Eur. J. Med. Chem. 35 (2000) 1043–1052

PII: S0223-5234(00)01189-2/REV

Review

Biologically active dihydropyrimidones of the Biginelli-type — a literature survey

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Received 10 October 2000

Abstract – In 1893, the synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate was reported for the first time by P. Biginelli. In the past decades, such Biginelli-type dihydropyrimidones have received a considerable amount of attention due to the interesting pharmacological properties associated with this heterocyclic scaffold. In this review, we highlight recent developments in this area, with a focus on the DHPMs recently developed as calcium channel modulators, α_{1a} adrenoceptor-selective antagonists and compounds that target the mitotic machinery. © 2000 Éditions scientifiques et médicales Elsevier SAS

dihydropyrimidones / dihydropyridines / cardiovascular disease / calcium channel modulators / benign prostatic hyperplasia / mitotic machinery

1. Introduction

Over 100 years ago, 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones of type **1** (DHPMs) were reported for the first time in the literature. In 1893, the Italian chemist Pietro Biginelli discovered a multicomponent reaction that produced these multifunctionalized dihydropyrimidones **1**, in a simple one-pot process (see *figure 1*) [1]. This efficient approach to partly reduced pyrimidines was largely ignored in the following decades and therefore, the pharmacological properties of this interesting heterocyclic scaffold remained unexplored. Since the early 1980s, however, interest in dihydropyrimidones of type **1** has increased significantly [2]. This was originally due to the apparent structural similarity of DHPMs to the well-known dihydropyridine calcium channel modulators of the Hantzsch type (e.g. **2**, DHPs, see *figure 2*) [3]. It was soon established that DHPMs exhibit a similar pharmacological profile to DHP calcium channel modulators of the nifedipine type and much activity has been observed in this area throughout the 1980s and 1990s [2–5]. More recently, interest has shifted from DHPM calcium channel modulators to other biologically active DHPM derivatives, e.g. α_{1a} adrenoceptor-selective antagonists, useful for the treatment of benign prostatic hyperplasia [6]. Again, the pharmacological activity in the area of α_1 adrenergic antagonists is based on activity found earlier in the DHP series of compounds. However, dihydropyrimidones of type **1** represent much more than just being aza-analogs of dihydropyridines of the Hantzsch type. The advent of combinatorial chemistry, which has proven particularly useful for multicomponent reactions such as the Biginelli condensation [7], allows the efficient generation of diverse DHPM compound libraries that have been subjected to high throughput screening (HTS) processes. Interesting biological effects have been discovered using HTS techniques. The recent identification of a DHPM analog as a potential new anticancer lead that is involved in blocking mitosis by inhibition of a kinesin motor protein is just one example [8].

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In this review, we provide a literature overview on the biologically active DHPM analogs. The focus of this article will be on recent pharmacological results in the area of DHPM calcium channel modulators and α_{1a} adrenoceptor-selective antagonists. Although several natural marine products, with interesting biological activities — such as the anti-HIV alkaloid batzelladine B [9] — containing the DHPM core, have recently been reported in the literature, these are not covered in the present article since much of the information on these cyclic guanidinium alkaloids has been presented in a recent review [10]. Since the synthesis of DHPMs **1** is relatively straightforward and has been the focus of other recent review articles [2, 7], only a brief account on synthetic methods will be given here. Patents are only cited if they contain valuable pharmacological information which otherwise has not been published.

2. Synthesis

Two different approaches have been employed in recent years to synthesize DHPM derivatives. The first method relies on the traditional Biginelli three-component protocol and involves the acid-catalyzed cyclocondensation of a 1,3-dicarbonyl component (**3**), with an aromatic aldehyde (**4**) and urea or thiourea derivative (**5**) (*figure 1*) [1, 2]. A major drawback of the original Biginelli protocols, using ethanol and catalytic HCl as reaction medium, has been the low yields that were frequently encountered when using sterically more demanding aldehydes or thioureas. In recent years, these problems have been largely overcome by the development of improved and more robust reaction conditions, involving e.g. Lewis-acid catalysis, solvent-free procedures or microwave-enhanced protocols [7].

