Russian Chemical Reviews **79** (4) 285 – 306 (2010) © 2010 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2010v079n04ABEH004122

The synthesis and physiological activity of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles

A V Ivachtchenko, O D Mitkin, M G Kadieva, S E Tkachenko

Contents

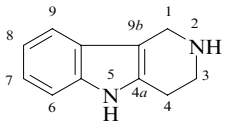
I.	Introduction	285
II.	Methods of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole synthesis	285
III.	Physiological activity of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles	299
IV.	Conclusion	305

Abstract. Data on the methods of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole synthesis has been surveyed. The synthetic accessibility of various derivatives of these heterocycles has been demonstrated. It has been shown that such compounds exhibit a broad spectrum of pharmacological activity and hold interest for medicinal chemistry. The bibliography includes 146 references.

I. Introduction

Advances in modern pharmacotherapy are in the first place associated with the development of innovative and efficacious pharmaceuticals. Most popular are drugs acting on novel, recently discovered targets. This fact gave rise, in particular, to a detailed study of the mechanisms of action of already known physiologically active molecules as well as of their metabolites,[1] chiral[2] and modified analogues.[3] Apparently, such investigations can result in both the creation of novel original drugs and new applications of known therapeutics.[4] In this regard, development of methods for the preparation of known classes of physiologically active compounds, synthesis of their new derivatives as well as detailed examination of their pharmacological profiles is a vital and promising task.

Heterocyclic compounds containing 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indolyl (or tetrahydro-γ-carboline) scaffold (**1**) have remained over many years the centre of attention of researchers specialized in the areas of organic and medicinal chemistry.



1

The most informative database of organic compounds 'SciFinder' (https://scifinder.cas.org) contains data on 9373 structures of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles (THPI), which were reported in 2150 scienific publications and 493 patents. In the series of THPI derivatives, compounds characterized by diverse and often unique physiological activities were discovered. However, the only review on the methods of synthesis of these heterocycles was published by Kost *et al.*[5] as far back as 1973.

Over the time elapsed since the publication of the review,[5] numerous facts have appeared on the syntheses of previously unknown THPIs bearing various substituents or fused with other heterocycles. In addition, our conceptions of the physiological activity of such compounds have been substantially broadened, in particular, effective pharmaceticals for the treatment of Central Nervous System (CNS) diseases have been devepoped based on them. For this reason it seemed pertinent not only to survey data on the methods of synthesis of THPIs, but also to address their biological properties in the present review.

II. Methods of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole synthesis

The methods of synthesis of this class of compounds have been developed since 1954. They can be divided into several logical parts: the formation of a pyrrole ring, the conversion of substituted indoles to yield a tetrahydropyridine ring, the reduction of the pyridine ring in γ-carbolines, the introduction of side chain substituents to the indole moiety and their modification.

A V Ivachtchenko, O D Mitkin, M G Kadieva, S E Tkachenko Chemical Diversity Research Institute, Rabochaya ul. 2a/1, 141401 Khimki, Moscow Region, Russian Federation. Fax (7-495) 626 97 80, ChemDiv, Inc. Nancy Ridge Drive 6605, 92121 San Diego, CA, USA. Fax (1-858) 794 49 31, tel. (7-495) 995 49 41, e-mail: av@chemdiv.com (A V Ivachtchenko), tel. (7-495) 995 49 41, e-mail: mod@chemdiv.com (O D Mitkin), tel. (7-495) 995 49 41, ext. 629, e-mail: kadieva@iihr.ru (M G Kadieva), (1-858) 436 15037, e-mail: set@chemdiv.com (S E Tkachenko)

Received 11 November 2009
Uspekhi Khimii **79** (4) 325 – 347 (2010); translated by A F Nasonov

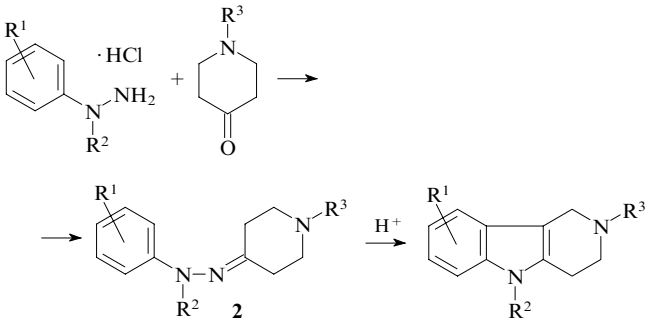
1. The Fischer rearrangement, the Heck and Nenitzescu reactions

The methods discussed below consist in condensation of piperidin-4-one and its derivatives with arylamines based on the Fischer rearrangement. It appears logical to consider THPI syntheses from anilines by the Heck and Nenitzescu reactions also in this section.

a. Syntheses based on phenylhydrazones (the Fischer rearrangement)

The Fischer reaction involving piperidin-4-one phenylhydrazones **2** in acidic media found a wide application in the preparation of THPIs. The key step of this process is an acid catalyzed rearrangement of the enehydrazine form of an arylhydrazone, proceeding *via* a 3,3-sigmatropic shift (the so-called 3,4-diaza-Cope rearrangement), followed by aromatization of the six-membered ring and formation of a pyrrole one.

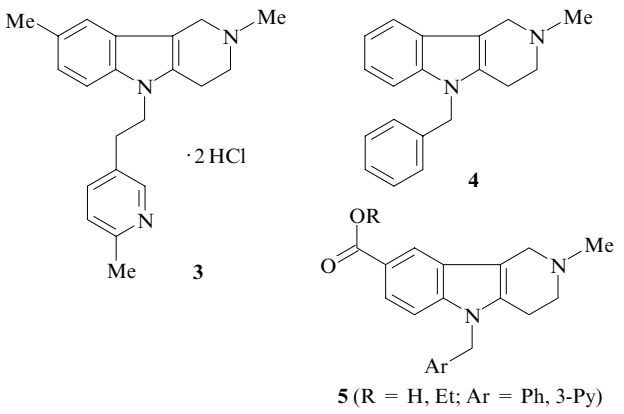
In a number of cases THPIs form even upon heating of a substituted phenylhydrazine hydrochloride with piperidin-4-one in alcohol[6–8] or pyridine.[9] Normally the reaction is carried out in acidic media, using HCl (Ref. 10) or its solution in AcOH,[11] CF_3CO_2H solutions in alcohol[12] or H_2SO_4 in dioxane.[13] A general purpose reagent is an HCl alcololic solution.[6,14–18] Sometimes better yields are achieved when using a preliminary prepared hydrazone **2**.[6,10]



R^1 = H, Alk, AlkO, Hal, $AlkO_2C$, $MeSO_2$, *etc.*;
R^2 = H, Alk, Ar; R^3 = H, Alk, AlkC(O), $AlkO_2C$.

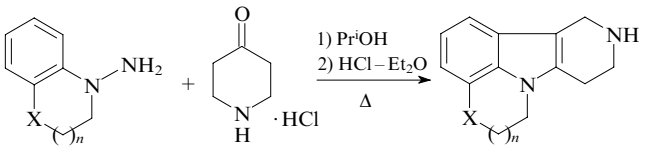
The choice of the acidity of the medium, as a rule, depends on the structural features of the hydrazine. Thus, the condensation occurs sufficiently readily if there is an electron-donating substituent at the *para*-position of the benzene ring of phenylhydrazine. In the presence of electron-withdrawing groups, however, the process frequently stops at the formation of a hydrazone, and its continuation requires more severe conditions. For example, using HCl solution in acetic acid 8-nitro substituted THPIs can be obtained in no more than 20% yield.[6] All phenylhydrazines are involved in the conversions under discussion, THPIs with required substituents at the indole nitrogen atom can also be obtained from *N*-substituted arylhydrazines.[7,19–21] The choice of the carbonyl component of the Fischer reaction is generally not limited: both the piperidin-4-one itself and its *N*-alkyl and *N*-acyl derivatives undergo this reaction successfully.

It is by this way that such well-known drugs as Dimebon (**3**)[22] and Diazoline (**4**),[21] as well as their analogues **5**[17] were synthesized for the first time.



5 (R = H, Et; Ar = Ph, 3-Py)

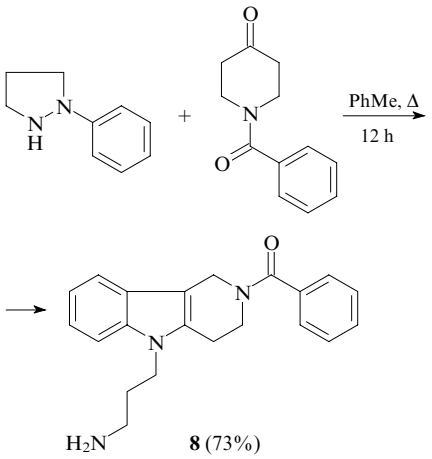
The possibility of the preparation of tetracyclic compounds **6a–d** in high yields was exemplified[23] by the reaction of bicyclic *N*,*N*-disubstituted hydrazine **7a–d** with piperidin-4-one hydrochloride in refluxing isopropyl alcohol.



7a–d **6a–d** (75%–90%)

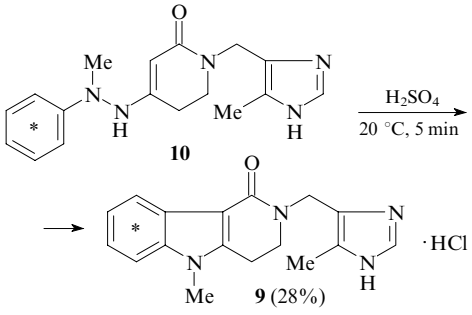
n = 1: X = S (**a**), CH_2 (**b**), O (**c**); *n* = 2, X = CH_2 (**d**).

Reflux of 1-phenylpyrazolidine with *N*-benzoylpiperidin-4-one in toluene with water distillation results in 5-(3-aminopropyl)-2-benzoyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**8**)[24] isolated as a salt with maleic acid.



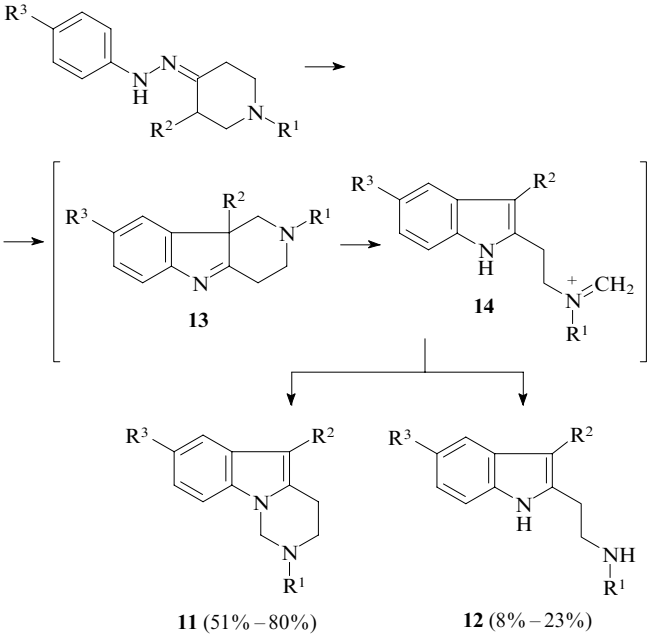
8 (73%)

Hydrazones existing in the enehydrazine form can undergo the Fischer reaction. As an example let us cite the synthesis of alosetron (**9**)[25] labelled with the ^{14}C isotope from the corresponding hydrazine **10** in a 28% radiochemical yield.



10 **9** (28%)

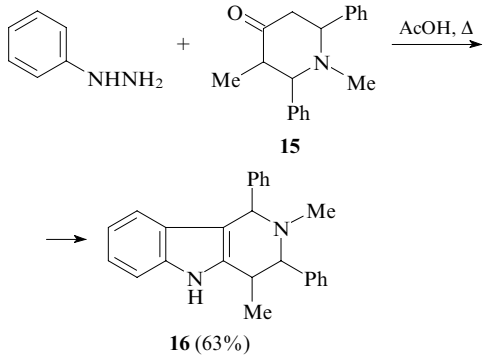
It should be noted that the Fischer cyclization of phenylhydrazones of 1,3-disubstituted piperidin-4-ones leads to a mixture of tetrahydropyrimido[1,6-*a*]indoles **11** and substituted 2-(1*H*-indol-2-yl)-*N*-ethylamines **12**[26, 27] rather than the expected products — 2,4-disubstituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles. According to the suggested reaction mechanism, intermediate **13** undergoes a retro-Mannich reaction to form iminium cation **14**, subsequent transformations of which do yield a mixture of the products **11** and **12**.



11 (51% – 80%) **12** (8% – 23%)

R^1 = Me, Bn; R^2 = Me, Ph; R^3 = H, Cl.

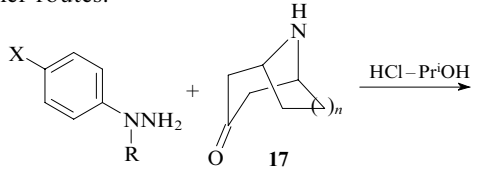
However, in the case of 1,3-dimethyl-2,6-diphenylpiperidin-4-one (**15**) as the starting compound, the route above does not take place. Thus, in the reaction[28] of compound **15** with phenylhydrazine the only product obtained was 2,4-dimethyl-1,3-diphenyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indole (**16**).



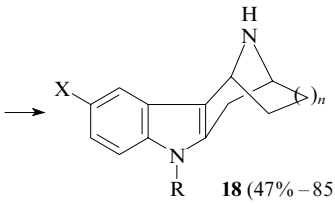
15

16 (63%)

Bridged piperidones **17**, for instance, tropinone and nortropinone, are smoothly and with acceptable yields converted to THPIs **18**, which are difficult to access by other routes.[29, 30]



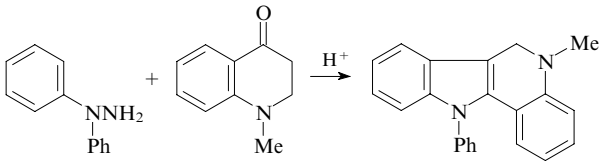
17



18 (47% – 85%)

R = H, Me, Ph; X = H, F; n = 1, 2.

From tetrahydroquinolinone **19**, substituted 6,11-dihydro-5*H*-indolo[3,2-*c*]quinoline **20** was prepared.[31]

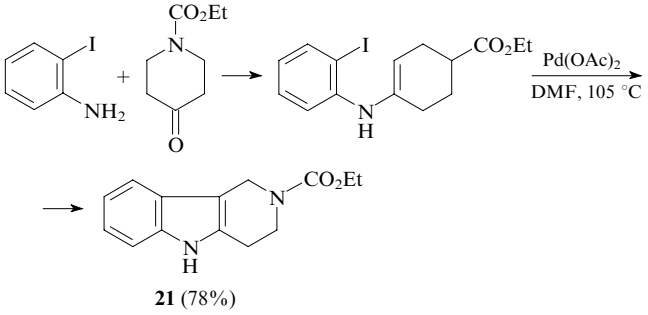


19 **20**

In conclusion of this section let us note that owing to the accessibility of starting compounds and mild process conditions the Fischer rearrangement is exploited in industrial processes for the manufacturing of many drugs containing a THPI moiety.

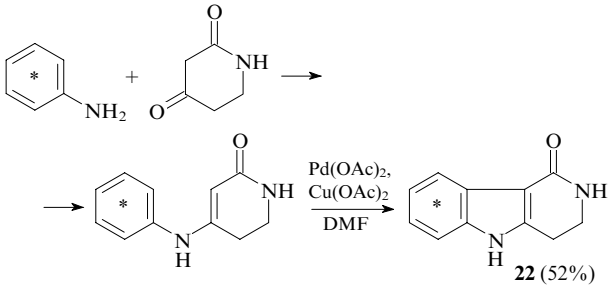
b. Syntheses based on the Heck reaction

Palladium-catalyzed coupling of alkenes with aryl halides, known as the Heck reaction, allows preparation of THPIs *via* intramolecular cyclization. The reaction proceeds *via* the formation of an enamine, and the choice of the amine is a determining factor for the efficiency of the process. Thus, the synthesis of 2-ethoxycarbonyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**21**)[32] from 2-iodoaniline and *N*-ethoxycarbonylpiperidin-4-one with the aid of the Heck reaction is a successful alternative to the Fischer rearrangement.



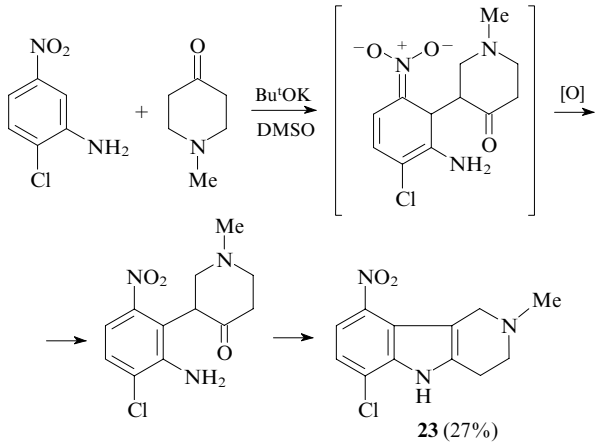
21 (78%)

A synthesis of isotope-labelled 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-one (**22**) by the oxidative Heck reaction has been described.[25] Under the reaction conditions, direct electrophilic palladation of the benzene ring occurs, followed by the catalyst regeneration on treatment with an oxidant — copper acetate.[33]



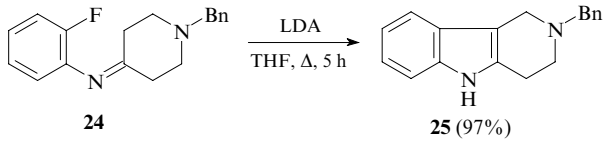
22 (52%)

The oxidative nucleophilic addition of *N*-methylpiperidin-4-one to 3-nitro-6-chloroaniline makes it possible, although in a low yield, to obtain 6-chloro-2-methyl-9-nitro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**23**)[34] which is difficult to access by other ways.



