do not incorporate heterocyle in the core unit, have also shown promise as α_{1A}-selective antagonists (49).

Conclusions

Several potent and highly selective α_{1A}-antagonists that belong to different structural classes were identified by the collaborative efforts of Synaptic and Merck. One compound (SNAP-6383) was shown to cause a dose-related increase in urine flow in humans, which was significantly higher than placebo in a randomized clinical trial. The results validate the hypothesis regarding the importance of α_{1A}-adrenoceptors in mediating the obstructive symptoms of BPH. A long-term (possibly head to head) study between a selective α_{1A}-antagonist and a nonselective alpha$_1$-antagonist will be needed to assess the real advantages for the selective α_{1A}-antagonist in terms of efficacy and side effects over the currently used nonselective α_1-antagonists.

Acknowledgements

The work described in this overview was a result of the excellent teamwork between the scientists from Synaptic Pharmaceutical Corporation and Merck Research Laboratories who contributed to this program. Personally, it was a great learning experience for me to be a part of the research team at Synaptic and I want to thank all the colleagues (their names appear in the original papers referenced in the manuscript) for their help. The project teams benefited tremendously from the guidance and support provided by Drs. Charles Gluchowski, Carlos Forray, Robert Taber and William Heydorn (Synaptic Pharmaceutical Corporation) and Drs. Roger Freidinger and Douglas Pettibone (Merck Research Laboratories) throughout this program.

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