GDAŃSK UNIVERSITY OF TECHNOLOGY
FACULTY OF CHEMISTRY

The author of the PhD dissertation: Milena Angelika Witkowska
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DOCTORAL DISSERTATION

Title of PhD dissertation: **Biologically active compounds based on the carbazole scaffold - synthetic and mechanistic aspects**

Title of PhD dissertation (in Polish): **Związki biologicznie czynne oparte na rdzeniu karbazolu- synteza i aspekty mechanistyczne**

Supervisor *signature*
Dr hab. Sławomir Makowiec

Gdańsk, 2021

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DESCRIPTION OF DOCTORAL DISSERTATION

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Keywords of PhD dissertation in Polish: leki przeciwdepresyjne, receptory 5-HT, karbazol, tetrahydrokarbazol, telomery, telomeraza, inhibitory telomerazy

Keywords of PhD dissertation in English: antidepressants, 5-HT receptors, carbazole, tetrahydrocarbazole, telomeres, telomerase, telomerase inhibitors

Summary of PhD dissertation in Polish: Rozprawa doktorska jest podzielona na trzy części: wstęp teoretyczny, badania własne oraz część eksperymentalną. Wstęp teoretyczny podzielony jest na cztery zasadnicze części w których opisano: receptory 5-hydroksytryptaminy, najpopularniejsze leki przeciwdepresyjne, nowe związki oparte na strukturze karbazolu wykazujące powinowactwo do receptorów serotoniny, telomery i telomerazę wraz z funkcjami jakie pełnią, strategie inhibicji aktywności telomerazy, karbazole zatwierdzone w leczeniu nowotworów, nowe pochodne karbazolu będące inhibitorami telomerazy oraz wybrane metody syntezy pochodnych tetrahydrokarbazolu i karbazolu. Główną częścią pracy są badania własne w których opisane są efekty eksperymentów w zakresie syntezy 1,2,3,4-tetrahydrocyklopenta[*b*]indoli, 1,2,4-trzypodstawionych pochodnych karbazoli oraz 1,2,3,6-czteropodstawionych pochodnych karbazoli. Część eksperymentalna zawiera procedury otrzymywania związków, analizę spektralną produktów oraz spis instrumentów, z których korzystano podczas realizacji tej pracy.

Summary of PhD dissertation in English: Doctoral dissertation is divided into three main parts: introduction, results and discussion and experimental. The introduction is divided into four main parts which describe: 5-hydroxytryptamine receptors, the most popular antidepressants, new compounds based on the carbazole structure with affinity for serotonin receptors, telomeres and telomerase with their functions, telomerase inhibition strategies, carbazoles approved in cancer treatment, new carbazole derivatives which are telomerase inhibitors and selected methods of synthesis tetrahydrocarbazole and carbazole derivatives. The main part of the work are results and discussion. In this chapter the effects of experiments in the synthesis of 1,2,3,4-tetrahydrocyclopenta[*b*]indoles, 1,2,4-trisubstituted carbazole derivatives and 1,2,3,6-tetrasubstituted carbazole derivatives are described. The experimental part includes procedures for the preparation of compounds, spectral analysis of products and a list of instruments that were used in the implementation of this work.

*) delete where appropriate.

Serdeczne podziękowania składam:

Mojemu Promotorowi dr hab. Sławomirowi Makowcowi za inspiracje do rozpoczęcia podróży po bezkresnym świecie syntezy organicznej, życzliwość i merytoryczne wsparcie na które zawsze mogłam liczyć.

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ABSTRACT

This doctoral dissertation is divided into three main parts: introduction, results and discussion and experimental.

The introduction is divided into four main parts. In the first subsection, entitled "Tetrahydrocarbazole derivatives in depression treatment" seven families of 5-hydroxytryptamine receptors are characterized, the most popular antidepressants are presented, and new compounds based on the carbazole structure with affinity for serotonin receptors were reviewed. In the next subsection, entitled "Carbazole derivatives in cancer therapy" the structure of telomere and telomerase with their functions are described, five strategies of inhibiting telomerase activity are presented, i.e. G-quadruplex stabilization, oligonucleotide inhibitors, gene therapy, small-molecule telomerase inhibitors and immunotherapy, the carbazoles approved for treatment tumors are reviewed, and novel carbazole derivatives that are telomerase inhibitors have been characterized. The last two sections include an overview of selected synthesis methods for tetrahydrocarbazole and carbazole derivatives.

