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Synthesis and structure–activity relationship of 2-(aminoalkyl)-3,3a,8,12b-tetrahydro-2*H*-dibenzocyclohepta[1,2-*b*]furan derivatives: a novel series of $5\text{-HT}_{2A/2C}$ receptor antagonists

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Abstract—Following the program started at Johnson & Johnson Pharmaceutical Research & Development searching for $5\text{-HT}_{2A/2C}$ antagonists we now report on the synthesis of a series of substituted 2-(aminomethyl)-3,3a,8,12b-tetrahydro-2*H*-dibenzocyclohepta[1,2-*b*]furan derivatives. The 5-HT_{2A}, 5-HT_{2C} and H_1 receptor affinities of the described compounds are reported. The mCCP antagonistic activity of a set of selected molecules is also reported.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter in the CNS and, since its discovery over 50 years ago, it has played an important role in the management of several CNS related disorders.[1,2] The 5-HT agonist *m*-chlorophenylpiperazine (mCPP) is known to induce symptoms of anxiety in various animal models.[3,4] As this mCPP-induced anxiety seems to be mediated via the 5-HT_{2C} receptor, it has been hypothesised that 5-HT_{2C} antagonists might be potential drugs for the treatment of anxiety and depression.[5,6] During the last years an increasing research effort has been devoted to discover new 5-HT_{2C} antagonists and/or agonists trying to better understand their potential as new therapeutic agents.[7] Recently, researchers at GSK have described a series of selective 5-HT_{2C} antagonists that have been shown to be active in animal models of anxiety and therefore might be considered as potential antidepressant/anxiolytic agents. A representative compound of this series is SB-243213 (**1**) (Fig. 1).[8] Furthermore, deramciclane (**2**) is a potent $5\text{-HT}_{2A/2C}$ antagonist that is currently in Phase III clinical trials for the treatment of anxiety disorders.[9]

Some years ago we started a program at Johnson & Johnson Pharmaceutical Research & Development, searching for potent and centrally active $5\text{-HT}_{2A/2C}$ receptor antagonists as potential anxiolytic/antidepressant agents.[10] As a result of our synthesis program, we have recently described series of 2-(aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine derivatives as novel $5\text{-HT}_{2A/2C}$ antagonists, that also showed high affinity for histamine-H_1 receptors.[11] One of those compounds, the *N*,*N*-dimethylaminomethyl derivative R107500 (**3**), was a potent mCPP antagonist as shown in our in vivo mCPP challenge test.[4,12]

Following with our synthesis program, we now report on the synthesis of the corresponding tetrahydrofuran analogues (**4**) of R107500. In this new class of compounds the isoxazolidine ring has been replaced by a tetrahydrofuran ring. This main modification has been combined with the introduction of different amines, as well as the replacement of the methylene linker between

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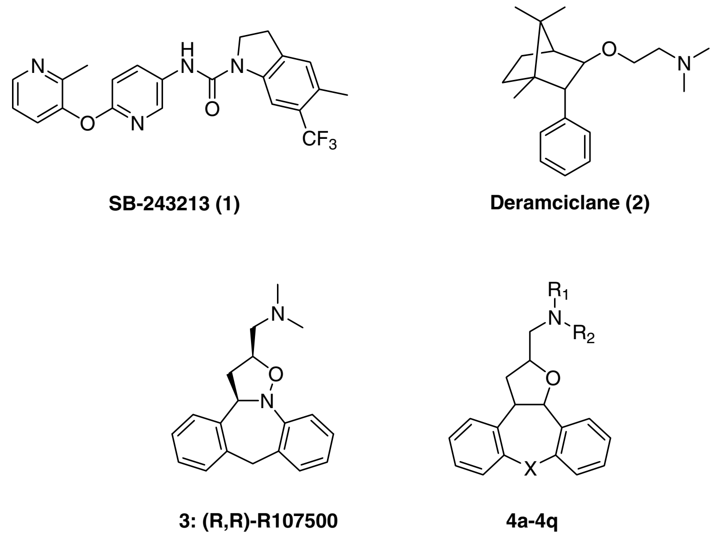


