Small changes for long term impact : optimization of structure kinetic properties : a case of CCR2 antagonists

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CHAPTER 2

INDANES – PROPERTIES, PREPARATION, AND PRESENCE IN LIGANDS FOR G PROTEIN-COUPLED RECEPTORS

This chapter was based upon:

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ABSTRACT

The indane (2,3-dihydro-1*H*-indene) ring system is an attractive scaffold for biologically active compounds due to the combination of aromatic and aliphatic properties fused together in one rigid system. This bicyclic structure provides a wide range of possibilities to incorporate specific substituents in different directionalities, thus being an attractive scaffold for medicinal chemists. Notably, many indane-based compounds are being used in the clinic to treat various diseases, such as indinavir, an HIV-1 protease inhibitor, indantadol, a potent MAO-inhibitor, the amine uptake inhibitor indatraline, and the ultra–long–acting β-adrenoceptor agonist indacaterol. Given the diversity of targets these drugs act on, one could argue that the indane ring system is a privileged substructure, just like indole, the nitrogen atom containing unsaturated version of it. In the present review the synthetic and medicinal chemistry of the indane ring system is described. In more detail, it contains a comprehensive overview of compounds bearing the indane substructure with G protein-coupled receptor (GPCR) activity, with particular emphasis on their structure–activity relationships (SAR).

INTRODUCTION

In the 1920's many compounds containing the 1,3-diketo-group or the enolic form of it were discovered to bear physiological activity, and combining this group with a phenol in the early 1930's resulted in a series of indan-1,3-diones showing bacteriostatic activity.[1] The compounds inhibited the proliferation of gram–positive bacteria and are very early representatives of pharmacologically active molecules based on the 2,3-dihydro-1*H*-indene structure **1** (also known as indane), which is also commonly found in indanones (such as indan-1-one **2**) or indandiones (such as indan-1,3-dione **3**) (Figure 1).

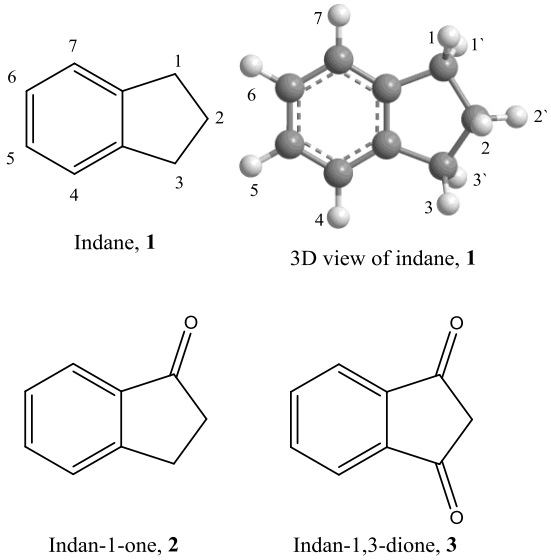
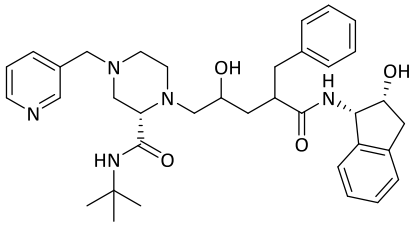


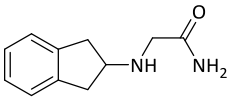
Figure 1. Chemical structures of indane ring system **1**, indan-1-one **2**, indan-1,3-dione **3**.

The indane ring system can be regarded as a fusion product of aromatic benzene and the aliphatic cyclopentane ring in one. This combination provides a broad diversity of chemical entities with indane as a core structure. Many different synthetic methods for the synthesis and diversification of indanes have been reported, which will be described below. Additionally, the ring system can accommodate substituents in six different directions on its aliphatic part and an additional four on the aromatic ring (see Figure 1, 3D view of indane) to add desired properties to such a molecule.

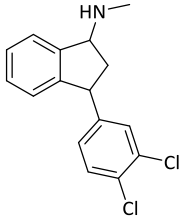
The indane substructure occurs in many natural products like pterosins,[2] or more hydrogenated forms of it in ionophores such as indanomycin,[3] and stawamycin.[4] This structural motif is also present in many marketed drugs, such as indinavir **4**,[5] an HIV-1 protease inhibitor, indantadol **5**,[6] a potent MAO-inhibitor, the amine uptake inhibitor indatraline **6**,[7] the anti-inflammatory clidinac **7**, antiarrhythmic agent indecainide **8**,[8] diuretic indacrinone **9**[9] and the anticoagulant hedulin **10**[10] (Figure 2). Given the big diversity of targets these drugs act on, one could argue that the indane ring system is a "privileged" substructure, just like indole, a nitrogen atom containing unsaturated version of it.[11] The activity of indane derivatives in biological systems and the wide variety of their actions make them an interesting moiety for medicinal chemistry.



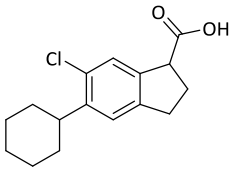
Indinavir, **4**



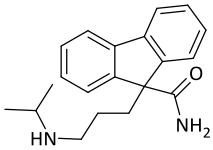
Indantadol, **5**



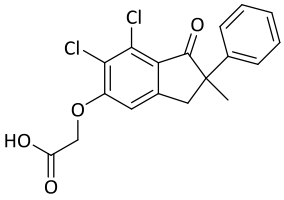
Indatraline, **6**



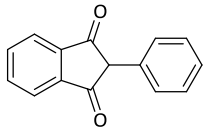
Clidinac, **7**



Indecainide, **8**



Indacrinone, **9**



Hedulin, **10**

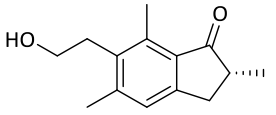
Figure 2. Examples of marketed drugs containing the indane ring system.

In this review, we aim to present the key chemical and pharmacological information on the indane ring system. In more detail, we will look at the activity of indanes on targets that have considerable importance in drug development – G protein–coupled receptors (GPCRs). The report is divided in the following sections: first the preservation and occurrence of the indane scaffold will be shown by discussing some of the natural products that contain this moiety. Additionally, synthetic routes to indanes are described as well as the possibilities of

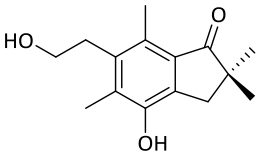
incorporating the indane system into a compound's chemical structure. Finally, an overview is given of compounds bearing the indane substructure with GPCR activity and inferences are made regarding their structure-activity relationships (SAR). This review excludes unsaturated indanes and polycyclic ring systems containing indane (e.g., 9*H*-fluorene, 1,2-dihydroacenaphthylene, indacenes and hydrogenated forms of these). SciFinder and Reaxys databases were used for a literature search based on the indane substructure. To retrieve the relevant literature on indanes with GPCR activity the following terms were used in different combinations as additional filters in the SciFinder database: *target*, *protein*, *G protein-coupled receptor*.

NATURAL OCCURRENCE OF INDANES

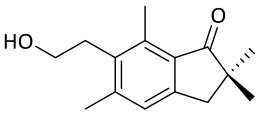
The indane scaffold is present across a wide range of species. One of the largest resources are *Pteridophyta* (ferns). Ferns produce more than 60 different structures that contain the indanone **2** scaffold, called pterosins. The structures and biological properties of these pterosins were first reviewed by Syrchina and Semenov.[12] The first identified pterosin is pterosin B **11** (Figure 3) with antimicrobial properties. Other compounds from the pterosin family have also been reported to have biological activity such as cytotoxicity against cancer cell lines[13] and antidiabetic activity.[14] Some of the pterosins have been used for centuries in oriental medicine like onitin **12**. Ho et al.[15] showed that onitin possesses smooth-muscle relaxant properties, suggested to take place through inhibition of a serotonin 5-HT receptor. More than a decade later Sheridan et al.[16] proposed that pterosin Z **13** (the dehydroxylated form of onitin) is acting through the inhibition of extracellular calcium influx through calcium channels or by interference with the calcium/calmodulin cascade of reactions within the cell.



Pterosin B, **11**



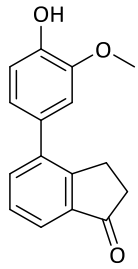
Onitin, **12**



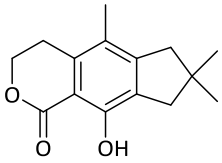
Pterosin Z, **13**

Figure 3. Indane derivatives found in *Pteridophyta*.