The main part of the work are results and discussion. In this chapter the effects of experiments in the synthesis of 1,2,3,4-tetrahydrocyclopenta[*b*]indoles, 1,2,4-trisubstituted carbazole derivatives and 1,2,3,6-tetrasubstituted carbazole derivatives are described. In the first stage of the research, the designed cyclopenta[*b*]indoles were first tested by molecular docking method in order to check the compatibility of the compounds with the serotonin TS3 transporter. Based on good receptor fit, the method of their synthesis was then developed. In the next stage of research, a new approach to the synthesis of carbazole derivatives containing substituents in the 1,2,4 positions was designed. On the basis of the collected material, a tentative mechanism of the studied cyclization process with the use of iodine and transition metal triflates was proposed. In the last stage of the research, the conditions for the synthesis of 1,2,3,6-tetrasubstituted carbazole derivatives with antitumor activity were developed. For this purpose, the previously described oxidative cyclization method with the use of manganese (III) acetate was used. The synthesized compounds were submitted for research in order to determine their antitumor activity.

The experimental part includes procedures for the preparation of compounds, spectral analysis of products and a list of instruments that were used in the implementation of this work.

TABLE OF CONTENTS

ABBREVIATIONS

5-HIAA	-	5-hydroxyindoleacetic acid
5-HT	-	serotonin
Ac	-	acetyl
acac	-	acetylacetone
ADP	-	adenosine diphosphate
AFP	-	alpha-fetoprotein
ALK	-	anaplastic lymphoma kinase
ALT	-	alternative lengthening of telomeres
AML	-	acute myeloid leukemia
Ar	-	aryl
ASM	-	aggressive systemic mastocytosis
BMVC	-	3,6-bis[2-(1-methylpyridinium)vinyl]carbazole diiodide
Bn	-	benzyl
Boc	-	tert-butyloxycarbonyl
bpy	-	2,2'-bipyridyl
cAMP	-	cyclic adenosine monophosphate
CAN	-	ceric ammonium nitrate
CD	-	circular dichroism
CNS	-	central nervous system
Cp	-	cyclopentadienyl
Cy	-	cyclohexyl
CYP	-	cytochrome
DA	-	dopamine
DACs	-	donor-acceptor cyclopropanes
DAPI	-	4′,6-diamidino-2-phenylindole
DAT	-	dopamine transporter
dba	-	dibenzylideneacetone
DCC	-	*N,N*′-dicyclohexylcarbodiimide
DCM	-	dichloromethane
DCU	-	*N*,*N*'-dicyclohexylurea
DDR	-	DNA damage response
DIPEA	-	*N,N*-diisopropylethylamine
DMA	-	dimethylacetamide
DMAP	-	*N,N*-dimethyl-4-aminopyridine
DMF	-	*N,N*-dimethylformamide

DMSO - dimethyl sulfoxide
DMU - *N,N*-dimethylurea
DNA - deoxyribonucleic acid
dppp - 1,3-bis(diphenylphosphino)propane
dpppf - 1,1′-bis(di-tert-butylphosphino)ferrocene
EMA - European Medicines Agency
Et - ethyl
FDA - Food and Drug Administration
GABA - γ-aminobutyric acid
GLOBOCAN - Global Cancer Observatory
GPCR - G protein-coupled receptors
GUS - Central Statistical Office of Poland
Hex - hexane/hexyl
HFIP - 1,1,1,3,3,3-hexafluoro-2-propanol
IARC - International Agency for Research on Cancer
IC50 - half maximal inhibitory concentration
i-Pr - isopropyl
KRN - National Cancer Registry of Poland
Ln - lanthanide
MAO - monoamine oxidase
MAOIs - monoamine oxidase inhibitors
MCL - mast cell leukemia
Me - methyl
MHC I - major histocompatibility complex class I
MIC - minimum inhibitory concentration
MLCT - metal-to-ligand charge-transfer
NA - noradrenaline
NBS - *N*-bromosuccinimide
NIS - *N*-iodosuccinimide
NMP - *N*-methyl-2-pyrrolidone
NMR - Nuclear Magnetic Resonance
NORT - Novel Object Recognition Test
NSCLC - non-small cell lung cancer
Nu - nucleophile
OS - oxidative stress
PARPs - poly(ADP-ribose)polymerases

Ph	-	phenyl
Pht	-	phthaloyl
Piv	-	pivaloyl
POT1	-	protection of telomeres 1
PPA	-	polyphosphoric acid
RAP1	-	repressor-activator protein 1
REM	-	rapid eye movement
RNA	-	ribonucleic acid
SERT	-	serotonin transporter
SSRI	-	selective serotonin reuptake inhibitors
TA	-	tartaric acid
TAA	-	tumor-associated antigen
TAA	-	tumor-associated antygen
TBP	-	telomere binding protein
TBTU	-	2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
t-Bu	-	tert-butyl
TCA	-	tricyclic antidepressants
TERC	-	telomerase RNA component
TERT	-	telomerase reverse transcriptase
Tf	-	trifluoromethanesulfonyl
TFA	-	trifluoroacetic acid
TFE	-	tetrafluoroethylene
THF	-	tetrahydrofuran
TIN2	-	TRF1 interacting nuclear factor 2
TLC	-	Thin Layer Chromatography
TMSCl	-	trimethylsilyl chloride
TNKS1	-	tankyrase 1
Tol	-	toluene
TPP1	-	tripeptidyl peptidase 1
TRF1/2	-	telomeric repeat binding factor ½
Trp	-	tryptophan
Ts	-	tosyl
WHO	-	World Health Organization
Z	-	benzyloxycarbonyl

