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(5S)-3-ARYL-5-(1-PIPERIDINYLMETHYL)-2-OXAZOLIDINONES, A NEW CLASS OF POTENTIAL NEUROLEPTICS WITH A HIGH AFFINITY FOR SIGMA RECEPTORS

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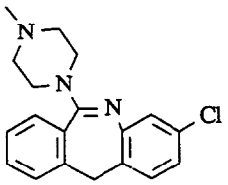
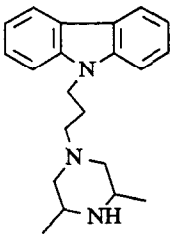
Abstract: The synthesis of 3,5-disubstituted 2-oxazolidinones, potential novel neuroleptic agents,is described. Like other "atypical" neuroleptics these compounds show high affinity for the σ-(SKF 10047)-receptor.Structure-activity relationships are discussed.

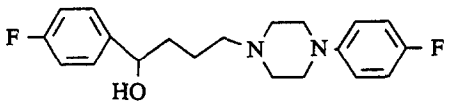
The fact that classical neuroleptics function as potent antagonists on the dopamine receptor (D2) is one of the essential supports of the dopamine hypothesis of schizophrenia[1]. Recently, however, atypical neuroleptics like clozapine with an apparently more complex mechanism of action have appeared[2].



Clozapine



Rimcazole



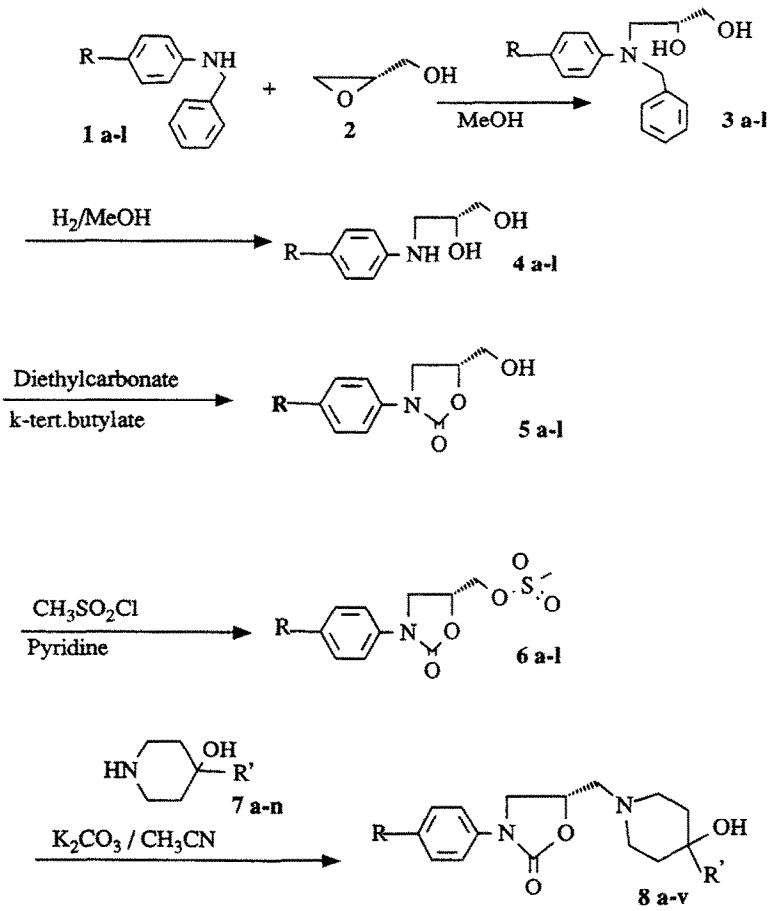
BMY 14802

BMY 14802, a compound characterized as a potential neuroleptic agent[3] with few side effects in animal experiments and rimcazole, that in addition has shown an antipsychotic clinical effect without extrapyramidal side effects[4], both possess a marked affinity for the σ-(SKF 10047-) binding site but do not bind to the dopamine receptor[5][6].

Even if the connection between this σ-affinity and the anti-psychotic effect of such compounds (and indeed the physiological significance of the σ-binding site as such) is anything but clear[7], it is none the less significant that a large number of new anti-psychotics all possess this affinity for the σ-binding site[8].

This interesting connection was reason enough for us to synthesize compounds with structural characteristics of a potential neuroleptic and to test these substances for their σ-affinity. The (5S)-3-aryl-5-(1-piperidinylmethyl)-2-oxazolidinones[9] were identified in this study as being new substances possessing an high degree of affinity for σ-binding sites.