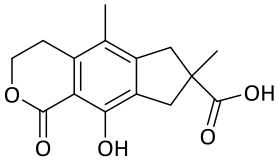
The indane system is also found in the stem bark of *Vatica pauciflora* as part of resveratrol oligomers (pauciflorol D and pauciflorol F)[17] where it is formed by polymerization of resveratrol.[18] Recently a new indanone containing compound has been isolated from the roots of *Uvaria afzelii*, named afzeliindanone **14** (Figure 4).[19] Another source of naturally occurring indanes are fungi and bacteria. For example, the fomajorins D **15** and S **16** were isolated from the fungus *Heterobasidion annosum*. Tripartin **17** containing a dichlorinated methyl group and inhibiting histone H3 lysine 9 demethylase (KDM4) was isolated from a culture broth of a *Streptomyces* species associated with larvae of the dung beetle *Copris tripartitus*.[20]



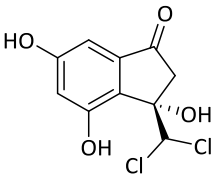
Azeliindanone, **14**



Fomajorin D, **15**



Fomajorin S, **16**



Tripartin, **17**

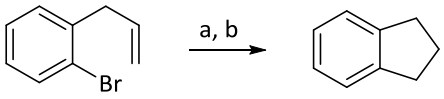
Figure 4. Indane derivatives found in *Uvaria afzelii* (afzeliindanone **14**), *Heterobasidion annosum* (fomajorins D **15** and S **16**), a culture broth of a *Streptomyces* species (tripartin **17**).

SYNTHESIS OF INDANE RING SYSTEM

As mentioned above the indane ring system is present in nature, but before it was identified in natural products, several synthetic routes had already been developed to produce indane-based structures. The first synthesis of an indandione, i.e. **3**, was described by Wislicenus in 1888 [21] and soon after the synthesis of indanone **2** by Gabriel and Hausmann[22] and indane **1** by Kramer and Spilker[23] was reported. However, nowadays more recent synthetic approaches are used to obtain indane compounds. The methods described below show different routes how to synthesize, modify and incorporate various substituents on the desired location of the indane ring system.

The unsubstituted indane can be acquired using a palladium–catalyzed cross–coupling reaction with B-alkyl-9-borabicyclo[3.3.1]nonane (Scheme 1) as reported by Miyaura et al.[24] A more general method for the formation of different cyclic systems including indane (Scheme 2) was developed by Katritzky et al.[25]

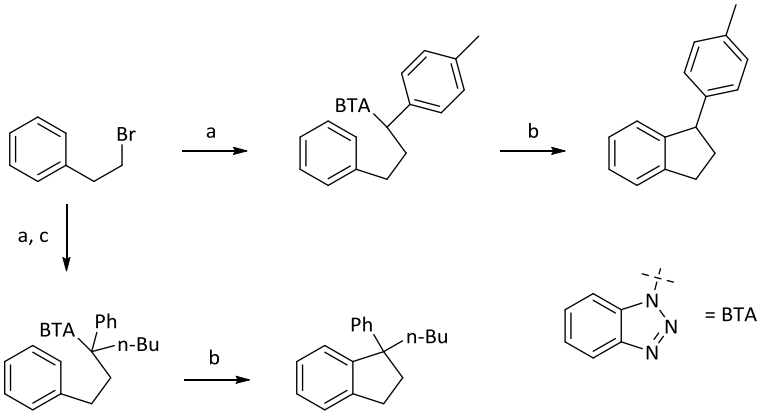
Scheme 1.



a) 9-BBN, THF, 0 C-rt, 4h; b) $PdCl_2$(dppf), NaOH 3 equiv.

These authors used (benzotriazol-1-yl)-methanes to act as 1,1-dipole synthon equivalents. With this method 1-monosubstituted or 1,1-disubstituted indanes can be synthesized. However, a significant formation of alkenes was observed during five-membered ring annulations.

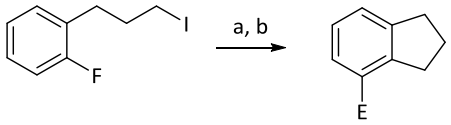
Scheme 2.



a) i) n-BuLi,1-benzyl-1*H*-1,2,3-benzotriazole, THF, -78 °C, 3 h; ii) rt, overnight;
b) i) $ZnBr_2$, 130 °C, 12 h; ii) 160 °C, 24 h;
c) n-BuLi, n-BuI, -78 °C, 3 h

Bailey and Longstaff[26] reported another method to arrive at the indane ring system and simultaneously incorporated a variety of different electrophiles selectively on the 4 position *via* an organolithium intermediate (Scheme 3).

Scheme 3.



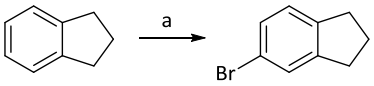
E^+	E
H_2O	H
CH_3OD	D
$Br(CH_2)_2Br$	Br
$ClCO_2C_2H_5$	$CO_2C_2H_5$
$(CH_3)_2NCHO$	CHO
PhCHO	PhCH(OH)

a) t-BuLi 3.2 equiv., n-pentane - Et_2O (4:1), -78 ^oC, 15 min; b) THF, warm, E^+

Indanes with substitution on the 5 position are usually acquired either via a direct halogenation (used in the synthesis of mGluR2 modulators)[27] (Scheme 4a) or via deoxygenation of 5-substituted indanones (Scheme 4b).[28] Mathison et al.[29] developed another method (Scheme 5) which allows to introduce an aldehyde group directly on the indane ring where it can be modified further on. However, this method yields a mixture of 4- and 5-substituted indanes in a 1:4 ratio.

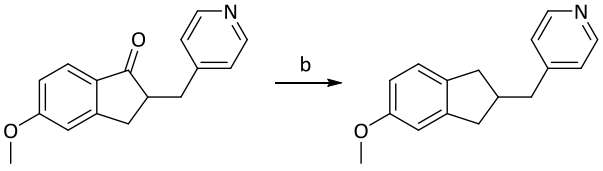
Scheme 4.

a)



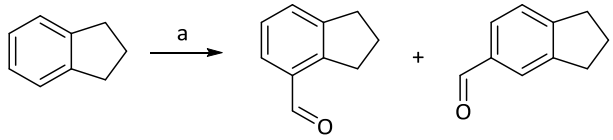
a) Al_2O_3, Br_2, 5 min, yield 33%

b)



b) i) KOH, $H_2N\text{-}NH_2{*}H_2O$, $HO(CH_2)_2OH$, reflux, 1.5 h, ii) 195^oC, 4 h

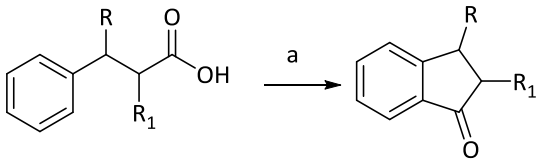
Scheme 5.



a) $TiCl_4$, Cl_2CHOCH_3, 0 ^oC, 30 min, yield: 84% (1:4 ratio)

The indanone structure **2** is much more versatile as a building block in medicinal chemistry. The ketone functional group can be directly used as the reactive center for different modifications or coupling reactions. A typical method for indan-1-one synthesis is based on intramolecular Friedel-Crafts acylation of phenylpropanoic acids. In this approach substituents on the propyl chain are translated into the corresponding 2- or 3-substituents on the indan-1-one. Recently Kangani and Day[30] reported conditions in which indan-1-ones are formed in high yields and short reaction times at room temperature in the presence of cyanuric chloride/pyridine/$AlCl_3$ (Scheme 6).

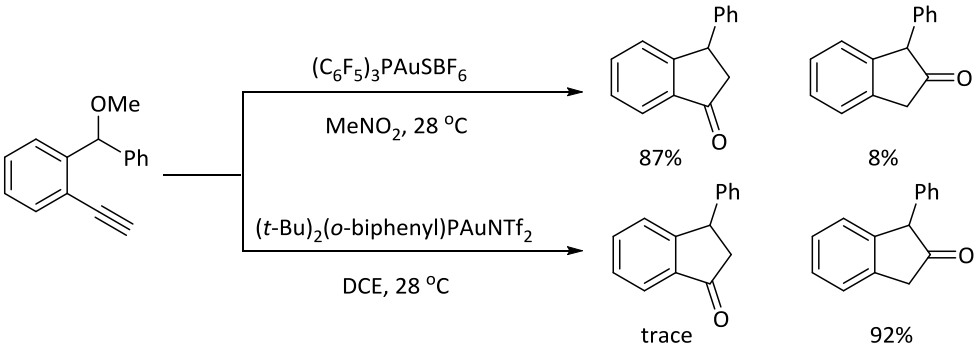
Scheme 6.



a) Cyanuric chloride, $AlCl_3$, Py, rt, 25 min

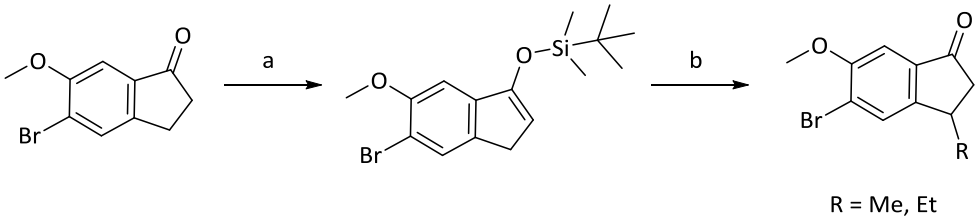
Very recently, Wang et al.[31] described selective syntheses of indan-1-ones and indan-2-ones from 2-ethynylbenzyl ethers with suitable catalysts and solvents (Scheme 7). Using [tris(pentafluorophenyl)phosphine]gold hexafluoroantimonate $[(C_6F_5)_3PAuSbF_6]$ in nitromethane ($MeNO_2$) preferably yielded indan-1-ones whereas [(ortho-biphenyl)di(tert-butyl)phosphine]gold triflimide $[(t\text{-}Bu)_2(o\text{-biphenyl})PAuNTf_2]$ in dichloroethane tended to form indan-2-one derivatives.

