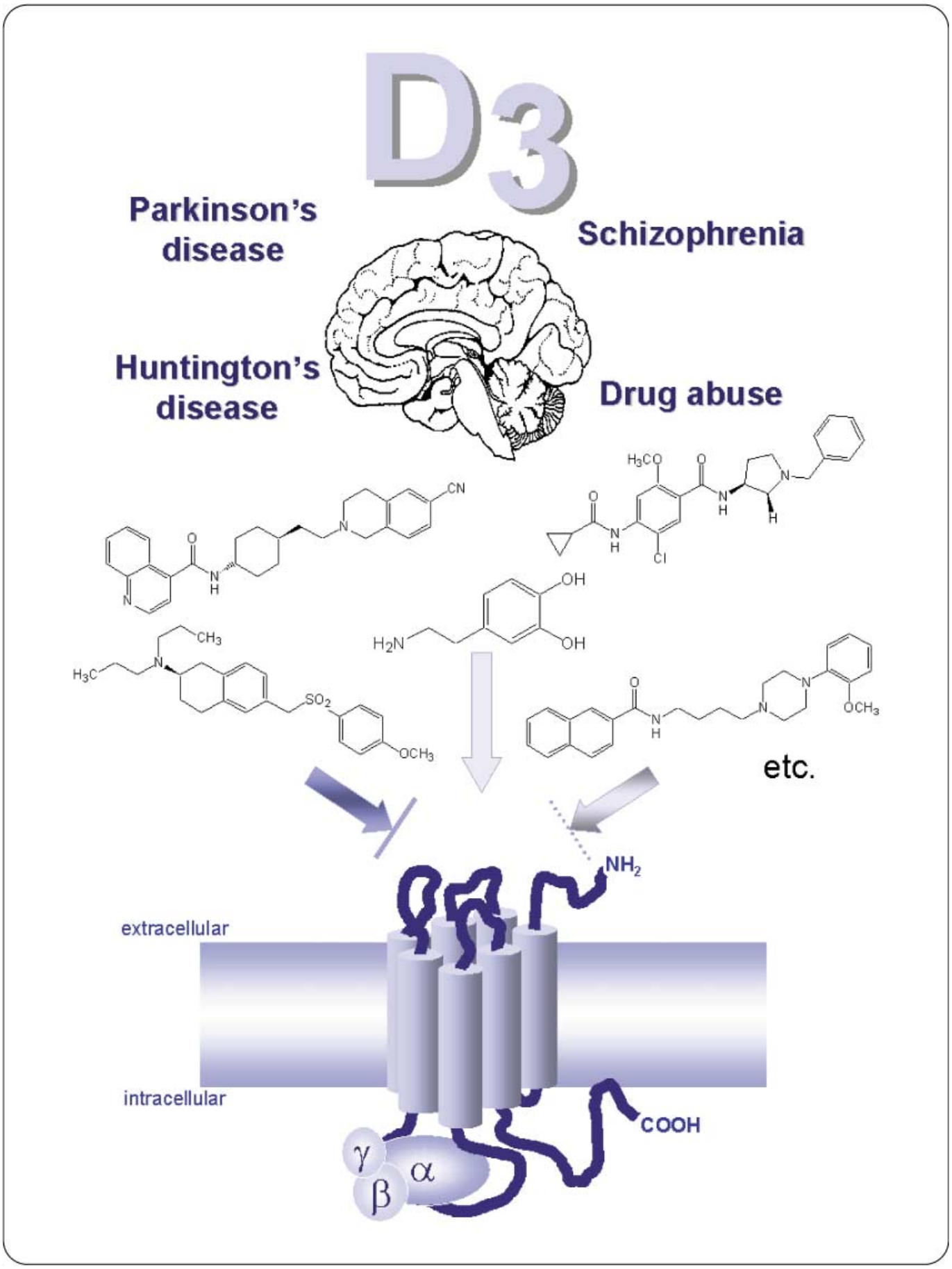

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Dopamine D_3 Receptor Ligands with Antagonist Properties

Anneke E. Hackling and Holger Stark*[a]

The dopamine D_3 receptor has been recognized to play an important role in the molecular mechanisms of various neuropsychiatric disorders. The development of new dopamine D_3 receptor selective antagonists is premised on the potentially improved therapeutic treatment of psychosis like schizophrenia. Partial agonists at dopamine D_3 receptors are supposed to be beneficial when administered to drug abusers or in Parkinson's disease. The structural basis for most compounds is at least a basic, aryl-substituted alkanamine part with an alkyl moiety, which in many compounds forms a spacer to another aryl residue. Structural variety among the amine moiety includes aminotetralins, tetrahydroisoquinolines, isoindoles, benzazepines, and aminoindans, as well as pyrrolidines, pyrroles, and 4-phenylpiperazines. Various ways for lead optimization are shown in different classes of compounds. Promising ligands with high D_3 receptor affinity often lack sufficient selectivity or display deficits in the required in vivo parameters. Structure–activity relationships for dopamine D_3 receptor antagonists and partial agonists are discussed here, along with the outlook for their potential therapeutic application.

KEYWORDS:

antagonist · dopamines · G-protein-coupled receptors · medicinal chemistry · neurotransmitters

1. Introduction

The biogenic amine dopamine is an essential neurotransmitter in the brain and periphery. Fundamental work in this area by A. Carlsson was recognized by the Nobel committee in 2000.[1] The cerebral dopaminergic system is implicated in a variety of physiological and pathophysiological processes. It comprises the regulation of motion, emotion, and cognition. An imbalance in dopaminergic neurotransmission and dopamine receptors underlies manifold neurological and psychiatric disorders, for example, Parkinson's disease, Huntington's disease, and schizophrenia.[2] Individual therapy for these disorders appeals to discriminating effects on one or several dopamine subreceptors.[3] Differential distribution of dopamine and distinct aminergic pathways related to specific projections of dopaminergic neurons reflect the functional diversity of the dopaminergic system at cellular level.[4, 5]

Dopamine receptor subtypes belong to the family of G-protein-coupled receptors and share the characteristic of seven transmembrane domains. Five dopamine receptor subtypes can be classified into two families, referring to analogies in sequence and in signal transduction. The D_1-like dopamine receptors include the dopamine D_1 and the D_5 receptors. They are characterized by activation of adenylyl cyclase mediated by a G_s protein, consequently effecting higher concentrations of the secondary messenger cyclic adenosine-3′,5′-monophosphate (cAMP), and under aspects of molecular biology by the lack of introns in their gene. The D_2-like receptor group consists of the dopamine D_2, D_3, and D_4 receptors, which couple to $G_{i/0}$ proteins and can inhibit adenylyl cyclase. In the genes of dopamine D_2-like receptors introns can be found. Distinguished from the D_1-like receptor family, the expressed D_2-like receptors bear a comparatively long third intracellular loop, a relatively long N terminus, and a short C terminus.[6] The D_2-like dopamine D_2 and D_3 subreceptors display a pronounced pharmacological similarity and homology in the sequence of amino acids, which is even increased up to 75 % when limited to the seven transmembrane domains.[7]

Among dopamine receptors, D_3 receptors are relatively few in number but show high abundance in brain regions associated with emotional and cognitive functions.[8] The highest incidence of dopamine D_3 receptors is reported in the nucleus accumbens and the islands of Calleja, where the D_3 receptor has been shown to be mainly postsynaptically located.[6, 9] A subset of dopamine D_3 receptors may be presynaptically located.[10] Signaling pathways of the D_3 receptor include increased extracellular acidification and modulation of expression of the transcription factor *c-fos*.[10] The neuroanatomical localization, mainly restricted to expression in distinct areas of the limbic system, evokes a special interest for the potential treatment of diverse neurological and psychiatric disorders, such as schizophrenia, Parkinson's disease, and cocaine abuse.[7, 11–13] For the characterization of the dopamine D_3 receptor and for further therapeutic application, the identification of highly affine and completely dopamine D_3 receptor discriminating ligands is still required.[14] Selective ligands facilitate the construction of receptor models, which, in return, may offer deeper insight into ligand–receptor interac-

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tions.[15] In vivo receptor imaging by positron emission tomography (PET) and single photon emission computer tomography (SPECT) with appropriate compounds allows the direct investigation of (not only) dopaminergic drug targets and drug action in living patients, thereby supporting the design of compounds with less unwanted effects.[16] Especially typical antipsychotics of the first generation, which mostly prefer the dopamine D_2 receptor, cause extrapyramidal side effects such as tardive dyskinesia.[17] In this field, not only are highly D_3 (and D_4) receptor selective compounds looked for, but also a mixed binding profile for other neurotransmitter receptors is desired for the so-called atypical antipsychotics devoid of extrapyramidal effects.[18] Non-dopaminergic antipsychotics have also been proposed and classified as third generation.[19] Since brain regions with low expression in motor divisions are mainly concerned, selective compounds with a dopamine D_3 receptor antagonist profile may give rise to beneficial antipsychotic activity without significant extrapyramidal side effects.[20] Dopamine D_3 receptor agonists, which are already in use for the treatment of Parkinson's disease, provide additional neuroprotective effects.[21] Partial dopamine D_3 receptor agonist action is supposed to alleviate craving symptoms during withdrawal, as mesolimbic dopamine pathways play an important role in the reinforcing properties of drugs of abuse,[22] and furthermore these agonists have potential in the treatment of levodopa-induced dyskinesia in Parkinson patients.[23, 24]

Structural analogies can be found among many dopamine D_3 receptor antagonists when applying a core scaffold, divided into three subunits (I – III): an aryl moiety (I), which is connected to an amide, heteroatom or heterocycle, possibly enabling hydrogen bonding, and further linked through an alkyl spacer (II) to a basic moiety (III) with various lipophilic residues. In this pattern I – II – III (aryl – spacer – basic moiety) at least one element may be missing.