I. INTRODUCTION

Heterocyclic compounds, due to the unique ability to mimic the structure of peptides and binding to proteins, are one of the most valuable sources of compounds with diverse biological activity[1,2]. Due to their unique properties, they are widely used in medicine[3].

A very important example of an aromatic heterocyclic compound, which is a key structural motif of many biologically active compounds, both natural and synthetic, is carbazole. It consists of two benzene rings (rings A, C) attached to both sides of a centrally located pyrrole ring (ring B)[4]. Carbazole derivatives can be divided into the following groups: carbazoles **1**, *N*-substituted carbazoles **2**, thienocarbazoles **3**, thiazolocarbazoles **4**, tetrahydrocarbazoles **5**, oxazolinyl carbazoles **6**, imidazocarbazoles **7**, benzofurancarbazoles **8** and benzopyrancarbazoles **9** (Figure 1)[5].

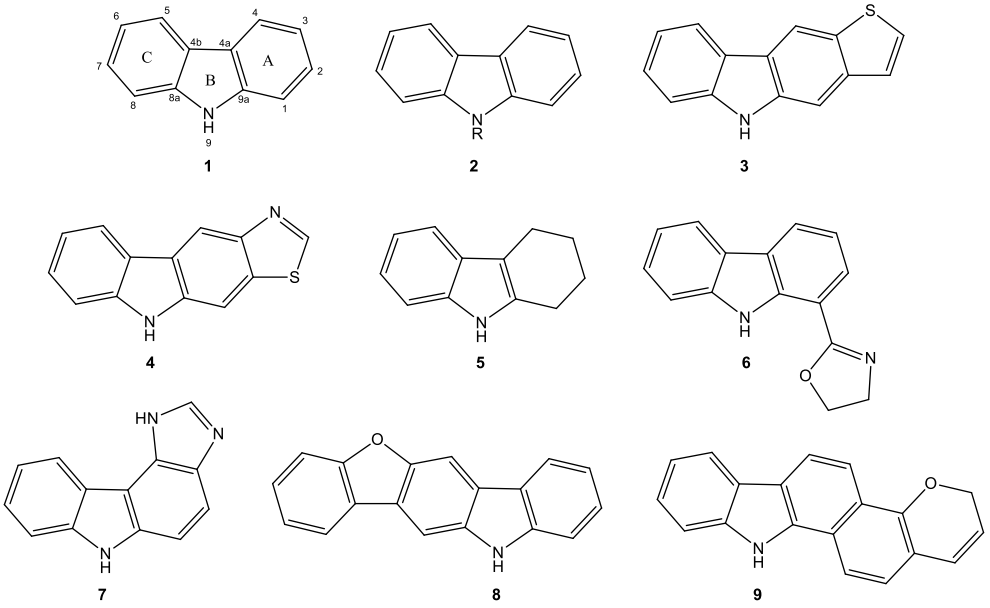


Figure 1. Carbazole derivatives

Carbazole was first isolated from coal tar in 1872 by Glaser and Graebe[6]. Ninety years later, the first naturally occurring carbazole was isolated, the alkaloid murrayanine from the *Murraya koenigii* Spreng[7]. As it turned out, this compound had antimicrobial properties, which initiated big interest in carbazole derivatives by scientists. Thanks to these discoveries, many carbazole derivatives were synthesized, which made it possible to learn about their pharmacological activities and use them as antiinflammatory[8], antibacterial[9,10], antifungal[11,12], antiviral[13], antitumor[14,15], anticonvulsant[16], antipsychotic[17,18], antidiabetic[19] etc.

Cancers, and suicides (often as a result of untreated depression), are at the forefront of causes of death, both in Poland and around the world[20,21]. According to GLOBOCAN estimates from 2018, 9.6 million people died because of cancer diseases in the world[22]. Whereas in Poland, according to the statistical data of the GUS and the KRN from 2013, cancers kill nearly 110 thousand people a year[23,24]. When it comes to suicides, the statistics are also not very good. Every year nearly 800 thousand people take their own lives[25]. In Poland in 2016 more people have committed suicide than are killed in car accidents. In 2016, the Police Headquarters recorded 9861 suicide attempts, of which 5405 (nearly 55%) of cases, ended in death[26].