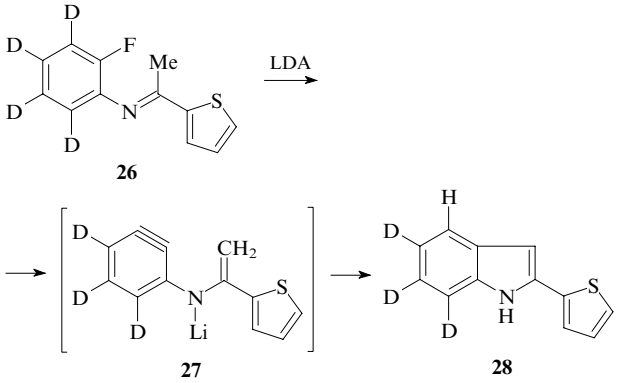
23 (27%)

The cyclization of 2-fluorophenylimine **24** occurring readily on treatment with 2.5 equivalents of lithium diisopropylamide (LDA) in boiling THF results in 2-benzyl-substituted THPI **25** in a nearly quantitative yield.[35]



24 **25** (97%)

By examining the conversion of tetradeutero-2-fluorophenylamine **26** in analogous conditions, it was established[35] that the reaction mechanism involves the formation of intermediate **27** of a dehydrobenzene structure. Indeed, the obtained indole **28** contained a hydrogen atom at position 4, which excludes the alternative mechanism, namely, the direct nucleophilic substitution of the fluorine atom in molecule **26**.



26 **27** **28**

c. The Nenitzescu reaction

Only one example of THPI synthesis by the Nenitzescu reaction is known.[36,37] It is the cyclocondensation of piperidin-4-one enol ethers with quinoneimine derivatives in the presence of Lewis acids, *viz*., the synthesis of 2,5,7,8-tetrasubstituted THPI **29** by the reaction of 2-methoxy-4-(*N*-phenylsulfonyl)-1,4-quinoneimine (**30**) with *N*-phenylsulfonylpiperidin-4-one enol methyl ether (**31**) in the presence of of Ti^{4+} salts (route *a*, Scheme 1).

It should be noted that upon catalysis with boron trifluoride etherate the mechanism of this reaction changes dramatically (route *b*, Scheme 1). In this case the only product, 2,6,8-trisubstituted 1,2,3,4-tetrahydrobenzo[4,5]-furo[3,2-*c*]pyridine **32**, is formed in a 85% yield. The distinct mechanisms are accounted for by non-identical coordination of Lewis acids to the quinoneimine **30**. Thus, the bidentate Ti^{4+} cation is coordinated with the carbonyl and methoxyl oxygen atoms (structure **33**), activating the C(5) atom of compound **30** for nucleophilic attack, whereas the monodentate boron binds to the more basic imine nitrogen atom (structure **34**), leading to the activation of the C(6) atom.

In our view, this example is of certain interest, albeit it does not reflect the potential of this method. Note that the methods discussed in sections II.1.a,b are focussed on the construction of an indole ring, while their possibilities in the directed synthesis of THPIs have not been studied in detail.

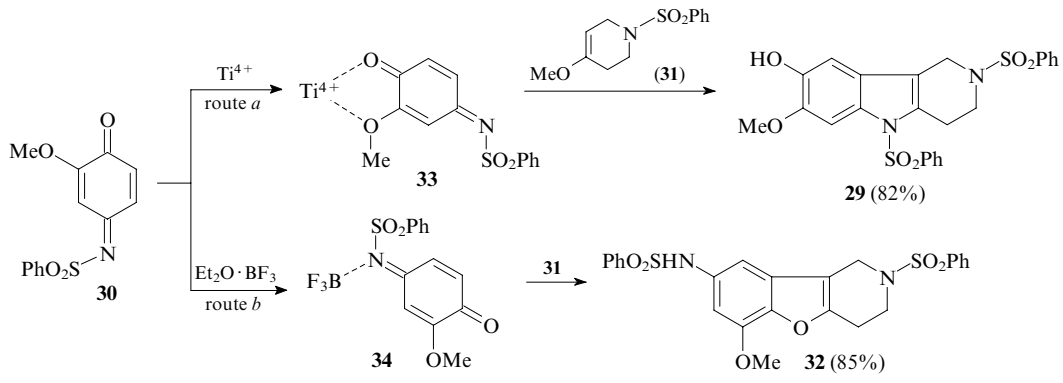
2. Syntheses based on substituted indoles to form a tetrahydropyridine ring

Known methods for the construction of the tetrahydro-1*H*-pyrido-[4,3-*b*]indole system based on indoles are distinguished by much greater diversity compared with the conversions of hydrazines and anilines, since they provide various options for the formation of the C−C and C−N bonds. Methods for the closure of the C(1)−C(9*b*), C(3)−C(4), and C(4)−C(4*a*) bonds as well as for the concerted formation of the C(1)−N(2) and C(1)−C(9*b*) bonds or the N(2)−C(3) and C(4)−C(4*a*) bonds have been reported.

a. Electrophilic substitutions in the pyrrole ring

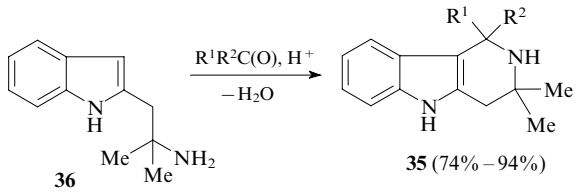
A high reactivity of pyrrole and its derivatives in electrophilic substitution reactions determines a wide application

Scheme 1



of these heterocycles in THPI syntheses. From this perspective the Pictet–Spengler and Friedel–Crafts reactions are of greatest interest, since these reactions enable heterocyclization at two different positions (2 and 3) of the indole molecule.

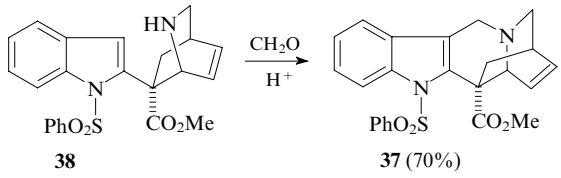
Condensation of aldehydes with 2-arylethylamines (substituted pyrroles in this case) in an acidic medium according to Pictet–Spengler [38–41] can be attributed to classical methods. As a rule, the reaction occurs under mild conditions in good-to-high yields and permits the preparation of sufficiently exotic heterocycles. For instance, useful synthons with free positions 2 and 5, 1,1,3,3-tetrasubstituted pyrido[3,4-*b*]indoles **35**, were obtained from 2-(1*H*-indol-2-yl)-1,1-dimethylethylamine (**36**) and carbonyl compounds.[40]



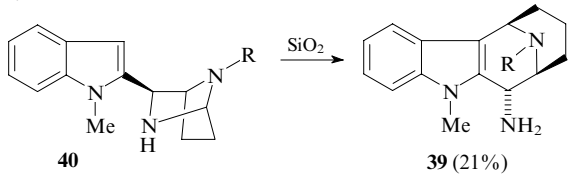
R^1 = H, Me, Et; R^2 = H, Me, Et, Ph, PhCH=CH, 4-HOC_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$.

The reaction takes place equally readily both in an acetate buffer (pH 4.7) at room temperature and on reflux of indole **36** hydrochloride solutions with aldehydes and ketones in a mixture of PhH–EtOH–H_2O.[40]

Of interest is the use [42] of the Pictet–Spengler reaction for the synthesis of THPI **37**, which is a structural analogue of indole alkaloids contained in the root of the African plant iboga (*Tabernanthe iboga* Baill). The azabicyclo[2.2.2]octene derivative **38** was employed as the starting compound.

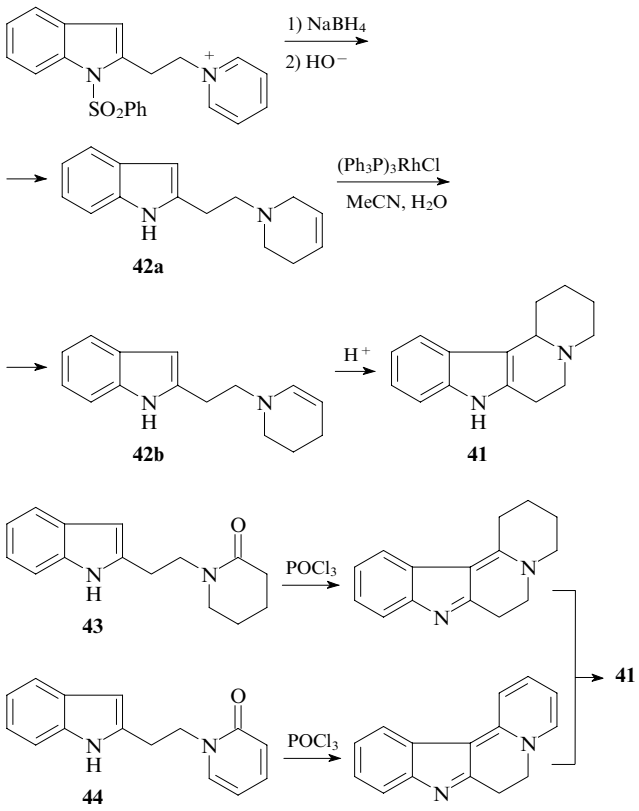


Structural rearrangements of indole-substituted aminals in an acidic medium also belong to the reactions under discussion. Thus, 'bridged' THPI **39** is formed in a small yield from aminal **40** already when applied to silica gel.[43] The optically active group R used for the diastereoselective synthesis of the aminal **40** can be removed by hydrogenation.

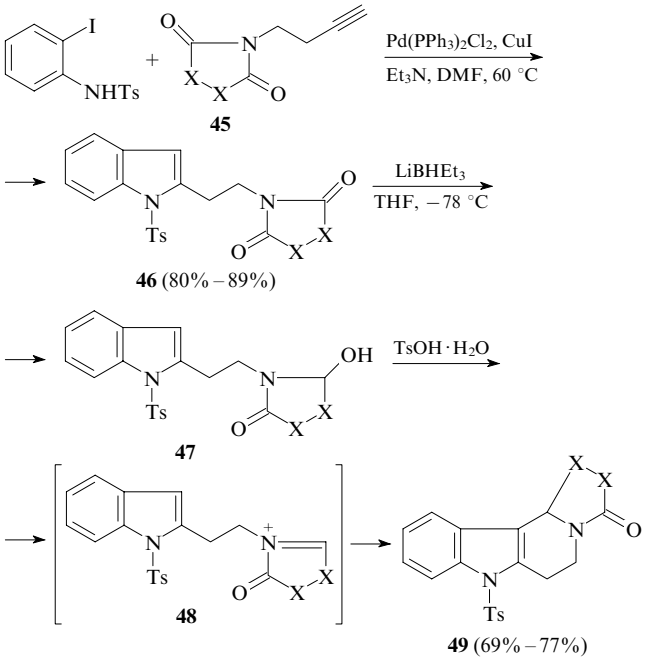


R = (*R*)-CH(Ph)CH_2OTBDMS (TBDMS is *tert*-butyldimethylsilyl).

A method of synthesis of a tetracyclic compound, 1,2,3,4,6,7,8,12*c*-octahydroindolo[3,2-*a*]quinolizine (**41**) from enamine **42b** has been proposed.[44] The latter was obtained by isomerization of cyclic allyl amine **42a** on a rhodium catalyst. Compound **41** can also be prepared on treatment of amide **43** and pyridone **44** with phosphorus oxychloride, followed by reduction of the formed 3-aminoalkylidene-3*H*-indoles with sodium borohydride.

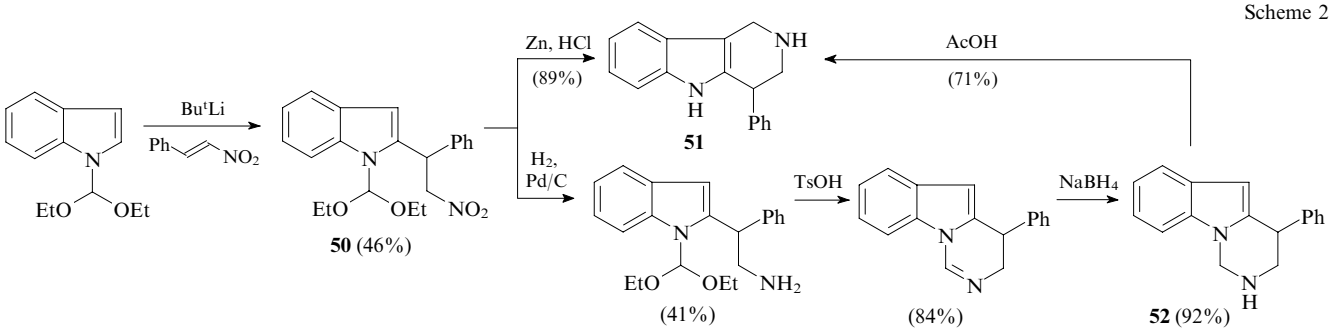


According to the publication,[45] THPI syntheses can proceed *via* the formation of acyl cations. Thus, indoles **46** were obtained from 2-iodo-*N*-(*p*-tolylsulfonyl)aniline and *N*-(but-3-ynyl)succinimides, -glutarimides and -phthalimides **45** by the Sonogashira reaction. For a partial reduction of the latter, lithium triethylborohydride ($LiBHEt_3$), known as 'superhydride', is employed. The heating of the obtained hydroxylactams **47** with $TsOH \cdot H_2O$ results in iminium intermediates **48**, which are converted to tetracyclic indoles **49** in good yields.



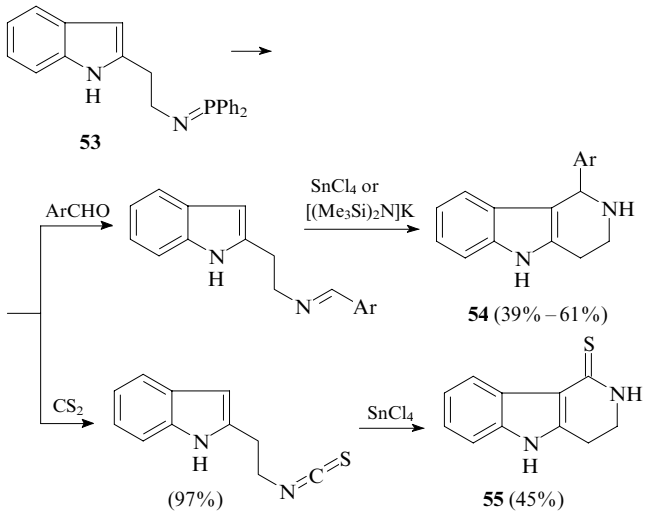
X–X = $(CH_2)_2$, $(CH_2)_3$, *o*-C_6H_4.

Scheme 2

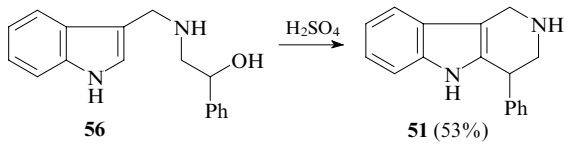


4-Phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**51**) was prepared by the reduction of 2-(2-nitroethyl)indole **50** in the Zn/H^+ system (Scheme 2).[46] As follows from the reaction scheme, the C(1) atom of the THPI **51** molecule was initially included in the acetal (diethoxymethyl) protecting group at the nitrogen atom of the starting indole **50**. Conversions of the compound **50** carried out under mild conditions permitted the isolation of the tetrahydropyrimido[1,6-*a*]indole **52** intermediate, which on treatment with AcOH undergoes a Pictet–Spengler rearrangement to THPI **51**.

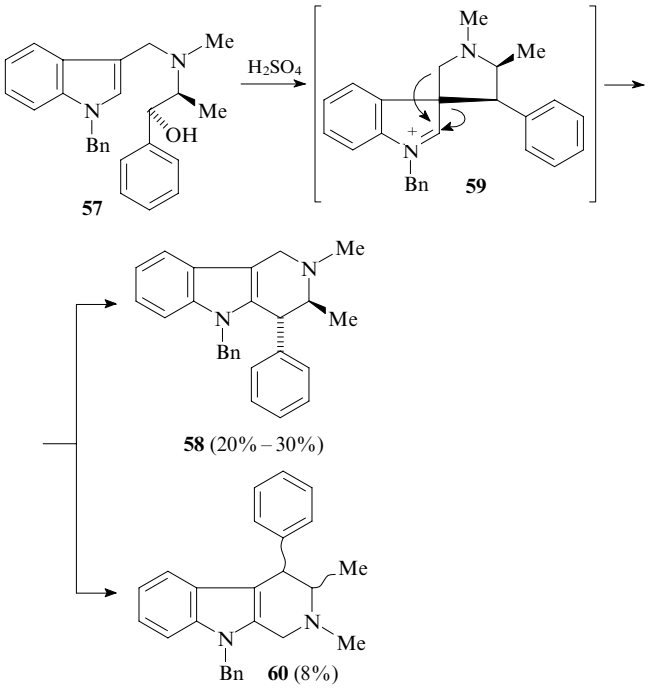
A reaction of iminophosphorane **53** with aldehydes was described,[47] leading to aldimines, which further cyclize to 1-aryl-2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indoles **54** in an acidic or basic medium *via* the Pictet–Spengler reaction mechanism. With carbon disulfide, indole **53** forms the corresponding isothiocyanate undergoing a Friedel–Crafts cyclization to 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-1-thione **55**. In both cases the product yields are moderate.



The involvement of readily available (by the Mannich reaction) indol-3-ylmethylaminoethanol **56** in the Friedel–Crafts cyclization allows[48] the preparation of 4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**51**) in a moderate yield.