The review starts with early developments and briefly mentions the first dopamine D_3 receptor agonists. Consequently dopamine D_3 receptor partial agonists and antagonists are structurally grouped according to their basic moieties. Structure – activity relationships are discussed with consideration of dopamine D_3 receptor affinity and selectivity in different classes of important ligands following larger variations of their chemical structures. Functional pharmacological aspects are only considered for selected compounds and are dealt with in a pursuing section. A short summary and an outlook terminate the overview of structures and functional pharmacology in the recent approach to develop highly potent and selective dopamine D_3 receptor antagonists and partial agonists.

Compounds cited in this article have been tested at least for D_3 and D_2 receptor affinity in binding assays with different radioligands, thereby evaluating D_3 receptor selectivity. Functional in vitro D_3 receptor activity has been preferably assessed by [^{3}H]thymidine incorporation after induction of mitogenesis[25] or extracellular acidification measured by microphysiometry.[26] Determination of in vivo potencies included various test systems, regarding distinguished behavioral, endocrine, or other physiological responses.[27–29] An antagonist profile may include partial agonism as well. The discrepancy of neutral antagonism and inverse agonism will not be addressed. Data and binding values for the compounds itemized refer preferably to initial publications or publications with data comparable to other systems cited here. Affinity is mostly given in inhibition constant (K_i) values.

Holger Stark studied pharmaceutical sciences at the Freie Universität Berlin, Germany, and completed his PhD degree in medicinal chemistry with W. Schunack, working on prodrugs and antagonists for histamine H_3 receptors in 1991. After a postdoctoral period working on non-peptidergic direct G-protein activators, he focused on research into dopamine D_2-like receptors. His Habilitation was finished in 1999 on the development of novel dopamine D_3 receptor ligands with different pharmacological properties. Since 2000/2001 he has held a professorship for pharmaceutical/medicinal chemistry at the Biozentrum of the Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany. His main work is engaged towards neurotransmitter research, mainly for the central nervous system (focusing on histamine and dopamine receptor subtypes as G-protein-coupled receptors) and for N-*methyl-*D*-aspartate (NMDA) receptors as cation channels. Along with the development of pharmacological tools and potential drugs for therapeutic use, special emphasis is put on inhibition of metabolic enzymes, prodrugs with improved pharmacokinetics, molecular modeling, different kinds of radioligands (PET, SPECT), and the pharmacological behavior of ligands having the complete range from full to inverse agonists. He and his collaborators are mainly involved in the generation of new leads for the aforementioned receptors and in the detection of high constitutive receptor activity in vivo, as well as looking into new dopamine D_3 receptor dependent ways to fight drug abuse and levodopa-induced dyskinesia.*

2. Early Developments

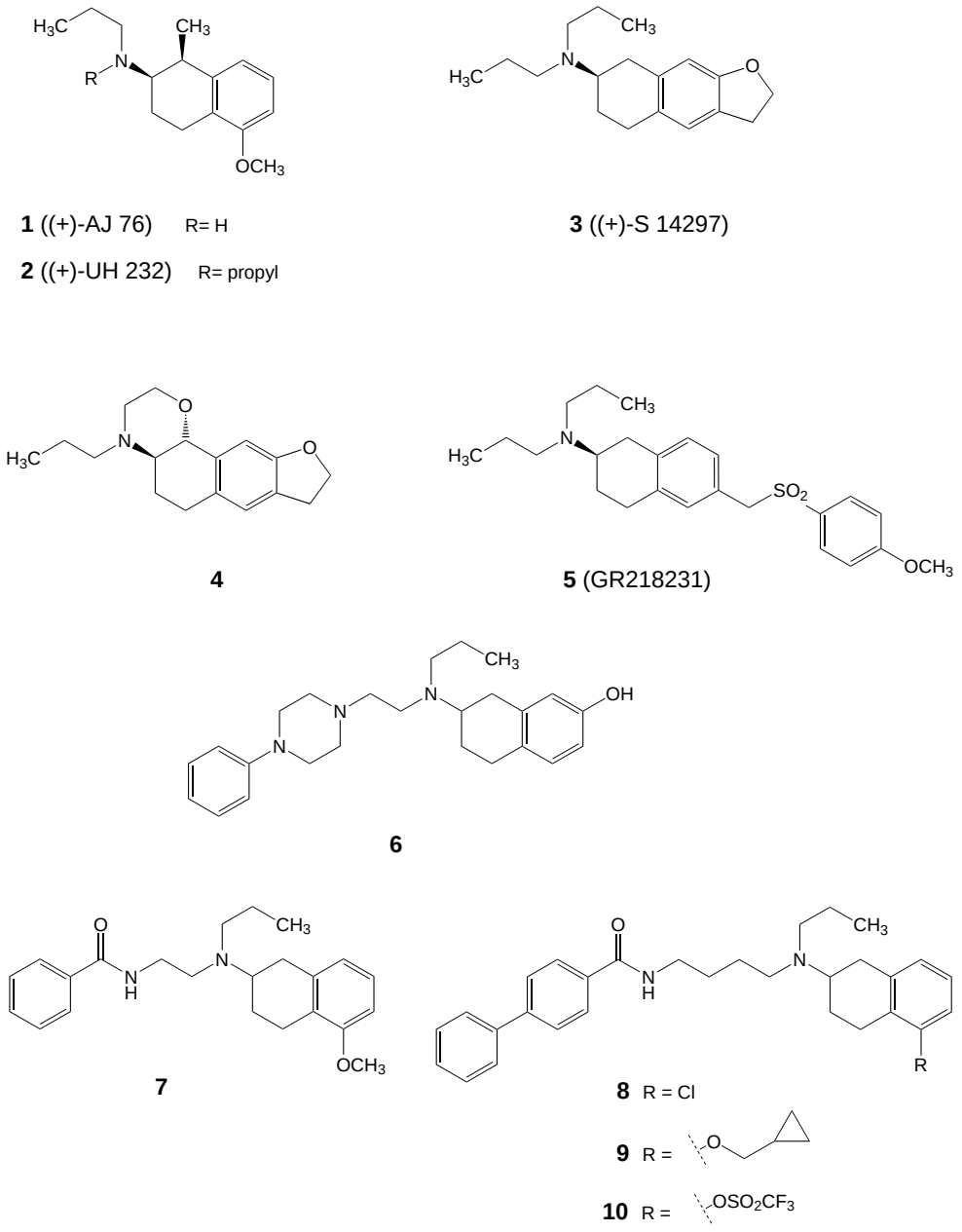
After cloning and identification of the rat dopamine D_3 receptor in 1990 by Sokoloff et al.,[30] dopamine itself was found to bind with at least 30-fold preference to this subreceptor compared to the dopamine D_2 receptor and other dopamine subreceptors. Several known ligands for dopamine receptors have been screened for their D_3 receptor binding affinities, by using [^{125}I]iodosulpiride in replacement studies. The compound 7-hydroxy-*N*,*N*-dipropyl-2-aminotetralin (7-OH-DPAT) was made out as a template for a D_3 receptor preferring radioligand, acting as an agonist. [^{3}H]7-OH-DPAT bound with subnanomolar affinity (0.7 nM) to dopamine D_3 receptors and displayed $\approx$100-fold selectivity for dopamine D_3 receptors against D_2 receptors and even higher rates against D_1 and D_4 receptors.[31] Later the (*R*)-(+) isomer of 7-OH-DPAT was identified as the eutomer (more potent enantiomer) with more than 200-fold higher affinity for do-

pamine D_3 receptors (0.57 nM) versus D_2 receptors.[32] Also, for the generally less D_3 receptor selective 5-hydroxy analogues a significant stereochemical influence on D_3 receptor affinity was manifested, with (*S*)-(−)-5-OH-DPAT being the active isomer.[33] The affinity-mediating aminotetralin moiety could also be used for the development of antagonists.

3. Antagonists Based on the Aminotetralin Structure

On the antagonist side, the 1,3,8-triazaspiro[4.5]decan-4-one derivative spiperone still maintained dopamine D_2 receptor preference while having subnanomolar binding at the D_3 receptor, whereas 5-methoxy-1-methyl-*N*-propyl-2-aminotetralin (**1**, (*R*)-(+)-AJ 76) and its *N*,*N*-dipropyl analogue **2** ((*R*)-(+)-UH 232)[34] exhibited slight D_3 receptor preference over D_2 (3- to 4-fold) and nanomolar (91 nM) to low nanomolar (9.2 nM) binding affinity, respectively (Scheme 1).[30] For compound **2** partial agonist activity was postulated.[35, 36]

The dihydrofurano-*N*,*N*-dipropyl-2-aminotetralin derivative **3** (S 14297) was described to block hypothermia in rats induced by the dopamine D_3 receptor agonist (+)-7-OH-DPAT and therefore determined as a functional D_3 receptor antagonist.[37] D_3 receptor affinity values were revealed at 13 nM with more than 20-fold preference against the D_2 receptor. The distinguished functional activity of **3** was investigated in several in vitro and in vivo tests. The potency was stereochemically restricted to the (*R*)-(+) isomer **3** with the corresponding racemate S 11566 being less



Scheme 1. *Aminotetralins with an* N*-alkyl residue. References:* ***1*** *and* ***2****;*[30] ***3****;*[37] ***4****;*[39] ***5****;*[41] ***6****;*[43] ***7****;*[46] ***8****,* ***9****, and* ***10****.*[47]

active, and did not reside in the *S* distomer (less potent enantiomer), (−)-*S* 17777.[28, 38]

Since compound **3** displayed more than 80-fold preference against D_1, D_4, 5-HT_{1A}, and M_1 receptors,[37] it seemed to deliver a promising template for a series of tetracylic analogues (5-HT receptor = serotonergic receptor; M receptor = muscarinic receptor).[39] One objective was to rigidize the basic moiety by incorporating the nitrogen into a fourth anellated ring. Adopting structural features from the selective D_3 receptor agonist PD 128907,[40] an oxygen was inserted into the additional ring to give a morpholino element. Different *N* substituents have been introduced, with a propyl chain being favorable in contrast to deteriorating ω-arylalkyl residues. All *cis* derivatives were inactive. Compared to **3**, the *trans*-morpholino compound **4**, having the same stereochemistry in the amino group, achieved slightly increased dopamine D_3 receptor affinity (10 nM) and selectivity (40-fold D_3 versus D_2).