Taking into account the ongoing problem in the treatment of cancer diseases and depression and the huge therapeutic potential of carbazole derivatives, it seems quite obvious to search for new compounds based on the carbazole core that can be used to treat the mentioned diseases.

1. Tetrahydrocarbazole derivatives in depression treatment

Depressive disorders have been ranked by the World Health Organization as one of the largest contributors to global disability. According to WHO data from 2015, about 300 million people suffer from depression (about 5-6% of the world's population), while in Poland were 1.9 million (about 5% of the Polish population) people suffering from this disease at the same time[27].

Depression is the response of the body generated by the central nervous system occurs in most people. The appearance of depression is associated with the interaction of such factors as: genetic predisposition, physical condition of the body and stress factors, mainly life events. In different cases of depression, we observe a different proportion of these three factors[28-30]. Unipolar depression (ie, a recurrent depressive disorder or a single episode of major depression) affects approximately 5-17% of the population throughout life[31]. The main peak incidence of unipolar depression is between the ages of 30 and 40. The average lenght of episode is approximately 6 months. A small number of people may only get one episode of depression in their lifetime. For some people, the space between the first and subsequent episodes of depression may be as long as 20-30 years. However, most often patients with recurrent depression have several episodes during their lifetime, and each subsequent episode increases the risk of another episode. In the course of the disease, in many patients there is a tendency to increase the frequency, duration of episodes, and to increase resistance to pharmacological treatment. We speak about chronic depression if the duration of an episode of depression is at least 2 years[28].

Depression can be treated with medications, psychotherapy, or through their combination. Psychotherapy teaches new ways of thinking and behaving, and helps to change habits that may have contributed to getting sick. Therapy can also help to understand difficult relationships or situations that may have caused depression[32]. Pharmacological treatment is currently the most important treatment for depression. Antidepressants have a therapeutic effect for the symptoms of the depressive syndrome occurring in the course of recurrent affective disorders, as well as on the symptoms of depression occurring in other mental disorders and neurological or somatic diseases[28]. The first drugs that turned out to be effective in the treatment of depressive disorders were monoamine oxidase inhibitors (MAOIs)[33]. The MAOI works by inhibiting the oxidation of monoamines, which results in an increase in extracellular levels of serotonin (5-HT), noradrenaline (NA) and dopamine (DA) in the brain. In the 1950s, a second class of antidepressants was developed - tricyclic antidepressants (TCAs). Their action is based on blocking the reuptake of 5-HT and NA, which increases the level of monoamines[34-36]. As both MAOIs and TCAs were the cause of many serious side effects, new solutions were sought. In the late 1980s, more pharmacologically specific antidepressants with fewer side effects were developed - selective serotonin reuptake inhibitors (SSRIs). SSRIs inhibit 5-HT reuptake, and long-term treatment increases the level of serotonin in the brain[37,38]. They are currently one of the most commonly used drugs in the world[39].

1.1 5-hydroxytryptamine receptors

Serotonin (*Figure 2*) was isolated and characterized for the first time in 1948 by Page and coworkers[40]. In 1953, Page and Twarog[41] discovered, that serotonin was present in the central nervous system. 5-hydroxytryptamine is a neurotransmitter that plays an important role in a number of physiological functions, such as pain, appetite, sex, emotions, sleep, memory and related disease states, such as depression, anxiety, schizophrenia, social phobia, panic and obsessive-compulsive disorders[42].

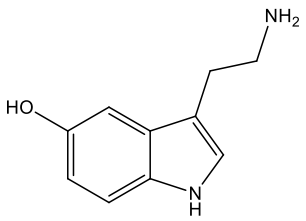


Figure 2 Serotonin (5-HT)

Serotonin is biosynthesized from tryptophan. First, this amino acid is converted to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase. The compound is then treated with aromatic L-amino acids decarboxylase to form serotonin. 5-HT metabolism occurs in two ways.

The first is the conversion of 5-HT by the monoamine oxidase enzyme (MAO) to 5-hydroxyindole acetaldehyde, which then produces 5-hydroxyindole-3-acetic acid (5-HIAA) by the action of aldehyde dehydrogenase. The resulting 5-HIAA is a marker of the carcinoid syndrome. The second way is to convert 5-HT to *N*-acetyl-5-hydroxytryptamine using the *N*-acetylase enzyme, then replace the hydroxyl group in the indole ring with a methyl group using the enzyme 5-hydroxyindole-*O*-methyltransferase and form melatonin (*Figure 3*). Melatonin is an important hormone that regulates the sleep cycle and also acts as an antioxidant[43,44].