The second procedure that has been used frequently is the so-called 'Atwal modification' of the

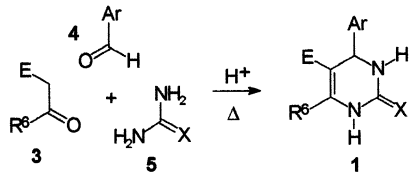

Figure 1. The Biginelli dihydropyrimidone synthesis.

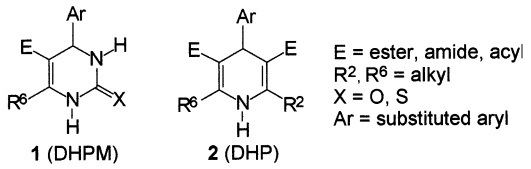

Figure 2. Structural comparison of Biginelli dihydropyrimidones (**1**, DHPMs) and Hantzsch dihydropyridines (**2**, DHPs).

Biginelli reaction (see *figure 3*). Here, an enone of type **6** is first condensed with a suitable protected urea or thiourea derivative **7** under mildly basic conditions. Deprotection of the resulting 1,4-dihydropyrimidine **8** leads to the desired DHPMs **1** [11, 12]. Although this method requires prior synthesis of enones **6**, its reliability and broad applicability makes it an attractive alternative to the traditional one-step Biginelli condensation. In addition, 1,4-dihydropyrimidines **8** can be alkylated or acylated regiospecifically at *N*3 by various electrophiles (**8**→**9**), thereby making the pharmacologically especially interesting DHPM analogs of type **10** (see below) readily accessible [13].

The large majority of DHPM analogs that have been reported in the literature so far have been prepared by either of the two protocols outlined above. More recently, both methods have also been adopted to solid-phase synthesis, with either the 1,3-dicarbonyl or the (thio)urea components attached to the solid support [7]. The combinatorial synthesis of DHPM compound libraries has, therefore, been made possible.

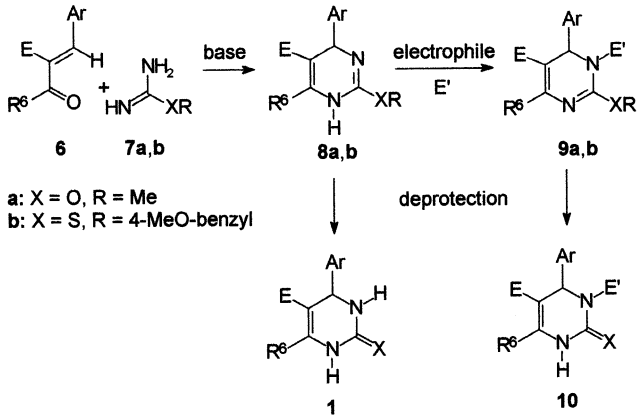

Figure 3. The 'Atwal-modification' of the Biginelli reaction.

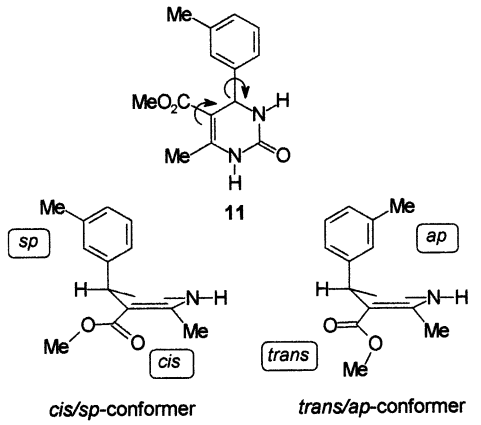

Figure 4. Conformational preferences of DHPM **11** (schematic representation, side view).