Among aminotetralin compounds, the *N*,*N*-dipropyl-2-aminotetralin derivative **2** was selected for further development, due to its lack of affinity for many non-dopaminergic receptors.[41] An advanced binding profile could be achieved with 6-(2-phenylethyl)-2-aminotetralins. Various 4-phenyl-substituted, racemic aminotetralins revealed dopamine D_3 receptor affinities below 3 nM and more than 100-fold selectivity for the D_3 receptor over the D_2 receptor.[41] Nonpolar substituents achieved superior binding properties. Within these structures negative aspects such as high lipophilicity and rapid in vivo clearance came across. With the objective to decrease lipophilicity but retain the advanced binding profile for the D_3 receptor, polar moieties were introduced into the linker. The (*R*)-(4-methoxyphenyl)sulphonylmethyl derivative **5** (GR218231) was evaluated as the eutomer and, with reduced lipophilicity, as the most selective compound in this series with ≈400-fold selectivity for the D_3 receptor over the D_2 receptor and 10000-fold selectivity over the D_1 and D_4 receptors (Scheme 1). Functional activity was only tested on D_2 receptors, where **5** showed low D_2 receptor antagonist potency. Replacement of the 4-methoxy group with an iodine substituent led to superior binding affinity below 0.2 nM and 120-fold D_3 receptor preference, which suggested the potential use of this compound as a radioligand. Unfortunately, other groups could only partly reproduce the exceptional selectivity ratio for **5** in heterologous expression systems.[36, 42]

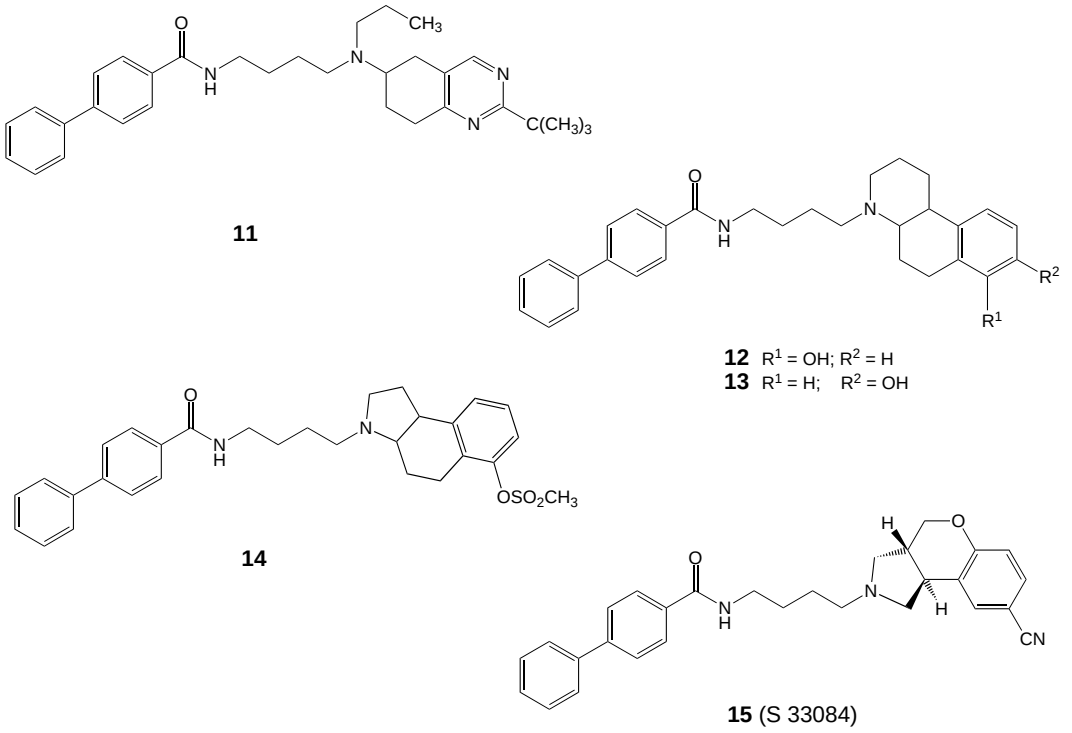
A very recently published hybrid approach combined 2-aminotetralin- and aryl-substituted piperazino moieties.[43] According to previous studies a tetramethylene linker was favorable for D_3 receptor affinity,[44, 45] but here best results could be obtained with a dimethylene spacer (**6**, Scheme 1). As a remarkable structural feature, the core structure contained only basic amines and a 7-hydroxy substituent on the aminotetralin, but no other heteroatoms. The racemic 7-hydroxy-*N*-(2-(4-phenylpiperazin-1-yl)ethyl-*N*-propyl-2-aminotetralin (**6**) bound with low nanomolar affinity (1.75 nM) and 120-fold selectivity for the dopamine D_3 receptor versus the D_2 receptor. Functional activities for the compounds need to be determined.

In an alternative approach to develop antipsychotic agents, a mixed dopamine D_2 and D_3 receptor as well as a 5-HT_{1A} receptor binding profile was favored. With this objective a series of aminotetralins with substituted benzamide residues was synthesized.[46] Substituted benzamides are a part of some known D_2 and D_3 receptor ligands, which share a dimethylene chain as the linker to a basic nitrogen (sulpiride, raclopride). Here the 2-benzamidoethyl moiety was attached to *N*-propyl-2-aminotetralin to enhance affinities for D_2, D_3, and 5-HT_{1A} receptors. Unsubstituted benzamides obtained the best results, with the unsubstituted 2-aminotetralin only surpassed in binding properties by the 5-methoxy-*N*-propyl-2-aminotetralin derivative **7** (Scheme 1), which revealed subnanomolar binding (0.58 nM) to dopamine D_3 but also to 5-HT_{1A} receptors (0.82 nM) and no pronounced selectivity against D_2 receptors. Intrinsic efficiencies have not been described yet.

More aminotetralins have been described with a biphenyl-4-carbamide moiety.[47] In this series, the known dopamine D_3 receptor agonist 5-OH-DPAT[33] was substituted instead of a 2-methoxyphenyl-piperazino moiety in the basic section of the known antagonist **42** (GR103691, Table 1),[44] the substructure of which was implied to be responsible for 5-HT_{1A} receptor affinity. Compared to its more D_3 receptor selective isomer (*R*)-(+)-7-OH-DPAT, in (*S*)-(−)-5-OH-DPAT the amino substituents were found to have greater influence on affinity. Therefore it seemed to be reasonable to combine this aminotetralin with the arylcarbamide and spacer moiety, 4-(4-phenylbenzoylamino)butyl, of compound **42**, which is crucial for its high D_3 receptor affinity and the antagonist profile. Diverging results for functional activity were obtained within this series of compounds.[47] Related to the lead structure 5-OH-DPAT, the 5-hydroxy-2-aminotetralins exhibited agonist activity, probably due to bioisosterism to the catechol structure and therefore activation of the receptor by hydrogen bonding between the 5-hydroxy group and a serine residue on transmembrane helix V. Among the optimized *N*-propyl series, the agonist profile depended on 5-aminotetralin substituents with the ability to build up similar hydrogen bonds. Compounds with 5-chloro (**8**), 5-cyclopropylmethoxy (**9**), or 5-trifluoromethylsulfonyloxy substitution (**10**) displayed affinities below 3 nM and 200- to 320-fold selectivity for the D_3 receptor, as well as an antagonist profile (Scheme 1). Later in vivo findings revealed rapid clearance of these compounds, due to *N*-dealkylation.[48]

In a related study of 2-aminotetralins, different known dopamine D_3 receptor agonists were taken as starting points and, as in the series above, connected through a tetramethylene spacer to a biphenylcarbamide residue (Scheme 2).[49] Similar results were obtained for functional activity, as only substituents in the 2-position of the 5,6,7,8-tetrahydroquinazoline ring, which were not enabling hydrogen bonding to receptor activation, led to antagonist properties. The best compound in this series was the 6-*tert*-butyl-quinerolane analogue **11** with low nanomolar D_3 receptor affinity (13 nM) and a D_2/D_3 selectivity ratio of 110.