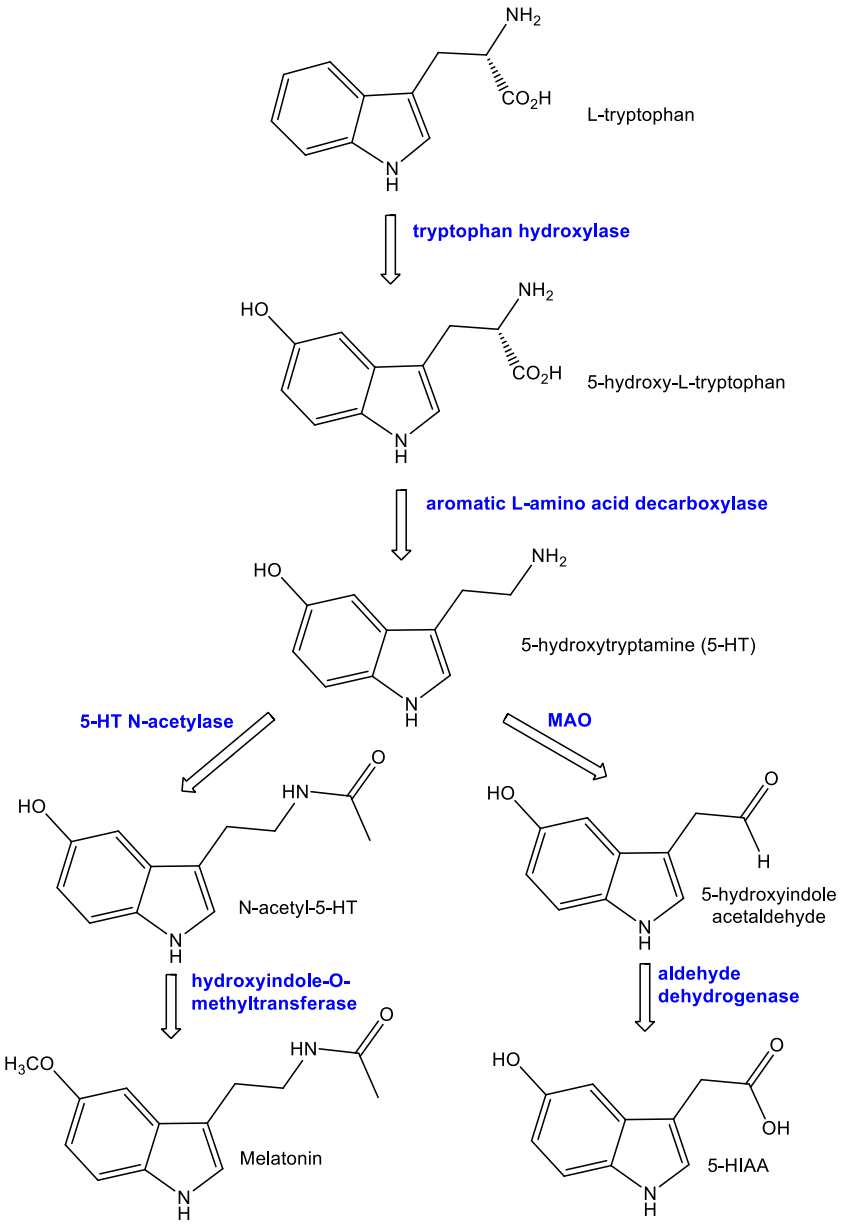


Figure 3 Biosynthesis of serotonin and its metabolites

Serotonergic system dysfunction has been considered a major factor in many mental illnesses since the 1950s[45]. Perhaps the strongest evidence for the role of the serotoninergic system in depressive disorders is the effectiveness of antidepressants targeting the serotonin transporter (SERT) - selective serotonin reuptake inhibitors. Knowledge of the structure and action of the serotonergic system is very important in understanding the effects of antidepressant therapy. The serotonergic neurons in the mammalian brain contain the most extensive and complex neurochemical network in the central nervous system. It has been estimated that the human brain contains approximately 250 thousand 5-HT neurons[46] clustered in the raphe nuclei in the brainstem[47]. Serotonergic neurons contact each other through chemical synapses to form a neural network. These cells are characterized by tonic activity that ceases during the rapid eye movement phase of sleep (REM)[48]. Although the serotonin system is regulated by many mechanisms, it is also involved in the self-regulation of serotonergic activity. The key control mechanism of 5-HT neurons is self-inhibition by 5-HT_{1A} autoreceptors, which will be discussed later in this dissertation. Given the complex nature of the serotonergic system and interaction with other neurochemical systems, numerous mechanisms may play a role in the development of depressive disorders. Proposed mechanisms include: low serotonin or postsynaptic receptors production, decreased neurons excitation or self-inhibition, decreased 5-HT synthesis, and/or tryptophan deficiency[49].

Following the development of the SSRIs, targets other than SERT received a lot of interest from scientists - namely the 5-HT receptors. Serotonin performs many physiological functions by interacting with many receptors. So far, seven subfamilies of 5-HT receptors (5-HT_1 - 5-HT_7) have been identified, with several subtypes within them. Six of the seven subtypes are G protein-coupled receptors, while the 5-HT_3 receptor is a ligand-gated ion channel[50].

