THE EFFECT OF AROMATIC SUBSTITUTION ON NEUROLEPTIC ACTIVITY IN 1-PIPERAZINO-3-PHENYLINDANS. A COMPARISON BASED ON A NEW D-2 RECEPTOR MODEL WITH CORRESPONDING 10-PIPERAZINO-10,11-DIHYDRODIBENZO-[*b*,*f*]THIEPINS

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Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

The validity of a new dopamine D-2 receptor interaction model based on conformational analysis and least-squares superimposition studies of the indan derivative tefludazine and the thiepin derivative octoclothepin was further tested by comparison of the effect of aromatic substitution on D-2 antagonistic activity in two series of indan and thiepin derivatives. The indan series include new derivatives substituted in the 4-, 7-, 2′- and 3′-position.

The substitution effects were largely parallel with one important exception: Only 6-substituted indans have significant neuroleptic activity while both 8- and 7-substituted thiepin derivatives have neuroleptic activity. In indans additional fluorination in the 2′- or 4′-position is demanded to give potent neuroleptic activity, while a 3′-fluoro-substituted derivative was inactive. Fluorination is not necessary in thiepins although 3-fluoro derivatives have a significant prolonged duration of action. Considering the differences in physico-chemical properties, metabolism and pharmacokinetics between the two series, the largely parallel substitution effects support the new D-2 receptor model.

Several years ago we discovered a new class of psychotropic compounds, the 1-piperazino-3-phenylindans. The discovery and structure-activity relationships (SAR) of these compounds are described in a recent review[1]. The SAR is illustrated in Fig. 1. In most cases the synthetic method leads to a mixture of four stereoisomers, which by fractional crystallization can be separated into *cis*- and *trans*-isomers; often these can be further separated into their enantiomers by crystallization of suitable diastereomeric salts.

The pharmacological and biochemical activities of the resulting stereoisomers are depending on their absolute configuration and on the substituents in their aromatic rings[1]. *1R,3S-trans*-isomers are generally antagonists of central dopamine (DA) D-2 receptors, α_1 adrenoceptors and serotonin-2 (5-hydroxytryptamine-2,

5-HT_2) receptors[2,3]. High potency is associated with 4'-fluoro substitution. Further, potent DA D-2 antagonism is dependent on a proper 6-substituent[2] (see below) while compounds without a substituent in this position, such as irindalone, are selective 5-HT_2 antagonists[3].

The corresponding 1*S*,3*R*-*trans*-isomers as well as 1*R*,3*R*-*cis*-isomers are inhibitors of the reuptake of DA and noradrenaline[2] (NA). The most potent members of this series are unsubstituted in the indan phenyl ring and have a 3',4'-dichloro substitution in the 3-phenyl ring[1,2]. Finally, 1*S*,3*S*-*cis*-isomers are inactive compounds[4].

In the process of understanding the structural basis for the observed D-2 antagonistic activity of the 1*R*,3*S*-isomers we focused on the structural similarity between the indans and the neuroleptic thiepin derivatives, octoclothepin and oxyprothepin. Comparison of the X-ray structures of the potent neuroleptics tefludazine[5] and oxyprothepin[6] led initially to the wrong conclusion, that the D-2 antagonistic activity of the indans was associated with the 1*S*,3*R* absolute configuration[2]. After the determination of the absolute configuration of irindalone[7] it became clear that the conclusion was wrong, and a renewed study of the conformational properties of indans and thiepins was initiated. After extensive conformational analysis and least-squares superimposition studies of tefludazine and octoclothepin it was possible to explain the previous misunderstandings and identify the possible D-2 receptor active conformations of the two compounds[8]. The superimposition of the suggested active conformations of 1*R*,3*S*-tefludazine and *S*-octoclothepin (Fig. 2) defines the spatial relationships of the pharmacophore elements (the phenyl rings, the distant piperazine nitrogen atom, and the nitrogen atom-nitrogen lone pair vector). These spatial relationships represent, in our opinion, a contemporary DA D-2 receptor interaction model[8,9]. We have since then accomodated D-2 antagonists of other chemical classes into the model[10] and Froimowitz have successfully employed this model in a study of dibenzocycloheptene and cyproheptadine derivatives[11].