Scheme 7.



Another method worth mentioning is how to incorporate substituents on 3 position of already made indan-1-ones. Azemi et al. described that 3-(*t*-butyldimethylsilyloxy)indene (generated from indanone) can be selectively deprotonated with lithium diisopropylamide and then reacted with an alkylating agent.[32] The silyl ether can be removed by quenching it with acid (Scheme 8). This approach was used by Vilums et al.[33] to generate the desired indanones as building blocks for CCR2 antagonists.

Scheme 8.



a) TBDMS-Cl, DBU, 0 °C-r.t.;
b) i) LDA, 1 h, -78 °C -> -35 °C, -> -78 °C, 1 h, corresponding alkyliodide; ii) 12 M HCl.

Incorporation of substituents on the phenyl ring of the indane system is usually done via Friedel–Crafts acylation; however, it can result in mixtures of regioisomers.

INDANES AND G PROTEIN-COUPLED RECEPTORS

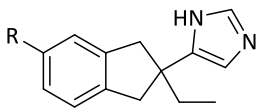
In a recent review Garland[34] discusses that 26% (437 of 1663) of marketed drugs that are listed in DrugBank are targeting G protein-coupled receptors. However, GPCRs or GPCR

related (e.g., receptor-activity modifying proteins or RAMPs) targets make only 7% (109 of 1479) of all the drugged targets. Apparently, GPCRs are privileged targets. GPCRs are very similar in overall structure, but the binding sites are tailored to accommodate their individual endogenous ligands, and, additionally, synthetic ligands, giving rise to ligand diversity. Ligands containing the indane substructure are among the ones with highest affinities for GPCRs and these are the subject of this review.

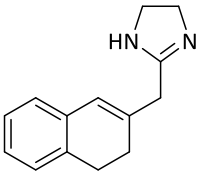
TARGETS IN DISEASES OF THE CENTRAL NERVOUS SYSTEM (CNS)

α_2-Adrenoceptor

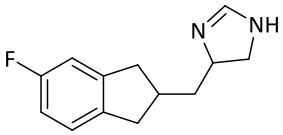
Alpha–2 adrenergic receptors (α_2–adrenoceptors) are involved in several central and peripheral nervous system processes, such as alertness, heart rate regulation, vasomotor control and nociceptive processing. Recent studies suggest that α_2–adrenoceptors are targets for the treatment of L–dopa–induced dyskinesia in Parkinson's disease. For example, fipamezole **18** (Figure 5) can be co–administered with the anti-parkinsonian drug L–dopa.[35] Fipamezole reduces the L–dopa–induced dyskinesia without affecting any other parkinsonian action of the drug; it even elongates the duration of L–dopa's action. It has high affinity for the human α_{2A} (K_i = 9.2 nM), α_{2B} (K_i = 17 nM), and α_{2C} (K_i = 55 nM) receptors, with lower affinity for the GPCRs histamine H_1 and H_3 and the non–GPCR serotonin transporter.[36] Its non–fluorinated analogue atipamezole **19**, which is used as an agent in reversing medetomidine–induced sedation–analgesia in veterinary practice, has an approximately 4–fold higher affinity for the α_{2A} (K_i = 2.2 nM), α_{2B} (K_i = 3.9 nM), and α_{2C} (K_i = 12 nM) receptors.



Fipamezole, **18** R = F
Atipamezole, **19** R = H



Napamezole, **20**



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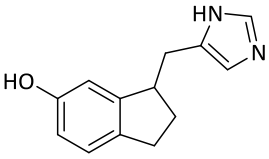


Fadolmidine, **22**

Figure 5. α_2 adrenoceptor ligands.

Another structurally similar α_2 adrenoceptor antagonist was designed to combine the properties of **18** with the monoamine uptake inhibition properties of napamezole **20**, thereby creating anti-depressant effects.[37] Compound **21** had the best balance between affinity for α_2 adrenoceptors and serotonin–norepinephrine reuptake inhibitor properties. The change from indane to indene affected only the α_2 adrenoceptors while a further change to benzofuran solely affected the serotonin reuptake inhibition. Additionally, the indane system displayed a much higher affinity (at least 8–fold) for the α_2 adrenoceptor compared to other bicyclic systems such as dihydronaphtalene, naphthalene and tetralin containing the same 4(5)-imidazoline substituent.

In contrast to these antagonists, fadolmidine **22** is an agonist of α_2 adrenoceptors[38] being developed for post-operative pain treatment (currently phase IIb).[39] Structurally, this agonist is very similar to the antagonists with the indane system as a core. The main difference is the position of the imidazole/imidazoline on the cyclopentane ring. The affinity of the compound is similar to that of the antagonists, with 2.5 nM, 0.6 nM and 0.3 nM for the human α_{2A}, α_{2B} and α_{2C} receptors, respectively. Fadolmidine is also a full agonist for α_{1A} and α_{1B} adrenoreceptors with EC_{50} values of 22 nM and 3.4 nM, respectively.[40]

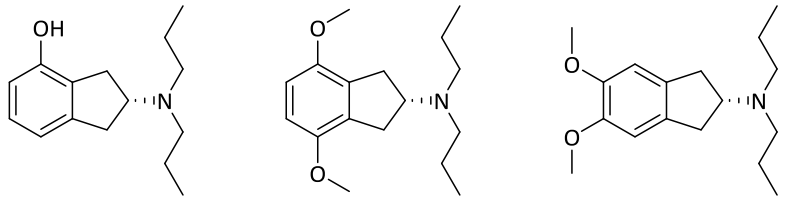
Thus, the indane system seems to be a preferred structure for α_2 adrenoceptor affinity and the location of imidazole/imidazoline rings determines the agonistic/antagonistic activity of the structures.

Dopamine Receptors

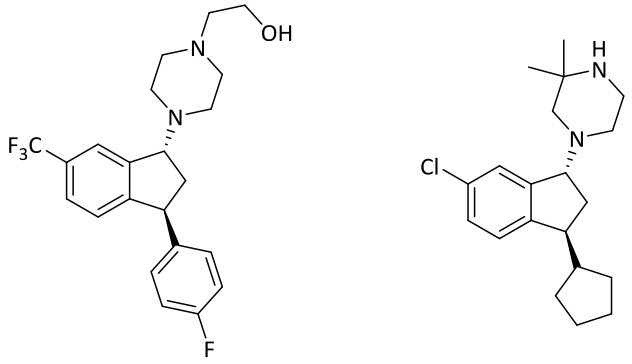
Central dopaminergic receptors are involved in many CNS diseases such as schizophrenia, depression and Parkinson's disease. The development of drugs targeting this receptor-type has therefore been a goal for several decades.

One of the earlier investigations was performed by Hacksell et al.[41] identifying 4-hydroxy-2-(dipropylamino)indan **23** (Figure 6) as a potent dopamine receptor agonist. When its biochemical and behavioral effects in rats and emesis in dogs were measured, this compound was found to have similar potency compared to the known highly active dopamine agonist apomorphine, but it was considerably less potent than its tetralin analogue. In the indane series, potency was significantly reduced when the hydroxyl group was placed at the 6-position, or when a methyl–spacer was positioned between the indane and amine.

Another agonist, RDS-127 **24**, was identified to preferentially activate dopamine autoreceptors as opposed to the post-synaptic dopamine receptors (D_2).[42] It was found to have a K_i of 10 nM when incubated with rat striatal membrane preparations, and was shown to be more potent than its tetralin analogue. Its structure is based on the core of **23**, only the 7-hydroxy substituent was replaced by a methoxy group and a 4-methoxygroup was added. This compound also has some serotonin (agonist) receptor activities.



23 RDS-127, **24** PNU 99194, **25**



Tefludazine, **26** **27**

Figure 6. Dopamine receptor ligands.