To compensate the severe drawback of rapid *N*-dealkylation found among *N*-propyl-2-aminotetralins, a series of fused aminotetralins was developed. With the aim of maintaining D_3 receptor affinity and selectivity but improving metabolic stability, the *N*-alkyl residue was formally fused to the aminotetralin structure in octahydrobenzo[*f*]quinolines and the corresponding hexahydro-1*H*-benzo[*e*]indoles.[48] The 7-hydroxy-octahydrobenzo[*f*]quinoline exposed a D_3 receptor affinity value of 1 nM and



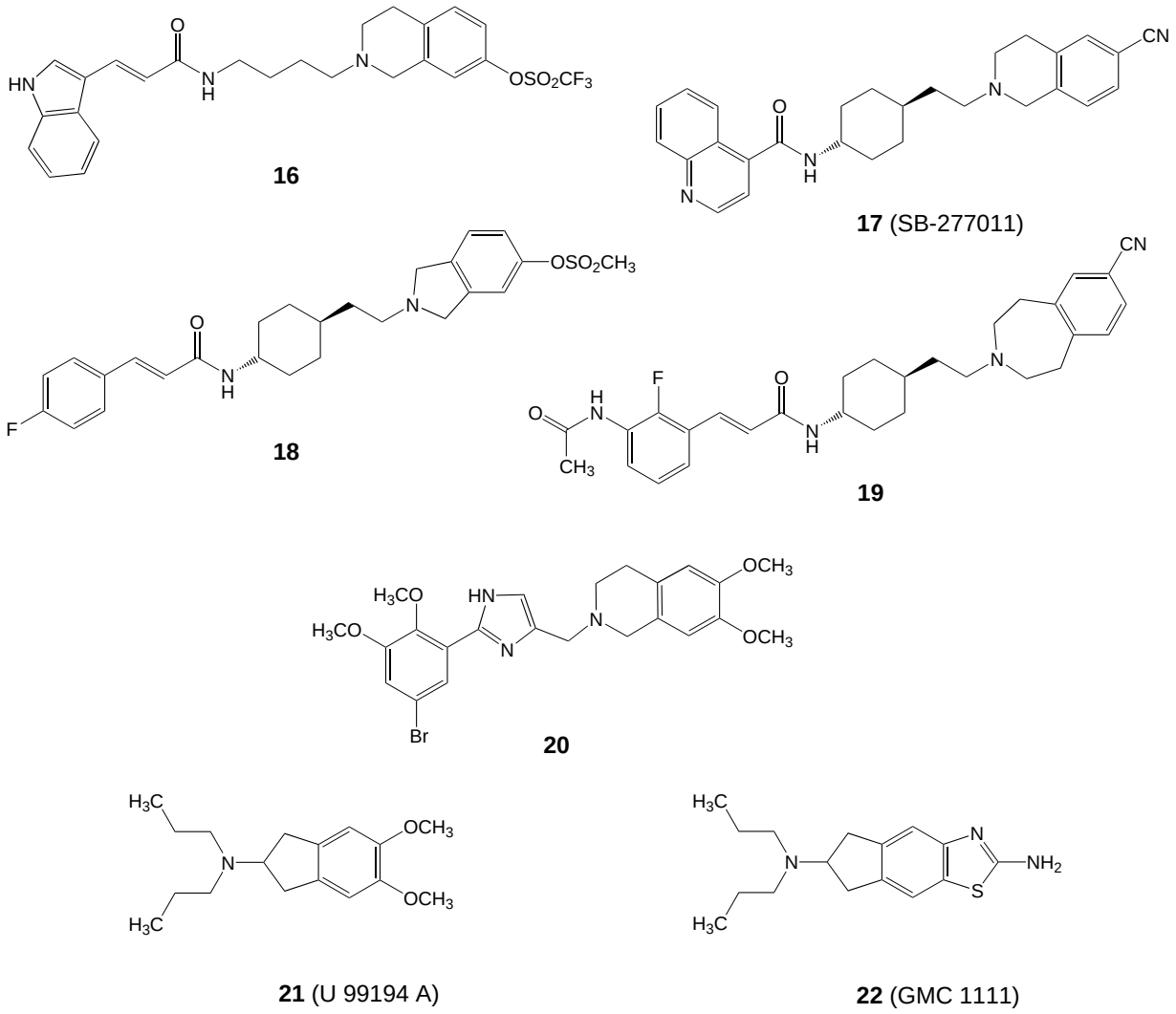
Scheme 2. *Aminotetralin-related compounds with an amide moiety. References:* ***11****;*[49] ***12****,* ***13****, and* ***14****;*[48] ***15****.*[50]

moderate D_3 receptor preference (22-fold versus D_2) only for the (*S*,*S*)-*trans* enantiomer of compound **12**, which indicates an important impact of chirality for these rigid compounds. This offers the perspective of even more enhanced binding properties for an isomer of the racemic (±)-*trans*-8-hydroxy analogue **13**, which attained more than 3-fold increased D_3 receptor selectivity but deteriorated D_3 receptor affinity (8 nM). Introduction of a methylsulfonyloxy group in the 6-position of the racemic (±)-*trans*-hexahydro-1*H*-benzo[*e*]indole **14** was performed to improve lipophilic parameters, and moreover deliver equivalent binding values (D_3 affinity 5 nM, 65-fold selectivity for D_3 versus D_2). Both latter compounds exhibited antagonist activity in an in vitro functional assay with microphysiometry.[48]

The cyano-substituted *N*-(4-(benzopyrano[3,4-*c*]pyrrol-2-yl)-butyl)biphenyl-4-carbamide **15** (S 33084) has been developed as another biphenyl derivative with a rigid tertiary amino moiety (Scheme 2). In comparison to the known dopamine D_3 receptor ligands (*S*)-(−)-5-OH-DPAT and (*R*)-(+)-7-OH-DPAT, only the *trans* derivatives within this series of benzopyrano[3,4-*c*]pyrroles behaved as conformationally constrained analogues.[50] Compound **15** was determined as an antagonist (0.3 nM) with more than 100-fold selectivity for cloned and native rat dopamine D_3 receptors versus D_2 receptors, and more than 200-fold selectivity versus 40 other binding sites, including hD_1, hD_4, and hD_5 receptors, as well as α_1 receptors and 5-HT_{1A} receptors (α receptor = α adrenoreceptor, hD receptor = human dopaminergic receptor).[36, 42] The corresponding radioligand [^{3}H]S 33084 exposed a binding profile that correlated very well with that of [^{3}H]spiperone.[51] Due to the considerable selectivity for the D_3 receptor, [^{3}H]S 33084 may be employed for the characterization of cloned as well as native receptor populations.

4. Tetrahydroisoquinoline, Benzazepine, Aminoindan Derivatives, and Related Compounds

An approach to compensate the rapid in vivo clearance of *N*-propyl-2-aminotetralin structures like **8**–**10**[47] was made. Supported by molecular modeling, a 7-substituted 1,2,3,4-tetrahydroisoquinoline was evaluated to give the best overlap fitting the 5-substituted 2-aminotetralin structure.[52] Already the unsubstituted tetrahydroisoquinoline derivative showed promising lower clearance compared to analogous *N*-propyl-2-aminotetralin derivatives. Improved binding affinities were obtained by introducing a 7-(trifluoromethylsulfonyloxy) substituent, which was consequently maintained within the whole series. In the arylcarbamide part of the molecule, modifications in the biphenyl residue revealed the importance of this shape with its coplanar conformation. A *trans*-cinnamide group was found to have similar spatial requirements and led to D_2/D_3 receptor selectivity increased up to 100-fold. As the 2-naphthylpropenamide analogue reached 200-fold selectivity but displayed high lipophilicity, an indol-3-ylpropenamide rest was alternatively introduced (**16**). Compound **16** revealed a D_3 receptor affinity value of 4 nM and pronounced selectivity for the D_3 receptor of 150-fold over the D_2 receptor (Scheme 3). Selectivity could be confirmed in an in vitro microphysiometry assay, which determined this compound as a potent antagonist. However, further studies disclosed low bioavailability in rats (7%) and only moderate selectivity over the 5-HT_{1B} and 5-HT_{1D} receptors.[53] Recently a related tetrahydroisoquinoline (ST 198) has been used for the characterization of dopamine autoreceptors subpopulation.[54]



Scheme 3. *Tetrahydroisoquinoline, isoindole, benzazepine, and aminoindan derivatives. References:* ***16****;*[52] ***17****;*[53] ***18****;*[58] ***19****;*[59] ***20****;*[60] ***21****;*[62] ***22****.*[63]

With the rationale to reduce lipophilicity and liability to metabolism of the 1,2,3,4-tetrahydroisoquinoline moiety, a series of compounds with alternative substituents and a modified alkyl linker was developed.[53] Replacement of the trifluoromethylsulfonyloxy substituent by a cyano group as another electron-withdrawing residue only led to improvement in oral bioavailability. Comparative analysis of known selective 5-HT_{1B} and 5-HT_{1D} ligands proposed the flexible butyl spacer to affect selectivity in a negative way. Consequently, introduction of a more rigid alkyl spacer structure stood to reason. A (*trans*-1,4-cyclohexyl)ethyl linker met these requirements and led to compounds with low nanomolar affinity and more than 100-fold selectivity for the D_3 receptor against the D_2 receptor. Inhibition of cytochrome P450 2D6 was also disclosed, which was put down to the 7-cyano-1,2,3,4-tetrahydroisoquinoline moiety. Shifting the cyano substituent from the 7- to the 6-position could diminish this severe drawback. On this structural basis the 4-quinolinyl derivative with a cyclohexylethyl spacer and 6-cyano-1,2,3,4-tetrahydroisoquinoline residue, compound **17** (SB-277011), was obtained, which combined nanomolar affinity (10 nM) and 100-fold selectivity for the dopamine D_3 receptor with relatively high oral bioavailability (43%) and central nervous system penetration in rats.[55] Compound **17** was proved as an antagonist in in vivo microdialysis and exhibited 100-fold selectivity when cross-screened over more than 60 other receptors and ion channels. These results gave reason to assume **17** was a potential compound for treating the negative symptoms of schizophrenia.[56] Despite the promising pharmacokinetics firstly obtained in rats, **17** revealed poor bioavailability in cynomolgus monkeys.[57] A high first pass effect, rather than malabsorption, is believed to cause this effect. A key factor discussed may be aldehyde oxidase, which possibly oxidizes the 4-quinolinyl ring of **17**. In rat and dog livers, aldehyde oxidase levels are low, contrary to high levels in monkey and human livers. Thus, the oral bioavailability of **17** was predicted to be low in humans.[57]

In continuing studies, the tetrahydroisoquinoline moiety of **17** was replaced by a 2,3-dihydro-1*H*-isoindole with the objective to maintain D_3 receptor affinity and improve the overall selectivity.[58] Referring to molecular modeling studies, a 5-substituted

2,3-dihydro-1*H*-isoindole can be superimposed on 6-substituted 1,2,3,4-tetrahydroisoquinolines. The analogous isoindole derivative of **17** displayed a deteriorated binding value (60 nM), whereas replacement in the aryl moiety to a 3-(3-methoxyphenyl)acrylamide delivered equivalent D_3 receptor binding values to **17** but reduced selectivity for the D_3 receptor over the 5-HT_{1D} receptor. Further variations led to the 3-(4-fluorophenyl)acrylamide derivative **18**, which turned out to be the compound with the most favorable binding properties in this series. Being an antagonist like **17**, compound **18** displayed slightly improved D_3 receptor affinity (5 nM), markedly improved selectivity for the D_3 receptor against the D_2 (100-fold), 5-HT_{1D} (270-fold), and other aminergic receptors (more than 200-fold), and a superior pharmacokinetic profile in rats.