Potent neuroleptic activity in indans or thiepins is associated with proper substitution in their respective 6- and 8-positions. It is an important aspect of the D-2 model that these positions and their "neuroleptic substituents" are coincident in the model (see Fig. 2). The highest activity in the indan series is obtained with the CF_3 substituent found in tefludazine[2,12] and also within the thiepins are 8-CF_3 substituted derivatives among the most potent[13]. Concerning the effect of substitution in other indan phenyl ring positions we have so far reported that 5-fluoro or 5-chloro derivatives are very weak or inactive[2,14]. Concerning substitution of the 3-phenyl ring we have reported that 4'-fluoro substitution is of crucial importance[2,3]. Compounds, which are unsubstituted in this ring, are weaker and alternative 4'-substitution (Cl, CH_3) results in weak or inactive compounds[2,3]. In this paper we present the effect of substitution in other positions of the indans such as the 4-, 7-, 2'- and 3'-positions together with new data on a number of the previously reported compounds. Within the thiepin series Protiva and coworkers have extensively reported

the effect of substitution in all positions of the thiepin ring system on neuroleptic activity[15]. Even though there is not a complete coincidence of all carbon atoms (and possible substituents) in the corresponding indan and thiepin phenyl rings (Fig. 2) it is still interesting, in relation to the D-2 model, to compare the effect of substitution in the two series. While one certainly would expect some differences between the two series, due to differences in metabolism and pharmacokinetics, one would on the other hand expect that possible steric effects of substituents in corresponding positions (Fig. 2) would have a qualitatively similar influence on D-2 antagonistic activity in the two series.

EXPERIMENTAL

Chemistry

The structures of the indan derivatives discussed in this article are shown in Fig. 3 and Table I together with the structures of thiepin derivatives with a similar substitution pattern. The indan derivatives *Ig*, *Ii*, *Il*, *Im*, *In* and *Io* (Table II) are reported for the first time. They were all prepared by methods previously reported, i.e. by alkylation of a 1-substiuted piperazine derivative with

TABLE I
Structure of indans (*I*) and thiepins (*II*)

No[a]	X	Y	R	Ref.	No[b]	X	Y	R	Ref.
Ia	H	H	C_2H_4OH	14	*IIa*	H	H	CH_3	15
Ib	6-Cl	H	CH_3	14	*IIb*	8-Cl	H	CH_3	15
Ic	6-F	4′-F	CH_3	1, 2	*IIc*	8-F	3-F	CH_3	16
Id	6-Cl	4′-F	C_2H_4OH	2	*IId*	8-Cl	3-F	CH_3	17, 18
Ie	6-CF_3	4′-F	C_2H_4OH	1, 2	*IIe*	8-CF_3	3-F	C_2H_4OH	13
If	6-iPr	4′-F	C_2H_4OH	2	*IIf*	8-iPr	3-F	C_2H_4OH	13, 15
Ig	4-Cl	4′-F	C_2H_4OH	new	*IIg*[c]	6-F	H	CH_3	19
Ih	5-Cl	4′-F	C_2H_4OH	14	*IIh*	7-Cl	H	CH_3	20, 21
Ii	7-Cl	4′-F	i-C_3H_7	new	*IIi*	9-Cl	H	CH_3	22
Ij	6-Cl	4′-Cl	C_2H_4OH	2	*IIj*	8-Cl	3-Cl	CH_3	23
Ik[d]	6-F	4′-Cl	C_2H_4OH	14	*IIk*	8-F	3-Cl	CH_3	23
Il	6-Cl	2′-F	i-C_3H_7	new	*IIl*	8-Cl	1-F	CH_3	[e]
Im	6-Cl	2′-Cl	i-C_3H_7	new	*IIm*[f]	8-Cl	1-Cl	CH_3	[e]
In	6-Cl	3′-F	C_2H_4OH	new	*IIn*	8-Cl	2-F	CH_3	17
Io	H	3′-Cl	C_2H_4OH	new	*IIo*	H	2-Cl	C_2H_4OH	24, 15c
Ip	H	3′,4′-Cl_2	C_2H_4OH	1, 2	*IIp*	H	2,3-Cl_2	C_2H_4OH	25

[a] All compounds are racemic *trans*-isomers (>95% isomeric purity), see Fig. 3 for numbering system; [b] racemates, see Fig. 3 for numbering system; [c] 6-Cl derivative described in ref.[20]; [d] isomeric mixture approx. 70% *trans*; [e] not reported; [f] 1-Cl derivative reported in ref.[20].