When the methoxy groups were moved from the 4,7- to 5,6-positions the compound behaved as a postsynaptic dopamine receptor antagonist (PNU 99194) **25**.[43] This compound selectively binds to the D_3 receptor and thereby predominantly has an effect on locomotor activity. Its K_i value for this receptor is 78 nM, 20 fold lower than for the D_2 receptor (1572 nM).[44]

A slightly bulkier molecule, tefludazine **26**, was found in a 1-piperazino-3-phenylindane series as a dopamine antagonist with high affinity.[45] These compounds have methyl phenidate and amphetamine antagonist activity and induce catalepsy in rats, indicating their antipsychotic activity, through D_1 and D_2 antagonism. Tefludazine has a K_i of 8.8 nM in rat striatal membranes, a binding affinity slightly higher than that of chlorpromazine, a known antipsychotic. Bogeso et al. showed that substituents such as chlorine, methyl or CF_3 and to a lesser extent fluorine at the indane 6-position are crucial for affinity. A variety of substituents on the piperazine moiety is tolerated, but the hydroxyethyl showed the best activity. The 4-fluoro substitution on the phenyl ring is important for the *in vivo* activity, most probably due

to increased metabolic stability. None of the *cis*-isomers were active dopamine antagonists, and only *trans*-isomers bound with high affinity to the dopamine receptor. At the same time it was found that many of the compounds in this series were potent dopamine uptake inhibitors and had high affinity for the $5HT_2$ receptor as an antagonist **26** with a K_i of 8.6 nM while having only sub–micromolar affinity for the α_1-adrenoceptor (IC_{50} = 670 nM).[46]

Another series from the same research group showed high affinity for the D_1 and D_2 receptors, next to $5HT_2$ and α–adrenoceptors.[47] In this series the *trans*-isomers were the active species. It was concluded that for the chiral center at the amine, one enantiomer contains the receptor blocking activity, whereas the other enantiomer is active as dopamine/norepinephrine uptake inhibitor. One of the most potent compounds in this series (**27**) was identified as a potential antipsychotic agent. D_1 and D_2 affinity were highest for small substituents on the 6-position of the indane moiety and much higher compared to 4-, 5- or 7-substituted structures. In addition, compounds with 6-fluoro and 6-chloro substituents preferred the D_1 receptor, whereas 6-CH_3 and 6-CF_3 favored the D_2 receptor. Exploration of the piperazine ring revealed that its optimal substituent is 3-Me. However, to avoid creating an additional chiral center, the 3 position was dimethylated, which yielded an increase in selectivity for the D_1 receptor. Formation of spirocycles at this position gave similar affinities, but a loss of selectivity for D_1/D_2. Larger substituents on the nitrogen atom such as *i*-propyl, hydroxy-ethyl and propyl did not markedly affect affinity for the dopamine receptors, in accordance with the tefludazine series. Finally, substitutions at the indane 3 position should be *trans*- oriented bulky groups, with the highest D_1 and D_2 affinity for the phenyl, 4-fluorophenyl and 3-thienyl moieties. Compound **27** had a K_i value of 0.84 nM and 7.1 nM for the D_1 and D_2 receptors, respectively. Affinities for the $5HT_{2A}$ (antagonist), $5HT_{2C}$ and α_1–adrenoceptors were also high with 1.9 nM, 0.28 nM and 25 nM, respectively.

In summary, a typical high affinity dopamine receptor ligand based on the indane scaffold contains an amine on the pentane ring and on the phenyl ring an electron donating group (EDG) – in the case of agonists **23**, **24**, and an electron withdrawing group (EWG) – in the case

of antagonists **26**, **27**. The optimal distance between the two appears to be four carbon atoms.

Serotonin Receptors

The serotonin receptor family (5HT receptor) is involved in a wide range of CNS processes and is a target for several diseases including anxiety, depression, psychosis and cognitive impairment. Therefore, investigations to develop ligands for these receptors have produced a plethora of compounds with affinity for one or several of the subtypes $5HT_1$ through $5HT_7$.

Millan et al.[48] reported S15535 **28** (Figure 7) as a highly selective $5HT_{1A}$ receptor ligand which acts as weak partial agonist with high affinity (K_i = 0.8 nM). However, this compound was rapidly metabolized *in vivo* and more stable compounds were searched for. A decade later Peglion et al.[49] described 2-(arylcycloalkylamine)-indan-1-ols as ligands of the $5HT_{1A}$ receptor for treatment of anxiety. Additional substituents on the indane system improved selectivity and oral bioavailability while keeping the high affinity. Substitutions at the 6 position of the indane yielded the highest affinity. With a methoxy group a K_i value of 0.45 nM was obtained, two- to threefold better than 6-NO_2 or 6-F, or the 5-OMe analogue. However, the 5-OMe compound **29** (K_i = 1 nM) was selected for further investigations due to its better metabolic bioavailability. In the case of substituents on the 2 position a 4-substituted-piperidin-4-ol was deleterious for the affinity. However, piperazine or piperidine moieties substituted with benzodioxane or benzopyran maintained the high affinity for the receptor. Similar to dopamine receptor ligands **26** and **27** the *trans*-isomers were most active on the $5HT_{1A}$ receptor.

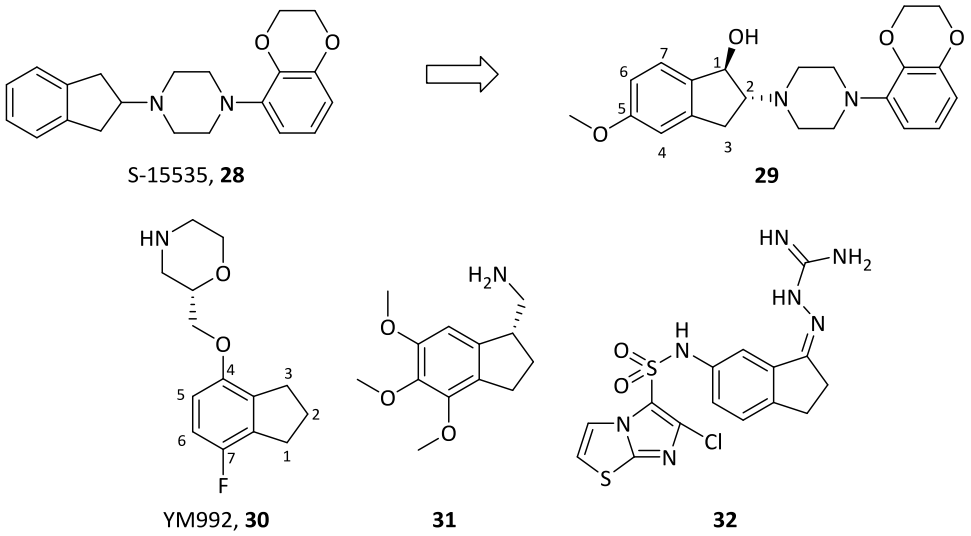


Figure 7. Serotonin receptor ligands.

YM992 **30** (Figure 7) was developed as a selective serotonin reuptake inhibitor (SSRI) with moderate (K_i = 86 nM) $5HT_{2A}$ affinity. Submicromolar (K_i = 200 nM and 680 nM) affinity was observed for the α_1–adrenoceptor and $5HT_{2C}$ receptor, respectively.[50] The substitutions on the indane system are located on positions 4 and 7 compared to positions 1, 2 and 5 in **29**, potentially explaining the lower receptor affinities. Additionally, the basic nitrogen in compound **30** is located much further form the indane than in other serotonin receptor ligands described in this review.

A mescaline analogue was synthesized to develop a $5HT_{2A}$ receptor agonist, and the conformationally restricted **31** was found to have a K_i value of 69 nM at cloned human receptors.[51] The more recently identified family of $5HT_6$–receptors was investigated as a target for indenes/indanes.[52] The SAR revealed compound **32** to have the highest affinity in the indane series for the human receptor (K_i = 1.2 nM). The 6-chloroimidazo[2,1-b][1,3]thiazole structural motif coupled to the sulfonamide in this compound was important for affinity, as the naphthyl and 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine analogues had over 20 fold lower affinity. The sulfonamide was preferentially located at the 5 or 6 position, as the

4 position abolished affinity. The guanylhydrazone could be replaced by an imidazolinylhydrazone group with only a marginal loss in affinity.

Melatonin Receptors

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that is secreted during darkness. It regulates the circadian rhythm and analogues of melatonin can be used to control diseases associated with circadian rhythm disorders.