A 2,3,4,5-tetrahydro-1*H*-3-benzazepine was suggested as a further alternative bioisosteric moiety with a good overlap to the 6-substituted 1,2,3,4-tetrahydroisoquinoline moiety of **17**. Therefore a series of 7-cyano-2,3,4,5-tetrahydro-1*H*-3-benz[d]azepines was prepared to investigate the effects of variations in the aryl moiety on dopamine D_3 receptor affinity and selectivity and on its pharmacokinetic profile.[59] Introduction of a substituted cinnamide residue led to increased D_3 receptor affinity and delivered two highly affine (3 nM) and selective (130- and 180-fold selectivity for D_3 over D_2 receptors) compounds (structures not shown). After oral administration in rats the 3-acetamide derivative displayed low systemic exposure and the more selective 3-methoxy derivative hardly any, probably due to metabolic instability. Resolving the metabolic drawback with a deactivating fluoro substituent, the 3-(3-(acetylamino)-2-fluorophenyl)acrylamide – benzazepine derivative **19** with low nanomolar affinity (4 nM) and a D_2/D_3 receptor selectivity ratio of 130 could be obtained. Compared to lead **17**, this compound exhibited equivalent systemic exposure in rats and selectivity for the D_3 over the D_2 receptor, as well as slightly increased D_3 receptor affinity.[59]

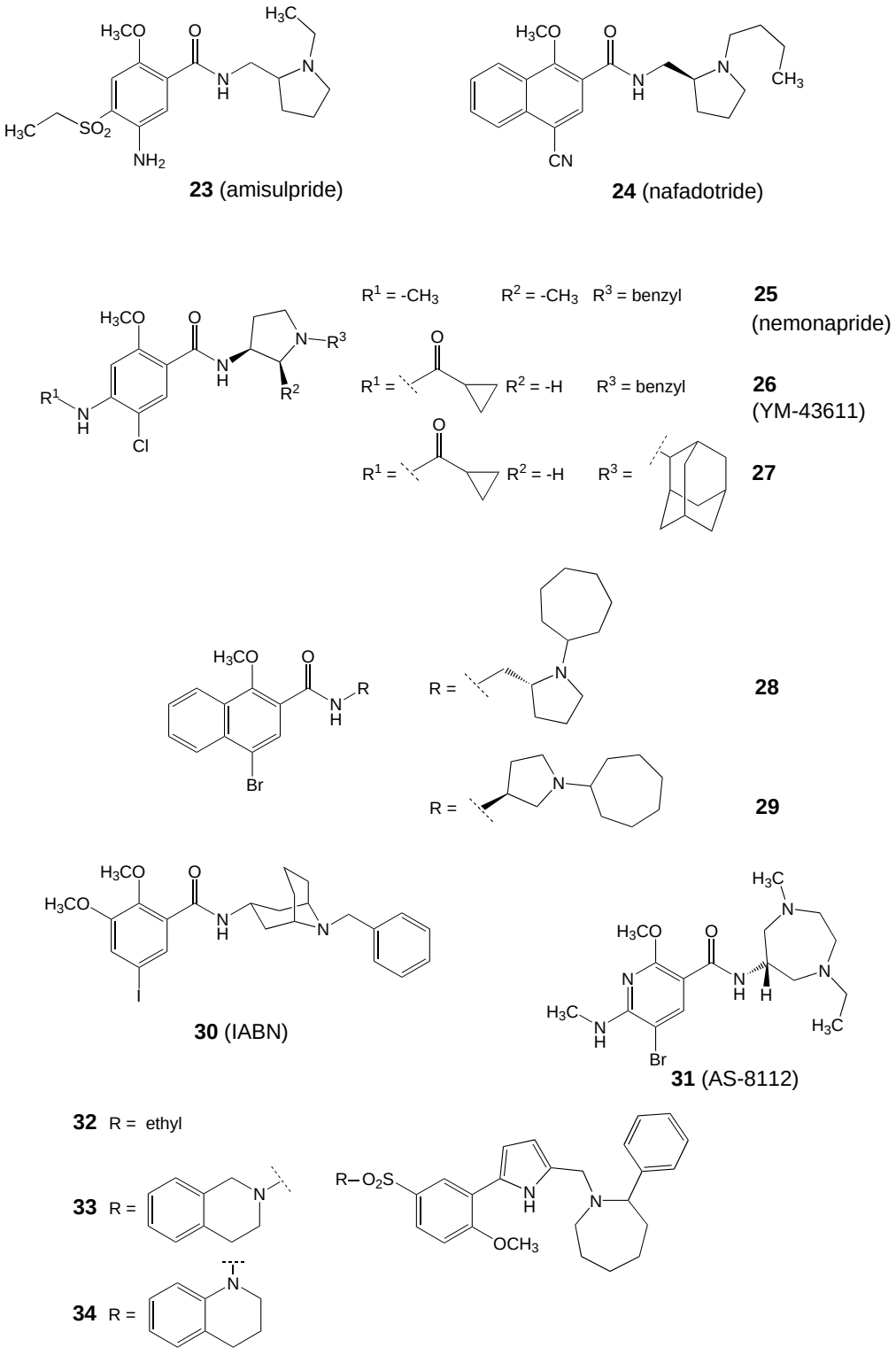
With the aim to evaluate the effect of modifications in the amide moiety of benzamide analogues on D_2 and D_3 receptor binding, a series of 2-(2,3-dimethoxyphenyl)-4-(aminomethyl)-imidazoles was prepared.[60] Replacement of the amide by an imidazole moiety led to no improvement in affinity or selectivity for the dopamine D_3 receptor, but provided a possible bioisostere. Introduction of a 1,2,4-oxadiazole effected a dramatic decrease in D_3 and D_2 receptor affinities. Consequently, the ability to form intramolecular hydrogen bonds between the *o*-methoxy oxygen atom and a proton donor, like NH in imidazole or amide bonds, was proposed as an important structural feature, which may force a coplanar conformation to the aromatic residue. In the imidazol-2-ylphenyl moiety, 5-bromo-substitution on the phenyl ring had a markedly beneficial effect on affinity and selectivity. Thus, compound **20** achieved the highest D_3 receptor preference (7-fold) and nanomolar D_3 receptor affinity (21 nM) in this series. Some analogues were more potent but displayed no selectivity for either the D_3 or D_2 receptor subtype. An impressively high impact on selectivity could be attributed to the structure of the basic amine residue. For enhanced binding affinity to D_3 and D_2 receptors, an aryl moiety positioned near the amine functionality seemed to be required, due to a postulated additional aromatic binding region at the receptor site.[61] Furthermore, binding appeared to be related to the basic property of the amine moiety, whereas a second basic amine turned out to be disadvantageous. As phenylpiperazino derivatives bear such a second amine and nevertheless show high binding affinity (see Table 1), one may speculate that the orientation of the receptor – ligand interaction is disturbed by another amino group only if protonated under physiological conditions.

The structure of 5,6-dimethyoxy-*N*,*N*-dipropylindan-2-amine (**21**, U 99194 A) was affiliated early on to a series of hydroxylated or methoxylated 2-aminoindans (Scheme 3).[62] In later binding assays **21** displayed nanomolar affinity (31 nM), 30-fold preference for the D_3 receptor site as compared to the D_2 receptor, and did not have appreciable affinity to the other monoaminergic, opioid, or adrenergic receptors tested.[29] No apparent intrinsic activity was found, either at the D_2 or at the D_3 receptor.[27] Nevertheless, in in vivo experiments **21** revealed weak activating properties. Contrary to the potential antipsychotic efficiency in animal models, the low metabolic in vivo stability and low oral bioavailability ($\leq$10% in rats) excluded **21** from being a viable drug candidate.[29] In a structurally related series of *N*-substituted 5,6-dimethoxyindan-2-amines the effects of variable amine substitution on D_3 receptor affinity and selectivity were investigated.[29] Here, selective D_3 receptor antagonists exclusively bore an *N*,*N*-dipropyl group at the 2-aminoindan. All other modifications on the *N*-alkyl residues resulted in almost inactive compounds. Compared to substitution at the 4-position of the indan-2-amine basic structure, substitution at the 5-position favored dopamine D_3 receptor preference, due to reduced D_2 receptor binding affinity. Improved metabolic stability could only be achieved for few derivatives, but no improved binding profile was obtained.