Scheme 1:



The compounds were synthesized as shown in scheme 1: Compounds (**3 a-l**) were obtained by reacting N-benzylated anilines (**1 a-l**) with S-glycidol (**2**) using regioselective ring-opening. Hydrogenolytic cleavage of the benzyl group gave rise to the formation of (**4 a-l**). Reaction with diethyl carbonate and potassium tert. butylate gave the oxazolidinones (**5 a-l**). These compounds were converted to the corresponding methanesulphonic esters (**6 a-l**) by means of methanesulphonyl chloride in pyridine. The desired oxazolidinones (**8 a-v**) were obtained by reaction with substituted 4-arylpiperidine-4-oles (**7 a-n**) (in turn obtained by reacting appropriate aromatic Grignard compounds with N-benzylpiperidine-4-one and subsequent debenzylation). On using R-glycidol instead of S-glycidol, the corresponding 5-R-configurated enantiomers (**9 a-v**) were obtained.

Compounds with a missing 4-hydroxy group in the piperidine ring were synthesized as follows: (**12**) was obtained by first converting 4-hydroxy-4-(3,4-methylenedioxyphenyl)-piperidine (**7a**) by means of H_2O-elimination in acid medium into 4-(3,4-methylenedioxyphenyl)-3,4-dehydropiperidine (**10**) and reacting with (**6a**) as in scheme 2. (**13**) was obtained from (**10**) by hydrogenating the double bond to give the intermediary 4-(3,4-methylenedioxyphenyl)-piperidine (**11**) and subsequent reaction with (**6a**) as in scheme 2.

Scheme 2:

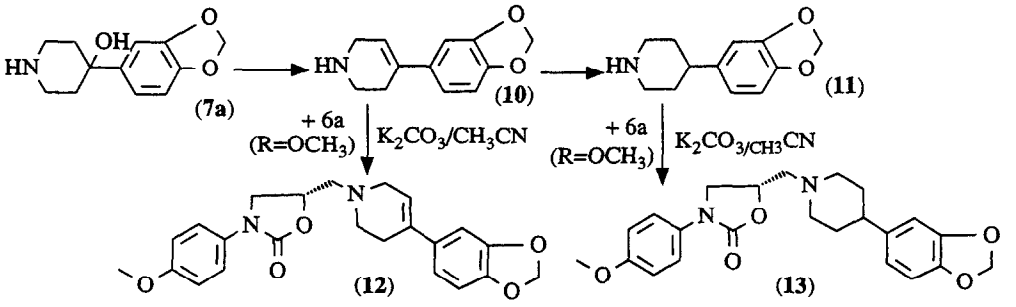


Table 1 illustrates to what degree the affinity of the oxazolidinones (which have in this case a constant substituent at the 3-position) is altered by variation of the aromatic group on the piperidine ring.

The data indicate that the type of substitution in the phenyl group has only a small influence on σ-affinity: In general, the K_i-value is between 10 and 30 nmol/l. The larger-volume group only, e.g. the one in compond (**8l**), gives rise to a decrease in affinity.

Table 1: Physical data and binding values of compounds **8 a-n** to the sigma receptor (guinea pig brain [3H]SKF10047)

Comp.	R	R'	mp °C	α_D^{20}	Sigma-binding K_i nmol/l
8 a	Methoxy	Phenyl	154-155	-14,2° ($CHCl_3$)	7
8 b	Methoxy	2-Thienyl	151-152	-15,8° ($CHCl_3$)	41
8 c	Methoxy	3-Thienyl	109-110	-28,3° (DMSO)	34
8 d	Methoxy	4-Fluorophenyl	108-110	-15,0° (DMSO)	14
8e	Methoxy	4-Chlorophenyl	140-141	-13,9° (DMSO)	21
8 f	Methoxy	4-Chloro-3-trifluorophenyl	127-128	-24,2° (DMSO)	15
8g	Methoxy	4-Methylphenyl	123-124	-27,9° (DMSO)	19
8 h	Methoxy	4-Methoxyphenyl	136-138	-12,9° ($CHCl_3$)	12
8 i	Methoxy	3,4-Dimethoxyphenyl	136-140	-25,9° (DMSO)	18
8 j	Methoxy	5-(1,3-Benzodioxolyl)	167-168	-27,9° (DMSO)	19
8 k	Methoxy	5-[(2,2-Dimethyl)-1,3-benzodioxolyl]	122-123	-26,8° (DMSO)	16
8 l	Methoxy	5-[(2,2-Pentamethylene)-benzodioxolyl]	157-159	-25,3° (DMSO)	62
8 m	Methoxy	6-(1,4-Benzodioxanyl)	156-157	-28,8° (DMSO)	31
8 n	Methoxy	5-(2,3-Dihydrobenzofuranyl)	147-148	-28,1° (DMSO)	17