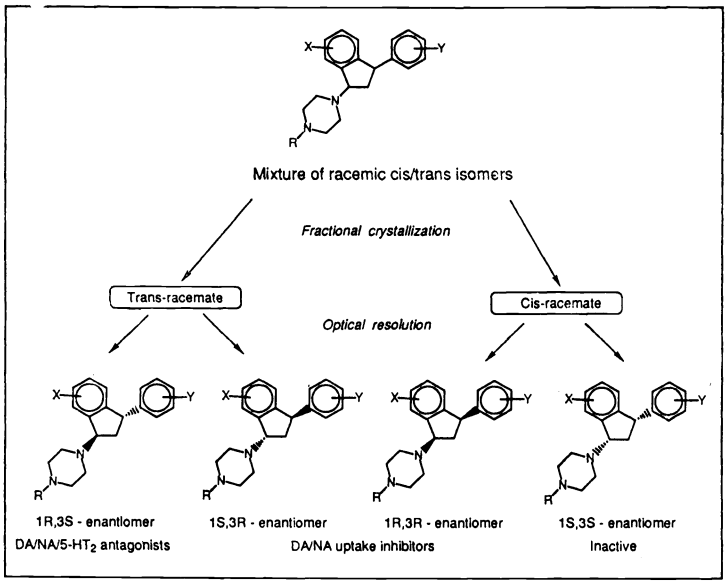

FIG. 1

Schematic illustration of the structure-activity relationships of 1-piperazino-3-phenylindans

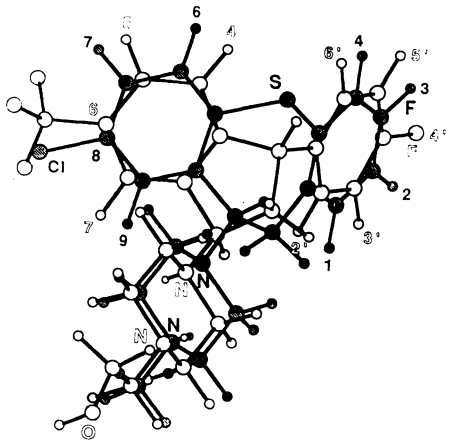

FIG. 2

A D-2 receptor model based on least-squares superimposition of the suggested active conformations of tefludazine (*Ie*, white atoms and numbers) and octoclothepin (*IId*, hatched atoms, black numbers)

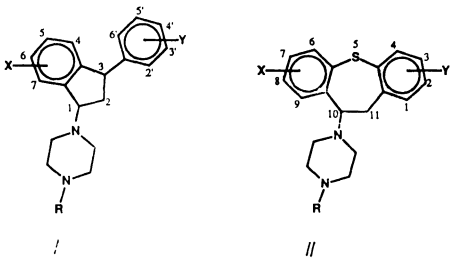

FIG. 3

The numbering system for indans (*I*) and thiepins (*II*) used in Table I

a suitable substituted 1-chloro-3-phenylindan[2,3,14]. The chloro indans were as usual obtained from 3-phenylindan-1-ols upon treatment with thionylchloride in a suitable solvent, such as ether or methylene chloride. The 3-phenylindan-1-ols were obtained by reduction of the corresponding 3-phenylindan-1-ones with sodium borohydride[2,3,14].

Preparation of 3-(3′-chlorophenyl)indan-1-one used for production of *Io* has previously been reported[26]. The indanones used for the preparation of the other new derivatives (Table II) were obtained from the corresponding 1-amino-2-methoxycarbonyl-3-cyano-3-phenyl-1*H*--indenes produced by a method which we have published recently[27]. This method allows introduction of aromatic substituents in positions inaccessible by previously reported methods for preparation of 3-phenylindan-1-ones[2,14,26].

Biochemical and Pharmacological Methods

DA D-2 receptor binding. Inhibition of ^{3}H-spiperone binding to DA D-2 receptors in rat striatal membranes was determined as described by Hyttel[28,29].