Representing the *N*,*N*-dipropyl-indan-2-amine group, known from D_3 receptor active compounds like pramipexole, compound **22** (GMC 1111) was attributed to a 2-aminothiazole moiety, which is a stable and lipophilic bioisosteric replacement of a phenol/catechol group (Scheme 3).[63] In functional mitogenesis assays both agonist and antagonist action was observed, combined with high oral bioavailability and long-lasting activity in rats. Compound **22** displayed partial agonism at D_2 receptors with an affinity value of 27 nM. At the D_3 receptor low nanomolar binding affinity (1.4 nM) and antagonism could be observed for **22**.

5. Pyrrolidine and Pyrrole Structures

As is evident from the structures in Schemes 1 – 3, arylcarbamides and arylacrylamides deliver a valuable structural basis for D_3 receptor ligands. The benzamide derivative **23** (amisulpride; Scheme 4) was characterized as a dopamine receptor antagonist with high and similar affinity for both the dopamine D_3 and D_2 receptor, (2.8 nM and 3.2 nM, respectively).[64] Although (*S*)-(−)-amisulpride is the eutomer and is 38- to 19-fold more potent than the *R*-(+) distomer, the racemate is used in clinical practice. Amisulpride has disinhibitory effects at lower doses and acts as



Scheme 4. *Pyrrolidine and pyrrole structures. References:* ***23****;*[64] ***24****;*[25] ***25****;*[67] ***26*** *and* ***27****;*[68] ***28*** *and* ***29****;*[69] ***30****;*[71] ***31****;*[72] ***32****,* ***33****, and* ***34****.*[75]

an antipsychotic drug at higher doses.[65] This pharmacological profile was assumed to be beneficial for both positive and negative symptoms of schizophrenia.[66]

The naphthamide derivative **24** (nafadotride) has been established as a potent D_3 receptor antagonist.[25] The levoisomer **24** displayed 20-fold higher, subnanomolar affinity for the dopamine D_3 receptor (0.3 nM) and enhanced D_3 receptor preference (10-fold versus D_2) compared to that of its dextroisomer. Binding to D_1 and D_4 receptors as well as to several other receptors appeared to be insignificant. In functional assays **24**

exerted no intrinsic activity and antagonized quinpirole-stimulated mitogenesis.[25]

Derived from the *N*-(pyrrolidin-3-yl)benzamide derivative nemonapride (**25**, YM-09151-2),[67] a very potent but only D_2-like receptor selective antagonist, a series of differently substituted analogues was synthesized and tested on the dopamine D_2, D_3, and D_4 receptors.[68] Variations of the substituent in the 4-position on the benzamide and of the amino substituent on the basic pyrrolidine ring were performed. Increased bulkiness of the substituent on the 4-amino group on the benzamide was tolerated best by the D_4 receptor, followed by the D_3 and the D_2 receptors. With regard to the *N*-pyrrolidine substituent, alicyclic derivatives could be clearly distinguished as favorable for dopamine D_3 receptor binding from corresponding benzyl or phenethyl derivatives. Increasing the bulkiness and the lipophilicity of this substituent consistently enhanced dopamine D_3 receptor selectivity over the D_2 receptor. Potent compounds were obtained that bore a cyclopropylcarbamide moiety and, at the pyrrolidine, a benzyl (**26**, YM-43611) or 2-adamantyl substituent (**27**; Scheme 4). Compounds **26** and **27** revealed low nanomolar binding affinity to dopamine D_3 (21 nM and 1.7 nM, respectively) and D_4 receptors (2.1 nM and 4.4 nM, respectively) and mild preference over the D_2 receptor (10-fold and 2-fold, respectively).

Related to dopamine D_3 receptor ligands with benzamide structures (**23**, **25** – **27**),[68] another series of naphthamide derivatives was presented.[69] The 4-bromo-1-methoxy-2-naphthamide core structure was linked directly or through a methylene bridge to an *N*-substituted piperidine, pyrrolidine (**28**, **29**), or 9-azabicyclo[3.3.1]nonane; in the two latter cases an ethyl chain was kept to the amide nitrogen. Here, the objective was to evaluate the structure – activity relationships of the *N* substituent. Most of the piperidines showed D_2 receptor preference. For pyrrolidines and 9-azabicyclo[3.3.1]nonanes the generally moderate D_3 receptor selectivities could not be related to the size of their *N* substituents. Comparison of stereochemical analogues indicated a considerable spatial impact on affinity and D_3 receptor selectivity. Both, the most selective compound in this series (*R*)-**28** (D_3 affinity 2.4 nM; D_2/D_3 ratio of 26), and the most potent compound (*S*)-**29**, with subnanomolar dopamine D_3 receptor affinity (0.2 nM; 9-fold preference over D_2), bore a cycloheptyl residue, which points out some advantage of this increased ring size (Scheme 4). All compounds displayed modest affinity (5 – 60 nM) for sigma σ_1 and σ_2 receptors.

N-(9-benzyl-9-azabicyclo[3.3.1]non-3-yl)-5-iodo-2,3-dimethoxybenzamide (**30**, IABN) has been developed as a ^{125}I-labeled structural analogue of the dopamine D_2-like receptor selective benzamide MABN.[70] It bound equipotently to the dopamine D_2 and D_3 receptors with subnanomolar affinity values (0.1 nM), and in a slightly less affine manner to the D_4 receptors.[71] No significant binding was found for dopamine D_1 or sigma σ_1 and σ_2 receptors. Due to missing apparent intrinsic activity at D_2 receptors, ^{125}I-IABN was recognized as an antagonist.

The 3-pyridinecarboxamide derivative **31** (AS-8112) with two basic structures was found to have high affinity for dopamine D_2, D_3, and 5-HT_3 receptors (IC_{50} values of 1.0, 2.5, and 1.3 nM, respectively).[72] Low affinity was found for other serotonergic and dopaminergic receptor subtypes.[73] Moreover, in ferrets and dogs **31** showed an improved centrally antiemetic profile, which was supposed to be mediated by combined D_2, D_3, and 5-HT_3 receptor antagonism.[74]

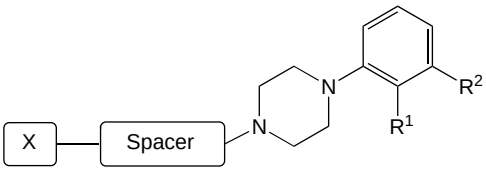
A series of 2,5-disubstituted 1*H*-pyrroles **32** – **34** with basic 2-phenylazepane and 2-methoxy-5-sulfonylphenyl moieties has been described as dopamine D_3 receptor antagonists (Scheme 4).[75] The precursor with 5-ethylsulfonyl substitution **32**, obtained from a previous series, delivered low nanomolar D_3 receptor binding affinity (1.3 nM) and 30-fold selectivity against the dopamine D_2 receptor.[76] Introducing a heteroatom (N, O) next to the sulfonyl group had a positive effect on the D_2/D_3 receptor selectivity ratio since this structural attribute decreased D_2 receptor affinity. Further improvement was achieved in sulfonamide structures when avoiding an acidic NH group in this position by additional alkyl substituents. Conformationally restrained structures resulted in either low nanomolar affinity value (2 nM for 1,2,3,4-tetrahydroisoquinoline **33**; 100-fold selectivity for D_3 versus D_2 receptors), or prominent D_3 receptor selectivity over D_2 (150-fold for 1,2,3,4-tetrahydroquinoline **34**; D_3 affinity 6.3 nM).[75]

6. 4-Phenylpiperazino Compounds

Structural analogues of the antagonists **24** (nafadotride), **28**, and **29** have been developed, in which the naphthamide is linked through an ethyl chain to a basic 4-phenylpiperazino moiety.[77] Affinity was maintained but selectivity could be improved for the dopamine D_3 versus D_2 receptors. As mentioned before, in the arylcarbamide moiety a methoxy group neighboring the amide was proposed to be required for a constrained confirmation as it may enable hydrogen bonds to the amide hydrogen. Nevertheless, this structural feature did not seem to be essential for highly affine D_3 receptor binding, as seen from various compounds in Table 1. Increasing the length of the alkyl spacer chain to trimethylene or tetramethylene led to deteriorated D_3 receptor affinity. Substitution in the phenylpiperazino residue was favorable in the *ortho* position, as was disubstitution in *ortho* and *meta* positions. In contrast to the structural template of compound **24** (see Scheme 4), compounds in this series were found to be antagonists as well as full to partial agonists. Due to its low nanomolar binding affinity, 4-bromo-*N*-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-1-methoxynaphthalene-2-amide (**35**) was observed to have partial D_2/D_3 receptor agonist activity, and also displayed moderate dopamine D_4 receptor affinity (Table 1).