Affinities to the σ-binding site on the other hand vary more strongly if - with the constant "piperidine portion" - the substitution pattern on the phenyl ring at position 3 of the oxazolidinone is altered (Table 2)

Table 2: Physical data and binding values of compounds **8 j-v** to the sigma receptor (guinea pig brain [3H]SKF10047)

Comp.	R	R'	mp °C	α_D^{20} (DMSO)	Sigma-binding K_i nmol/l
8 j	Methoxy	5-(1,3-Benzodioxolyl)	167-168	-27,9°	19
8 o	H	5-(1,3-Benzodioxolyl)	138-139	-27,0°	5
8 p	Fluoro	5-(1,3-Benzodioxolyl)	172-173	-23,4°	16
8 q	Chloro	5-(1,3-Benzodioxolyl)	163-165	-28,6°	3
8 r	Hydroxy	5-(1,3-Benzodioxolyl)	213-215	-26,8°	24
8 s	Ethoxy	5-(1,3-Benzodioxolyl)	139-141	-24,8°	15
8 t	Cyclopropylmethoxy	5-(1,3-Benzodioxolyl)	164-166	-24,5°	2
8 u	Trifluoromethoxy	5-(1,3-Benzodioxolyl)	123-124	-24,0°	1
8 v	Acetoxy	5-(1,3-Benzodioxolyl)	160-161	-25,4°	250

The K_i-values vary here between 1 and 250 nmol/l. The chloro-,cyclopropylmethyloxy- and trifluoromethoxy-groups are particularly advantageous (compounds **8q**, **8t** and **8u**). The introduction of a hydroxyl group leads to compound **8r** which has a strong affinity for the σ-binding site. Etherification (compounds **8j** and **8s**) does not alter the biological activity; esterification in contrast (compound **8v**) decreases the activity.

The biological activity is influenced not only by these alterations at the periphery of the molecule, but also by configurational and structural changes at the core. Table 3 illustrates the effect of configuration of the molecule on the σ-binding values.

Table 3: Stereochemistry and binding values of selected compounds to the sigma receptor (guinea pig brain [3H]SKF10047)

Comp.	Stereochemistry	α_D^{20} ($CHCl_3$)	Sigma-binding K_i nmol/l
8 a	S	-14,2°	7
9 a	R	+14,6°	34
8 d	S	-14,1°	15
9 d	R	+14,0°	300
8 e	S	-13,9°	21
9 e	R	+12,8°	270
8 h	S	-13,0°	12
9 h	R	+13,7°	120

The four examples illustrated here show that the compounds with 5S-configuration demonstrate a higher affinity (by about one order of magnitude) to the σ-binding site than their antipodes.

Table 4 shows how structural changes at position 4 of the piperidine ring also influence the biological activity:

Table 4: Physical data and binding values of compounds **8j**,**12** and **13** to the sigma receptor (guinea pig brain [3H]SKF10047)

Comp.	mp °C	α_D^{20} (DMSO)	Sigma-binding K_i nmol/l
8 j	167-168	-27,9°	19
12	198-199	-27,5°	170
13	158-160	-27,2°	19

Whilst the replacement of the hydroxyl group by a hydrogen atom in compound (**8j**) has no effect on the biological activity (see compound **13**), a more significant decrease in activity is observed on inserting a double bond into the piperidine by dehydration.(Compound **12**)

In summary,the (5S)-3-aryl-5-(1-piperidinylmethyl)-2-oxazolidinones can be said to represent a new class of compounds exhibiting strong affinity for the σ-binding site whilst remaining relatively robust in this respect as far as minor structural changes are concerned. Even within such a class of compounds, the suitability of a particular compound as a potential pharmaceutical product has to be decided on the basis of its principal effect and possible side-effects demonstrated in animal testing. Within this class of substances, compound **8j** was shown in animal testing to be advantageous as potential neuroleptic agent (details to be published elsewere).

Table 5 illustrates that this compound is comparable with some other recent "atypical" neuroleptic agents as far as binding capacity is concerned (binding spectrum extends from distinct to strong binding to the σ-binding site and weak to no binding to the dopamine D2-receptor):

Table 5: Binding values of compound **8j** and reference compounds to the sigma receptor and to the D_2-receptor (guinea pig brain [3H]SKF10047 and rat striatum[3H]spiperone)

Comp.	Sigma-binding K_i nmol/l	D_2-binding IC_{50} nmol/l
8 j	19	4000
Remoxipride	55	1400
Rimcazole	680	> 10 000
BMY 14802	71	4900

The hydrochloride of compound **8j** with the internal company designation EMD 57445 is being further investigated.

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