Compounds **33** and **34** (Figure 8) were developed as melatonin analogues,[53] with binding affinities on chicken brain melatonin (MT) receptors of 16 nM and 7.6 nM, respectively. Their tetralin analogues had approximately 20 fold higher affinity, and the benzocycloheptane analogues had similar affinity, whereas the cyclobutane analogues had a lower affinity. Compounds with a butyramido substituent (such as **34**) had higher affinity than when substituted with a propionamido (**33**) or acetamido moiety, indicating the receptor favors longer lipophilic side chains. Moreover, as for the serotonin and dopamine receptors, the melatonin receptor has marked enantioselectivity for these compounds. The (+)-enantiomer of **33** had a K_i value of 3 nM, compared to 456 nM for the (-)-enantiomer. These features seem to be important for melatonin receptor affinity as an agonist, as will also become apparent in the next examples.

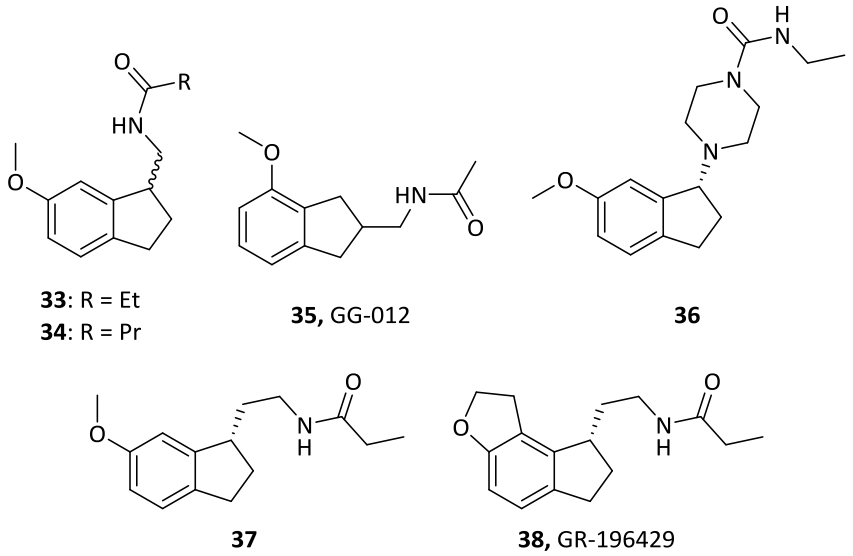


Figure 8. Melatonin receptor ligands.

Drijfhout et al. tested several compounds for melatonin receptor agonism.[54] GG-012 (compound **35**) was a partial agonist with high binding affinity (K_i = 9.5 nM) for the chicken retina melatonin receptors, 5–fold higher than its tetralin analogue. Additionally, in another paper,[55] a derivative of compound **35** that is lacking the methylene spacer between the indane and amide was found to have no affinity for the receptors, stressing the importance of the distance between the amide and methoxy group, equal to the distance seen in **33** and **34**.

Mattson et al. reported on piperazine amides attached to benzyl, indenyl and naphthalene groups as MT_2 receptor selective agents.[56] Compound **36** was reported to have high affinity and the best selectivity for the cloned human MT_2 receptor (hMT_1, IC_{50} = 200 nM, hMT_2, IC_{50} = 1.7 nM). The indanes in general had higher affinity than the more flexible benzyl or the bulkier tetralin and naphthyl analogues (20-30 fold). The compounds showed stereospecificity in their binding. Only R-enantiomers were active, whereas the S-enantiomers showed no activity at the MT receptors. The *n*-, *c*- and *i*-propyl substituents instead of ethylamine on the carbonyl piperazine yielded the highest affinity for the MT_2 receptor; however, the selectivity for the MT_1 receptor was decreased. Smaller substituents, such as methyl and ethyl, or larger substituents such as n-butyl reduced affinity.

Two other series of indanes were synthesized as therapeutic agents for sleep disorders, one describing the SAR of indane derivatives[57] the other the SAR of indeno–furans,[58] both yielding agonists with very high affinity. The K_i values on human melatonin receptors (MT_1) were 0.041 nM and 0.014 nM for **37** and **38**, respectively, even higher than that of melatonin itself (0.082 nM). Again, the geometry of substituents on the 1 position of the indane system plays an important role in binding affinity. The same configuration as in **36** is preferred for **37** and **38**.

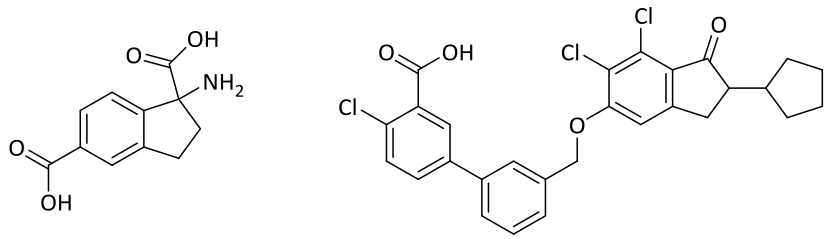
In the indane series, the *S*-enantiomers had more than 100–fold higher affinity than the R-enantiomers. The indane system itself provided twofold higher affinity over a similar tetralin series, and more than 70–fold higher affinity than the 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene derivative. The amide alkyl group should be ethyl or propyl, as seen before, whereas *iso*-propyl resulted in a decrease in affinity. Exchanging $-CH_3$ to $-CF_3$ on the amide led to a 5–fold increased affinity, yielding the most potent compound in the series with a K_i value of 0.012 nM. The length of the spacer between the indane and amide was also of importance, with optimal affinity provided by an ethyl spacer. Propyl and methyl spacers reduced affinity 20–fold and 1000–fold, respectively. Lastly, the methoxy group was substituted for ethoxy, propoxy and iso-propoxy groups, but this decreased affinity in this order. The 6-methoxy group yields a 7–fold increase in affinity. The authors argued that the H–bond can be formed only if the methyl group on the oxygen points towards the 7 position of the indane, giving access of the oxygen's lone pair for hydrogen bonding. It was concluded that substitution on the 7 position (but not the 5 position) prevents this conformation from occurring and therefore reduces affinity markedly.

Using this finding, Uchikawa et al. developed the second series of tricyclic indanes, such as compound **38**.[58] The methoxy group was fixed into the preferred position by incorporating it in a furan, 1,3-dioxolane, oxazole, pyran, morpholine, or 1,4-dioxane ring systems. In order to maintain affinity, the tricyclic system with the oxygen at the 6 position needed to be angular (6,7 position), not linear (5,6 position), underlining the hypothesis of the lone pair on the oxygen being accessible for hydrogen bonding as described before. The 1,6,7,8-tetrahydro-2*H*-indeno[5,4-b]furan ring system (compound **38**) resulted in the highest affinity. According

to the docking study,[58] an additional positive feature of compound **38** over melatonin is the indane system, which is located in the hydrophobic pocket at the bottom of the binding site, contributing to the high affinity of the MT_1 receptor.

Metabotropic Glutamate Receptor

There are three groups of metabotropic glutamate receptors, of which group one (mGluR1 and 5) is involved in increasing NMDA receptor activity while group two (mGluR2 and 3) and three (mGluR4, 6-8) inhibit neurotransmission. The mGluR1 is a potential target for neuroprotection via inhibition by an antagonist.[59] Pellicciari et al. [60] developed an mGluR1 selective antagonist called 1-aminoindan-1,5-dicarboxylic acid (AIDA, **39**) (Figure 9) which is a conformationally restricted analogue of the (carboxyphenyl) glycine derivatives. It inhibited glutamate-stimulated phosphoinositide hydrolysis in BHK cells expressing mGluR1 with an IC_{50} of 7 µM. From the very limited SAR performed it became apparent that one of the two carboxylic acids should be at the 5 position of the indane in order to give the antagonistic effect on mGlu1. However, the compound showed also modest agonist action on mGlu5 receptors.



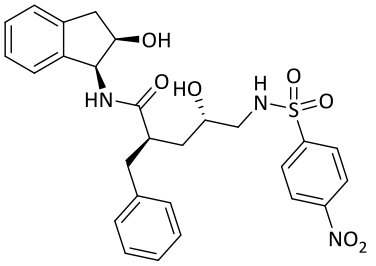
AIDA, **39** **40**

Figure 9. Metabotropic glutamate receptor ligands.

The group two receptors might act as a target for epilepsy, anxiety and schizophrenia treatment, especially through selective targeting of mGluR2.[61] However, one of the main problems in the development of selective compounds for mGluR2 over mGluR3 is the high degree of sequence homology between group two mGluRs, especially at the (extracellular) glutamate binding site. Therefore, instead of targeting the orthosteric (glutamate) binding

site, emphasis these days is on allosteric modulators binding into the transmembrane domain of the receptor. Bonnefous et al. have reported a new class of selective mGluR2 positive allosteric modulators (PAM`s) based on biphenyl–indanones. Compound **40** was identified to have the highest potency for the human mGluR2, with an EC_{50} value of 5 nM.[62] The indanone moiety provided receptor selectivity; for high potency there must be substitutions on the 6 and/or 7 position of the indanone and a cyclopentyl at the α-position of the ketone. Additionally, in the biphenyl system, the central phenyl and methylene group are best unsubstituted. The acid on the second phenyl is preferentially at the *meta*-position, and electron–withdrawing substituents on the *para* position improve affinity additionally.