3. Geometry and conformation

A prerequisite for any understanding of the interaction of DHPMs with known biological targets at the molecular level is the knowledge of the molecular geometry and accessible conformations of the DHPMs in question. The conformational features of DHPMs have therefore been studied extensively by computational (semiempirical and ab initio), X-ray diffraction and NMR studies [14–19]. In general, DHPMs of type **1** are conformationally rather flexible molecules, in which the aryl rings and the ester groups can rotate and the conformation of the dihydropyrimidine ring can change (*figure 4*). For the model compound **11**, for example, four distinct local minima were found (AM1, HF/3-21G) for geometries, where (a) the ester group is in coplanar arrangement with the double bond of the dihydropyrimidine ring (carbonyl group *cis* or *trans* with respect to the C5=C6 double bond); and (b) where the methyl substituent on the C4-aryl ring adopts either a *syn*- (sp) or antiperiplanar (ap) orientation with respect to C4–H (*figure 4*) [14]. In all four conformations, the aryl ring is positioned axially, perpendicular to and (nearly) bisecting the half-boat-like dihydropyrimidine ring (no minima were found for equatorially arranged C4-aryl rings). The lowest energy conformer generally is the *cis*/sp conformer, however, the other rotamers are usually only a few kcal/mol higher in energy. Coupled with the relatively low calculated rotational barriers [14], it can be concluded that in a biological environment all four distinct minimum geometries are accessible, with no clear preference for one particular conformer. This general trend has been confirmed for a variety of DHPM structures [14–18]. It should be noted that the overall conformational and structural preferences observed for DHPMs are quite similar to those found for dihydropyridines of type **2** [20], again demonstrating the close structural relationship of the two heterocyclic systems.

4. Calcium channel modulators

4-Aryl-1,4-dihydropyridines (DHPs, e.g. nifedipine, **12**) are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975, have become almost indispensable for the treatment of cardiovascular diseases, such as hypertension, cardiac arrhythmias or angina [21]. More than 25 years after the introduction of nifedipine (**12**), many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market (e.g. nicardipine, amlodipine, felodipine, etc.) [22].

The cardiovascular activity of DHPMs was first recognized by Khanina et al. in 1978, who reported on β-aminoethyl esters of type **13** (*figure 5*) that exhibit moderate hypotensive activity and coronary dilatory properties [23]. The same group later also disclosed difluoromethoxy-substituted analogs of type **14**, showing similar levels of cardiovascular activity [24, 25]. During the mid 1980s, interest originally focused on 4-aryl-1,4-dihydropyrimidine-5-carboxylate calcium channel blockers which closely mimic the dihydropyridine (DHP) scaffold, e.g. **15** [26], **16** [27] and **17** [3]. These analogs were shown to be potent calcium blockers, however, most did not show significant antihypertensive activity in vivo [3]. Further structural modifications on the dihydropyrimidine ring led to DHPMs bearing an ester group at N3 (e.g. **18–21**) [28–30], thereby more closely resembling nifedipine-type dihydropyridines (**12**). DHPM **18**, for example, displayed not only more potent and longer lasting vasodilative action, but also a hypotensive activity with slow onset as compared with DHPs [28]. Among the most potent derivatives in a series of N3 substituted DHPMs described by Atwal et al. was the thiourea derivative **21** [30]. Although the calcium channel blocking activity of this DHPM was comparable to DHPs, it was devoid of antihypertensive activity in vivo [30]. The lack of oral activity of these derivatives has been rationalized by their rapid

metabolism [30]. Further modification of the substituent at N3 subsequently led to the development of orally active long-lasting antihypertensive agents, such as DHPMs **22** (SQ 32926) [4] and **23** (SQ 32547) [5]. In the case of DHPM **22**, the superior oral antihypertensive activity (compared to **21**) was explained by its improved oral bioavailability, resulting from the increased chemical stability of the urea functionality. Compound **22** was shown to be both more potent and longer acting than nifedipine as an antihypertensive agent; the in vivo potency and duration being comparable to the long-acting DHP amlodipine [4]. Similar pharmacological properties were established for the basic analog **23** [5]. Both compounds have antiichemic properties in animal models [31].

Apart from the monocyclic DHPM derivatives displayed in *figure 5*, several groups have also reported that fused analogs, which incorporate hetero- or carbocyclic rings attached to either the C5/C6 or the C2/N3 positions of the dihydropyrimidine nucleus possess calcium channel blocking activity [32–40]. Some of those bicyclic derivatives (e.g. **24–27**) are shown in *figure 6*.