1.1.1 5-HT_1 receptors

The subfamily consists of 5 receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}) coupled with $G_{i/0}$ protein (GPCR, ang. *G protein-coupled receptors*), which inhibit the action of cyclase adenylate by reducing the concentration of cyclic adenosine monophosphate (cAMP)[51].

5-HT_{1A} occurs mainly in the raphe nuclei as presynaptic autoreceptors and in many structures of the limbic system, especially in the hippocampus, where they play the role of postsynaptic receptors. These receptors are coupled with several intracellular signaling pathways. Two of them deserve special attention: negative coupling with adenylate cyclase and opening of potassium channels[50]. As mentioned above, 5-HT_{1A} plays an important role in the self-regulation of the serotonergic system. Serotonergic activation of these receptors leads to the opening of potassium channels in the plasma membrane and cell hyperpolarization, which

results in a reduction in the rate of neuronal discharge[52]. The activation of 5-HT_{1A} autoreceptors by endogenous 5-HT plays a fundamental role in the physiological control of the activity of ascending 5-HT neurons. During wakefulness, 5-HT neurons exhibit a slow and regular rate of discharge. On the other hand, under conditions of overexcitation, near cell bodies, there is an increased release of 5-HT. More serotonin activates 5-HT_{1A} autoreceptors and helps to maintain a low and regular action potential of 5-HT neurons. Thus, 5-HT_{1A} autoreceptors act as physiological safety valves that help maintain homeostasis. This negative feedback mechanism plays a harmful role in the mechanism of action of antidepressants. The administration of SSRIs in the initial phase of treatment causes a very large increase in extracellular serotonin, which activates 5-HT_{1A} receptors and reduces the action potential of 5-HT cells and the final release of serotonin. The effectiveness of this mechanism decreases with prolonged treatment and is likely due to 5-HT-induced desensitization of 5-HT_{1A} autoreceptors, allowing for a significant increase in extracellular serotonin[49]. Moreover, 5-HT_{1A} receptors play an important role in depressive disorders. Autopsy studies of patients suffering from depression have suggested an increased density of 5-HT_{1A} autoreceptors[53,54]. Additionally, genetic studies have shown that people with increased density or activity of 5-HT_{1A} autoreceptors are more sensitive to mood disorders and less likely to respond to medications[55,56]. Two new compounds have been recently developed, vilazodone and vortioxetine. They act by inhibiting 5-HT reuptake and show partial agonism of 5-HT_{1A}[57,58].

5-HT_{1B} receptors, like 5-$HT_{1A,}$ are also negatively coupled to adenylate cyclase. They are located on serotonergic axons where they locally regulate synthesis and release of serotonin. Just like in case of 5-HT_{1A} receptors, administration of an SSRI in the initial phase of treatment activates 5-HT_{1B} and reduce the serotonin release. On the other hand, longterm use of SSRIs leads to desensitization of 5-HT_{1B} autoreceptors[59]. These receptors also play a role in depressive disorders. Two common genetic polymorphisms of 5-HT_{1B} receptors: G861C[60] and C129T[61] are associated with depression and affective disorders. Antagonists of 5-HT_{1B} receptor have been shown to be effective in preclinical models of depression[62].

In the case of the rest 5-$HT_{1\text{-like}}$ receptors (5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}) the clinical relevance is not fully understood. Although there is limited preclinical evidence linking some of them with depressive disorder. Whale and coworkers[63] research from 2001 shows the impaired sensitivity of the postsynaptic 5-HT_{1D} receptors in patients with depression. Similarly, another postmortem studies have shown a much higher density of 5-HT_{1D} receptors in the globus pallidus in patients suffering from depression[64].

1.1.2 5-HT$_2$ receptors

This subfamily consists of 3 receptors: (5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$) coupled with G$_{q/11}$ protein. These receptors are distributed throughout the brain, but with the highest density in the neocortex[51].

5-HT$_{2A}$ is located in the cortex on GABAergic interneurons and glutamatergic neurons[65,66]. Several clinical trials have shown that atypical antipsychotics and the antidepressant mirtazapine, which have an affinity for 5-HT$_{2A}$ receptors, increase the response to SSRIs in treatment-resistant patients[67-69]. Intrestingly, the chronic use of 5-HT$_{2A}$ antagonists results in down-regulation of 5-HT$_{2A}$ receptors, which is predicted to be beneficial in the treatment of depression[70].