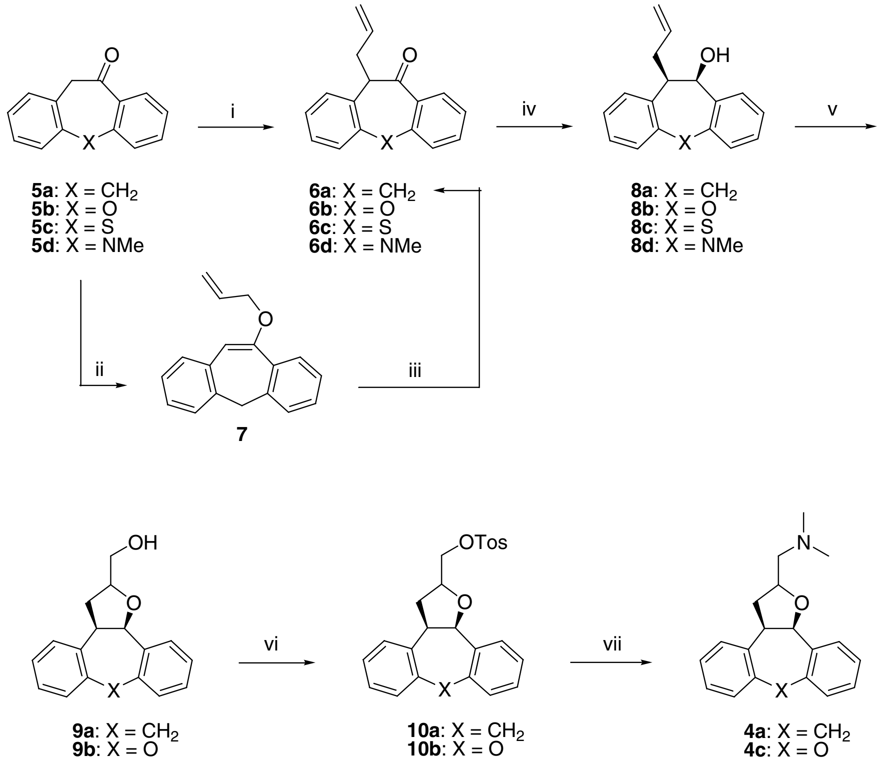
Figure 1.

the two aromatic rings by different spacers. The isolation of the enantiomers of the most active racemate allowed us to discover **16b** (JNJ17297709) as a new candidate for further pharmacological characterisation.

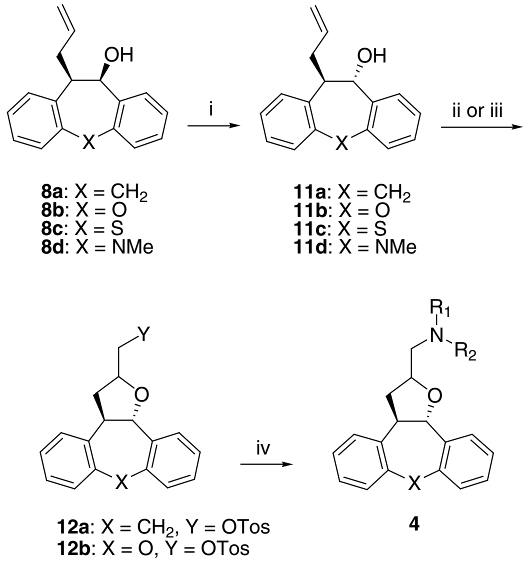
2. Chemistry

The synthesis of the target compounds **4** was achieved by two general methods (Schemes 1 and 2), depending on the desired relative stereochemistry at positions 3a, 12b (*cis*-fused or *trans*-fused tetrahydrofuran analogues).