Antagonism of methyl phenidate-induced gnawing behaviour in mice. The experiments were performed as described by Pedersen and Christensen[30]. Test compounds were injected i.p. (or s.c.) 2 h before methyl phenidate (60 mg/kg) and two mice were placed on corrugated cardboard in each gnawing cage (12 × 25 cm). Five to nine pairs of animals were used per dose. The ability to inhibit methyl phenidate-induced gnawing was evaluated after 1 h by inspection of the corrugated cardboard.

TABLE II

Physico-chemical data of new indan derivatives

Compound[a]	M.p., °C (salt)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
Ig	268–270 (2 HCl)	$C_{21}H_{26}Cl_3FN_2O$ (447·8)	56·32/56·18	5·86/6·04	6·26/6·23
Ii	237–241 (2 HCl)	$C_{22}H_{28}Cl_3FN_2$ (445·8)	59·21/59·16	6·34/6·47	6·28/6·00
Il	198–200 (dimaleate)	$C_{30}H_{34}ClFN_2O_8$ (605·1)	59·55/59·47	5·66/5·68	4·63/4·49
Im	276–279 (2 HCl)	$C_{22}H_{28}Cl_4N_2$ (462·3)	57·16/56·91	6·11/6·07	6·06/5·99
In	177–180 (2 HCl, H_2O)	$C_{21}H_{28}Cl_3FN_2O_2$ (465·8)	54·15/53·84	6·06/5·78	6·01/6·00
Io	158–160 (dimaleate)	$C_{29}H_{33}ClN_2O_9$ (589·0)	59·13/59·26	5·65/5·64	4·76/4·78

[a] All compounds are racemic *trans*-isomers (>96% isomeric purity); see Fig. 3 and Table I for structural formula.

Cataleptogenic effect in rats. Catalepsy was measured on a vertical wire grid each hour 1—6 h after test drug administration and was defined as being present after at least 15 s immobility. The maximum effect between 1—6 h after administration is reported. A total of 8—12 animals were used per dose.

RESULTS AND DISCUSSION

The affinities for DA D-2 receptors and the neuroleptic activities (methyl phenidate antagonism, catalepsy) of the indans *Ia*—*Ip* are shown in Table III together with

TABLE III

Biochemical and pharmacological activity of indans and related thiepins

Indans				Thiepins		
Compound	Binding[a] D-2(^{3}H-SPI)	Methyl phenidate[b] antg., mice 2 h	Catalepsy, rats[c] max. eff. 0—6 h	Compound	Catalepsy, rats[d] max. eff. 0—5 h	Reference
Ia	2 800	>100	>51	*IIa*	45	21
Ib	61	66 (26—165)	>92	*IIb*	4·3	17
Ic	91	11 (7·3—17)	200 (118—340)	*IIc*	3·1	16
Id	20	2·8 (1·6—5·0)	3·3 (1·7—6·6)	*IId*	3·8	17, 18
Ie	10	0·071 (0·015—0·33)	0·27 (0·19—0·38)	*IIe*	1·1	13
If	14	9·6 (5·1—18)	17 (8·9—32)	*IIf*	2·0	13
Ig	220	>89[e]	[f]	*IIg*	>100	19
Ih	2 200	>89	[f]	*IIh*	4·5[g]	21
Ii	39	>90	>2·8[e]	*IIi*	>10[g]	22
Ij	190	>86	>86[e]	*IIj*	30	23
Ik	450	>89	[f]	*IIk*	>50	23
Il	6·8	1·3 (0·48—3·5)	3·2 (1·6—6·4)	*IIl*	[h]	
Im	480	>87[e]	>11[e]	*IIm*	[h]	
In	460	>86[e]	>11[e]	*IIn*	3·4	17
Io	6 200	[f]	>34[e]	*IIo*	>50	24
Ip	6 900	>86	[f]	*IIp*	>50	25

[a] Results are expressed as IC_{50} values in nM. All results are the logarithmic mean of at least two determinations, each with five concentrations of test compounds in triplicate. [b] Doses are expressed in μmol/kg i.p., 95% confidence interval stated in brackets. [c] Doses are expressed in μmol/kg p.o., 95% confidence interval stated in brackets. [d] Doses are expressed in mg/kg p.o. [e] Administration s.c. [f] Not tested. [g] Administration i.p. [h] Not reported.