5-HT$_{2B}$ is largely expressed in peripheral tissues and its presence in the mammalian brain is limited[71]. Despite limited knowledge about the functions of 5-HT$_{2B}$ in the central nervous system, Diaz et al.[72] research from 2012 indicates their participation in the action of SSRIs. These studies also report the presence of 5-HT$_{2B}$ receptors in dorsal raphe 5-HT neurons and their role in the release of serotonin.

5-HT$_{2C}$ receptors are found mainly in the hippocampus, cortex, substantia nigra, choroids plexus and cerebellum[73] and play an important role in the control of mood, appetite, motor function, sleep and sexual function[74]. These receptors are located in the somatodendrial zone and on axon terminals[75]. Longterm use of SSRIs, like in the case of 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors, leads to receptor desensitization. Preclinical studies have shown that both selective and nonselective 5-HT$_{2C}$ antagonists enhance the neurochemical effects of SSRIs on extracellular serotonin levels and significantly increase the antidepressant effect of the SSRIs[76,77]. Furthermore, 5-HT$_{2C}$ receptors are involved in the modulation of dopaminergic activity[78].

1.1.3 5-HT$_3$ receptors

5-HT$_3$ receptors are found throughout the brain and central nervous system. A relatively high concentration of the receptors can be found in the spinal cord and brainstem, where it regulates the pharyngeal reflex. 5-HT$_3$ works by directly gating an ion channel-inducing rapid depolarisation, which in turn releases neurotransmitters and/or peptides[49]. Additionally, 5-HT$_3$ receptors control the GABAergic system. Different types of GABAergic interneurons express these receptors. Physiological stimulation of 5-HT neurons stimulates GABAergic neurons located in the cortex and possibly those in the hippocampus, resulting in inhibition of adjacent excitatory neurons via GABA$_A$ (ionotropic receptor) and GABA$_B$ (metabotropic receptor)

receptors[79]. The use of 5-HT_3 receptor antagonists in depressive disorders did not bring the expected results. Nevertheless, there is some evidence that antidepressants interact with 5-HT_3[80,81]. For example, blockade of 5-HT_3 by ondansetron enhances the increase in extracellular serotonin production in the rat forebrain[57]. Intrestingly, various antidepressants are non-competitive 5-HT_3 receptor antagonists, which may contribute to their antipsychotic efficacy[82].

1.1.4 5-HT_4 receptors

5-HT_4 are located mainly in substantia nigra, hippocampus, globus pallidus, nucleus accumbens, putamen and caudate nucleus[83]. 5-HT_4 interacts with the p11 protein, the presence of which is necessary for the 5-HT_{1B} and 5-HT_4 receptor mediated antidepressant activity[84]. Based on preclinical studies, it has been found that the administration of 5-HT_4 antagonists (RS67333 and prucalopride) reduces the idle time during the Porsolt test (forced swim test), which makes 5-HT_4 an excellent target for future antidepressant therapies. Moreover, these compounds modify rat brain parameters considered to be key markers of antidepressant activity, i.e. an increase in tonus of 5-HT_{1A} postsynaptic receptors in the hippocampus, desensitization of 5-HT_{1A} autoreceptors and an increase in CREB phosphorylation. Significantly, these effects occurred after 3 days of treatment, while with SSRIs therapy, they are observed after 2-3 weeks[85].

1.1.5 5-HT_6 receptors

5-HT_6 are postsynaptic receptors most expressed in the olfactory tubercle, striatum, cortex and nucleus accumbens[86]. There is evidence of the role of these receptors in learning and memory[87], so in the future they may be used to improve cognition[88]. The 5-HT_6 receptors also play an important role in the treatment of depression. Preclinical studies conduced in 2008 prove that the 5-HT_6 antagonist SB-399885 exerts an antidepressant effect confirmed by Porsolt test and tail suspension test in rats and mice. In addition, these studies showed that the combination of ineffective doses of SB-399885 and imipramine, bupropion, moclobemide or desipramine had antidepressant effect[89]. This means that inhibition of the 5-HT_6 receptor enhances the effect of currently used antidepressants.

1.1.6 5-HT_7 receptors

5-HT_7 are the receptors with highest expression in the cortex thalamus, hypothalamus and hippocampus[90]. They play a significant role in regulating the mood, circadian rhythm and sleep[91]. Some antidepressants[92] and antipsychotics[93] have shown high affinity for 5-HT_7 receptors, which initiated research into their antidepressant effect. Preclinical trials conduced in in 2006 in rodents prove that the 5-HT_7 antagonist - SB-269970 has antidepressant and

anxiolytic effects[94]. It is worth mentioning that, aripiprazole, which is a neuroleptic drug with high affinity for 5-HT_7 receptor, is sometimes used to enhance the effects of traditional antidepressants[95,96].