Detailed pharmacological studies by Rovnyak et al. with a large set of DHPM analogs have led to a general structure–activity relationship for N3-functionalized DHPM calcium channel blockers of type **19–23** [5]. Thus, *ortho* and/or *meta* aromatic substitution, essential for optimal activity in vitro, was proposed. Similarly, the C5 ester alkyl group was found

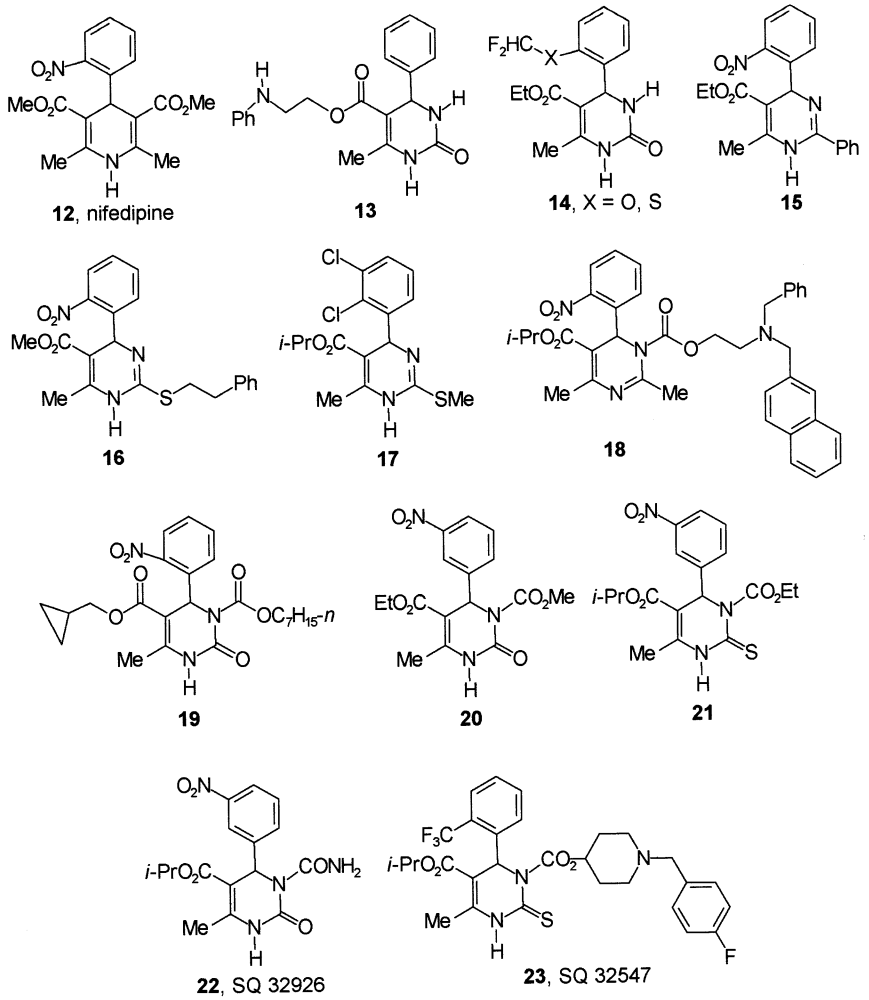

Figure 5. Structures of DHPM calcium channel modulators.

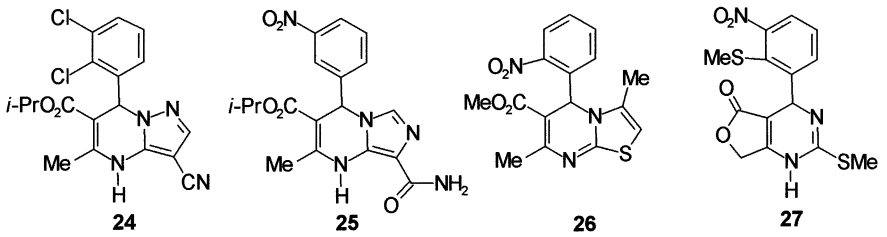

Figure 6. Bicyclic DHPMs with calcium modulatory activity.

to be a major determinant of potency. Additionally, a substituent on N3 of the dihydropyrimidine ring was found to be a strict requirement for activity and the order of potency for the 2-hetero atom was S > O > N (*figure 7*).

Of critical importance for the biological activity of most of the DHPMs shown in *figure 5* is the absolute stereochemistry at the C4 stereocenter. Pharmacologic studies with resolved enantiomers have demonstrated that, for example, for DHPM **21** a > 1000-fold difference in potency can be observed [30]. For the orally active antihypertensive DHPM derivatives **22** and **23**, it was established that the desired antihypertensive effect resides solely in the (*R*)-enantiomer [4, 5].