Chain elongation and variation of the arylcarbamide moiety resulted in tricyclic D_3 receptor antagonists incorporating the dichlorinated 4-phenylpiperazino moiety as common structural feature.[78, 79] The 9*H*-fluoren-3-carbamide derivative **36** (NGB 2904) and its biphenylen-2-carbamide analogue **37** (NGB 2849) displayed high D_3 receptor affinity and more than 150-fold selectivity for the D_3 receptor over all other dopamine subreceptors (Table 1).[78] The latter compound exhibited also moderate affinity for the 5-HT_2 receptor. Spacer length reached its optimum at four carbons, compared to three and five carbons. The 9-oxo-9*H*-fluorene-4-carbamide derivative **38**

Table 1. *Dopamine D_2 and D_3 receptor affinities for 4-phenylpiperazino compounds.*



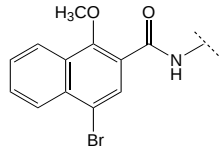
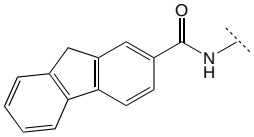
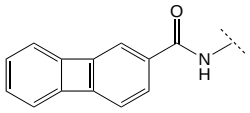
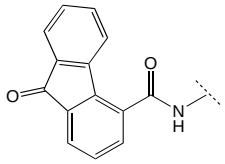
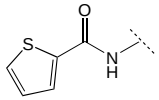
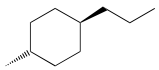
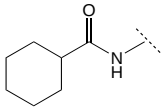
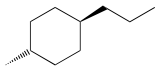
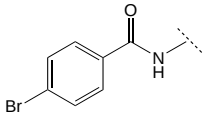
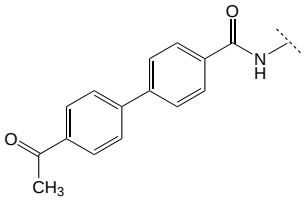
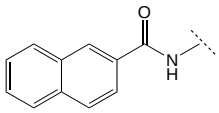
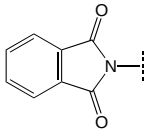
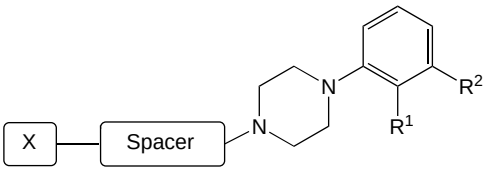
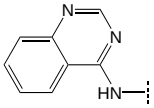
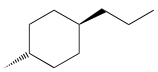
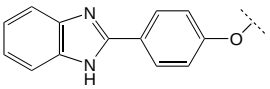
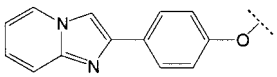
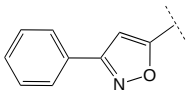
No.	X	Spacer	R^1	R^2	$K_i(D_2)$ [nM][a]	$K_i(D_3)$ [nM][a]	ratio[b] D_2/D_3	Ref.
35		$(CH_2)_2$	Cl	Cl	[c]	8	–	[77]
36		$(CH_2)_4$	Cl	Cl	217	1.4	155	[78]
37		$(CH_2)_4$	Cl	Cl	262	0.9	290	[78]
38		$(CH_2)_4$	Cl	Cl	89	1.4	64	[79]
39			Cl	Cl	0.6	0.02	30	[80]
40			H	H	38	0.14	270	[80]
41		$(CH_2)_4$	OCH_3	H	40	0.5	80	[44]
42		$(CH_2)_4$	OCH_3	H	40	0.3	126	[44]
43		$(CH_2)_4$	OCH_3	H	61	0.9	68	[81]
44		$(CH_2)_4$	OCH_3	H	50	38	1.2	[85]

Table 1. *(Continued).*



No.	X	Spacer	R^1	R^2	$K_i(D_2)$ [nM][a]	$K_i(D_3)$ [nM][a]	ratio[b] D_2/D_3	Ref.
45			H	H	3.2	0.02	160	[86]
46		$(CH_2)_3$	H	H	406	1.5	270	[87]
47		$(CH_2)_4$	OCH_3	H	13	0.32	41	[45]
48		$(CH_2)_4$	OCH_3	H	1727	9.5	181	[94]

[a] Inhibition constant K_i values tested on heterologous binding assays. [b] Ratio D_2/D_3 is the quotient of K_i (D_2): K_i (D_3). [c] 35% response at 10 μM.[77]

slightly differed in structure from **36**. Compound **38** is being evaluated in models of psychostimulant abuse, to assess whether its high lipophilicity is pharmacokinetically problematic.[79] Very recently a related 4-(4-(2,3-dichlorophenyl)piperazino)butyl derivative having a 2-benzothiophenecarbamid moiety (FAUC 365) has been described as an antagonist possessing an extraordinary D_2/D_3 receptor selectivity ratio of 7200 (D_3 affinity 0.5 nM).[95]

Alkyl- and arylcarbamides with a cyclohexylethyl spacer and basic 4-phenylpiperazino residue were synthesized and tested; they revealed remarkable affinity for the dopamine D_3 receptor.[80] Once more, a stereochemical impact was observed for the structures, with a *trans*-cyclohexyl substitution pattern being more selective for the D_3 receptor than the *cis* analogues. Additional substitution at the amide nitrogen had a negative effect on affinity for both D_2 and D_3 receptors. The 2-thienylcarbamide derivative **39** achieved remarkable picomolar D_3 receptor affinity and modest selectivity for D_3 against D_2 receptors. The cyclohexylcarbamide derivative **40** with an unsubstituted phenylpiperazino residue was more selective for the D_3 receptor with subnanomolar affinity and selectivity of 270 for the D_3 over the D_2 receptor. In functional assays on mitogenesis **39** turned out to be an antagonist, whereas **40** proved to be a partial agonist at dopamine D_3 receptors, with [^{3}H]thymidine incorporation at 44% of the level of the full dopamine agonist quinpirole (≅ intrinsic activity of 0.44). Both compounds were satisfactorally selective against α_1, α_2, 5-HT_{1A}, and 5-HT_{2A} receptors.[80]

More phenylpiperazines have been synthesized, exhibiting ≈100-fold selectivity for the dopamine D_3 receptor over D_1, D_2, and D_4 receptors.[44] A 4-bromobenzamide-arylpiperazino derivative (**41**) showed subnanomolar affinity for D_3 as well as considerable affinity for the 5-HT_{1A} and α_1 receptors whilst being selective against other dopamine receptor subtypes. Optimization for selectivity led to 4′-acetylbiphenyl-*N*-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-4-carbamide (**42**, GR103691), which displayed subnanomolar binding affinity, but significantly deteriorated selectivity over 5-HT_{1A} receptors and α_1 adrenoreceptors. Decreasing or increasing the length of the tetramethylene spacer from dimethylene to pentamethylene markedly reduced dopamine D_3 receptor affinity in most series. First an in vivo test in rats indicated a potential atypical antipsychotic profile for **42**. In later studies **42** turned out to have only low activity in vivo, determined on various test systems for D_3, D_2, and 5-HT_{1A} receptors. Rapid metabolism, poor blood–brain barrier penetration, or other factors were considered to be responsible for the general lack of in vivo response for **42**.[14]

The naphthamide derivative **43** (BP 897) showed a noteworthy pharmacological profile (Table 1).[81] The characterization of this 4-(2-methoxyphenyl)piperazino derivative with a tetramethylene spacer comprised subnanomolar binding to and 70-fold preference for the human dopamine D_3 receptor as compared to the D_2 receptor. For D_1, D_4, α_1, α_2, 5-HT_{1A}, and 5-HT_7 receptors no marked preference was manifested. The pattern of functional activity obtained was quite heterogeneous and unique. Thus, in vitro **43** shared a selective, potent, but partial D_3 receptor agonism (intrinsic activity of ≈0.6 versus the dopamine intrinsic activity of 1), with a weak antagonism for the D_2 receptor. In vivo it acted either as agonist or antagonist, depending on the system tested.[35, 82] Compound **43** proved to be effective in reducing cocaine-seeking behavior in rats without having rewarding

effects itself[83] and in the treatment of levodopa-induced dyskinesia.[23, 24]

Quite early related phenylpiperazines linked through a tetramethylene chain to an aromatic amide or imide, like **44** (NAN 190), have been described as high affinity and selective 5-HT_{1A} receptor antagonists.[84] When tested at the dopamine site, these compounds disclosed remarkable affinity for the dopamine D_3 receptor.[85]

Among the 4-phenylpiperazino group, the following compounds (Table 1) showed clearly that an amide or imide moiety was not essential for high D_3 receptor affinity. Within a series of aminopyrimidines directly connected to a cyclohexylethyl spacer, the 4-aminoquinazoline derivative **45**, displaying an aromatic amidine substructure instead of amide, achieved an enhanced affinity for dopamine D_3 receptors, whilst having modest affinity for D_2 and weak affinity for 5-HT_{1A} receptors (74 nM).[86] Analogues have been tested in functional assays as antagonists or partial agonists at D_2 and 5-HT_{1A} receptors, indicating a comparable profile for **45**.

Modification of the amide moiety into an aryl – alkyl – ether led to highly affine compounds with partial agonist activity at the dopamine D_3 receptor.[87] Among those 2-(4-(propyloxy)phenyl)-benzimidazole structures, the unsubstituted phenylpiperazino derivative **46** showed low nanomolar binding affinity for the dopamine D_3 receptor and remarkably high selectivity versus the D_2 receptor (Table 1). Results of a second messenger assay in vitro indicated agonist properties, despite an antagonist profile in vivo. Various substitutions of the aromatic moiety in phenylpiperazines mostly reduced the D_3 receptor preference.

A related series of 4-(2-methoxyphenyl)piperazino derivatives with the structural feature of a substituted phenoxyalkyl spacer of variable length was described.[45] Conformational analysis was performed with variations in the heterocyclic 4-phenoxy substituent and length of the alkyl spacer, whilst maintaining the 4-(2-methoxyphenyl)piperazino group. For the alkyl spacer clear structure – activity relationships could be observed with two methylene groups being disadvantageous, three methylene groups displaying improved values, and a tetramethylene chain as optimal for high dopamine D_3 receptor binding as well as for D_3 versus D_2 receptor preference ($(CH_2)_2 < (CH_2)_3 < (CH_2)_4$). Furthermore the tetramethylene spacer had an enhancing influence on the considerable 5-HT_{1A} receptor affinity. Among the heterocyclic modifications, a nitrogen-containing substructure seemed to be beneficial for improved D_3 receptor ligand binding. As long as they bore a tetramethylene chain, all fused imidazole derivatives showed subnanomolar binding affinities and reasonable D_3 receptor preference. The imidazo[1,2-α]pyridin-2-yl-4′-phenyl-ether derivative **47** displayed the best values within this series and showed 42-fold D_3 over D_2 receptor preference. Functional activity has not been determined yet for this series.