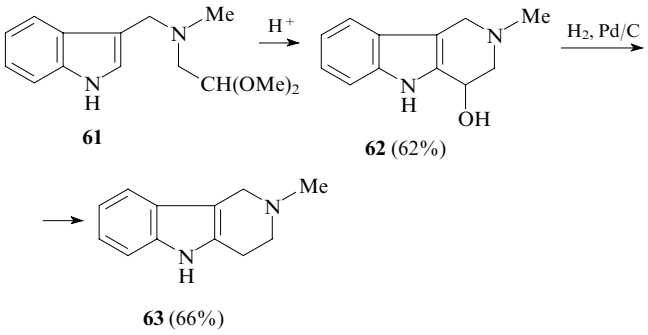


The cyclization of ephedrine derivative **57** to product **58** occurs with the retention of the configuration of the carbon attached to the phenyl substituent,[49] although, at first glance, the configuration of this atom must have undergone changes regardless of the reaction mechanism (S_N1 or S_N2).



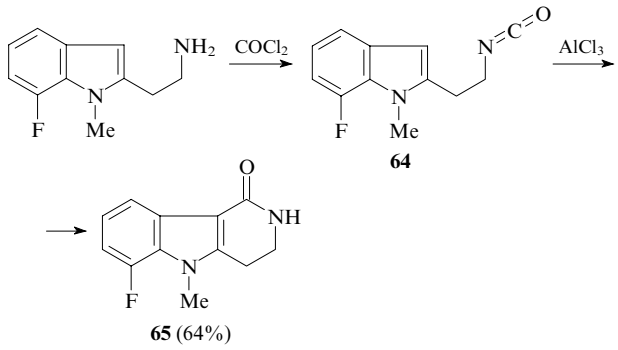
The reaction is supposed to occur *via* the formation of spirocyclic transition state **59** with two inversions: the more nucleophilic C atom at position 3 of indole **57** reacts first, subsequently a stereoselective reaction at position 2 takes place. As evident from the scheme, the opening of the spirocyclic intermediate **59** can occur not only at the C–Ph fragment, but also at the C–N one. In the latter case β-carboline **60** is formed. The isolation and identification of this by-product served as a proof of the suggested reaction mechanism.[49] Note that the yields of the major product and by-product are small (8%–30%), which, apparently, provides space also for other hypotheses about the reaction mechanism.

Mannich base **61** obtained from aminoacetaldehyde acetal easily cyclizes to 4-hydroxy-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**62**) in a dilute HCl, which is further reduced to 2-methyl derivative **63**.[50]



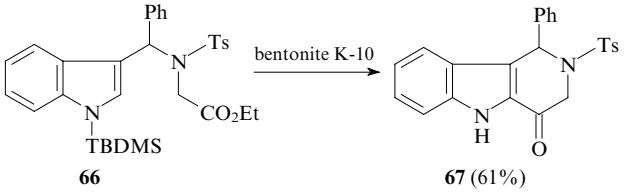
61 **62** (62%) **63** (66%)

For the construction of a THPI heterocyclic scaffold isocyanate **64** can also be used. When treated with $AlCl_3$ it cyclizes to 6-fluoro-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-one (**65**).[25]



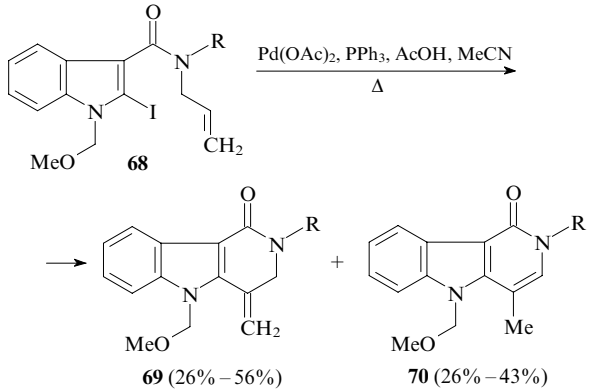
64 **65** (64%)

Compound **66** protected at position 1 with a *tert*-butyldimethylsilyl group cyclized to 1-phenyl-2-toluenesulfonyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-4-one (**67**) on bentonite clay.[51]



66 **67** (61%)

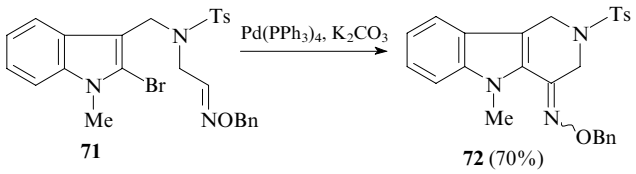
A wide use of homogeneous catalysts containing Group VIII metals of the Periodic system in the synthesis of a variety of heterocyclic compounds could not miss THPI derivatives. For instance, the Heck cyclization of allylamides **68** appears to be a promising approach to THPI synthesis, despite the fact that target products **69** partially isomerize to more stable pyridones **70** under these conditions.[52]



68 **69** (26% – 56%) **70** (26% – 43%)

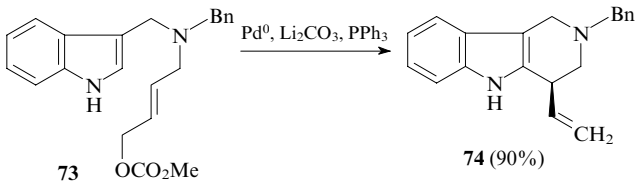
R = H, Me, All, Ph.

It is reported[53] that the replacement of the allylamides **68** with oxime ethers of the **71** type enables one to avoid the isomerization described above. Thus, on long reflux (48 h) of compound **71** in dioxane pyridoindole **72** was obtained (*E*/*Z*-isomer ratio is 30 : 70).



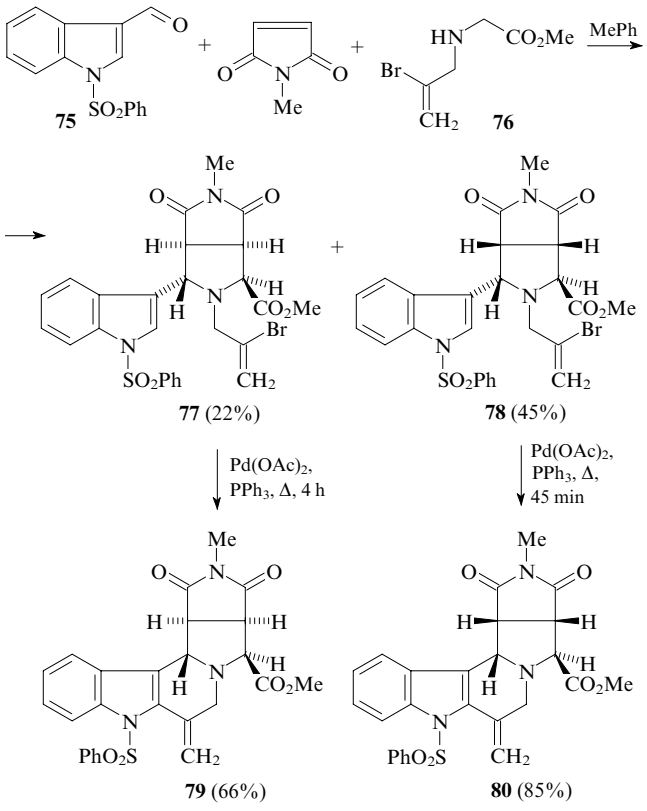
71 **72** (70%)

An advantage of organometallic catalysis is the possibility of a stereoselective reaction, which has a particular significance in the preparation of analogues of natural alkaloids. Such an approach proved successful[54] for the intramolecular cyclization of indole **73** to chiral 2-benzyl-4-vinyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**74**) in a high yield and with 93% enantiomeric purity.



73 **74** (90%)

An example of the construction of a piperidine ring *via* intramolecular cyclization of vinyl halides in the presence of $Pd(OAc)_2$ has been reported.[55] The process can be performed 'one-pot', following 1,3-dipolar cycloaddition. Thus, 1-phenylsulfonyl-1*H*-indole-3-carbaldehyde (**75**) reacts with *N*-substituted glycine ester **76** and *N*-methylmaleimide in refluxing toluene (15 h) to form a mixture of isomers **77** and **78** (in a ratio of 1 : 2), which were separated



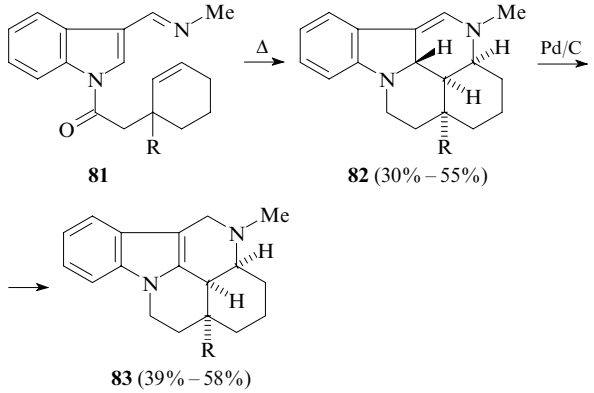
75 **76** **77** (22%) **78** (45%) **79** (66%) **80** (85%)

by chromatography. On heating in MeCN in the presence of Pd^{2+}, compounds **77** and **78** are converted to THPIs **79** and **80**, respectively.

b. Formation of the pyrido[4,3-*b*]indole system as a result of cycloaddition reactions

Synthesis methods for some polycyclic compounds containing a THPI core include cycloaddition reactions.

The intramolecular Diels–Alder reaction of 3-formimidoylindoles **81** permits the preparation of compound **82** in moderate yields.[56] The latter isomerizes to pentacyclic THPIs **83** with a loss of one of the chiral centres.

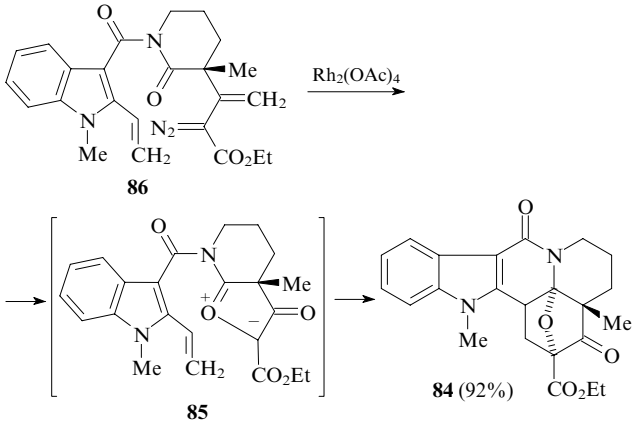


81 **82** (30% – 55%)

83 (39% – 58%)

R = Me, Et.

Aside from [4 + 2]-cycloaddition reactions a synthesis of THPI **84** by [3 + 2]-bipolar addition was described.[57] Zwitterion **85** results from diazo ester **86** *via* the formation of a rhodium complex and cyclizes to pentacycle **84**. The reaction is carried out in benzene at room temperature for 72 h, The product **84** was obtained in a high yield upon chromatographic purification.



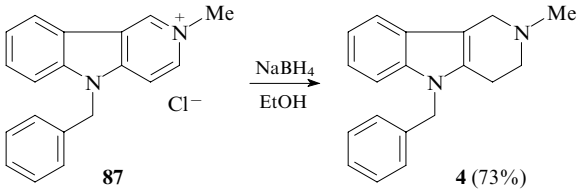
86

85 **84** (92%)

Undoubtedly, the methods discussed in this section are on the whole much more complex and laborious compared with the 'assembly' of the tetrahydropyrido[4,3-*b*]indole nucleus from indoles. For this reason preference is commonly given to the Fischer syntheses of THPIs, while the cycloadditions are employed if a rearrangement occurs in a low yield.

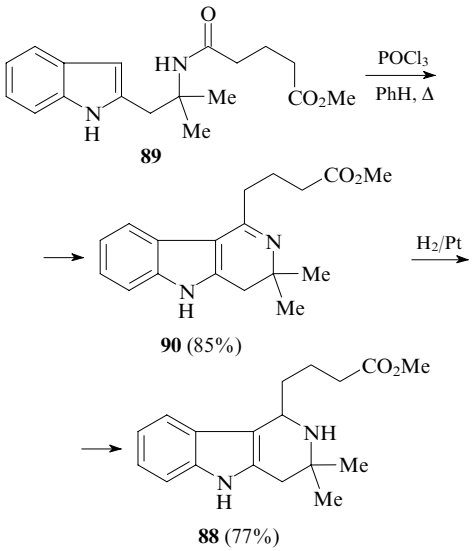
3. Reduction of the pyridine nucleus in pyrido[4,3-*b*]indoles

Reduction of the pyridine nucleus in the corresponding γ-carboline molecule is a convenient route to various THPIs from their aromatic analogues. 2-Alkylcarbolinium **87** salts are reduced especially easily and in good yields.[58] This approach was successfully applied to the synthesis of the drug Diazolinel (**4**).[59]



87 **4** (73%)

Reduction of dihydrocarbolines is often the final stage of a THPI synthesis. For example, compound **88** is prepared by the Bischler–Napieralski cyclodehydration of indole **89,** followed by hydrogenation of the dihydro-γ-carboline **90** formed.[60]

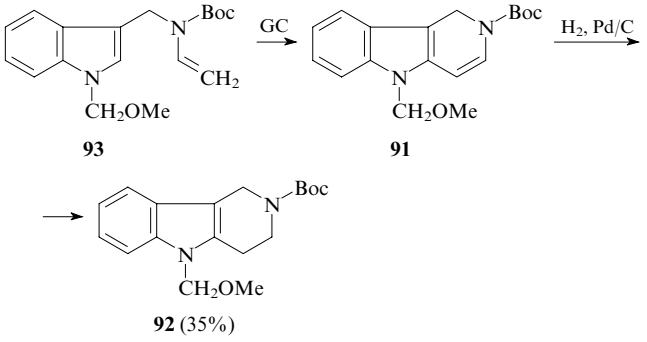


89

90 (85%)

88 (77%)

Similarly the reduction of 2,5-dihydropyridoindole **91** to 2-*tert*-butoxycarbonyl-5-methoxymethyl-2,3,4,5-tetrahydropyrido[4,3-*b*]indole **92** was accomplished.[61] Compound **91** is synthesized from indole **93** by a metathesis reaction in the presence of Grubbs' ruthenium catalysts (GC) that tolerate a wide range of functional groups under these conditions.



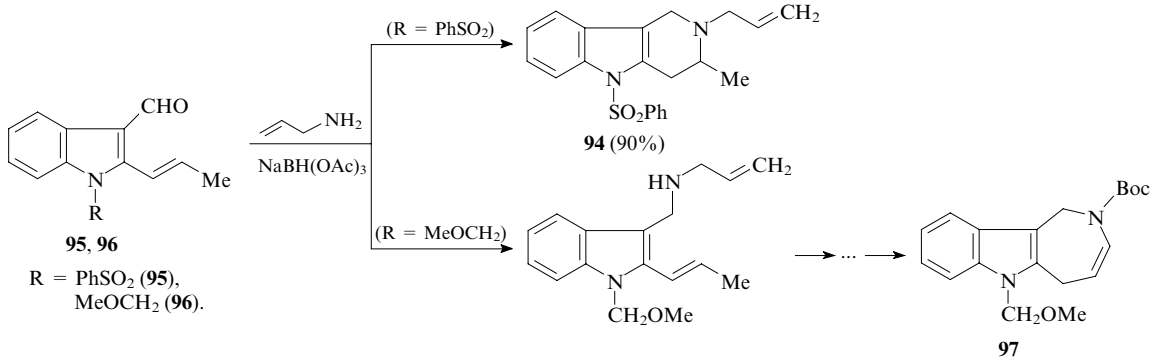
93 **91**

92 (35%)

Boc is *tert*-butyloxycarbonyl.

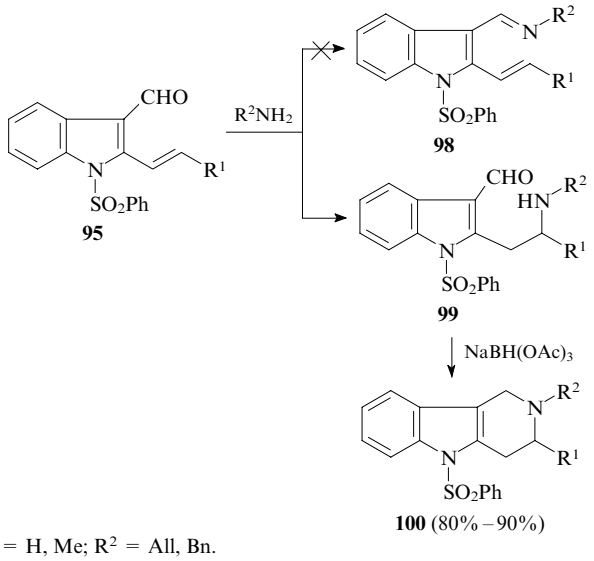
A synthesis of THPI **94** was reported [62] as an unexpected product of the reductive amination of 2-propenylindole-3-carbaldehyde **95**. In the classical variant the reductive amination of *N*-methoxymethyl-2-propenylindole-3-carb-

Scheme 3



aldehyde **96** with allylamine after subsequent transformations results in a metathesis product, 1,2,5,6-tetrahydroazepino[4,3-*b*]indole **97**. However upon replacement of the *N*-methoxymethyl protective group with *N*-phenylsulfonyl, 2-allyl-3-methyl-5-phenylsulfonyl-2,3,4,5-tetrahydropyrido[4,3-*b*]indole (**94**) is produced in a high yield (Scheme 3).

An examination of the reaction discussed [62] allowed the initial hypothesis about the intermediate formation of an azomethine of the **98** type to be excluded. Since the *N*-phenylsulfonyl group in indoles **95** decreases electron density on the adjacent vinyl group, the competitive Michael reaction becomes predominating. The latter yields exclusively indoles **99**, which, in their turn, cyclize to THPI **100** by an intramolecular reductive amination mechanism.