Being inherently asymmetric, the dihydropyrimidine nucleus provides an ideal molecular tool with which to probe structural and functional aspects of calcium channel function, in particular with analogs of type **17**, that only possess a single ester group at C5. Despite many studies on the structure–function relationships of DHP derivatives [20, 41], there still remains debate concerning the conformational requirements of DHP interactions at the receptor and, in particular, the molecular distinctions between antagonist and agonist activity. Based on pharmacological studies made with a set of uniquely designed, conformationally restricted, single enantiomer DHPM analogs (*figure 8*), Rovnyak et al. proposed a new binding site model for DHP/DHPM calcium channel modulators in 1995 (*figure 9*) [19]. The competitive binding behavior of DHPs (e.g. nifedipine, **12**) and DHPMs **28–30** at the same receptor was proven by radioligand receptor binding assays.

In their model [19], Rovnyak et al. proposed that calcium channel modulation (antagonist versus agonist activity) is dependent on the absolute configuration at C4, whereby the orientation of the C4-aryl group (*R*- or *S*-configuration) acts as a 'molecular switch' between antagonist (aryl-group up) and agonist (aryl-group down) activity (*figure 9*). Furthermore, in the receptor-bound conformation, the substituted aryl ring should be positioned axially, perpendicular to and bisecting the boat-like dihydropyridine/pyrimidine ring, with the 4-aryl substituent (*X*) preferring the *syn*-periplanar (relative to C4–H) orientation. A *cis*-carbonyl ester orientation (with respect to the C5–C6 dihydropyrimidine double-bond) was also found mandatory for optimum calcium channel modulatory activity. Importantly, only the 'left-hand side' of the DHP/DHPM molecule was proposed to be essential for activity, providing a rationale for the similar pharmacological profile observed for DHP and DHPM calcium channel modulators. Although the Rovnyak model is internally consistent, it should be noted that it contradicts other proposed DHP pharmacophor models [20, 42–45], which suggest that both ester functionalities in DHPs are required for binding affinity.

Calcium channel modulatory activity has also been reported for other conformationally restricted DHPM derivatives [18, 46, 47].

In the context of studying potential pharmacophore models, the C5 nitro substituted DHPM calcium channel modulators of type **31** (*figure 10*) reported by Remennikov et al. [48–50] should be of particular interest, since these are aza-analogs of the potent calcium antagonist/agonist Bay K 8644. However, details of the pharmacological activity of individual enantiomers, for example DHPM **31**, have not been

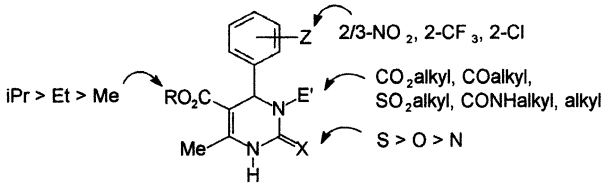

Figure 7. General structure–activity relationship of DHPM calcium channel blockers [5].

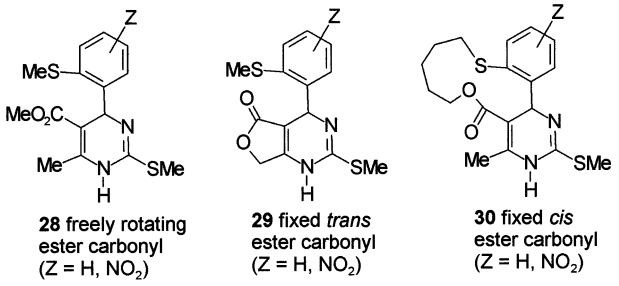

Figure 8. DHPM mimics designed by Rovnyak et al. [19] to define receptor-bound conformations and interactions of calcium channel modulators.

disclosed so far [49]. Weak calcium channel modulatory activity has also been described for a number of other DHPMs of type **1** [51–55].

5. α_{1a}-Adrenergic receptor antagonists

Benign prostatic hyperplasia (BPH) is a progressive enlargement of the prostate, resulting in a number of obstructive and irritative symptoms [56]. The incidence of BPH increases with advancing age, such that ca. 70% of males, >70 years-old, manifest symptoms associated with BPH [57]. Nonselective α_1-adrenoceptor antagonists, e.g. terazosin, are currently being approved pharmaceuticals commonly employed for the treatments of BPH [58]. It has been reported, however, that the functional potency of a number of α_1 antagonists correlates well with the binding affinity for α_{1a} subtype at the cloned human receptors. Therefore, efforts are being made to develop α_{1a}-selective antagonists as attractive drug candidates for the treatment of BPH with fewer undesirable side effects that may be associated with the other subtypes.