Vasoactive Intestinal Polypeptide Receptor 2



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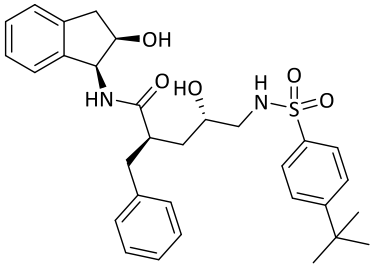

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Figure 10.Vasoactive intestinal polypeptide receptor 2 ligands.

Vasoactive intestinal polypeptide receptor 2 ($VAPC_2$) is a member of the secretin receptor family (class B GPCRs). $VAPC_2$ is involved in sustaining circadian rhythm,[63] regulation of immune responses,[64] schizophrenia[65, 66] and upregulation of basal metabolic rate.[67] Thus far there are only two known small molecule ligands for the $VAPC_2$ receptor discovered by Chu et al.[68] Compound **41** (Figure 10) was the only hit from a high-throughput screen of 1.67 million compounds. After a structure similarity search another analog, compound **42**, was found. Both compounds showed antagonistic activity on the $VAPC_2$ receptor. Compound **41** was the more potent inhibitor with an IC_{50} value of 2.3 µM and selective towards the $VAPC_2$ receptor. The change of the electron–withdrawing nitro group to the lipophilic, electron–donating *t*-

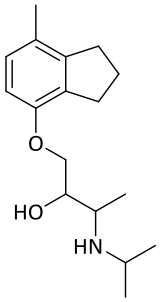
butyl group in **42** led to a small degree of activation of $VAPC_1$ receptors at higher concentrations, while maintaining the antagonist activity on the $VAPC_2$ receptor.

INFLAMMATORY DISEASE TARGETS

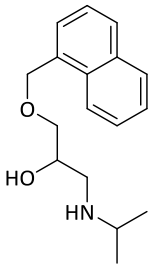
β_2–Adrenergic Receptor

One of the beta-adrenergic receptors is the β2–adrenoreceptor, involved in smooth–muscle relaxation, blood vessel dilation, control of the heart rate and the digestive system among others. It is especially of interest in asthma and COPD as a target for bronchodilation.

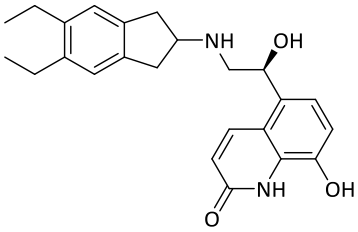
In 1980 indane derivative ICI-118,551 **43** (Figure 11) was identified as a selective antagonist for the β_2–adrenoreceptor, and has mostly served as a research tool ever since as β_2–adrenoreceptor blockade is not regarded as therapeutically useful.[69] **43** is quite similar to propranolol, a non–selective beta blocker, and is the indane analogue of α-methyl substited propranolol (**44**). It is thought that the structure gets its selectivity and potency through three aspects. Firstly, **43** is as potent as its naphthalene analogue α-methylpropranolol, but is five times more selective for the β_2–adrenoreceptor. The indane ring therefore must give a preference to the β_2–adrenoreceptor over the β_1–adrenoreceptor. Secondly, the oxymethylene bridge between the ring and the propanolamine is of importance for potency as the same structure is seen in propranolol and other potent beta–blockers, but not in the less potent ethanolamine compounds H35/25 and butoxamine. Lastly, selectivity for the β_2–adrenoreceptor is enhanced through the additional methyl group in the propanolamine moiety, as α-methylpropranolol, H35/25 and butoxamine are more selective than propranolol and contain this feature too.



ICI-118,551, **43**



Propanolol, **44**



Indacaterol, **45**

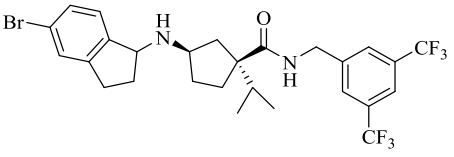
Figure 11. β_2 adrenergic receptor ligands.

Recently, a potent and selective agonist for the β_2–adrenoreceptor was developed (indacaterol **45**).[70, 71] It is marketed as an inhaled ultra-long acting bronchodilator, and is especially aimed at asthma and COPD treatment. It has the highest affinity for the β_2–adrenoreceptor in the series, however, the affinity values vary in different reports (K_i = 76 and 16 nM).[70, 71] The indane scaffold was chosen for this compound in order to easily substitute the phenyl in the indane to regulate lipophilicity (for long–term activity *via* possible membrane binding causing a high local concentration around the receptor). This part of the molecule allows big variations due to the remote position from the key epinephrine mimicking part. The di-ethyl substitution pattern was chosen to keep the indane part symmetrical and a–chiral for simplicity. The SAR can then be broken down into three parts, when compared to the non-selective β_2–agonist epinephrine. Compound **45** has a 8-hydroxyquinolinone catechol mimetic, as a replacement for the catechol moiety of epinephrine and an ethanolamine linking group, which remained unchanged. These are the crucial parts for agonist activity at the β_2–receptor. The third part is the amino substituent, in which the N-methyl group of epinephrine is replaced by a 5,6-diethyl indanyl moiety. The 5,6-disubstitutions led to higher affinity than 4,7-disubstitutions. Dimethyl substitution decreased affinity compared to the unsubstituted indane, whereas diethyl substitution gave the highest affinity, slightly higher than di-*n*-propyl and di-*n*-butyl. Lastly, introduction of a methyl group at the 2 position of the indane ring increased affinity by 10 fold compared to **45**, however, β_1–affinity was increased even more, and thereby selectivity was lost.

Chemokine Receptor 2

Chemokines are a class of chemoattractant cytokines, and their main action is to control the activation and trafficking of leukocytes and other cell types in a range of inflammatory and non-inflammatory conditions. One of these, chemokine ligand 2 (CCL2), acts on memory T cells, monocytes, and basophils.[72] It creates a chemotactic gradient and activates the movement of immune cells to the site of inflammation by binding to its cell–surface receptor, chemokine receptor 2 (CCR2).[73] Pre–clinical models of inflammatory diseases (e.g., atherosclerosis,[74] asthma,[75] multiple sclerosis,[76] rheumatoid arthritis,[77] neuropathic pain[78]) have pointed to a critical role of the CCR2 and CCL2.

Recently, Vilums et al.[79] reported a new approach in hit–to–lead optimization for CCR2 antagonists. This report suggests that next to SAR, one should also use structure-kinetic relationships (SKR) to yield compounds with good affinity and optimal drug-target binding kinetics already at the early stages of the drug discovery cycle. It was discovered that the constrained indane system yielded better affinity than more flexible alkyl linkers, but the affinity was worse than that of aliphatic heterocycles. However, in the SKR study the indane derivative showed the longest residence time and was used for further optimization which yielded compound **46** (Figure 12) with high affinity and long residence time (K_i = 3.6 nM, RT = 135 min). Substituents on the 5 position improved affinity in general, but only halogens like Cl and Br also prolonged the residence time.



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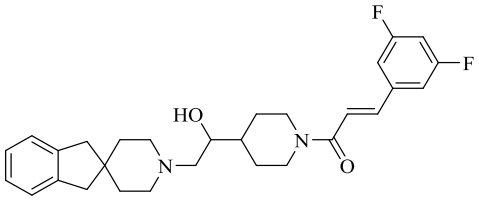

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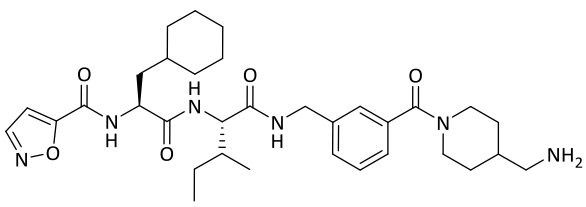
Figure 12. Chemokine receptor 2 antagonists.

In a patent application[80] Bristol–Myers Squibb disclosed several CCR2 antagonists with indene and indane (**47**) structures. Not much has been published yet about these compounds,

however, it is anticipated that they will have high affinities due to their resemblance to other CCR2 antagonists, such as reported in several GSK patents.[81, 82] The indene/indane group would fill the needed hydrophobic space of the 'end group', which requires at least one aromatic ring for affinity at the receptor.