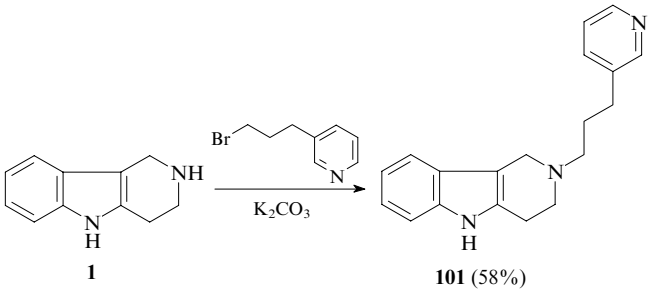


R^1 = H, Me; R^2 = All, Bn.

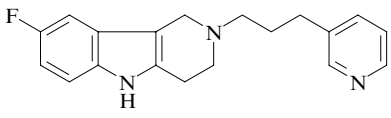
4. Reactions at nitrogen atoms in 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles

a. Reactions at the N(2) atom

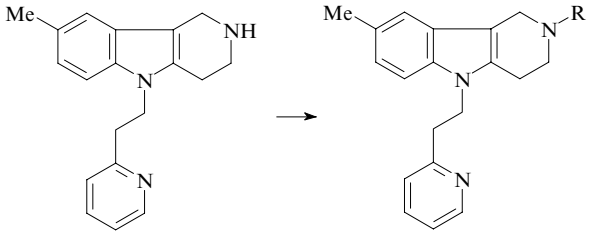
In the molecule of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indole the nitrogen atom at position 2 readily undergoes conversions that typify secondary amines, including alkylation by a host of alkyl halides.[63] Thus, the alkylation of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole (**1**) with 3-(3-bromopropyl)pyridine resulted [48] in 2-[3-(pyridin-3-yl)propyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole (**101**).

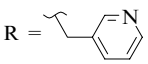
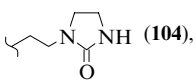


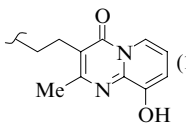
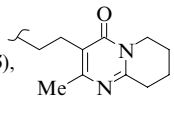
The compound **101** is a close analogue of the antipsychotic drug Gevotroline (**102**) bearing a fluorine atom at position 8.



Other examples of alkylation products can be THPIs **103**–**106**. The reaction of starting THPI **107** with the corresponding alkyl halides in DMF on treatment with K_2CO_3 occurs in good yields.[64]

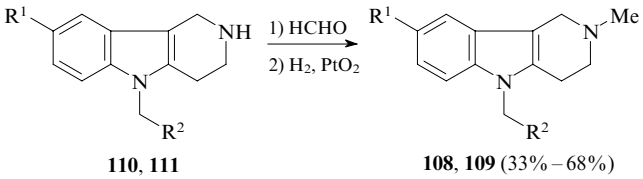


R =  (**103**),  (**104**),

 (**105**),  (**106**).

Alkylation at position 2 of THPIs is easiliy accomplished by reductive amination of aliphatic and aromatic aldehydes and ketones. For instance, 2-methyl substituted THPIs **108**, **109** were prepared in moderate-to-good overall yields on treatment of the corresponding THPIs **110**, **111**

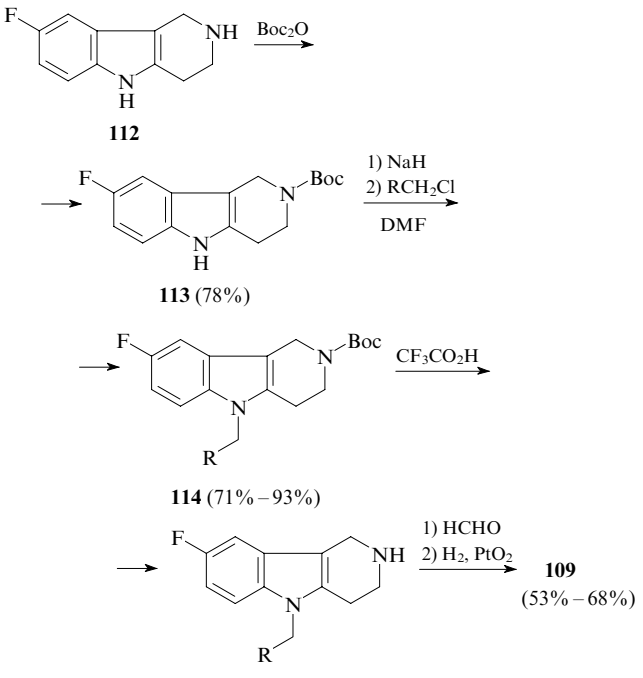
with formaldehyde, followed by *in situ* catalytic reduction of intermediate 2-hydroxymethyl derivatives.[11, 18]



110, **111** **108**, **109** (33% – 68%)

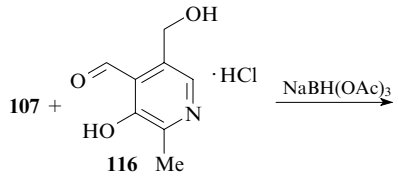
R^1 = H (**108**, **110**): R^2 = Ph, 2-Py, 3-Py, 4-Py;
R^1 = F (**109**, **111**): R^2 = Ph, 2-Py, 3-Py, 4-Py, EtO_2C, 4-$EtO_2CC_6H_4$.

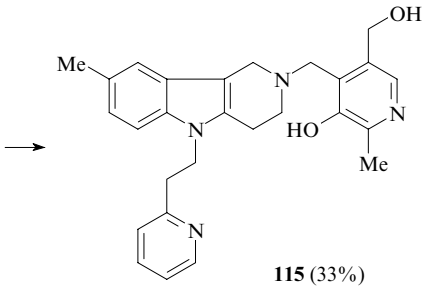
2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indoles are easily acylated at the N(2) atom,[8, 65] including the formation of Boc-derivatives.[11, 18] This reaction is very convenient for subsequent introduction of substituents to positions 2 and 5 of the heterocycle. For example, when preparing 2-methyl-8-fluoropyridoindoles **109** the starting 8-fluoro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indole (**113**) is converted to Boc-derivative **114**, which is then alkylated with alkyl halides in the presence of NaH. After unmasking the Boc-protective group in urethanes **111** the secondary amino group is methylated.[11, 18]



R = Ph, 2-Py, 3-Py, 4-Py, EtO_2C, 4-$EtO_2CC_6H_4$.

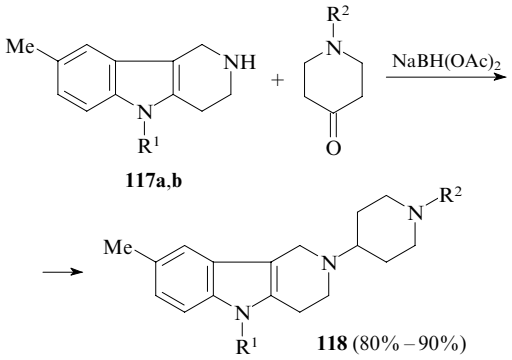
Reductive amination of aromatic aldehydes can also be carried out 'one-pot'. Thus, the synthesis of THPI **115** comprises several conversions. First, 5-pyridylethylated tetrahdyropyridoindole **107** is brought into reaction with 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carbaldehyde hydrochloride (**116**), then the intermediate being formed is reduced *in situ* to product **115**.[64]





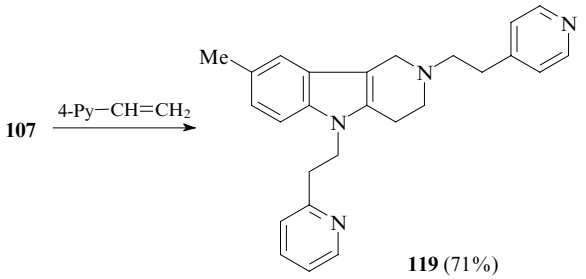
115 (33%)

'One-pot'-reaction of compounds **117a**,**b** and *N*-substituted piperidin-4-one results in 2,5,8-trisubstituted THPIs **118** in high overall yields.[64, 66 – 69]

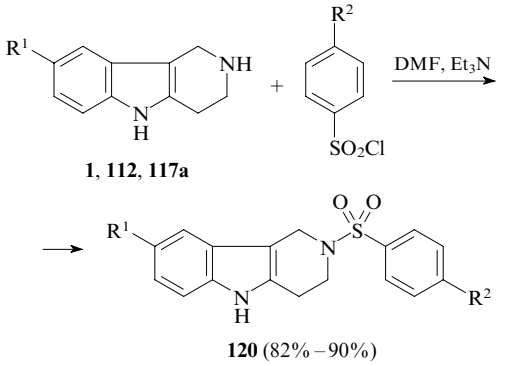


R^1 = H (**117a**), Ts (**117b**); R^2 = Me, Boc.

Pyridoindole **107** protected at position 5 can be brought into a 2-pyridylethylation reaction.[64] A long reflux of compound **107** with 4-vinylpyridine in a mixture of AcOH and EtOH gives 8-methyl-[2-(4-pyridyl)ethyl]-5-[2-(pyridyl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**119**).



Tetrahydropyridoindoles **1** (R^1 = H), **112** (R^1 = F) and **117a** (R^1 = Me) quickly (in 30 min) react at room temperature with sulfonyl chlorides, producing THPIs **120** in high yields.[67]

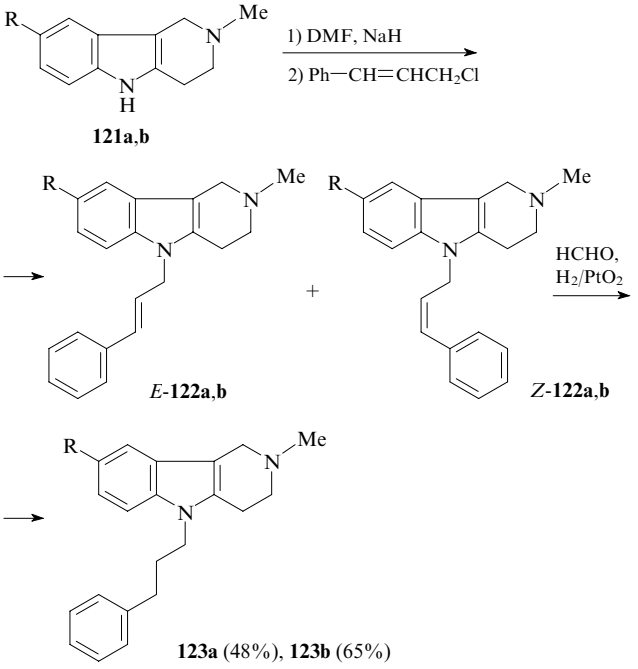


R^1, R^2 = H, Me, F.

b. Reactions at the N(5) atom

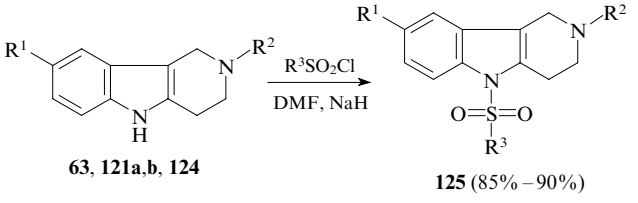
Alkylation of the indole nitrogen in THPIs occurs smoothly when treated with NaH at room temperature. The alkylation products, as a rule, are formed in good yields.[69]

E and *Z* isomers of 2-methyl-5-(3-phenylallyl)-2,3,4,5-tetradydro-1*H*-pyrido[4,3-*b*]indoles **122a**,**b** were obtained by a long-lasting alkylation of indolyl-anions produced on treatment of compounds **121a**,**b** with NaH in DMF by cinnamyl chloride. The hydrogenation of the latter leads to 2-methyl-5-(3-phenylpropyl) derivatives **123a**,**b**.[70]



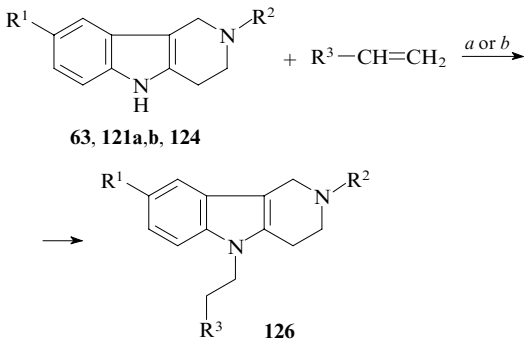
R = Me (**a**), F (**b**).

Sulfonyl chlorides already at 20 °C substitute[66] the hydrogen atom at position 5 of compounds **63** (R^1 = H, R^2 = Me), **121a**,**b** [R^2 = Me: R^1 = Me (**a**), F (**b**)] and **124** rapidly giving 5-sulfonyl-THPI **125** in high yields.



R^1 = H, Me, F, Br, $PhSO_2$; R^2 = Me, Boc, 1-methylpiperidin-4-yl, 1-Boc-piperidin-4-yl; R^3 = Ph, 4-MeC_6H_4.

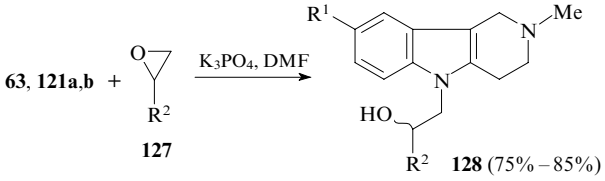
Pyridylethylation of THPIs at the indole nitrogen proceeds smoothly enough if position 2 of the molecule is protected. A variety of 5-(2-pyridylethyl)tetrahydropyridoindole **126** derivatives were obtained by reaction of vinylpyridines with compounds **63** (R^1 = H, R^2 = Me), **121a**,**b** [R^2 = Me: R^1 = Me (**a**), F (**b**)] and **124** catalyzed by metallic Na or NaH (5–15 h, the yields being 10%–55%). The process is performed particularly easily and in high (62%–85%) product yields in the biphasic system DMSO–60% aqueous KOH in the presence of tetrabutylammonium sulfate (TBAS) as a phase-transfer catalyst.[64, 67, 68, 71]



(*a*) Na, EtONa or NaH, DMSO (yields 10%–55%);
(*b*) KOH, DMSO, H_2O, $(Bu^n_4N)_2SO_4$ (yields 62%–85%);
R^1 = H, Me, F, Br, F_3C, HO_2C, MeO; R^2 = Me, Boc, 1-piperidin-4-yl, 4-$MeC_6H_4SO_2$, 4-$FC_6H_4SO_2$; R^3 = 2-Py, 3-Py, 4-Py, 6-methylpyridin-3-yl, pyrazin-2-yl.

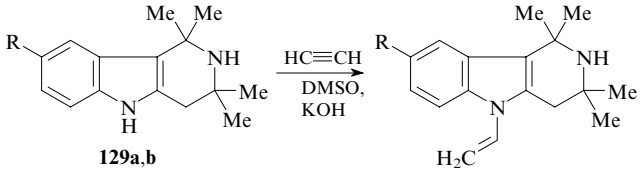
An analogous reaction of pyridoindoles **63** (R^1 = H, R^2 = Me), **124** with ethyl acrylate results in THPI **126** (R^3 = CO_2Et).[18, 67]

When treated with propylene oxide or styrene oxide (**127**), compounds **63** (R^1 = H) and **121a**,**b** (R^1 = Me, F) are readily converted to the corresponding 5-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **128**.[70]



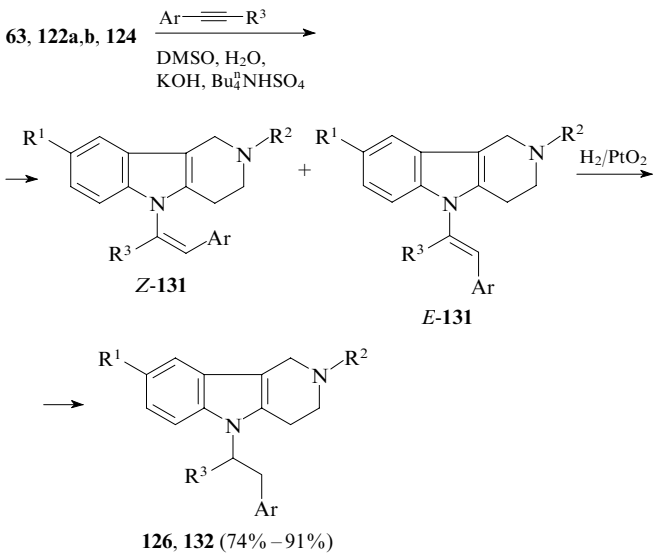
R^1 = H (**63**), Me (**121a**), F (**121b**); R^2 = Ph, Me.

Addition of pyrido[3,4-*b*]indoles **129a**,**b** to acetylene in a superbasic medium to produce 5-vinyl THPI derivatives **130a**,**b** in high yields is also reported.[72] The N(2) atom bearing no substituent is not involed in the reaction, obviously, due to sterical hindrance.



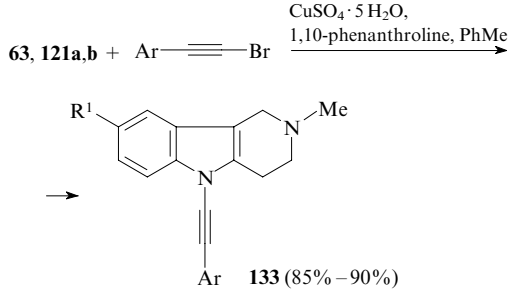
R = H (**a**), Me (**b**).