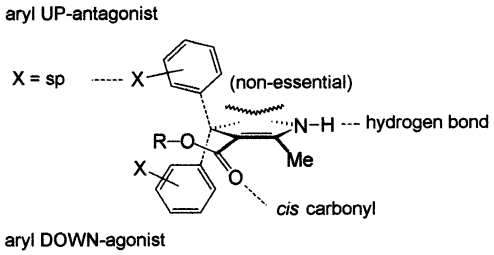

Figure 9. Structural and steric aspects of 1,4-dihydropyridine interaction, according to Rovnyak et al. [19].

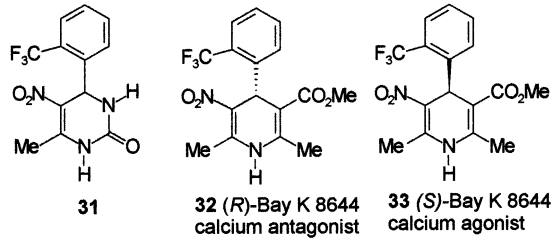

Figure 10. Comparison of structures for DHPM **31** and Bay K 8644.

Soon after the cloning and expression of the three different α_1 receptor subtypes, the DHP calcium channel blocker niguldipine (**34**) (*figure 11*) was shown to be a potent antagonist of the α_{1a} receptor subtype. Structural modifications of the DHP skeleton led to SNAP 5089 (**35**) [59] and SNAP 5540 (**36**) [60], which maintained potency and selectivity versus other α receptor subtypes, but had attenuated or no calcium channel activity [59, 60]. Some of the compounds that belong to this class, however, exhibit less than optimal pharmacokinetic profiles.

In a further modification step, the DHP core was therefore replaced by a DHPM scaffold, as in SNAP 6201 (**37**), in order to avoid problems derived from the propensity of DHPs towards oxidation. The difluoro analog SNAP 6201 showed good binding affinity (<1 nM) and excellent subtype selectivity (>300-fold) for the α_{1a} receptor, no cardiovascular effects and a good pharmacodynamic profile [61]. However, in vitro and in vivo evaluation of SNAP 6201 showed its major metabolite, 4-methoxycarbonyl-4-phenylpiperidine, to be a potent μ-opioid agonist. Modification of the linker in SNAP 6201 gave several compounds with good α_{1a} binding affinity and selectivity, e.g. **38**. Importantly, the piperidine fragments here, e.g. 4-methyl-4-phenylpiperidine, were essentially inactive at the μ-opioid receptor [62]. In an alternative approach, a different template, devoid of agonist activity at the μ-opioid receptor, was identified, namely the 2-carboxamidophenylpiperazine residue. The corresponding DHPM **39** maintained a binding and functional profile comparable to that of SNAP 6201 [63]. In an effort to develop analogs that resembled the DHP scaffold even closer, the dihydropyrimidin-2-one unit in compounds **37–39** was also replaced by a 2-methyl-dihydropyrimidine core, leading to derivatives such as compound **40**, which,

however, displayed suboptimal pharmacokinetic profiles [64]. In a related study, it was demonstrated that furo[3,4-*d*]pyrimidones of type **41** are metabolites of e.g. DHPM **39**, that also show subtype-selective antagonism of the α_{1a} receptor [65].

The conversion of the central heterocycle from the symmetrical 1,4-dihydropyridine (**34–36**) to an inherently asymmetric dihydropyrimidine skeleton offers two logical sites of attachment of the piperidine/piperazine containing side chain. Apart from attachment at N3 of the dihydropyrimidine ring, as exemplified by DHPMs **37–41**, the piperidine/piperazine side chain can also be linked via an amide bond to the C5 carboxy functionality, e.g. as in compound **42**. DHPMs of this type were shown to generally have good binding affinity (< 1 nM) and excellent subtype selectivity (> 100 fold) for the α_{1a} receptor [6]. In vivo testing of these compounds in both rat and dog models confirmed the results from receptor studies and suggest that DHPMs of this type have significant potential to relieve the symptoms of BPH without eliciting effects on the cardiovascular system [6].