Firstly, the reaction of the corresponding tricyclic ketones **5a**,[13] **5b**,[14] **5c**[14] and **5d**[15] with sodium hydride, followed by addition of allyl bromide afforded the α-allylated ketones **6a–d** in good to moderate yields (Scheme 1). Ketones with an heteroatom linker between the two phenyl rings (**5b–d**) were allylated in satisfactory yields (80–92%). On the other hand, dibenzosuberone



Scheme 1. Reagents and conditions: (i) NaH, THF, 0 °C, 2 h then allyl bromide, 0 °C to rt, overnight, 42–92%; (ii) allyl bromide, K_2CO_3, DMF, 60 °C, 8 h, 90%; (iii) toluene, 230 °C, 10 h, 98%; (iv) Red-Al, THF, −30 °C to rt, 6 h, 87–96%; (v) MCPBA, CH_2Cl_2, hydroquinone (cat.), rt, 10 h, 83–95%; (vi) tosyl chloride, NEt_3, CH_2Cl_2, rt, 8 h, 82–90%; (vii) dimethylamine, CaO, THF, 120 °C, overnight, 77–86%.



Scheme 2. Reagents and conditions: (i) *p*-nitrobenzoic acid, DIAD, PPh_3, THF, 0 °C to rt 12 h, then LiOH, rt, overnight, 77–89%; (ii) MCPBA, CH_2Cl_2, hydroquinone (cat.), rt, 10 h, 83–97% then tosyl chloride, NEt_3, CH_2Cl_2, rt, 9 h, 80–87%; (iii) IPy_2BF_4, CH_2Cl_2, rt, 5 min, 90–95%; (iv) NHR_1R_2, CaO, THF, 120 °C, overnight, 70–83%.

(**5a**) led to the corresponding *C*-allylated compound **6a** in only 42% yield due to the competition with double *C*-allylation and *O*-allylation reactions.[16] This problem was resolved performing the *C*-allylation reaction in a two step sequence: treatment of the ketone **5a** with allyl bromide in DMF at 60 °C, using K_2CO_3 as base, occurred with complete regioselectivity, affording the *O*-allylated product **7** in 90% yield; the Claisen rearrangement of the allyl vinyl ether **7** led quantitatively to the desired α-allylketone **6a**. The reduction of ketones **6a–d** with Red-Al at −30 °C in THF gave the expected *cis*-alcohols **8a–d** with complete diastereoselectivity and excellent yields (Scheme 1). The determination of the relative configuration of the alcohols **8a–d** was carried out by means of NOE difference experiments. The epoxydation/cyclisation of the *cis*-β-allylic alcohols **8a** and **8b** with *meta*-chloroperbenzoic acid (MCPBA) occurred with almost no selectivity, affording the corresponding *cis*-fused tetrahydrofuran derivatives **9a** and **9b** as 3:2 mixtures of diastereoisomers. Finally, transformation of the tetracycles **9a** and **9b** into the *cis*-fused target compounds **4** was carried out by reaction of the alcohol group with tosyl chloride in dichloromethane, and subsequent thermal displacement of the tosyl group by dimethylamine in THF at 120 °C (oil bath temperature), conducted in a standard Parr pressure reaction vessel.

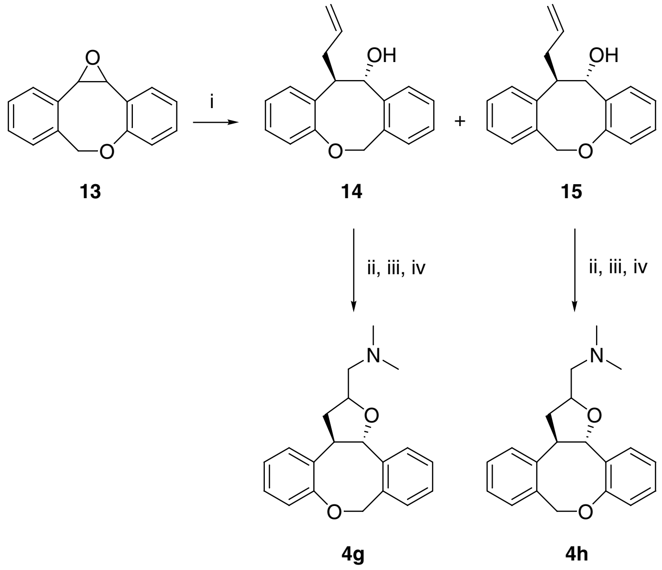
The synthesis of the *trans*-fused tetrahydrofuran analogues, is outlined in Scheme 2. The required *trans*-β-allylic alcohols **11a–d**, were prepared by Mitsunobu inversion reaction of the *cis*-alcohols **8a–d** with *p*-nitrobenzoic acid,[17] followed by ester hydrolysis, in good overall yields (77–89%). The cyclisation reaction of the *trans*-alcohols **11a** and **11b** was performed with MCPBA, providing mixtures 1:1 of the expected 2-hydroxymethyltetrahydrofurans, that were transformed in the tosyl derivatives **12a** and **12b**[18] by treatment with tosyl chloride in dichloromethane. Attempts of cyclisation of the *trans*-β-allylic alcohols **11c–d** with MCPBA were unsuccessful, affording complex mixtures of oxidation products. In these cases, the use of IPy_2BF_4 (bis(pyridine)iodonium(I)tetrafluoroborate; Barluenga's reagent)[19] instead of MCPBA as cyclisating agent led to the 2-iodomethyltetrahydrofurans **12c** and **12d** with excellent yields (90% and 95%, respectively), as equimolecular mixtures of diastereoisomers. Final conversion of compounds **12a–d** into the corresponding *trans*-fused 2-aminomethyltetrahydrofuran derivatives **4** was effected by heating with the corresponding amine in THF at 120 °C (oil bath temperature) using a standard Parr pressure reaction vessel.