Very recently a series of piperazinylalkylisoxazoles was reported to include several low nanomolar binding (2.6 – 27 nM) dopamine D_3 receptor ligands with more than 180-fold preference for the D_3 over the D_2 receptor. The isoxazole was taken as an alternative bioisostere and linked to a trimethylene or tetramethylene spacer, the latter being clearly favorable for D_3 receptor binding. Special interest is attracted by 1-(2-methoxyphenyl)-4-(4-(3-phenylisoxazol-5-yl)butyl)piperazine (**48**) with its D_3 receptor preferring (181-fold over D_2, 21-fold over D_4) and low nanomolar D_3 binding profile.[94]

7. Functional Pharmacology of Selected Dopamine D_3 Receptor Antagonists and Partial Agonists

Several functional assays have been performed on compound **3** (S 14297; Scheme 1). The complete blockade of 7-OH-DPAT-induced hypothermia in rats indicated an antagonist profile in vivo for the aminotetralin derivative **3**.[38] Furthermore, it elicited neither prolactin secretion nor catalepsy in rats; these are characteristic actions of dopamine D_2 receptor antagonists.[38] As compound **3** did not significantly enhance dopamine release, D_3 autoreceptors were suggested to control dopamine synthesis and release.[28] The existence of dopamine D_3 autoreceptors seems to be clear in special brain areas,[10] but their functional importance still is a matter of debate. In some cases the influence of D_3 heteroreceptors localized on non-dopaminergic neurons cannot be excluded. The cataleptic actions of haloperidol were abolished by **3**, but an influence on conditioned avoidance response, as paradigm for antipsychotic properties, was not observed.[88] With the D_3 receptor antagonists **21** (U 99194 A) and **24** (nafadotride) compound **3** shared stimulatory behavioral properties in habituated rats, but had no effect on locomotor activity in actively exploring rats.[29] On the other hand, **3** was suggested to possess partial agonist properties, due to stimulation of mitogen-activated protein kinase.[89] Although presenting a reasonable combination of substantial D_3 receptor affinity and selectivity as well as satisfactory bioavailability,[14] the moderate interactions of **3** at σ_1 and muscarinic receptor sites compromised its use as an experimental pharmacological tool.[36, 38]

The antagonist profile of the biphenyl derivative **15** (S 33084; Scheme 2) has been determined on various functional features. Compound **15** competitively antagonized dopamine-induced [^{35}S]guanosine-5′-*O*-(3-thio)triphosphate ([^{35}S]GTPγS) binding in cell lines expressing hD_3 and hD_2 receptors.[36, 50] It also concentration-dependently abolished dopamine-induced stimulation of D_3 receptor coupled mitogen-activated protein kinase.[36] More functional tests have been performed to investigate the influence of dopamine D_3 receptors on diverse effects and behaviors. The induction of hypothermia by the agonists 7-OH-DPAT and PD 128907 was dose-dependently attenuated, as were 7-OH-DPAT-induced penile erections; these factors indicate an influence of D_3 receptors.[90] In contrast to that, **15** had little effect on 7-OH-DPAT-induced yawning and hypophagia, behaviors that are assumed to be mediated by D_2 receptors.[90] The proposal of principal D_2 receptor activation in therapy against Parkinson's disease with dopamine agonists seemed to be supported by the failure of **15** to block contralateral rotation elicited by the preferential D_3 receptor agonist quinpirole in unilateral substantia nigra-lesioned rats.[90] In models of potential antipsychotic activity **15** was inactive with regard to conditioned avoidance behavior, the hyperlocomotor response to amphetamine and cocaine in rats, and apomorphine-induced climbing

in mice.[90] Furthermore, **15** neither elicited catalepsy nor inhibited methylphenidate-induced gnawing or induced prolactin secretion in tests predictive of extrapyramidal motor or endocrine side effects in rats.[90] The benefit of compound **15** can be seen as a tool for further investigation of the physiological and pathophysiological role of dopamine D_3 receptors rather than in therapeutic application.

In in vivo experiments **21** (U 99194 A; Scheme 3) acted as a prominent activator of locomotor activity in rats, but on the other hand more or less failed to induce an increase in dopamine release.[27] One possible explanation for this observation was the blockade of release-inhibitory dopaminergic autoreceptors or postsynaptic dopamine receptors involved in the suppression of some aspects of psychomotor activity.[27] Strikingly, in a following functional test on rats **21** acted as an activator of locomotion, whereas the higher D_3 receptor selective antagonist **42** (GR103691) and the less selective compound **24** (nafadotride) were both ineffective on spontaneous behavior.[91] Besides a D_2-like receptor agonism and influence on D_1-like receptors, a putative non-dopaminergic response has to be taken into consideration.

Compound **22** (GMC 1111; Scheme 3) exhibited a mixed dopamine receptor agonist/antagonist profile in functional assays.[63] In rats unilaterally lesioned with 6-hydroxydopamine (6-OH-DA) it caused an activation of rotation, which was suggestive of agonism at postsynaptic dopamine receptors. The increase in dopamine turnover in rat striatum was assigned to the blockade of presynaptic dopamine receptors and implied antagonist action. Therefore **22** displayed dopamine D_2 receptor partial agonism but D_3 receptor antagonism.

For nafadotride (**24**; Scheme 4) dopamine agonist activity was not detected in vitro at either the dopamine D_2 or D_3 receptors. In in vivo models for rodents, paradoxical behavior stimulant properties were observed, shared with the D_3 receptor preferring antagonists (+)-AJ 76 (**1**) and (+)-UH 232 (**2**).[34] Contrary to haloperidol, a D_2 receptor preferring antagonist, low-dosage treatment of **24** (maximum 1 mg kg^{-1}) increased spontaneous locomotion of habituated rats and climbing behavior of mice.[25] About 100-fold higher dosage was required to evoke catalepsy in rats, like that obtained with haloperidol, and to antagonize apomorphine-induced climbing in mice.[23] This biphasic behavioral pattern may be attributed to the limited selectivity for dopamine D_3 receptors, as low dosage of **24** evoked D_3 receptor blockade and higher dosage also blocked D_2 receptors. A potential therapeutic application in schizophrenia with alleviation of the negative symptoms was implied.[25]

The efficiency of the antipsychotic amisulpride (**23**; Scheme 4) against both the negative and positive symptoms of schizophrenia was assigned to the preferential blockade of effects involving presynaptic D_2/D_3 receptor mechanisms and limbic structures.[92] Even at high doses (100 mg kg^{-1}, intraperitoneal) **23** did not induce catalepsy.

Compound **43** (BP 897; Table 1) evoked agonist effects on rotations in 6-OH-DA-lesioned rats and antagonist effects on c-*fos* gene expression in the islands of Calleja in rats.[81] The hypothesis for the dual activity observed may rest on various models of receptor activation. On the basis that efficiency of a ligand is not only related to its intrinsic property, but also to receptor G-protein-coupling efficiency, diversity in functional response may be put down to various tissues with different receptor reserve.[81] Most probably the level of the endogenous transmitter is also involved in the direction of the response. Crucial for the potential therapeutic applications were the findings that **43** significantly reduced conditioned cue-controlled cocaine-seeking behavior in rats in a dose-dependent manner, which was prevented by pretreatment with the antagonist nafadotride (**24**). The effects obtained were dissociative and limited to the starting, cocaine-unaffected interval of a session, whereas no effect on cocaine-induced increase in responding was perceived.[81] Attenuation of the stimulus effect was achieved for cocaine and *D*-amphetamine, but not for heroin. As a further positive aspect in the pharmacological profile, **43** displayed no intrinsic reinforcing effects itself in monkeys, due to its mixed partial agonist/antagonist properties. These data supported the potential therapeutic benefit of **43** in the treatment of cocaine craving and the vulnerability to relapse as well as in the recently started clinical development.[83] Other groups proved **43** to be a D_3 receptor antagonist. In microphysiometry and radioligand test systems, it was found to have a primary antagonist effect on human D_2 and D_3 receptors.[35] The authors proposed that inhibition of cocaine-seeking behavior depended on antagonist properties. Congruent results were obtained from studies with an electrophysiological in vivo assay in rats,[82] whereas discrepancy in in vitro tests might be due to heterologous expression systems.

A more recent therapeutic target for **43** is the proposed coadministration to levodopa in Parkinson's disease.[93] The majority of patients suffering from Parkinson's disease develop dyskinesia as a severe side effect of long-term levodopa treatment. As an overexpression of dopamine D_3 receptors was suggested to underlie this phenomenon, a compound with partial D_3 receptor agonism should prevent patients from dyskinesia due to normalizing excessive D_3 receptor stimulation. Furthermore, the agonist attribute of **43** may contribute to the therapeutic effect of levodopa or, at least, do not oppose it.[93] Promising results were obtained from a test on monkeys, where BP 897 (**43**) was able to attenuate levodopa-induced dyskinesia after oral administration.[23]

8. Summary and Outlook

In the field of dopamine D_3 receptor ligands, numerous developments have been observed during the last decade. Promising compounds with high affinity for the D_3 receptor often do not display sufficient selectivity over the D_2 or other neurotransmitter receptors, and only few compounds fulfill the crucial requirements on pharmacokinetic parameters for drugs when tested in vivo. Therapeutic options for dopamine D_3 receptor antagonists and partial agonists are proposed in the treatment of psychosis, schizophrenia, drug addiction, and Parkinson's disease, with the complete pharmacological receptor profile of compounds taken into consideration. Although it

may seem that the ideal drug candidate has not been discovered yet, major progress in D_3 receptor drug development for different diseases is expected for the near future.

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