6. Mitotic Kinesin inhibitors

A common strategy for cancer therapy is the development of drugs that interrupt the cell cycle during the mitosis stage. Compounds that perturb microtubule shortening (depolymerization) or lengthening (polymerization) cause arrest of the cell cycle in mitosis due to perturbation of the normal microtubule dynamics necessary for chromosome movement. A variety of such drugs that bind to tubulin and thus inhibit spindle assembly are currently used in cancer therapy (e.g. paclitaxel, docetaxel) [66].

By screening a 16 320-member library of diverse small molecules, Mayer et al. have recently identified the structurally rather simple DHPM **43** (*figure 12*) as a novel cell-permeable molecule, that blocks normal bipolar mitotic spindle assembly in mammalian cells and therefore, causes cell cycle arrest [8]. By combining several screening assays, it was established that DHPM **43** — termed monastrol — blocks mitosis by specifically inhibiting the motor activity of the mitotic kinesin Eg5, a motor protein required for spindle bipolarity. Monastrol is the only cell-perme-

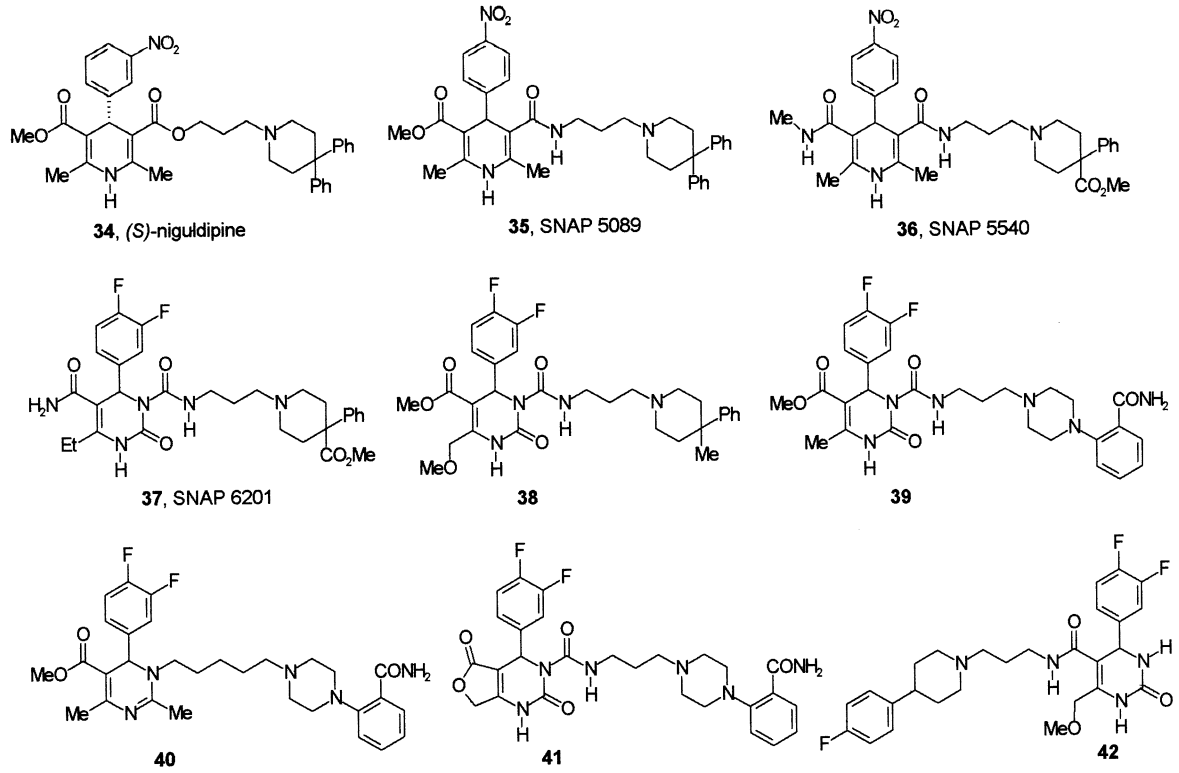

Figure 11. DHP and DHPM derivatives as selective α_{1a} adrenergic receptor antagonists.