The influence of the length of the spacer between the two aromatic rings was investigated with the synthesis of the dibenzo[*b*,*f*]oxazine derivatives **4h** and **4i** (Scheme 3). The ring opening of the epoxide **13**[20] with allylmagnesium bromide gave a 3 to 1 mixture of regioisomers **14** and **15**, respectively, that were separated by HPLC chromatography. The structure and the relative stereochemistry of each regioisomer was assigned by 2D-HMQC, 2D-HMBC and 2D-NOESY experiments. Finally, the targeted dimethylamino derivatives **4h** and **4i** were obtained by a reaction sequence similar to that described in Schemes 1 and 2. Thus, treatment of the *trans*-β-allylic alcohols **14** and **15** with MCPBA, followed by reaction with tosyl chloride and final thermal displacement of the corresponding tosyl groups with dimethylamine, afforded **4h** and **4i** in good yields (68% and 60%, respectively, after three steps) as mixtures 1:1 of diastereoisomers.

3. Biological results and discussion

The affinities of the compounds for the 5-HT_2 receptors were measured by means of radioligand binding studies conducted with: (a) human cloned 5-HT_{2A} receptor, expressed in L929 cells using [^{125}I]R91150 as radioligand[21] and (b) human cloned 5-HT_{2C} receptor, expressed in CHO cells using [^{3}H] mesulergine as radioligand.[22] The experiments to measure the affinities for the H_1 receptor were conducted with human cloned H_1 receptors expressed in CHO cells, using [^{3}H]pyrilamine as radioligand.[20] The experiments to measure the in vivo activity of the compounds in our mCPP challenge test were performed in male Wistar rats, weighing between 200 and 220 g, following the method described by Meert et al.[4] The test compounds were administered subcutaneously.

Antagonistic effects on the H_1 receptor are not associated with therapeutic efficacy in depression or anxiety, but may contribute to potential sedative effects of those drugs.[23] Therefore this interaction should be taken into account for the future development of any of these compounds. Tables 1 and 2[24] show the affinities for the



Scheme 3. Reagents and conditions: (i) allylmagnesium bromide, THF, reflux, 3 h. (ii) MCPBA, CH_2Cl_2, hydroquinone (cat.), rt, 10 h; (iii) tosyl chloride, NEt_3, CH_2Cl_2, rt, 8 h; (iv) dimethylamine, CaO, THF, 120 °C, overnight, 60–68% (three steps).

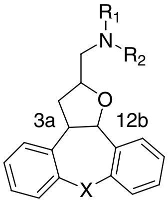
5-HT_{2A}, 5-HT_{2C} and H_1 receptors of the synthesised compounds. The mCCP antagonistic activity of a set of selected molecules is also reported in Table 2.