Mixtures of *E* and *Z* isomers of 5-vinyl derivatives **131** were prepared in medium-to-high yields upon reaction of compounds **63** (R^1 = H, R^2 = Me), **121a**,**b** [R^2 = Me: R^1 = Me (**a**), F (**b**)] and **124** with aryl- and hetarylacetylenes in the system DMSO–60% KOH in the presence of TBAS as a catalyst (the overall yields are 65%–80%). Further hydrogenation leads to 5-(2-arylethyl)tetrahydropyridoindoles **126** (R^3 = H) and **132** (R^3 = Me).[67, 73, 74]



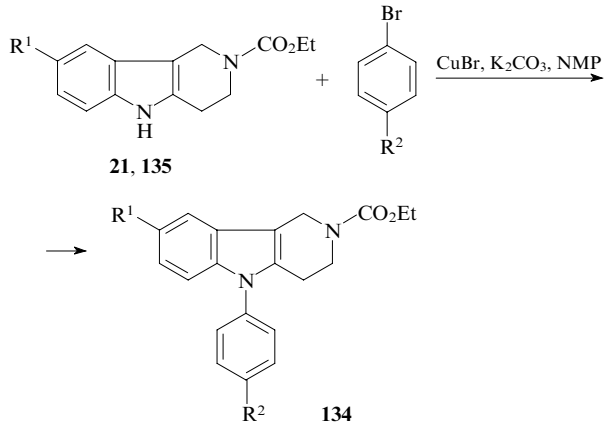
R^1 = H, Me, MeO, F, F_3C; R^2 = Me, 4-$MeC_6H_4SO_2$; R^3 = H, Me;
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$F_3CC_6H_4$, 2-Py, 3-Py, 4-Py.

Recently the preparation of 5-ethynylpyridoindoles **133** by reactions of compounds **63** (R = H) and **121a**,**b** (R = Me, F) with bromoethynylbenzene [70] and 3-(bromoethynyl)pyridine [74] in PhMe occurring in the presence of $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline was reported.



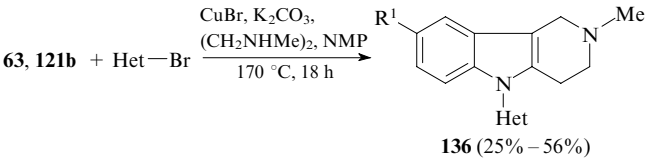
R = H, Me, F; Ar = Ph, 3-Py.

The Ullmann reaction [20, 65, 75] turned out to be a convenient method for the synthesis of THPIs **134**. The interaction of compounds **21** (R^1 = H) and **135** (R^1 = F) with bromobenzene and its 4-fluoro derivative is conducted in *N*-methylpyrrolidone (NMP) at 200 °C in the presence of CuBr and K_2CO_3 in conditions that are typical for this reaction.



R^1 = H, F, Cl, Br, Me, MeO; R^2 = H, F.

In an analogous way compounds **136** were obtained from pyridoindoles **63**, **121b** and bromazines in low-to-moderate yields.[74]



R^1 = H (**63**), F (**121b**); Het = 2-Py, 3-Py, 4-Py, pyrimidin-5-yl.

5. Substituent modifications in and subtitution reactions of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles

Modification of substituents in a THPI molecule is one of the most widespread methods for the synthesis of various derivatives. In most cases such reactions occur readily and in good yields. In this way many compounds that are difficult to access were obtained.

An illustrative example of the effective modification of an ester group in THPIs is the conversion of 8-substituted ethyl 3-(2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-5-yl)propionates **137** to the corresponding acids (**138**), benzyl esters (**139**) and amides (**140** – **142**) (Scheme 4).[18]

First, from ethyl esters **137**, acids **138** were prepared in high yields, which were further derivatized to benzyl esters **139**, using the *N*-hydroxybenzotriazolecarbodiimide activation of the carboxyl group. Amide **140** (R^1 = F) was obtained by aminolysis of the corresponding ester **137** with methylamine, whereas amides **141** were prepared by condensation of acids **138** with amines in the presence of a condensing agent, the nature of which considerably affected the product yields. Acid **142** is produced upon alkaline hydrolysis of the corresponding amide. With isolated exceptions the yields of the desired tetrahydropyrido[3,4-*b*]indoles are medium to high, despite the relatively long (12 – 24 h) duration of the majority of the processes under discussion.

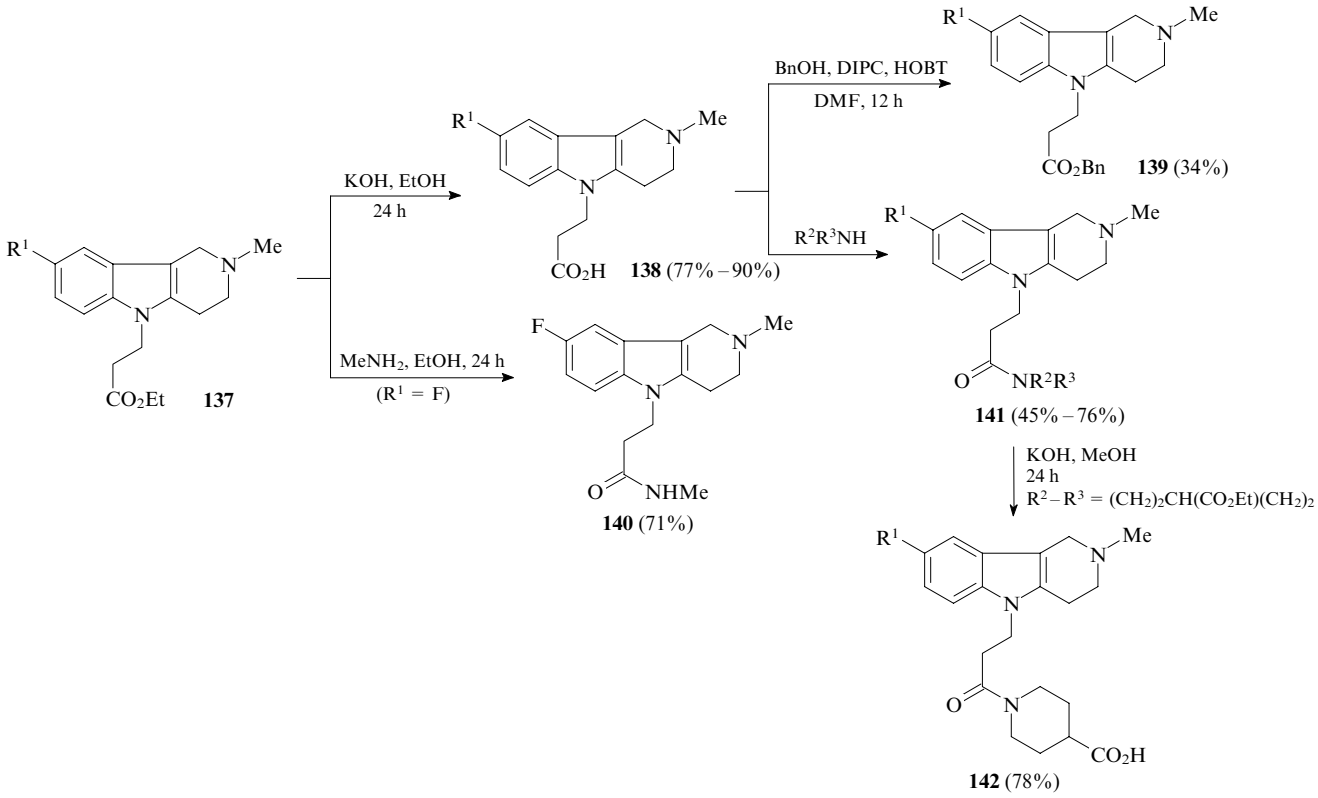
A possibility of the modification of the sulfo group in THPIs **143** with free position 2 have been demonstrated [76] (Scheme 5). The authors synthesized the corresponding sulfonyl chlorides (**144**), sulfinic acid (**145**), sulfonamides (**146**) and sulfones (**147**).

The sulfonic acids **143** react with $POCl_3$ in sulfolane to form the target sulfonyl chlorides **144** in high yields. The compounds **144** were isolated and used for further conversions as hydrogen sulfates. Their reactions with secondary amines at room temperature rapidly yield sulfonamides **146**. Upon reduction of the sulfonyl chloride **144** (R = Me) with Na_2SO_3 in the presence of $NaHCO_3$ as a relatively weak base, 2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-sulfinic acid **145** was obtained. Using a strong base (for example, NaOH) the hydrolysis of the sulfonyl chlorides **144** to the sulfonic acids **143** becomes the predominating reaction.

Crude sulfinic acid **145** (the purity being 80% – 85%, the impurities being exclusively inorganic salts) served as the starting compound in a CuI-catalyzed coupling with aryl and hetaryl iodides, resulting in sulfones **147** in small yields.

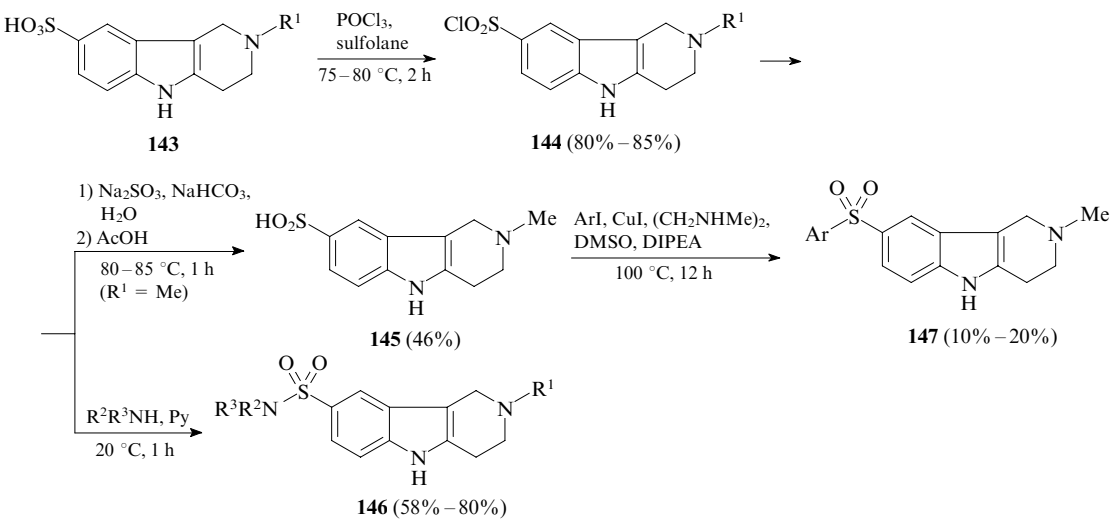
8-Sulfonyl THPI derivatives can be obtained not only by the Fischer reaction, but also by nucleophilic substitution of the bromine atom in the aromatic ring, catalyzed by Cu(I) salts. In this way 8-bromo-THPI **148** when treated with a salt of sulfinic acid is converted to 8-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indole **149** (Scheme 6).[6]

Scheme 4



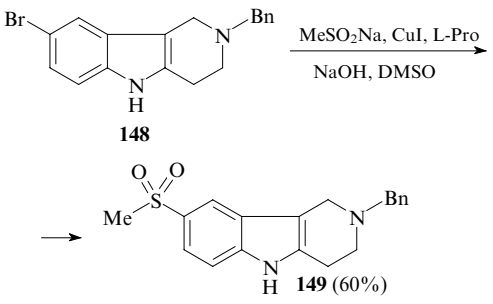
R^1 = H, Me, F, F_3C, MeO; R^2, R^3 = H, Me; $R^2–R^3$ = $(CH_2)_2CH(CO_2Et)(CH_2)_2$, $(CH_2)CH(CO_2Et)(CH_2)_3$;
DIPC is diisopropyl carbodiimide, HOBT is *N*-hydroxybenzotriazole.

Scheme 5



R^1 = Me, Bn; R^2 = Me, 3-FC_6H_4; R^3 = H, Me; $R^1–R^2$ = $(CH_2)N(Me)(CH_2)_2$; Ar = Ph, 3-FC_6H_4, 3-Py, 4-Py; DIPEA is diisopropyl(ethyl)amine.

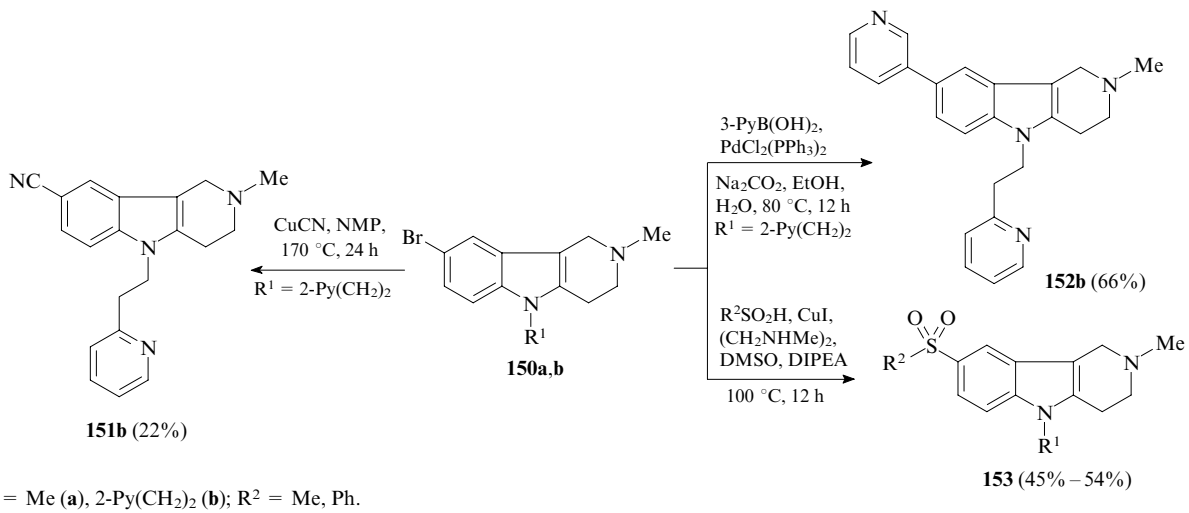
Scheme 6



Substitution of the Br atom in position 8 of compounds **150a**,**b** yielded 8-cyano- (**151b**), 8-pyridin-3-yl- (**152b**) and 8-methyl(aryl)sulfonyl derivatives (**153a**,**b**) (Scheme 7).[68]

Nitrile **151b** was synthesized on treatment of bromide **150b** with copper cyanide in NMP at 170 °C. A The reaction of THPI **150b** with 3-dihydroxyboranylpyridine in the presence of a palladium catalyst in an alkaline aqueous-alcoholic medium leads to THPI **152b**. In conditions that are analogous to those described above (see Scheme 1), the reaction of bromides **150a**,**b** with 4-substituted sulfinic acids

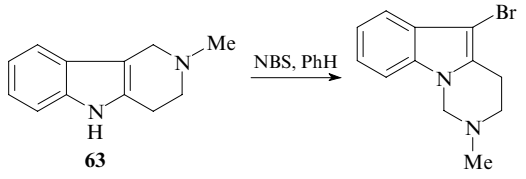
Scheme 7



R^1 = Me (**a**), 2-Py$(CH_2)_2$ (**b**); R^2 = Me, Ph.

results in 8-substituted diaryl sulfones **153a**,**b**. The authors [68] substantially broadened the battery of 8-bromo-THPIs available *via* the Fischer reaction that are employed for the synthesis of a variety of 8-functional derivatives.

This is particularly important since preceding attempts to accomplish an aromatic electrophilic substitution in THPIs (in contrast to the other indoles) resulted exclusively in tetrahydropyridine moiety destruction products. Until now examples of a successful nitration of such compounds are unknown, whereas on bromination of 2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**63**) with *N*-bromosuccinimide (NBS) the attack occurs exclusively at position 9*b* and after recyclization gives 5-bromo-2-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]indole (**154**).[77]



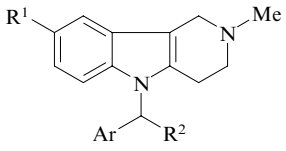
III. Physiological activity of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles

For more than 60 years now 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles have been the focus of attention of medicinal and pharmaceutical chemists, first of all owing to their antihistamine,[21,78–84] antidopaminergic [75,81] and antiserotonergic [18,48,82] actions. Antiallergic remedies,[21,78,79] neuroleptics,[12,75,81] drugs for treatment Alzheimer's [83,84] and Huntington's [85] diseases were developed based on these compounds. Among THPI derivatives, angiogenesis inhibitors were found, which can be useful in the treatment of malignant tumors, diabetic retinopathy, *etc*.[86,87] In addition, these compounds exhibit analgesic,[15] antiinflammatory,[88] local anaesthetic,[89] antidepressant,[90] antibacterial [65] effects, *etc*.

1. Antiallergic properties

The quest for novel antiallergic drugs in the mid-1950s led researchers at Bayer AG to 5-substituted 2-methyl-2,3,4,5–tetrahydro-1*H*-pyrido[4,3-b]indoles. It turned out that such compounds are highly effective H_1-histamine receptor antagonists.[21,78,79] For instance, Diazoline (synonyms Diazolin, Diazolinum, Incidal, Mebhydrolin, Mebhydrolini Napadisylas, Omeril, Bexidal, Fabahistin, *etc*.), being 5-benzyl-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole naphthalene-1,5-disulfonate, nowadays still finds application in medical practice for the treatment of a wide range of allergic diseases.[91]

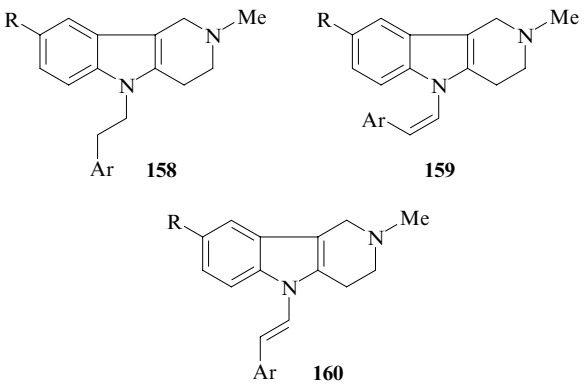
More detailed studies revealed [7,76,88,89] that in the series of compounds **155**–**157** 5-benzyl derivatives with R^1 = H, Me, F, Cl possess maximal antihistamine properties, while 5-benzyl-8-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole hydrochloride **157** (R^1 = F, R^2 = H, Ar = Ph) is not inferior to Diazoline in potency [the inhibition constants (IC_{50}) are 22 and 27 nmol litre^{-1}, respectively [11,92–94]].