Protease–Activated Receptor 2

Four protease–activated receptors (PAR`s) are among the most unusual receptors in the vast super–family of GPCR`s due to their manner of activation. There are no known endogenous extracellular ligands for these receptors. Instead, they are activated via proteolytic cleavage of their *N*-terminus by serine proteases. The remainder of the N-terminus folds back onto the receptor and induces intramolecular activation of the PAR.[83] The PAR_1 subtype has been most investigated, because it is activated by thrombin, suggesting it as a potential target in cardiovascular diseases. In contrast, PAR_2 is resistant to thrombin, but can be activated by trypsin, tryptase or cathepsin G and has been linked to inflammatory and proliferative disorders.[83, 84]



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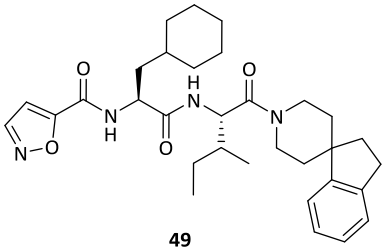


49

Figure 13. Protease–activated receptor 2 ligands.

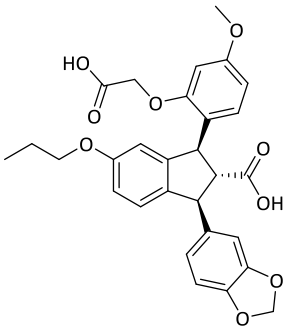
Recently, Barry et al reported the discovery of selective agonists and antagonists of PAR_2.[85] The authors truncated the known PAR_2 agonist SLIGRL-NH_2 by three amino acids and derivatized both ends of the tripeptide to yield agonist **48** (Figure 13) with sub-micromolar potency (EC_{50} = 0.28 µM). The removal of the primary amine on the piperidine ring altered the agonistic effect into antagonism of PAR_2. A spiroindanepiperidine group coupled directly to the terminal amide group of the tripeptide yielded the most potent antagonist **49**.

CARDIOVASCULAR DISEASE TARGETS

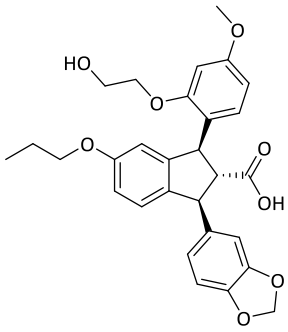
Endothelin Receptor

The endothelin receptors ET_A, ET_B and ET_C are mainly involved in the cardiovascular system regulating vasoconstriction and -dilation. They are used as a target in hypertension[86] and renal failure[87].

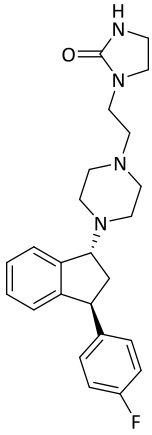
In the 1990's a research group from SmithKline Beecham Pharmaceuticals developed several antagonists for the ET_A and ET_B receptor with an indane core structure.[88, 89] Through molecular modeling of the peptide endothelin–1 (ET-1), the natural ligand of these receptors, important side chains for binding were identified. The 1 and 3 positions on the indane ring are substituted with phenyl groups, possibly mimicking two aromatic side chains of ET-1. Additionally, the carboxylic acid at position 2 plays an important role in binding as the corresponding methyl ester had no measurable affinity for the ET receptors. Introduction of electron–donating substituents on the 1- and 3-phenyl groups improved affinity, with both phenyls *para*-substituted with methoxy groups giving a marked increase in affinity. A 3,4-methylenedioxy instead of one of these methoxy groups improved the affinity even more, as did substitutions at the 6 position of the indane. To mimic the C-terminal carboxylic acid of ET-1, a carboxylic acid was introduced with a methylenoxy spacer to the *ortho*-position of one of the phenyl rings. This resulted in structure **50** (SB 209670) (Figure 14), the (+)-enantiomer being more potent than the (-)-enantiomer, with a K_i value on human ET_A and ET_B receptors of 0.43 nM and 15 nM, respectively. However, despite its high affinity, a shortcoming with this compound was its limited bioavailability. Therefore compound **51** (enrasentan) was developed, changing only the oxyacetic acid at the 2 position of the phenyl ring into an alcohol. This slightly reduced the affinity for ET_A, but improved the selectivity over the ET_B receptor by 10 fold and also improved bioavailability, resulting in binding affinities of 1.1 nM and 111 nM for ET_A and ET_B receptors, respectively.



SB 209670, **50**



Enrasentan, **51**



Irindalone, **52**

Figure 14. Endothelin receptor ligands **50**, **51** and serotonin receptor ligand **52**.

Serotonin Receptor

Apart from serotonin receptors in the brain as discussed above, there are also peripheral receptors, such as peripheral $5HT_2$ receptors. These receptors could be used as antihypertensive targets when blocked with an antagonist.

As described for the compounds targeting serotonin receptors in the CNS, several features are crucial for affinity to these receptors. All these elements are present in the dopamine and $5HT_2$ antagonist tefludazine **26**. One of its characteristics, the substitution on the 6 position of the indane, is less important for serotonin receptor affinity. Hence, Bogeso et al.[90] used tefludazine without its 6-CF_3 substitution as a starting point to target selectively the peripheral $5HT_2$ receptors. Additionally, their compounds had some α_1–adrenoceptor antagonistic affinity, although less than for $5HT_2$. These combined effects may be responsible for the antihypertensive effects of these drugs. The SAR showed that the 4-fluoro substituent on the phenyl is crucial for activity of the compounds, as in tefludazine, since other substituents, including hydrogen, yielded inactive compounds. Substitutions at the piperazine ring were important for tuning central and peripheral activity, to the extent that a 1-ethyl-2-imidazolidinone moiety abolished neuroleptic activity and kept peripheral activity indicated

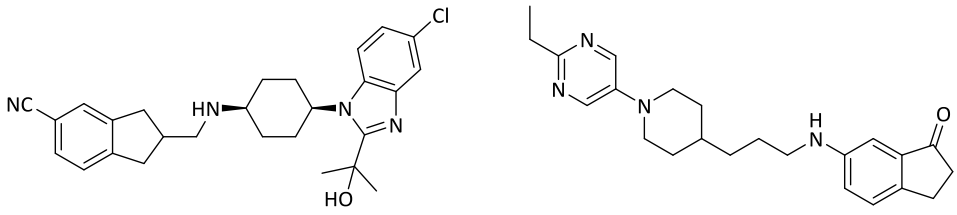
by the compound's antihypertensive effects in rats. Additionally, the (+)-enantiomer was found to be much more active resulting in compound **52** (irindalone) (Figure 14), with IC_{50} values of 3.4 nM, 400 nM and 26 nM for $5HT_2$, dopamine (DA) and α_1–receptors, respectively.

TARGETS OF METABOLIC DISEASES

Melanin Concentrating Hormone Receptor

The melanin concentrating hormone receptor exists as two subtypes in humans, MCH-R1 and MCH-R2 and is involved in feeding behaviour and energy homeostasis. Inhibition of this receptor could therefore be a new way of treating obesity and metabolic syndromes.[91, 92]

An indane–derived chemical class was identified as a promising lead for an antagonist of the MCH-R1[93] and its optimization was published recently.[94] The indane moiety was found to be superior for receptor selectivity over cyclopentyl, cyclobutyl, cyclopropylmethyl and dihydrobenzofuran. A bromine or CN at the 6 position of the indane gave higher affinity for the MCH-R1, with the CN group giving the highest potency and selectivity. This group was then linked to a benzimidazole group by several linkers, the *cis*-4-methyleneaminocyclohexane giving the best results. This investigation showed that the *cis*-conformation was highly preferred over the *trans*- conformation and that the methylene spacer between the indane and NH is important for activity. The selected compound **53** (Figure 15) has a K_i value of 3 nM for the human MCH-R1, but was not further developed because of potent hERG inhibition, activities which could not be dissociated.



53 **54**

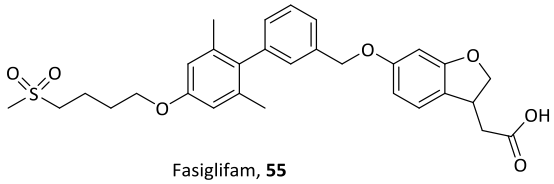
Figure 15. Melanin concentrating hormone receptor antagonist **53** and GPR119 agonist **54**.

GPR119

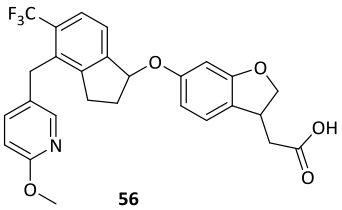
A relatively new GPCR termed GPR119 has been identified as a potential target for the treatment of obesity and diabetes. An agonist for this receptor was discovered and after optimization indanone **54** was found to have the desired effect of plasma glucose control in rodents.[95] Different bicyclic scaffolds were investigated and the indanone scaffold was identified as giving the highest affinity for GPR119. The nitrogen on the 6 position of the indanone was important for agonist activity. In addition, a propyl–spacer to the piperidine gave the best affinities. The EC_{50} value of the most potent compound **54** for human GPR119 was 51 nM.