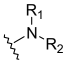
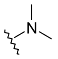
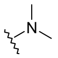
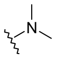
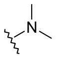
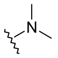
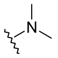
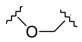
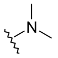
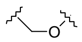
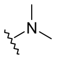
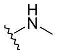
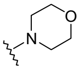
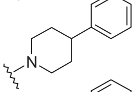
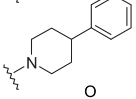
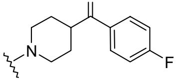
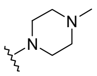
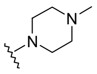
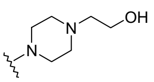
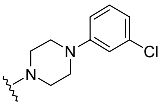
Initially, the effect of the stereochemistry at the tetrahydrofuran fusion positions (3a, 12b) was investigated by comparison of diastereoisomeric mixtures of the *cis*-fused analogues **4a** ($X = CH_2$) and **4c** ($X = O$) with their corresponding mixtures of the *trans*-fused stereoisomers **4b** and **4d**. While the *cis*-fused diastereoisomers evinced a remarkable decrease of the affinity for all receptors, compared to **3**, the *trans*-fused isomers presented better binding values than their corresponding *cis*-fused pairs. It should be noted that compound **4b**, being a mixture of two racemic diastereoisomers, was equipotent to **3** at the H_1 receptor and about 9- and 7-fold less potent at the 5-HT_{2A} and 5-HT_{2C} receptors, respectively. Having this in mind, we decided to explore the substitution of the methylene bridge between the two aromatic rings of the *trans*-fused analogue **4b**, by different heteroatomic linkages. Thus, the methylene spacer was replaced by an oxygen atom (**4d**), sulfur atom (**4e**) and N–Me group (**4f**). As can be deduced from the data shown in Table 1, none of these changes improved the binding affinities of **4b**. The influence of these substitutions specially affected the affinity for the H_1 receptor, being the affinities of the three analogues **4d**–**f** at least 6-fold less potent than the corresponding carbon-analogue **4b**. The binding affinities for 5-HT_{2A} were comparable in the case of the dibenzoxepine (**4d**) and dibenzothiepine (**4e**) analogues (1.7- and 1.4-fold less potency, respectively), and a more pronounced decrease was observed for the dibenzoazepine **4f** (about 4-fold less potent). In contrast, the dibenzoazepine analogue **4f** showed the best affinity for the 5-HT_{2C} receptor (about 2-fold less active than **4b**). The influence of the enlargement of the seven membered ring present on the structure of **4b** was also studied by comparison with the eight membered heterocyclic analogues **4g**,**h**. These modifications resulted in compounds showing much less affinity for the three receptors.

The replacement of the *N*,*N*-dimethylamino fragment in **4b** by several amines was also studied. The *N*-methylamine derivative **4i** showed similar binding values for 5-$HT_{2A/2C}$ receptors (about 2-fold less potent), being significantly less active in respect to the H_1 receptor (13-fold less affinity). The introduction of cyclic amines such as morpholine (**4j**), 4-substituted piperidines (**4k**,**m**) and 4-alkyl- and 4-arylpiperazines (**4n**,**p**,**q**) was not allowed in terms of activity and, in general, led to a pronounced loss of affinity for the 5-HT_2 receptors. This lack of activity, was confirmed as well in the case of the dibenzothiepine derivatives **4l** and **4o** where the *N*,*N*-dimethylamino group had been substituted by a 4-phenylpiperidine and a 4-methylpiperazine, respectively.

Based on the in vitro data shown in Table 1 for this preliminary exploration of the novel series of tetrahydrofuran derivatives, we decided to evaluate the four possible enantiomers of the *trans*-fused dimethylamino derivative **4b**. Thus, the diastereoisomeric mixture **4b** was resolved by chiral HPLC chromatography into the corresponding enantiomerically pure stereoisomers **16a**–**d**.[25] The biological results obtained are summarised in Table 2. A pronounced difference of activities between the enantiomers of the two *trans*-fused diastereoisomeric forms was observed both in vitro and in vivo. Enantiomers **16b** and **16d** were clearly more potent than their respective pairs **16a** and **16c**. To confirm the in vitro affinity for 5-HT_{2C} the compounds were evaluated in vivo in the mCPP challenge test. All enantiomers showed a good in vivo activity, after subcutaneous administration, in concordance with the in vitro values. The best in vivo activity was observed for **16b** whose ED_{50} was 0.04 mg/kg after subcutaneous administration.