155–**157**

155: R^1 = H, Cl, Br; R^2 = H; Ar = Ph, 4-MeOC_6H_4, 4-ClC_6H_4, 2-Py, Bn;
156: R^1 = H, Me, Cl, Br; R^2 = H, Me; Ar = 2-Py, 3-Py, 6-Me-3-Py, 4-Py;
157: R^1 = F, F_3C; R^2 = H; Ar = Ph, 2-Py, 3-Py, 4-Py.

The research showed that in order to manifest antihistamine activity, compounds of the THPI series must have a bulky substituent at the indole nitrogen atom. Indeed, 5-(2-arylethyl)- (**158**) [68,73,74,95,96] and 5-(2-arylvinyl)tetrahydropyrido[4,3-*b*]indoles (**159**, **160**) [73,75] proved highly efficacious H_1-receptor (H_1-R) antagonists. Among them compound **158** (R^1 = Cl, Ar is 6-methylpyridin-3-yl) and 2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole dihydrochloride (**3**) should be distinguished as the known pharmaceuticals Dorastine and Dimebon. The latter is the most potent compound in the series of the indoles of the type **158**. This is a unique drug used today as an H_1-histamine receptor blocker.[65]



158 **159** **160**

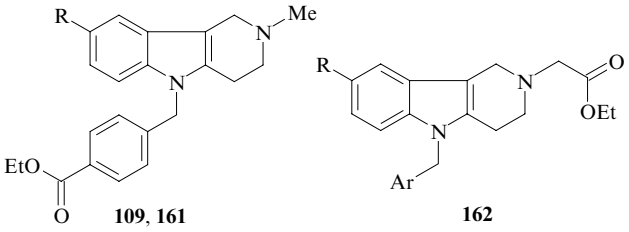
R = H, Cl, F, F_3C, Me, MeO, Ar, Het.

According to Mashkovskii,[91] Dimebon exerts antiserotonergic, anticholinergic, local anaesthetic and sedative effects, prevents the development of anaphylactic shock, reduces itching, the intensity of local exudative manifestations, and vascular permeability. The drug is practiced in the therapy of acute allergic reactions, pollinoses, hives, hay fever, food allergy, cosmetic and drug allergies, Quincke's edema, *etc*.

It is noteworthy that among THPIs bearing an arylalkyl substituent at the indole nitrogen, compounds with a methylene bridge between the indole nitrogen atom and the aryl substituent (**155**–**157**)[11,80,92,93] exert the greatest antihistamine effect, whereas among THPIs with a pyridinealkyl substituent, compounds with a $(CH_2)_2$ unit (**158**)[68,73,74] exhibit the greatest potency.

It should be noted that in the case of unsaturated analogues only the *Z* isomers **159** exert an apparent antihistamine action, whereas the *E* isomers **160** possess no noticeable acivity.[73] THPIs, in which an aryl fragment is attached to the indole nitrogen atom directly or *via* an acetylene unit, proved also inactive.[75]

THPIs **109** (R^1 = F, R^2 = 4-$EtO_2CC_6H_4$), **137**, **161** and **162** containing ester groups also manifest a high antihistamine potency.[97,98]

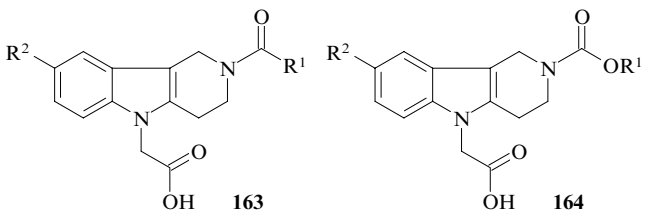


109, **161** **162**

R = H, F, F_3C, Me, MeO.

'Structure–antihistamine activity' relationship studies in the THPI series allowed the determination of the impact of substituents at positions 2, 5 and 8 of the heterocycle on the H_1-antagonist activity.[11,68] It was established that the maximum effect was produced by the following substituents: a methyl group at position 2, Bn- and XCH_2CH_2-groups at position 5 and H, F, Cl atoms or a methyl group at position 8.

The antiallergic effect of 2-acyl- (**163**) and 2-alkoxycarbonyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-5-ylacetic acids (**164**) is determined by another mechanism: being $CRTH_2$-receptor antagonists these compounds suppress the allergic inflammation brought on by prostaglandin D2.[99]

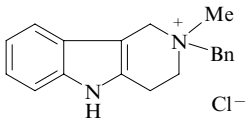


163 **164**

R^1 = H, Alk, Alkenyl, cyclo-Alk, Ar;
R^2 = H, Alk, AlkO, Hal, N≡C, O_2N, HC(O).

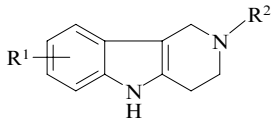
2. Effect on the central and peripheral nervous systems

The impact of THPIs on the nervous system was for the first time discovered as far back as 60 years ago,[100] in a study of properties of 2-benzyl-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium (**165**) chloride, which manifested a high curare-like activity in frogs.



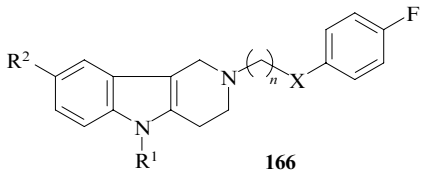
165

Later a high antiserotonergic activity in *in vitro* experiments was found for the disubstituted THPIs of the general formula[14]



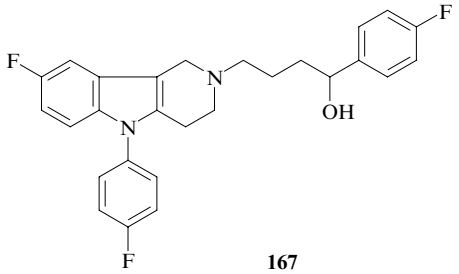
R^1 = H, Alk, AlkO, HO, Cl, Br, F_3C; R^2 = H, Alk.

Further investigations showed that THPIs **166** interact with dopamine receptors (D-R), which makes them promising antipsychotics.[8,75,81] 'Structure–activity' relationship study in the discussed series of compounds revealed the most active one among them, with respect to D-R. It was 8-fluoro-5-(4-fluorophenyl)-2-[4-hydroxy-4-(4-fluorophenyl)butyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indole (**167**) (the Flutroline drug, see Refs 8 and 75) having also demonstrated the highest neuroleptic effect in experiments *in vivo* and *in vitro*.



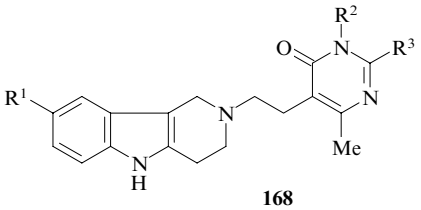
166

n = 2–4; R^1 = H, Me, Ph, 4-FC_6H_4; R^2 = H, Me, MeO, Cl, F;
X = CH_2, CH(OH), $CH(CO_2R^3)$ (R^3 = C_mH_{2m+1} (*m* = 1–6), C(O).



167

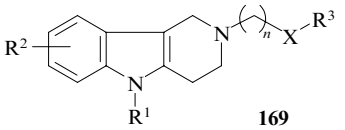
Clinical trials confirmed the high efficacy of Flutroline (**167**) as an antipsychotic drug for the treatment of schizophrenia.[101] However this drug did not find clinical use due to extrapyramidal side effects (see http://www.psychotropics.dk). In the series of 2-(ω-aroylalkyl) tetrahydropyrido[4,3-*b*]indoles, derivatives **166a**,**b** [$R^1 = R^2 = H$, X = C(O); $n = 3$ (**a**), 5 (**b**)] were discovered. Their pharmacological profile includes dopamine (D_2-R) and adrenergic receptors (α_{2A}-R), the potency of compound **166a** with respect to α_{2A}-R being 10 times higher than that with respect to D_2-R, whereas that of compound **166b** being 100 times higher.[102] Tetrahydro-1*H*-pyrido[4,3-*b*]indoles **168** exhibited an activity with respect to 5-HT_2-R and α_{2A}-R.[90]



168

R^1 = H, Me, F, Cl; R^2–R^3 = $(CH{=}CH)_2$, $(CH_2)_nS$ (n = 2–4), C(Me)=CHS, CH=CHS.

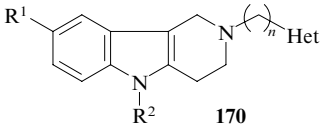
Later it was found that a number of THPIs **166** exert a high potency with respect to serotonin 5-HT_{2A}- and 5-HT_{5A}-receptors,[63,103] and their analogues **169** are ligands of 5-HT_{2A}, 5-HT_{2C} and 5-HT_{5A} receptors.[104]



169

n = 1, 2; R^1 = H, Me, Et, Bn; R^2 = H, 6-MeO, 8-MeO, 6-Cl, 8-Cl; R^3 = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$H_2NC_6H_4$, 4-$O_2NC_6H_4$, HO, 1-naphthyl, 2-naphthyl; X = C(O), CH_2, $(CH_2)_2$, CH(OH), O.

2-(ω-Hetarylalkyl)tetrahydro-1*H*-pyrido[4,3-b]indoles **170**, which are structural analogues of compounds **166**, possess no selectivity and manifest a high affinity to serotonin 5-HT_2-receptors.[48]



170

n = 1, 2; R^1 = H, Cl, F; R^2 = H, 4-FC_6H_4; Het = 2-Py, 3-Py, 4-Py, pyrazin-2-yl, 5-dimethylaminopiperazin-1-yl, pyrimidin-2-yl, piperazin-1-yl.

'Structure–activity' relatioship study in the series of THPIs **170** revealed a pronounced correlation of their biological properties with the nature of substituents at positions 2 and 5 of the heterocycle. For example, removal of a substituent from position 5 in compounds **170** sunstantially descreases their potencies with respect to D_2- and 5-HT_2-receptors (*cf*. the activities of compounds **170a** and **170b**,**c**[48] bearing the free indole nitrogen atom) (Table 1).

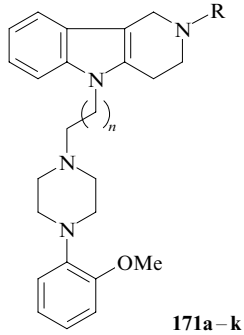
A detailed examination of the pharmacological profile of THPIs **170c** demonstrated a broad spectrum of activity including adrenoreceptors α_1 (IC_{50} = 420 nmol litre^{-1}) and α (K_i = 8500 nmol litre^{-1}), dopamine D_2 (IC_{50} = 150 nmol litre^{-1}), muscarinic (IC_{50} = 31900 nmol litre^{-1}), serotonin 5-HT_2 (IC_{50} = 355 nmol litre^{-1}) and sigma-receptors (IC_{50} = 80 nmol litre^{-1}).[105]

Table 1. The antagonist activity of tetrahydropyridoindoles **170a**–**c** with respect to D_2- and 5-HT_2-receptors.

Compound	n	R^1	R^2	Het	K_i/nmol litre^{-1} (see [a])	
					D_2	5-HT_2
170a	2	F	4-FC_6H_4	2-Py	7	3.6
170b	2	F	H	2-Py	26	73
170c	3	F	H	3-Py	104	136

[a] Inhibition constant.

2-Substituted 5-{ω-[4-(2-methoxyphenyl)piperazin-1-yl]-alkyl}-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **171a**–**k** exhibit a high activity with respect to serotonin 5-HT_{1A}- and 5-HT_{2A}-receptors (Table 2).[106] 2-Acyl substituted [R = Ac (**171c**,**f**,**j**), Bz (**171k**)] compounds were found to be most potent. Turning from 2-acyl substituted to either 2-unsubstituted (R = H) or 2-alkyl derivatives (R = Me, Bn in the series of THPIs **171**) is accompanied by a decrease in affinity to serotonin, especially to receptor 5-HT_{2A} (see Table 2). Note that compounds **171j**,**k** exhibit a sufficiently high activity with respect to 5-HT_{1A}- and 5-HT_{2A}-receptors.



171a–**k**

Table 2. The antagonist activity of tetrahydropyridoindoles **171a**–**k** with respect to 5-HT_{1A}- and 5-HT_{2A}-receptors.

Compound	n	R	K_i/nmol litre^{-1}	
			5-HT_{1A}	5-HT_{2A}
171a	2	H	105	4082
171b	2	Bn	134	739
171c	2	Ac	33	272
171d	3	H	42	1672
171e	3	Bn	64	1429
171f	3	Ac	8.7	99
171g	4	H	112	1378
171h	4	Me	22	260
171i	4	Bn	75	1624
171j	4	Ac	40	20
171k	4	Bz	34	43

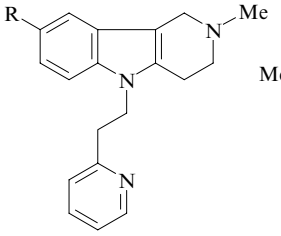
Recently THPIs were established[107] to interact with serotonin 5-HT_6-receptors. 'Structure–activity' relationship study demonstated[64,66–68,70,76] the determining role of the substituent at position 8 of compounds **172a**–**h** in manifesting the discussed features (Table 3). Thus, in the determination of the functional antagonist activity of compounds **172a**–**h** in the HEK-293 cell culture with expressed

Table 3. The antagonist activity of tetrahydropyridoindoles **172a**–**h** with respect to 5-HT_6-receptors.

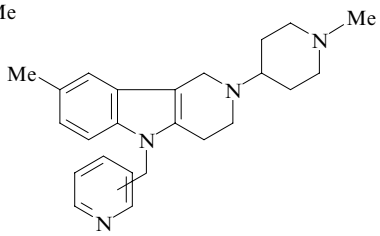
THPI	R	IC_{50}/μmol litre^{-1} (see [a])
172a	H	15.75
172b	Me	0.86
172c	MeO	8.36
172d	F	2.98
172e	Br	1.04
172f	F_3C	1.59
172g	NC	7.47
172h	3-Py	43.20

[a] In this case IC_{50} stands for the concentration of a substance, which provides a 50% descrease in the activity of adenylate cyclase bound to 5-HT_6-receptors.

5-HT_6-receptors their potencies (IC_{50}) lowered from 0.86 (for R = Me, **172b**) through 15.75 (for R = H, **172a**)[1] to 43.2 μmol litre^{-1} (for R = 3-Py, **172h**).[64] Note that compounds **173a**–**c** were completely inactive.



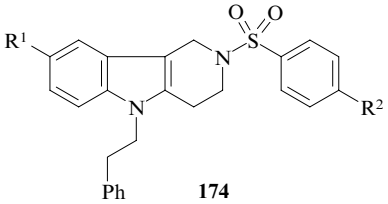
172a–**h**



173a–**c**

Isomers: 2-Py (**a**), 3-Py (**b**), 4-Py (**c**).

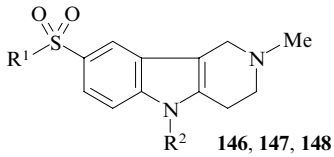
By the example of 5-HT_6 receptors 'structure–activity' correlation was studied in a series of THPIs bearing sulfonyl fragments at positions 2, 5 and 8 of the heterocycle. It was found that 2-arylsulfonyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **120** (R^1 = Me, F; R^2 = H, Me) and **174** were inactive as functional antagonists,[66] while the influence of 5-arylsulfonyl derivatives **125** (R^1 = H, Me, F, Br; R^2 = Me; R^3 = Ph, 4-MeC_6H_4) can be assessed as weak: IC_{50} = 4.9 μmol litre^{-1} for compound **125** (R^1 = Me, R^3 = Ph).[70]



174

R^1 = Me, F; R^2 = H, Me.

A move of the sulfonamide or sulfonyl group from position 2 to position 8 of the heterocycle sharply changes the properties under discussion. Some 8-sulfo derivatives exhibit features of highly active 5-HT_6-receptor anatgonists (Table 4).[66]



146, **147**, **148**

Table 4. The antagonist activity of sulfo-containing tetrahydropyridoindoles with respect to serotonin 5-HT_6-receptors.

Compound	R^1	R^2	IC_{50} /μmol litre^{-1}
146	3-FC_6H_4NH	H	0.015
147	Ph	H	0.078
	3-FC_6H_4	H	0.085
153	Ph	2-Py$(CH_2)_2$	0.615

3. Action on multiple biotargets (pharmacological profile of compounds). The 'magic shotgun' concept

Last investigations[108–111] indicated that some THPIs effectively act on multiple biotargets rather than on a single one, *i.e.* they have quite a broad spectrum of pharmacological activity.