catalepsy data reported in the literature for corresponding thiepins *IIa–IIp* (see Table I for definition of structures). Of course it would have been preferable also to have receptor binding data for the thiepin series, but such data have only been published in very few cases. On the other hand, there is generally a good correspondence between D-2 receptor binding and catalepsy[31]. The catalepsy data shown in Table III are maximum effects after p.o. administration of test compound for both series. However, the methods for measuring catalepsy are different meaning that the absolute numbers are not directly comparable. Generally speaking, our test procedure will probably give *lower* ED_{50} values for the thiepins (for *IIb*, octoclothepin, we find an ED_{50} of 4·6 μmol/kg (p.o.) = 2·1 mg/kg). The importance of the 6-substituent for D-2 affinity in the indans appears clearly by comparing the binding figures for *Ia* and *Ib*. A further substitution of *Ib* with fluorine in the 4′-position (*Id*) increases the D-2 affinity threefold and has a dramatic influence on the activity in vivo which is increased 24 times (methyl phenidate test) and > 28 times (catalepsy). It has never been proved that the 4′-fluorination protects against a metabolic 4′--hydroxylation, but it is tempting to suggest so based on the results just mentioned. Interestingly, 2′-fluorination increases D-2 affinity even more (*Il*) and results in a similar high potency in vivo. If the 4′-hydroxylation hypothesis is correct this indicates that also a 2′-fluorination might protect against this metabolic inactivation. In contrast, the 3′-fluoro derivative (*In*) has a much lower D-2 affinity and is inactive in vivo. Possible conformational consequences of 2′- and 3′-fluorination in relation to the suggested receptor active conformation depicted in Fig. 2 have not been studied, but it is difficult to imagine that 3′-fluorination would have a more dramatic influence on the 3-phenyl ring than 2′-fluorination. The inactivity of *In* could then be due to "forbidden" steric interactions with the D-2 receptor. In the case of the 2′-fluoro derivative, the fluoro atom would be situated either in the 2′- or the 6′-position in Fig. 2. This is either near to the thiepin ring carbon atom or the thiepin ring sulfur atom, in other words, in an area where there will be "enough space" at the receptor site.

Corresponding thiepin data, however, does not convincingly seem to support a hypothesis of an unfavourable steric interaction near the 3′-position (or 5′-position in Fig. 2). Both the 2-fluoro-derivative *IIn* (ref.[17]) and the 3-fluoro derivative *IId* (refs[17,18]) of octoclothepin (*IIb*) have potent neuroleptic activity (Table III). On the other hand, the 3′- and the 5′-positions in the indans are also close to the 1- or 4-positions in the thiepins (Fig. 2). Although fluorination effects in the thiepins have been studied extensively[15b] 1- or 4-fluoro derivatives of *IIb* have not been reported. Therefore, the hypothesis of unfavourable steric interaction cannot completely be discarded.

We have previously in detail discussed the SAR of various 6-substituents in the indans (4′-fluoro substituted compounds)[2,12]. Optimum activity is obtained with 6-CF_3 substitution (*Ie*, tefludazine). Although the D-2 affinity of *Ie* is only doubled,

compared to the 6-chloro derivative *Id*, the neuroleptic activity has increased 12–40 times. We have previously suggested that this might be due to pharmacokinetic differences[2]. The 6-CF_3 substituted derivatives including tefludazine are also the only compounds with a long duration of action[32] having significant neuroleptic activity even after 24 h.

In the thiepin series the effects of various substituents in the 8-position have been extensively investigated (ref.[15] and references cited there). An important difference from the indans is that compounds without fluoro atoms in the other ring have potent neuroleptic activity (*IIb*, octoclothepin), even the completely unsubstituted derivative *IIa* (perathiepin) has some cataleptogenic effect (although the compound was too weak to be clinically effective[15c]). The same is true for other classical tricyclic neuroleptics, such as phenothiazines or thioxanthenes[33,34]. A priori, a tricyclic ring system seems to fit better at the receptor site, while the indane ring system obviously needs a 6-substituent to do the same.