GPR40

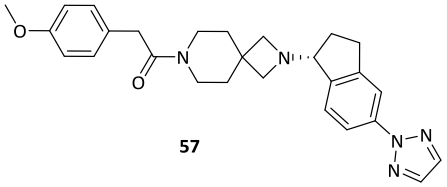
GPR40 (also known as free fatty acid receptor 1) is highly expressed in the pancreas and is a potential therapeutic target for diabetes. Itoh et al.[96] described that long-chain free fatty acids (FFAs) are the endogenous ligands for GPR40. Furthermore, by activating GPR40 FFAs amplify glucose–stimulated insulin secretion from pancreatic β cells. Takeda Pharmaceuticals developed fasiglifam **55** (Figure 16), a GPR40 agonist that showed significant glucose–lowering effects in patients with type 2 diabetes by stimulating glucose–dependent insulin secretion.[97] However, recently Takeda announced termination of fasiglifam development due to liver safety concerns.[98] Boehringer Ingelheim has filed a patent application that describes more potent indanyl analogues of fasiglifam as GPR40 agonists. Compound **56** showed the best potency in the series having an EC_{50} value of 1 nM[99] (compared to fasiglifam's EC_{50} = 14 nM).[100]



Fasiglifam, **55**



56



57

Figure 16. GPR40 agonists **55**, **56** and growth hormone secretagogue receptor inverse agonist **57**.

Growth Hormone Secretagogue Receptor

Growth hormone secretagogue receptor (GHSR) and its endogenous ligand ghrelin are expressed in pancreas where they are involved in regulation of glucose–induced insulin release. Blockade of the GHSR/ghrelin axis results in enhancement of glucose–induced insulin release from perfused pancreas, whereas addition of exogenous ghrelin suppresses it.[101] This suggests that antagonism of the ghrelin receptor enhances insulin release thereby normalizing the glycemic control in high–fat diet–induced obesity and counteracting the progression of type 2 diabetes. Pfizer has developed a series of small–molecule inverse agonists for GHSR based on a 2,3-dihydro-1H-inden-1-yl-2,7-diazaspiro[3.6]nonane scaffold as potential treatment of type 2 diabetes.[102] Compound **57** (Figure 16) had the best affinity in the series (K_i = 3.1 nM). This scaffold tolerates a wide variety of different chemical groups on the acetamide side, while substituents on the indenyl ring should be aromatic rings with at least a nitrogen atom on the 2 position.

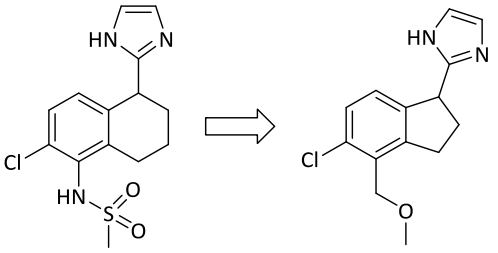
MISCELLANEOUS TARGETS

α_1–Adrenoceptor

The α_1–adrenoceptors have several subtypes that are very similar in structure. The α_{1A}, α_{1B} and α_{1D} receptors are all acting mainly on smooth muscle cells leading to vasoconstriction,

bronchospasms and decreased motility in the GI–tract. Subtype α_{1A} receptor selective agonists have been shown to be efficacious in *in vivo* models of stress urinary incontinence (SUI).[103] However, full α_{1A} receptor agonists possess a slender therapeutic index over α_{1A} induced cardiovascular effects. Therefore partial agonism and organ specificity are desired characteristics in SUI treatment.

In the search for a compound with these features, indanes and tetrahydronaphthalenes coupled to a 2-imidazole were investigated.[104] The tetrahydronaphthalene derivative **58** (Figure 17) had an attractive pharmacological profile, combining good potency, low E_{max}, good selectivity and *in vitro* metabolic stability. However, according to Conlon et al.[105] α_{1A} partial agonists mediate their effect *via* a central pathway rather than directly on the urethral smooth muscle, thus CNS penetrant partial agonists are desired for *in vivo* efficacy. Compound **58** has a high total polar surface area (TPSA = 83 Å^2) with an associated P-glycoprotein-mediated efflux, which could have a negative impact on the crossing of the blood–brain barrier (BBB).[106] As the indane derivatives were found to be more potent than the tetrahydronaphthalene congeners, it was decided to continue with the indane core and decrease the TPSA value by exchanging the sulfonamide group to an isostere with smaller TPSA penalty. After thorough SAR evaluation compound **59** (PF-3774076) was generated bearing a 4-methylenemethoxy group (EC_{50} = 31 nM, TPSA = 38 Å^2) instead of sulfonamide. Additionally, the chlorine substituent on the 5 position of the indane reduced the compound's E_{max} value and gave the wanted partial agonism. Unfortunately, **59** did not offer the necessary degree of selectivity over cardiovascular events when assessed in *in vivo* models of cardiovascular function.



58 **59**

Figure 17. α_1–Adrenoceptor ligands.

The structure of **59** bears resemblance to some of the α_{2A}, dopamine, serotonin and melatonin ligands. Fadolmidine **22** for example has the same location for the imidazole on the 1 position of the indane, only with an additional methyl–spacer. This α_2–receptor agonist is also a α_1 receptor full agonist and the selectivity of **59** compared to **22** seems to be due to the bulk of the substitution on position 4.

Prostaglandin F Receptor

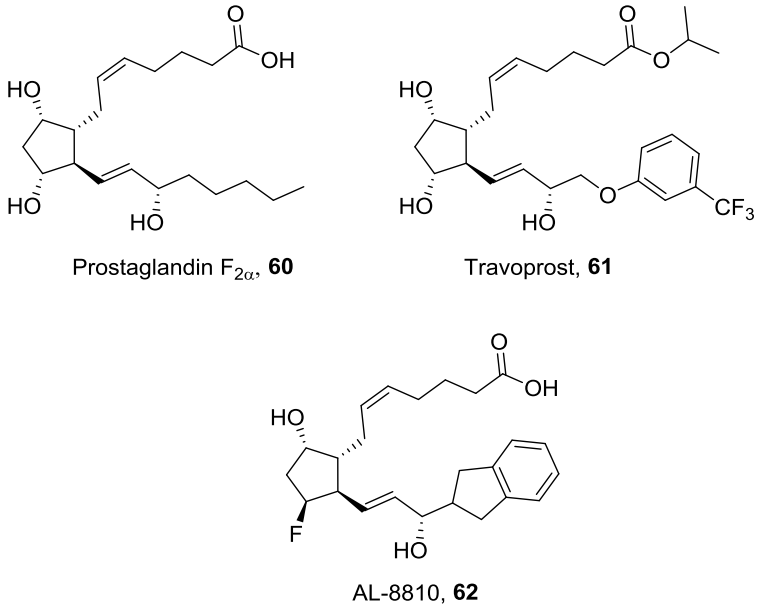


Figure 18. Prostaglandin F receptor ligands.

The endogenous ligand of the prostaglandin F receptor (FP receptor) is prostaglandin $F_{2\alpha}$ (PGF2α, **60**). It is involved in many physiological responses, such as the regulation of parturition (including luteolysis),[107] intraocular pressure,[108] cardiac hypertrophy[109] and kidney function.[110] The FP receptor agonist travoprost **61** (analogue of prostaglandin $F_{2\alpha}$ **60**) (Figure 18) is used to treat glaucoma and ocular hypertension. However, the 2-indane analogue of prostaglandin $F_{2\alpha}$ (AL-8810, **62**) is a low–efficacy FP receptor agonist and can be used as selective functional antagonist.[111] Although AL-8810 has low potency, it proved useful in studying PGF2α-mediated up-regulation of the nerve growth factor IB.[112]

CONCLUSIONS

In the above sections, we summarized the major targets of the GPCR protein superfamily where the indane system is used as the core structure in the development of high affinity ligands for these targets. Compounds containing this structure are used in the treatment of a wide variety of diseases through an even wider variety of mechanisms of action. Some of these compounds show very high affinities towards Class A and Class C GPCRs, possibly in part because of the good fit of the indane moiety itself. Additionally, the distinct shape of the indane, due to the fused aromatic and aliphatic rings, makes it a useful scaffold to orient substituents on it. On top of that, the scaffold can be used to mimic constrained alkyl linkers between the phenyl ring and other substituents on the 1 and 2 positions of indane. Apparently these features can be very well accommodated by many GPCRs, suggesting the indane moiety is a privileged structure. Last but not least, using the indane system as the core structure provides 'freedom to operate' to the medicinal chemist. It allows to introduce substituents in ten different directions to find the "perfect–fit" for every substituent, generating very selective and high affinity ligands for GPCRs.

ACKNOWLEDGMENTS

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