Thus, for instance, Diazoline (**4**) initially regarded by pharmacologists exclusively as an antihistamine drug proved to have a broad pharmacological profile. It acts on a variety of receptors: adrenergic (α_{1A}, α_{1B}, α_{1D}, α_{1A}, α_{2A}, α_2), dopamine (D_1, D_{2L}, D_{2S}, D_3), serotonin (5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, 5-HT_7), sigma-receptors (σ_1, σ_2), on calcium and sodium channels, norepinephrine (NET) and dopamine (DAT) transporters.[112] Presumably, it is this feature that governs the effect of the drug on CNS, which can give rise to excitement, dizziness, drowsiness, delayed motor and mental responses. The presence of these symptoms considered earlier just as adverse effects suggests a possibility of the use of Diazoline for the treatment of CNS diseases.[113]

A similar pharmacological profile was also revealed[64] for Dimebon (**3**) (Fig. 1). It was established that Dimebon is a blocker of the L-type calcium channels (IC_{50} = 57 μmol litre^{-1}),[114] an antagonist of NMDA-receptors *in vivo* (ED_{50} = 42 mg kg^{-1}),[115] a weak inhibitor of choline esterases AChE (IC_{50} = 45 μmol litre^{-1}) and BuChE (IC_{50} = 7.9 μmol litre^{-1}),[116] as well as an inhibitor of transition pores of mitochondrial permeability.[117] The drug prevents the neurotoxic action of β-amyloid on a neuron culture (ED_{50} = 25 μmol litre^{-1}),[112] exhibits mitochondrial[118] and other types of activity.[119, 120]

According to the indicated attributes, Diazoline, Dimebon and many other THPIs both approved for use as pharmaceuticals and drug candidates satisfy the so-called 'magic shotgun concept',[121] and the mechanism of their biological effects is associated with a superposition of various types of pharmacological activity (action on receptors, ion-channels, enzymes, *etc.*).[108] According to this concept, non-selective drugs interacting with several molecular targets simultaneously are most apt for treating depression, schizophrenia and other disorders of the nervous system of complex aetiology.

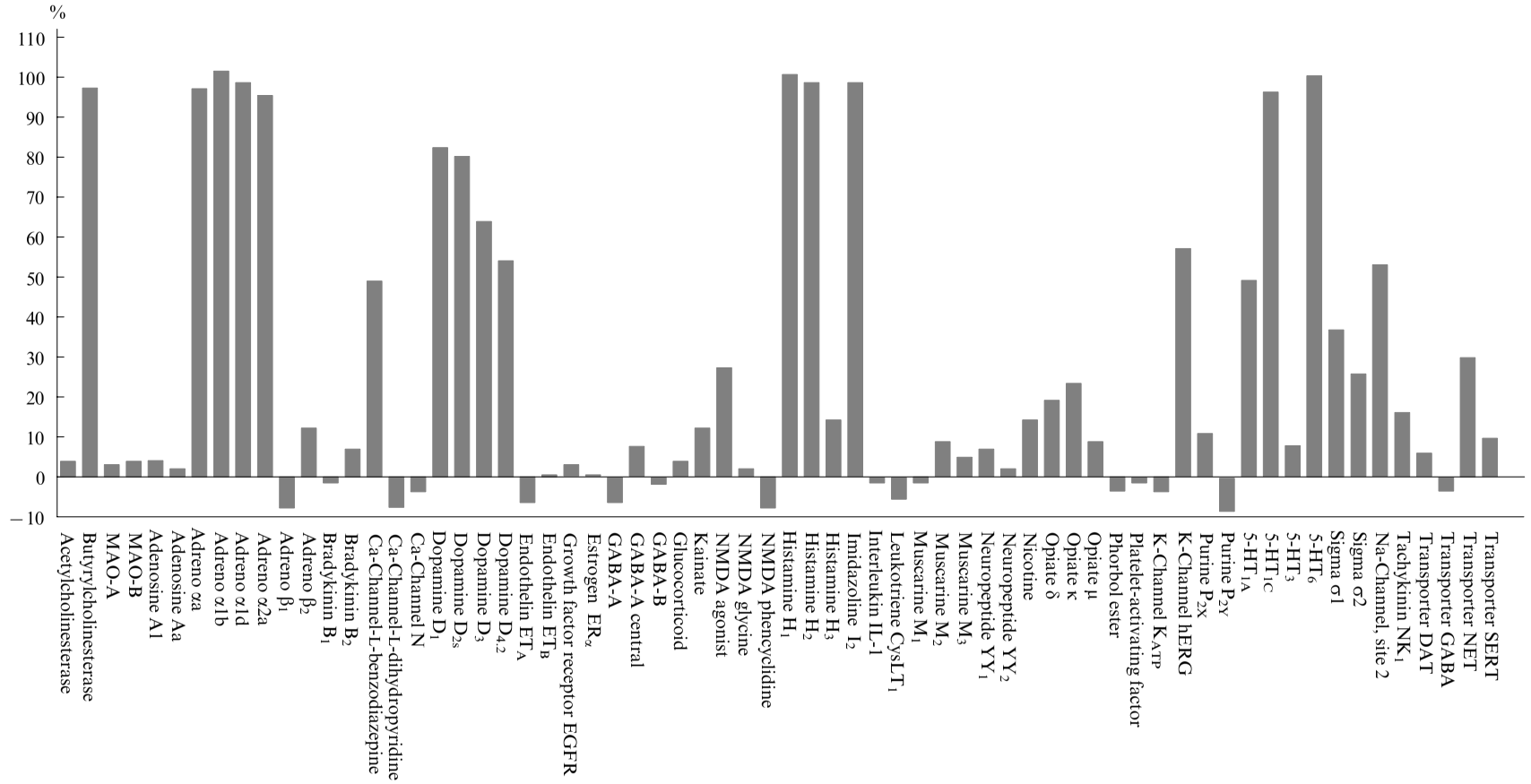


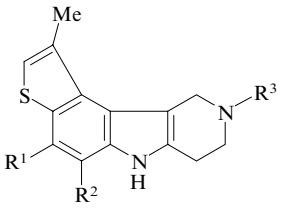
Figure 1. The pharmacological activity spectrum of Dimebon.
The axis of abscissas lists therapeutic targets (enzymes, receptors, ion channels, transporters), in which competitive displacement of specific radioligands by Dimebon was studied; the axis of ordinates provides the amount of a radioligand displaced from the ligand–target complex at a Dimebon concentration of 10 μmol litre^{-1}.

For the present-day medicine Dimebon is of interest as an anti-aging medication,[122] a drug for the treatment of anxiety disorders [123] and schizophrenia.[124] One should also mention the antiarrhythmic properties of this unique medicine, which are determined, supposedly, by blockage of sodium and especially calcium channels. It was found that Dimebon extends the refractory period, exerts a negative dromotropic effect,[125, 126] and a moderate coronary vasodilating effect.[127]

Currently, Dimebon demonstrated excellent results in Phase II clinical trials in the therapy of Alzheimer's [84] and Huntington's [128] diseases.However, the first outcomes of the Phase III six-month clinical trials of Dimebon for the treatment of Alzheimer's disease proved negative (http://www.news-medical.net/news/20100303/Pfizer-Medivation-announce-results-of-two-dimebon-Phase-3-trials-in-AD-patients.aspx). 598 Patients at the average age of 74.4 participated in these trials. Unfortunately, the investigators found no significant differences between the status of patients having received this drug and that of patients having received placebo. Obviously, a thorough analysis of all the data is required for further advancement of Dimebon to clinical practice.

4. Other types of pharmacological activity

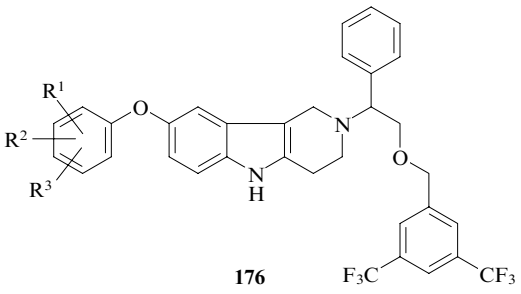
Compounds **175** [129, 130] are characterized by their antidepressant properties. The most studied compounds of this series are Triflucarbine [131] (**175**; $R^1 = F$, $R^2 = H$, $R^3 = Et$) and Tienocarbine [132] (**175**; $R^1 = R^2 = H$, $R^3 = Me$). The mechanism of their antidepressant action includes interaction with serotonin and dopamine receptors.[131] It was demonstrated [133] that Triflucarbine is also an effective calmodulin antagonist.



175

R^1, R^2 = H, Hal; R^3 = H, Alk.

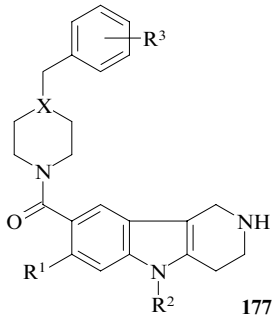
Compounds **176** are promising in treating some inflammatory (for example, rheumatoid polyarthritis) and vascular diseases (venous insufficiency), while not being antagonists of 5-HT_{1B} and 5-HT_{1D} receptors.[134, 135]



176

R^1, R^2, R^3 = H, Hal, F_3C, NC, HO_2C, Me, *etc.*

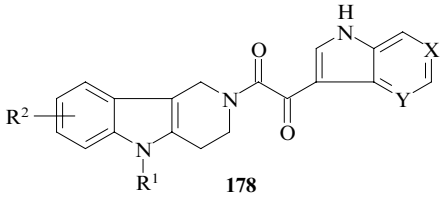
Tetrahydropyrido[4,3-*b*]indoles **177** are patented as inhibitors of p38α-kinase, an enzyme involved in the development of many inflammatory processes.[136]



177

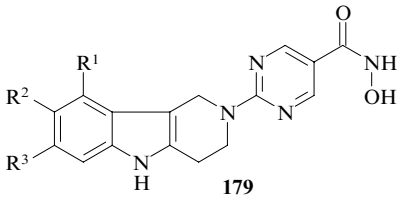
X = CH, N; R^1 = H, Hal, MeO, *etc.*; R^2 = H, Alk, *etc.*; R^3 = H, Alk, *etc.*

Compounds **178** suppress the penetration of the HIV-1 immunodeficiency viruses into cells by blocking the specific gp120 protein.[137] Tetrahydropyrido[4,3-*b*]indoles **179**, **180** as histone deacetylase (HDAC) inhibitors prevent cell proliferation and can be used in an effective therapy of cancer.[138, 139]



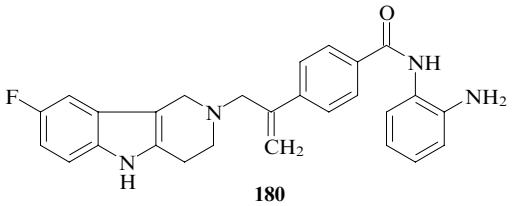
178

X, Y = CH, N; R^1 = H, Alk, Ar; R^2 = H, Hal, MeO, *etc.*



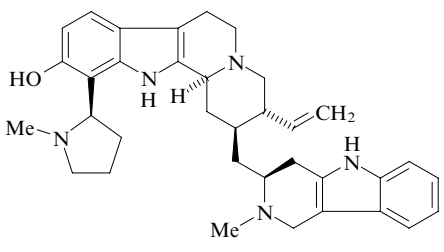
179

R^1, R^2 , R^3 = H, Alk, Hal, MeO, *etc.*



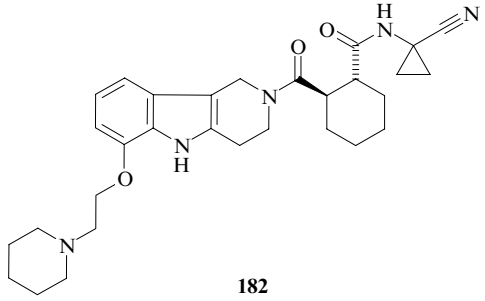
180

Some THPI derivatives manifest apparent antitumour properties. In particular, the strychnopentamine alkaloid (**181**) isolated from the Tanzanian shrub *Strychnos usambarensis*, is an efficacious apoptosis inductor, antimitotic agent and is considered as a promising oncolytic agent.[140] Note that this alkaloid combines γ- and β-tetrahydrocarboline fragments in its structure.

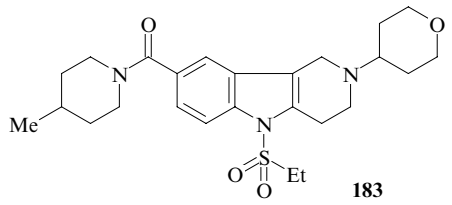


181

Compound **182** and a series of its analogues are patented as cathepsin K cysteine protease inhibitors (K_i = 325 pmol litre^{-1}). They are regarded as potential drugs for the treatment of osteoporosis, arthritis, neuropathic pain, *etc*.[141] The selective CB_1cannabinoid receptor agonist (**183**) (AZ-599)[142] and its analogues[143] are proposed as novel analgesic medications.



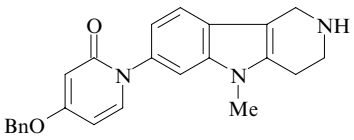
182



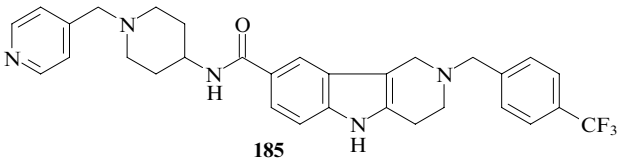
183

A new promising approach to the treatment of obesity and related diseases, particularly diabetes, is the employment of melanin-concentrating hormone receptor (MCHR) antagonists as drugs. An example of such an antagonist is THPI **184**.[144]

A promising method for the treatment of metabolic diseases, for instace atherosclerosis and type II diabetes seems to be stimulating the adiponectin signaling pathway, in particular by using 5′-ATP-activated protein kinase AMPK activators. One of the AMPK-activators is tetrahydropyrido[4,3-*b*]indole **185**.[145]



184



185

IV. Conclusion

Owing to a unique variety and combination of biological properties THPIs are of great interest to medicinal chemists and pharmacologists from the perspective of the search for a new generation of drugs for the treatment of a wide range of diseases. An additional argument for the selection of the compound **1** scaffold for the design of new molecules is the fact that while having apparently a broad spectrum of physiological activity, THPIs exhibit quite a low toxicity.

It should be noted that THPIs belong to one of the well-studied classes of heterocycles during the last 60 years. As follows from Fig. 2, the number of scientific publications on the chemistry and physiological activity of THPIs remains virtually constant for the last 9 years long. It suggests relentless attention to these compounds as well as the fact that THPIs should be regarded as typical 'privileged structures'.[146]

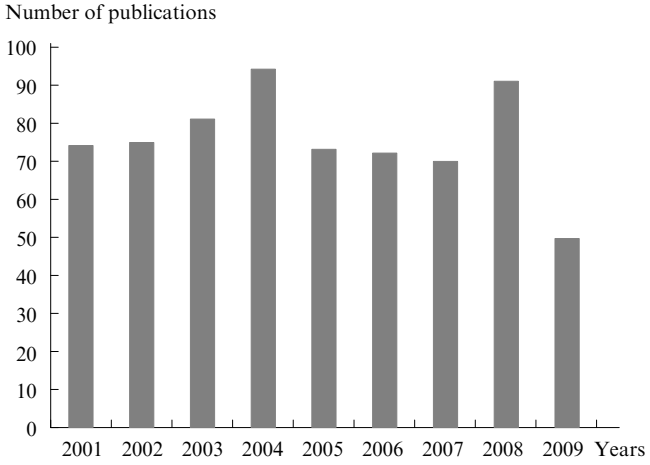


Figure 2. Diagram of the number of publications on THPIs during the last decade.

The advances in the synthesis of such systems were governed by high physiological activities of many derivatives. Based on them highly efficacious pharmaceuticals were designed, and innovative drug canidates that currently undergo clinical trials were developed.

Considerable progress in the synthesis of THPIs began when it had been demonstrated that starting compounds for this class of heterocycles can be easily available molecules. Promising and sufficiently straighforward methods for the preparation of such compounds were developed (rearrangements and isomerizations in acidic media, hydrogenation at atmospheric pressure, reduction, *etc*.). The possibility of further three- or four-step transformations of some functional groups already introduced to the heterocycle was demonstrated, which provided a basis for applying combinatorial chemistry principles and the preparation of large chemical compound libraries for the screening of new compounds.

To date molecular design of a large number of THPIs has been carried out. In many cases 'structure – biological activity' relationship studies have also been conducted for these compounds.

It can be reasonably assumed that data published in patent literature as well as in scientific and technological publications do not in full measure reflect the potential of THPIs as starting molecules for further modification and as promising physiologically active objects. Further synthesis research in order to result in previously unknown derivatives is warranted. In addition, the problem of THPI's molecular design using QSAR (or QSPR) methods for finding novel highly active compounds remains vital.

Thus, further investigation into synthetic pathways to THPIs and into possibilities of using them as a base for the design of a new generation of drugs is a promising field of the chemistry of heterocylcic compounds.