In the thiepin series the effect of fluorination in the 3-position is first of all a prolongation of the effect of some derivatives (cataleptogenic effect of *IId* and *IIf* lasts more than 24 h) (refs[13,15b,17]), while the influence on the maximum effect (catalepsy) is much less dramatic than in the indan series. In contrast to the indan case it has been proved that the 3-hydroxy derivatives are important, active metabolites of the thiepins[15]. Therefore, 3-fluorination is a rational strategy for making longer acting compounds. 2-Fluorination (*IIn*) does not lead to a prolongation of the effect, even though the 2-hydroxy derivatives have been found as metabolites[15b]. In 2-fluorinated derivatives the fluoro atom rather seems to mimic a hydrogen atom. Also in the thiepin series the 8-CF_3 derivatives are (e.g. *IIe*) among the most potent. Curiously, *IIe* is not a long-acting compound[13] like tefludazine (*Ie*). On the other hand, the 8-isopropyl derivative (*IIf*, isofloxythepine) is a potent and long-acting neuroleptic compound[13,15b–c], while the corresponding indan derivative *If* is short-acting and much weaker than *Ie*. Of course, these differences are in no way in conflict with the D-2 receptor model (Fig. 2), but is probably a natural consequence of differences between the physico-chemical properties, pharmacokinetics, and metabolism of indans and thiepins.

The exchange of the 4′-fluoro atom in the indans or the 3-fluoro atom in the thiepins with the larger chloro atom (compounds *Ij*, *Ik*, *IIj* and *IIk*) has a marked negative effect on the D-2 affinity (indans) and the neuroleptic activity of the compounds. Only *IIj* has a weak cataleptogenic activity[23]. Because a chloro atom also would protect against metabolic hydroxylation it is very likely that the loss of activity is due to an unfavourable steric interaction at the receptor site. Also the exchange of the 2′-fluoro atom in *Il* with a chloro atom results in an inactive compound with a low D-2 affinity (*Im*). Unfortunately, the corresponding 1,8-dichloro or 4,8-dichloro disubstituted thiepin derivatives have not been reported, but the 1-chloro derivative is inactive and the 4-chloro derivative is weakly active compared

with *IIa* and *IIb* (rotating rod)[20]. This seems to indicate that also in this area a chloro atom is too large to be accomodated at the receptor site. In indans a 2'-chloro atom might also have an unfavourable influence on the conformation of the 3-phenyl ring.

Concerning the effect of substitution in other positions than the 6-position of the indan phenyl ring we have previously reported that the 5-fluoro derivative of *Ic* and the 5-chloro derivative (*Ih*) of *Id* were without neuroleptic activity in vivo[2,14]. In fact, as seen in Table III, *Ih* has a hundred times lower D-2 affinity than *Id*. Therefore, it is very surprising that a similar complete loss of activity is *not* seen in the corresponding 7-substituted thiepins[20,21]. The 7-chloro derivative *IIh* is only slightly less cataleptogenic than *IIb*. Also, the 7-fluoro and the 7-trifluoromethyl derivatives are only 2–10 times less potent in inducing catalepsy than their respective 8-substituted counterparts[21] (data not shown). The lack of receptor binding data of the thiepin derivatives makes it difficult to analyze this important difference between indans and thiepins any further. However, as this is the first important example (besides the inactivity of the 3'-fluoro derivative *In* mentioned above) without parallel substitution effects in the two series it deserves further investigation.

The effect of 4- and 7-substitution in the indan phenyl ring is reported for the first time. The 4-chloro derivative *Ig* has ten times lower D-2 receptor affinity than *Id* and is completely inactive in vivo. The corresponding 6-chloro substituted thiepin has been reported[20] to be weakly active in the rotating rod model (80 times weaker than *IIb*). The 6-fluoro derivative *IIg* is completely without neuroleptic effect[19]. Also in this case the parallel substitution effects might indicate unfavourable steric interactions at the receptor site.

The 7-chloro derivative *Ii* does have significant affinity for the D-2 receptor, but is nevertheless without any effect in vivo. The corresponding 9-chloro substituted thiepin *IIi* induced catalepsy in 2 out of 10 animals in a dose of 10 mg/kg i.v. (ED_{50} for *IIb* is reported to be 2·4 mg/kg after i.v. administration[22]). This indicates a potential for a weak neuroleptic effect. Also here the substitution effects seem to be parallel in the two series. One may wonder whether the chloro substitution in this position might have an unfavourable influence on the orientation of the piperazine ring (Fig. 2), although the relatively high D-2 affinity of *Ii* speaks against such a hypothesis.