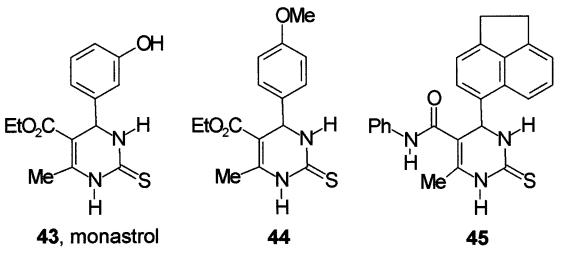

Figure 12. Structures of DHPMs targeting the mammalian mitotic machinery.

able molecule currently known to specifically inhibit mitotic kinesin Eg5 and can therefore be considered as a lead for the development of new anticancer drugs. Interestingly, the closely related DHPM **44** did not effect mitotic kinesin Eg5 or arrest cells in mitosis.

In addition to the mitotic kinesin Eg5 inhibitor monastrol, screening of the original library of 16 320 compounds in phenotype-based screens also led to the related DHPM structure **45** which showed the colchicine-like property of destabilizing microtubules [67].

Although the antimitotic activity of monastrol itself is not very high — being a micromolar inhibitor of Eg5 — structural variants could prove to have better activity. Racemic monastrol has been resolved into its individual enantiomers, but pharmacological data on these have not been reported [17].

7. Miscellaneous biological effects

As early as the 1940's DHPMs of type **1** were shown to possess antiviral activity [68]. Eventually, the nitrofuryl-substituted analog nitractin (**46**) (*figure 13*) was developed, which displayed good activity against the viruses of the trachoma group [69–71], in addition to showing modest antibacterial activity [72]. Other structurally simple DHPMs were screened as antitumor agents and found to be active against, for example, Walker carcinosarcoma in rats and mice [73–75]. Pyrimidine-5-carboxamides of type **47** were claimed to have anticarcinogenic activity [76], while other derivatives were reported to have blood platelet aggregation inhibitory activity [77, 78], or were shown to inhibit the uptake of adenosine by thrombocytes [79]. Fused DHPMs, such as thiazolo[3,2-*a*]-pyrimidine **48** and pyrimido[2,1-*b*][1,3]thiazine **49** were reported to have antiinflammatory activity [80–82], also found in other DHPM derivatives [83]. More recently, thiazolo[3,2-*a*]pyrimidine **50** has been found to be a micromolar group 2 metabotropic glutamate receptor antagonist [84]. Fungicidal activity toward *Aspergillus niger* and *A. ochraceus* was demonstrated for simple 2-thioxo DHPMs [85]. A recent patent disclosed the structures of DHPMs with neuropeptide Y (NPY) antagonistic activity [86].

8. Conclusions

Dihydropyrimidines (DHPMs) of the Biginelli-type have come a long way since their discovery in 1893 and the first patent on DHPM derivatives in 1930, describing agents for the protection of wool against moths [87]. During the last 20 years extensive studies on the pharmacology of this ring system have been reported, with an initial focus on developing calcium channel blockers that possess superior pharmacological profiles to Hantzsch-type dihydropyridines. Now, at the beginning of the 21st century, DHPMs represent an interesting class of compounds in their own right. Because of the pharmacological potency of the DHPM scaffold, novel dihydropyrimidines, with important biological properties, will undoubtedly be discovered in the future by combining combinatorial synthesis and high throughput screening (HTS) techniques.

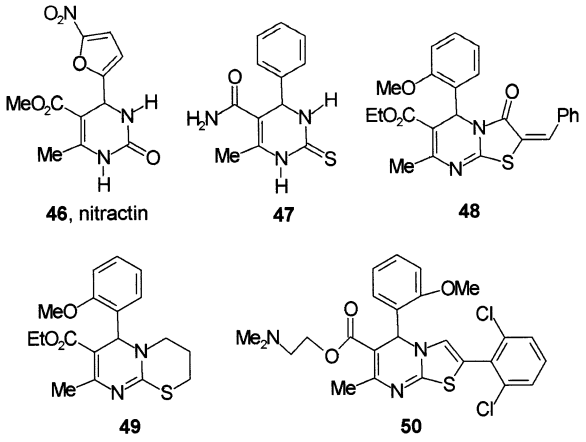

Figure 13. Structures of DHPMs **46**–**50**.

Acknowledgements

Our work in the area of dihydropyrimidine chemistry is generously supported by the Austrian Academy of Sciences (APART 319), the Austrian Science Fund (P-11994-CHE) and the 'Jubiläumsfonds der Österreichischen Nationalbank' (Project 7904).

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