References

1. A-E F Nassar, R E Talaat *Drug Discov. Today* **9** 317 (2004)
2. I Agranat, H Caner, J Caldwell *Nat. Rev. Drug Discov.* **1** 753 (2002)
3. L Hu *IDrugs* **7** 736 (2004)
4. A Burns, R Jacoby *Lancet* **372** 179 (2008)
5. A N Kost, M A Yurovskaya, F A Trofimov *Khim. Geterotsikl. Soed.* 291 (1973) [a]
6. A Bridoux, L Goossens, R Houssin, J-P Hganichart *J. Heterocycl. Chem.* **43** 571 (2006)
7. N G Tsyshkova, F ATrofimov *Khim.-Farm. Zh.* **5** (9) 14 (1971) [b]
8. C A Harbert, J J Plattner, W M Welch, A Weissman, B K Koe *J. Med. Chem.* **23** 635 (1980)
9. W M Welch *Synthesis* 645 (1977)
10. L A Aksanova, I N Pidevich, L M Sharkova, N F Kucherova *Khim.-Farm. Zh.* **2** (7) 3 (1968) [b]
11. A V Ivachtchenko, O D Mit'kin, M G Kadieva, E S Dubrovskaya, I M Okun', S E Tkachenko *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **52** (10) 31 (2009)
12. L Zhang, W Meier, E Wats, T D Costello, P Ma, C L Ensinger, J M Rodgers, I C Jacobson, P Rajagopalan *Tetrahedron Lett.* **36** 8387 (1995)
13. M E Lizarzaburu, S J Shuttleworth *Tetrahedron Lett.* **45** 4781 (2004)
14. C J Cattanach, A Cohen, B Heath-Brown *J. Chem. Soc., C* 1235 (1968)
15. R G W Spickett *J. Med. Chem.* **9** 436 (1966)
16. N F Kucherova, N K Kochetkov *Zh. Obshch. Khim.* **26** 3149 (1956) [c]
17. WO 2008112280; *Chem. Abstr.* **149** 378917 (2008)
18. A V Ivachtchenko, O D Mit'kin, I V Kuznetsova, M G Kadieva, A N Ivchenko *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **52** (10) 38 (2009)
19. A N Kost, E V Vinogradova, F A Trofimov, T I Mikhanova, V I Nozdrich, K S Shadurskii *Khim.-Farm. Zh.* **1** (7) 25 (1967) [b]
20. V A Zagorevskii, N F Kucherova, N M Sharkova, T I Ivanova, S M Klyuev *Khim. Geterotsikl. Soedin.* 1353 (1975) [a]
21. U Hörlein *Chem. Ber.* **87** 463 (1954)
22. A N Kost, E V Vinogradova, Kh Daut, A P Terent'ev *Zh. Obshch. Khim.* **32** 2050 (1962) [c]
23. T Lee, A J Robichaud, K E Boyle, Y Lu, D W Robertson, K J Miller, L W Fitzgerald, J F McElroyb, B L Largent *Bioorg. Med. Chem. Lett.* **13** 767 (2003)
24. M K Eberle, G G Kahle, S M Talati *Tetrahedron* **29** 4045 (1973)
25. S R Prakash, K M Cable, I D Correa, I Fellows, S Montgomery, J J Newman, I Waterhouse, G N Wells, D R Sutherland *J. Label. Compd. Radiopharm.* **36** 993 (1995)
26. C J Cattanach, A Cohen, B Heath-Brown *J. Chem. Soc., C* 359 (1971)
27. A Ebnöther, P Niklaus, R Süess *Helv. Chim. Acta* **52** 629 (1969)
28. V Padmavathi,T V R Reddy, K A Reddy, A Padmaja, D B Reddy *Indian J. Chem., Sect. B* **44** 2527 (2005)
29. R E Mewshaw, R G Sherrill, R M Mathew, C Kaiser, M A Bailey, E W Karbon *J. Med. Chem.* **36** 343 (1993)
30. R E Mewshaw, L S Silverman, R M Mathew, C Kaiser, R G Sherrill, M Cheng, C W Tiffany, E W Karbon, M A Bailey, S A Borosky, J W Ferkany, M E Abreu *J. Med. Chem.* **36** 1488 (1993)
31. J T Braunholtz, F G Mann *J. Chem. Soc.* 381 (1955)
32. C-y Chen, D R Lieberman, R D Larsen, T R Verhoeven, P J Reider *J. Org. Chem.* **62** 2676 (1997)
33. H Iida, Y Yuasa, C Kibayashi *J. Org. Chem.* **45** 2938 (1980)
34. N Moskalev, M Barbasiewicz, M Makosza *Tetrahedron* **60** 347 (2004)
35. L V Kudzma *Synthesis* 1661 (2003)
36. T A Engler, J Wanner *J. Org. Chem.* **65** 2444 (2000)
37. T A Engler, J Wanner *Tetrahedron Lett.* **38** 6135 (1997)
38. N Valls, V M Segarra, X López, J Bosch *Heterocycles* **29** 231 (1989)
39. F A Trofimov, V I Garnova, A N Grinev, N G Tsyshkova *Khim. Geterotsikl. Soedin.* 72 (1979) [a]
40. N N Komzolova, N F,Kucherova, V A Zagorevskii *Khim. Geterotsikl. Soedin.* 668 (1968) [a]
41. K Bhandari, V A Murti, P C Jain, N Anand *Indian J. Chem., Sect. B* **17** 246 (1979)
42. R J Sundberg, J D Bloom *J. Org. Chem.* **46** 4836 (1981)
43. S Cutri, A Diez, M Bonin, L Micouin, H-P Husson *Org. Lett.* **7** 1911 (2005)
44. M Salas, I K Al-Khawaja, M J Thomas, J A Joule *J. Chem. Res. (S)* **7** 218 (1988)
45. R Grigg, V Sridharan, D A Sykes *Tetrahedron* **64** 8952 (2008)
46. J Kraxner, P Gmeiner *Synthesis* 1081 (2000)
47. P Molina, J Alcantara, C Lopez-Leonardo *Tetrahedron* **52** 5833 (1996)
48. M Abou-Gharbia, U R Patel, M B Webb, J A Moyer, T H Andree, E A Muth *J. Med. Chem.* **30** 1818 (1987)
49. M Decker, R Faust, M Wedig, M Nieger, U Holzgrabe, J Lehmann *Heterocycles* **55** 1455 (2001)
50. J M Bobbitt, C L Kulkarni, C P Dutta, H Kofod, K N Chiong *J. Org. Chem.* **43** 3541 (1978)
51. J H Wynne, W M Stalick *J. Org. Chem.* **68** 4845 (2003)
52. E M Beccalli, G Broggini, A Marchesini, E Rossi *Tetrahedron* **58** 6673 (2002)
53. H Ohno, A Aso, Y Kadoh, N Fujii, T Tanaka *Angew. Chem., Int. Ed.* **46** 6325 (2007)
54. M Bandini, A Melloni, F Piccinelli, R Sinisi, S Tommasi, A Umani-Ronchi *J. Am. Chem. Soc.* **128** 1424 (2006)
55. R Grigg, T Coulter *Tetrahedron Lett.* **32** 1359 (1991)
56. Y Shimoji, T Hashimoto, H Yanagisawa *Heterocycles* **36** 123 (1993)
57. A Padwa, S M Lynch, J M Mejta-Oneto, H Zhang *J. Org. Chem.* **70** 2206 (2005)
58. N N Smolyar, A S Volchkov, Yu M Yutilov *Khim.-Farm. Zh.* **35** (9) 514 (2001) [b]
59. Yu M Yutilov, N N Smolyar, A S Volchkov *Khim.-Farm. Zh.* **34** (12) 33 (2000) [b]
60. N N Novikova, I D Silenko, N F Kucherova, V A Zagorevskii *Khim. Geterotsikl. Soedin.* 1630 (1976) [a]
61. M L Bennasar, T Roca, M Monerris, D García-Díaz *J. Org. Chem.* **71** 7028 (2006)
62. M L Bennasar, E Zulaica, S Alonso *Tetrahedron Lett.* **46** 7881 (2005)
63. N Khorana, A Purohit, K Herrick-Davis, M Teitler, R A Glennon *Bioorg. Med. Chem.* **11** 717 (2003)
64. A V Ivachtchenko, O D Mit'kin, V M Kisil', S E Tkachenko, in *XLV Vserossiiskaya Konferentsiya po Problemam Matematiki, Informatiki, Fiziki i Khimii (Tez. Dokl. Sektsii Khimii), Moskva, 2009* [The XLVth All-Russian Conference on Problems of Mathematics, Informatics, Physics and Chemistry (Abstracts of Reports of Chemistry Section) Moscow, 2009] p. 95
65. M A Seefeld, W H Miller, K A Newlander, W J Burgess, D J Payne, S F Rittenhouse, T D Moore, W E DeWolf, P M Keller, X Qiu, C A Janson, K Vaidya, A P Fosberry, M G Smyth, D D Jaworski, C Slater-Radosti, W F Huffman *Bioorg. Med. Chem. Lett.* **11** 2241 (2001)
66. A V Ivachtchenko, O D Mit'kin, V M Kisil', E B Frolov, S E Tkachenko *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **52** (10) 79 (2009)
67. A V Ivachtchenko, O D Mit'kin, V M Kisil', E B Frolov, S E Tkachenko *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **52** (10) 84 (2009)
68. A V Ivachtchenko, E B Frolov, O D Mitkin, V M Kysil, A V Khvat, I M Okun, S E Tkachenko *Bioorg. Med. Chem. Lett.* **19** 3183 (2009)
69. F A Trofimov, A N Kost, N G Tsyshkova, K S Shadurskii, E V Vinogradova *Khim.-Farm. Zh.* **1** (3) 22 (1967) [b]
70. A V Ivachtchenko, E B Frolov, O D Mit'kin, S E Tkachenko, A V Khvat *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **52** (10) 55 (2009)
71. A N Kost, M A Yurovskaya, T V Mel'nikova, O I Potanina *Khim. Geterotsikl. Soedin.* 207 (1973) [a]

72. B A Trofimov, R N Nesterenko, A I Mikhaleva, A B Shapiro, I A Aliev, I V Yakovleva, G A Kalabin *Khim. Geterotsikl. Soedin*. 481 (1986) [a]
73. A V Ivachtchenko, E B Frolov, O D Mitkin, S E Tkachenko, I M Okun, A V Khvat *Bioorg. Med. Chem. Lett*. **20** 78 (2010)
74. A V Ivachtchenko, E B Frolov, O D Mitkin, V M Kysil, A V Khvat, S E Tkachenko *Arch. Pharm*. **342** 740 (2009)
75. C A Harbert, J J Plattner, W M Welch, A Weissman, B K Koe *Mol. Pharmacol*. **17** 38 (1979)
76. A V Ivachtchenko, O D Mitkin, S E Tkachenko, I M Okun, V M Kysil *Eur. J. Med. Chem*. **45** 782 (2010)
77. K S Bhandari, V Snieckus *Synthesis* 327 (1971)
78. Br. P. 733123; *Chem. Abstr*. **50** 57189 (1956)
79. BRD P. 930444; *Chem. Abstr*. **52** 113832 (1958)
80. US P. 3522262; *Chem. Abstr*. **73** 120600 (1970)
81. B K Koe, A Weissman, J J Plattner, C A Harbert, W I M Welch *Pharmacologist* **21** 180 (1979)
82. Yu G Verkhovskii, L P Kokina *Farmakol. Toksikol*. 209 (1968)
83. Russ. P. 2106864; *Byull. Izobret*. (8) 323 (1998)
84. R S Doody, S I Gavrilova, M Sano, R G Thomas, P S Aisen, S O Bachurin, L Seely, D Hung *Lancet* **372** 207 (2008)
85. WO 2007041697; *Chem. Abstr*. **146** 395317 (2007)
86. WO 2006058088; *Chem. Abstr*. **145** 27846 (2006)
87. WO 2005089764; *Chem. Abstr*. **143** 347332 (2005)
88. US P. 3535326; *Chem. Abstr*. **74** 125428 (1971)
89. D A Kharkevich *Farmakol. Toksikol*. 6 (1967)
90. WO 1999012926; *Chem. Abstr*. **130** 237551 (1999)
91. M D Mashkovskii *Lekarstvennye Sredstva* (Pharmaceutical Drugs) Vol. 1 (Khar'kov: Torsing, 1998)
92. Russ. P. 2339637; *Byull. Iizobret*. (33) 818 (2008)
93. WO 2008123800; *Chem. Abstr*. **149** 448357 (2008)
94. WO 9715225; *Chem. Abstr*. **126** 338861 (1997)
95. USSR author's certificate 1138164; *Chem. Abstr*. **102** 198010 (1985)
96. WO 2009055828; *Chem. Abstr*. **150** 494843 (2009)
97. Russ. P. 2338745; *Byull. Izobret*. (32) 799 (2008)
98. WO 2008115098; *Chem. Abstr*. **149** 378711 (2008)
99. WO 2005095397; *Chem. Abstr*. **143** 367289 (2005)
100. V Boekelheide, C Ainsworth *J. Am. Chem. Soc*. **72** 2132 (1950)
101. A A Kurland, A Nagaraju, T E Hanlon *J. Clin. Pharmacol*. **22** 441 (1982)
102. WO 2000037466; *Chem. Abstr*. **133** 74013 (2000)
103. A M Ismaiel, M Dukat, D L Nelson, V L Lucaites, R A Glennon *Med. Chem. Res*. **6** 197 (1996)
104. N Khorana, C Smith, K Herrick-Davis, A Purohit, M Teitler, B Grella, M Dukat, R A Glennon *J. Med. Chem*. **46** 3930 (2003)
105. S H Snyder, B L Largent *J. Neuropsychiatry* **1** 7 (1989)
106. J Boksa, S Charakchieva-Minol, B Duszyñska, R Bugno, A Klodziñska, E Tatarczyñska, E Chojnacka-Wójcik, A J Bojarski *Pol. J. Pharmacol*. **55** 1013 (2003)
107. Russ. P. 2329044; *Byull. Izobret*. (20) 793 (2008)
108. WO 2009082268; *Chem. Abstr*. **151** 123969 (2009)
109. S E Tkachenko, A I Ivachtchenko, A V Khvat, Y V Lavrovsky, I M Okun, in *Proceedings of the 1st International Conference on Drug Design and Discovery, Dubai, 2008* p. 187
110. S E Tkachenko, A I Ivachtchenko, A V Khvat, Y V Lavrovsky, I M Okun, in *Proceedings of the 11th International Conference on Alzheimer's Disease and Related Disorders, Chicago, 2008* P2-478
111. S E Tkachenko, A V Khvat, Y V Lavrovsky, I M Okun, A I Ivachtchenko, in *Proceedings of the XXth International Symposium on Medicinal Chemistry, Vienna, 2008* P021
112. Russ. P. 2374245; *Byull. Izobret*. (33) 618 (2009)
113. Russ. P. 2227028; *Byull. Izobret*. (11) 459 (2004)
114. N N Lermontova, A E Redkozubov, E F Shevtsova, T P Serkova, E G Kireeva, S O Bachurin *Byull. Eksperim. Biol. Med*. **132** 545 (2001)
115. V V Grigor'ev, O A Dranyi, S O Bachurin *Byull. Eksperim. Biol. Med*. **136** 535 (2003)
116. N N Lermontova, N V Lukoyanov, T P Serkova, E A Lukoyanova, S O Bachurin *Byull. Eksperim. Biol. Med*. **129** 640 (2000)
117. S O Bachurin, E P Shevtsova, E G Kireeva, G F Oxenkrug, S O Sablin *Ann. N.Y. Acad. Sci*. **993** 334 (2003)
118. D Hung, in *Proceedings of the 11th International Conference on Alzheimer's Disease and Related Disorders, Chicago, 2008* S4-04-05
119. I Okun, S E Tkachenko, A Khvat, O Mitkin, V Kazey, A V Ivachtchenko *Curr. Alzheimer Res*. **7** 97 (2010)
120. M Yamashita, T Nonaka, T Ara, F Kametani, V L Buchman, N Ninkina, S O Bachurin, H Akiyama, M Goedert, M Hasegawa *FEBS Lett*. **583** 2419 (2009)
121. B L Roth, D J Sheffler, W K Kroeze *Nat. Rev. Drug Discov*. **3** 353 (2004)
122. Russ. P. 2283108; *Byull. Izobret*. (25) 441 (2006)
123. Russ. P. 2338533; *Byull. Izobret*. (22) 694 (2008)
124. Russ. Appl. 2006101999; *Byull. Izobret*. (22) 26 (2007)
125. P A Galenko-Yaroshevskii, O A Chekanova, V V Skibitskii, V V Bartashevich, A I Khankoeva, T I Polyashova *Byull. Eksperim. Biol. Med*. **119** 375 (1995)
126. P A Galenko-Yaroshevskii, I L Cherednik, V V Bartashevich, Yu R Sheikh-Zade, A I Khankleva *Byull. Eksperim. Biol. Med*. **124** 691 (1997)
127. P A Galenko-Yaroshevskii, Yu R Sheikh-Zade, O A Chekanova, E R Melkumova, V V Bartashevich, A I Khankoeva *Byull. Eksperim. Biol. Med*. **121** 506 (1996)
128. K Kieburtz, M McDermott, T S Voss, J Corey-Bloom, L M Deuel, E R Dorsey, S Factor, M D Geschwind, K Hodgeman, E Kayson, S Noonberg, M Pourfar, K Rabinowitz, B Ravina, J Sanchez-Ramos, L Seely F Walker, A Feigin *Arch. Neurol*. **67** 154 (2010)
129. US P. 3718657; *Chem. Abstr*. **79** 5320 (1973)
130. BRD P. 3311342; *Chem. Abstr*. **102** 62210 (1985)
131. R A Glennon, J De Vry, D G Spencer, T Glaser *Pharmacol. Biochem. Behav*. **37** 769 (1990)
132. J Castaner, H Koch *Drugs Fut*. **8** 516 (1983)
133. L Hegemann, R Fruchtmann, B Bonnekoh, B H Schmidt, J Trabler, G Mahrle, R Muller-Peddinghaus, L A van Rooijen *Arch. Dematol. Res*. **283** 456 (1991)
134. WO 2005095396; *Chem. Abstr*. **143** 367440 (2005)
135. WO 2007009485; *Chem. Abstr*. **146** 163297 (2007)
136. US P. 6448257; *Chem. Abstr*. **137** 216937 (2002)
137. WO 2005117868; *Chem. Abstr*. **144** 22907 (2005)
138. WO 2006088949; *Chem. Abstr*. **145** 271746 (2006)
139. WO 2005121073; *Chem. Abstr*. **144** 69625 (2005)
140. J Quetin-Leclercq, B Bouzahzah, A Pons, R Greimers, L Angenot, R Bassleer, H Barbason *Planta Med*. **59** 59 (1993)
141. WO 2009001129; *Chem. Abstr*. **150** 98296 (2009)
142. Y-X Cheng, X Luo, M Pourashraf, M Tomaszewski *Drugs Fut*. **33** (Suppl. A) P031 (2008)
143. WO 2006101434; *Chem. Abstr*. **145** 377318 (2006)
144. WO 2009089482; *Chem. Abstr*. **151** 173472 (2009)
145. WO 2009076631; *Chem. Abstr*. **151** 56830 (2009)
146. A Patchett, R Nargund *Ann. Rep. Med. Chem*. **35** 289 (2000)

[a] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[b] — *Pharm. Chem. J. (Engl. Transl.)*
[c] — *Russ. J. Gen. Chem. (Engl. Transl.)*