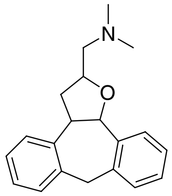
Table 1. 5-$HT_{2A/2C}$ and H_1 binding affinities of 2-aminomethyl-3,3a,8,12b-tetrahydro-2H-dibenzocyclohepta[1,2-*b*]furan derivatives[a]

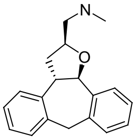
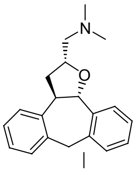
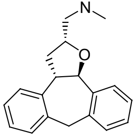
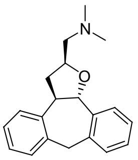


Compound	X		Stereochemistry (3a,12b)	5-HT_{2A} K_i (nM)	5-HT_{2C} K_i (nM)	H_1 K_i (nM)
3 (R107500)	—	—	—	2.5	1	0.64
4a	CH_2		*cis*	102	166	27
4b	CH_2		*trans*	21.7	6.7	0.7
4c	O		*cis*	92.6	183	32.6
4d	O		*trans*	37	31	14
4e	S		*trans*	30.7	24.7	4.3
4f	N–CH_3		*trans*	80.7	12.9	6
4g			*trans*	90.5	32.5	9.6
4h			*trans*	1064	123.5	20.6
4i	CH_2		*trans*	48.6	9.7	9.3
4j	CH_2		*trans*	433	27	2.36
4k	CH_2		*trans*	1088	42.7	29.7
4l	S		*trans*	68.7	239	47.1
4m	CH_2		*trans*	433	17	1.9
4n	CH_2		*trans*	433	677	3
4o	S		*trans*	17.3	120	1.2
4p	CH_2		*trans*	86.5	170	3.7
4q	CH_2		*trans*	56	107.4	471

[a] The activity of compounds was confirmed in an independent experiment. A difference in pIC_{50} up to 0.6 (SD <0.5) was considered as reproducible and therefore accepted.

Table 2. 5-$HT_{2A/2C}$ and H_1 affinities and activity in mCPP challenge test of 2-*N*,*N*-dimethylaminomethyl-3,3a,8,12b-tetrahydro-2H-dibenzocyclohepta[1,2-*b*]furan derivatives[a,b]



Compound	Stereochemistry	5-HT_{2A} K_i (nM)	5-HT_{2C} K_i (nM)	H_1 K_i (nM)	mCPP (sc) ED_{50} (mg/Kg)
3(R107500)	(*R*,*R*)	2.5	1	1	0.04
16a 	2*S**,3a*S**,12b*R**	74.1	15.9	3.5	2.2
16b 	2*R**,3a*R**, 12b*S* *	2.5	0.93	0.54	0.04
16c 	2*R**,3a*S**,12b*R**	104	28	3.74	1.26
16d 	2*S**,3a*R**,12b*S**	19.6	3.25	0.63	0.06

[a] The activity of compounds was confirmed in an independent experiment. A difference in pIC_{50} up to 0.6 (SD <0.5) was considered as reproducible and therefore accepted.

[b] ED_{50} values and corresponding 95% confidence limits were determined according to the modified Spearman–Kaerber estimate using theoretical probabilities instead of empirical ones. This modification allows to tabulate the ED_{50} and its confidence interval as a function of the slope of the log dose–response curve.

In conclusion, we have found that the replacement of the isoxazolidine ring of **3** by a tetrahydrofuran led to the discovery of novel series of compounds showing potential anxiolytic and/or antidepressant properties. The isolation and evaluation of the enantiomers of the most promising compound within this series (**4b**) led to the identification of the enantiomer **16b** (JNJ17297709), which showed an equipotent activity in the in vivo mCPP test as the reference compound R107500. Further exploration of JNJ17297709 in order to broaden the SAR around its structure is in progress and it will be reported in due course.

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24. All the compounds in Table 1 were assayed as mixtures of either *trans*-fused (1:1) or *cis*-fused (3:2) diastereoisomers.
25. The relative stereochemistry of the three chiral centres in **16a–d** was ascertained by means of 2D-NOESY experiments; the absolute configuration of the enantiomerically pure form has not been determined.