Compound *Ip* (Lu 17–133) is an example of the *trans*-isomers which are potent inhibitors of the reuptake of DA and NA (refs[1,2]) (Fig. 1). In other words, this compound is a potential antidepressant compound. Not only has it a very low affinity for D-2 receptors, but also for e.g. D-1, 5-HT_2, α_1 and muscarinic receptors[35]. The close analogue *Io* is also a potent DA/NA-uptake inhibitor, (IC_{50} DA uptake inhibition: 44 nM, NA uptake inhibition: 19 nM (ref.[36])), but, as expected, it has no affinity for postsynaptic receptor sites. Like the thiepin *IIo*, this compound can in a certain sense be regarded as an analogue of the atypical neuroleptic compound clozapine.

Clozapine is structurally closely related to *IIo*, the only difference being the structure of the tricyclic ring system (dibenzo[*b*,*e*]-1,4-diazepine system instead of the dibenzo-[*b*,*f*]thiepin ring system). Accordingly, *IIo* (docloxythepin) was developed as a non-cataleptogenic clozapine analogue. Despite its lack of antistereotypic and cataleptogenic activity it was shown to have some effect on DA turnover, like clozapine. Because of toxicological problems it has never been tested in schizophrenic patients, so it is unknown whether it has antipsychotic effect or not[15c].

The mechanism behind the antipsychotic effect of clozapine is still unclear, but it is a fact that clozapine has affinity for a variety of other receptors than dopamine D-2 receptors. For example, clozapine is a potent 5-HT_2 antagonist, α_1 adrenoceptor antagonist and muscarinic antagonist[37]. It is possible that clozapine's "mixed profile" is important for its unique clinical effect. If this is true it is very unlikely that compounds like *Io* and *Ip* should have "atypical" neuroleptic effects together with their potential antidepressant effects. On the other hand, it is more than likely that affinity for other receptor sites are preserved in thiepins with substituents in 2-position such as *IIo*, making it a rational strategy for finding "atypical" compounds in this series.

Compound *IIp* is also noncataleptogenic, but had very weak effect on DA turnover, compared to *IIp* (ref.[25]). However, as an analogue of *Ip* it might have potential antidepressant properties not as a dopamine uptake inhibitor (a property not found in tricyclic compounds[1]) but as an NA uptake inhibitor. Octoclothepine (*IIb*) is a potent NA uptake inhibitor[1,8,9] where the NA uptake inhibition resides in the *S*-enantiomer, which also is the more cataleptogenic enantiomer[9]. Therefore, there might be a chance to separate uptake inhibition from neuroleptic effects in compounds like *IIp*. On the other hand, *IIf* and oxyprothepin (X = SCH_3, R = $(CH_2)_3$.OH) are weak NA uptake inhibitors, while methiothepin (X = SCH_3, R = CH_3) like *IIb* is very potent[36]. This indicates that piperazine substituents larger than methyl might not be accomodated at the NA uptake site. In that case the N-methyl derivative of *IIp* might be a selective NA uptake inhibitor.

CONCLUSIONS

Comparison of the biochemical and pharmacological activities of a series of indans (including a number of new derivatives) with the corresponding closely related thiepins has supported and extended a new D-2 receptor model concept as follows:

1. In indans neuroleptic activity is found only in derivatives substituted in the 6-position. 7-Substituted derivatives retain some D-2 receptor affinity. Furthermore, the neuroleptic activity is dependent on a fluorine atom either in the 4'- or the 2'--position. Fluorination in the 3'-position results, for some unknown reasons, in loss of D-2 affinity.

2. In thiepins a suitable substituent in the 8-position is sufficient for potent neuroleptic activity. Additional fluorination has a less dramatic effect as compared to the indan series.

3. The SAR of derivatives with various substituents in the 6- or 8-positions in indans or thiepins, respectively, are largely parallel, but minor differences are found, probably due to differences in physico-chemical properties, pharmacokinetics and metabolism.

4. Thiepins with a substituent in the 6- or the 9-position are inactive like the corresponding 4- or 7-substituted indans.

5. Further investigations are needed to explain why 7-substituted thiepins have potent neuroleptic effect, while corresponding 5-substituted indans are inactive.

6. Replacement of fluorine with chlorine in the 4'-position in indans and the corresponding 3-position in thiepins lead to inactive compounds in both series.

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