1.2 Selective serotonin reuptake inhibitors

SSRIs are probably the most prescribed antidepressants in the world[39]. These drugs have revolutionized the treatment of depression due to their high efficacy with no significant side effects compared to tricyclic antidepressants and monoamine oxidase inhibitors. An additional advantage of these drugs is their broad therapeutic profile. In addition to the antidepressant effect, they are also effective in the treatment of anxiety disorders, such as panic disorder, posttraumatic stress disorder, obsessive-compulsive disorders, social phobia, eating disorders and many others. Understanding the mechanism of action of an SSRI requires knowledge of the reuptake process (*Figure 4*). Information in the brain is sent between neurons through synapses (connections between nerve cells). The presynaptic neuron (sending information) secretes serotonin into the synaptic cleft, where it is recognized by receptors on the surface of the postsynaptic neuron, which on the basis of this stimulation can further send a nerve impulse (action potential). In healthy people, when serotonin is no longer bound by receptors on the surface of the postsynaptic neuron, it is "sucked" by the serotonin transporter (SERT or 5-HTT) into the presynaptic neuron where it is stored for reuse[97].

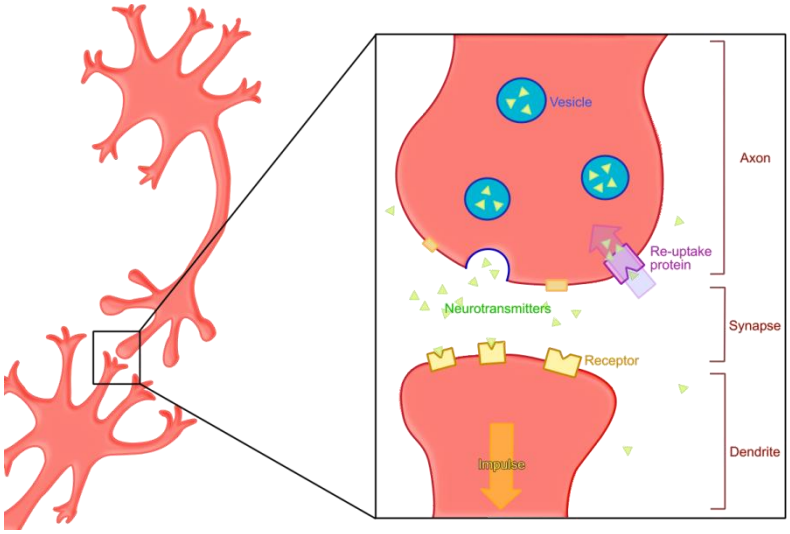


Figure 4 Reuptake of the neurotransmitter in the synaptic cleft („Reuptake both" by Sabar)

SSRIs are used when the amount of serotonin produced is insufficient or the SERT works harder and faster than usual. SSRIs work by blocking the 5-HTT transporter, which

results in serotonin remaining in the synaptic cleft for longer, where it can stimulate the postsynaptic neuron for longer, which can send impulses more often[97].

Currently, six drugs from the group of selective serotonin reuptake inhibitors are in use: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram. These drugs differ in their strength and specificity of their action on the serotonin transporter. Some of them, besides the inhibition of serotonin transporter, exert additional pharmacological effects, which cause certain differences in the clinical profile of the action of these drugs in various types of depression and other disorders. These SSRIs have different elimination periods from the system and have different effects on the cytochrome CYP-450 enzymes, which is important when they are dosed and combined with other drugs[28]. The biological half-life of citalopram, fluvoxamine, paroxetine and sertraline is approximately 20-35 hours, which means that after a break of several days, drugs that may interact with this SSRIs can be used. This period for fluoxetine is long (about 250 hours), which requires a 2-3 week break when there is a need to use drugs that interact with fluoxetine[98].

1.2.1 Citalopram

Citalopram is a racemic bicyclic phthalate derivative widely used in the treatment of depression (*Figure 5*). Also found use in the treatment of obsessive-compulsive disorders, separation anxiety, social anxiety disorder, panic disorder and premenstrual dysphoric syndrome. It was introduced to medicine in 1989 by the Danish pharmaceutical company H. Lundbeck under the trade name *Cipramil*[99]. In 2018, it was in the top ten of the most popular antidepressants on the US market (28 million prescriptions)[100].

The first antidepressant effect of citalopram occurs after 1-4 weeks of use. However, the full effect is achieved after 8-12 weeks of treatment[101]. Citalopram, right after escitalopram (form all SSRIs drugs), has the greatest selectivity of action on serotonin uptake compared to the action on norepinephrine or dopaminę uptake. It also shows very low affinity for various receptors, e.g. dopaminergic (D_1 and D_2), serotonergic (5-HT_{1A}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}), muscarinic, adrenergic (α_1, α_2, β), , γ-aminobutyric acid (GABA), histamine (H_1), cholinergic and benzodiazepine[102].

The oral bioavailability of citalopram is high (approximately 80%) and is unaffected by food consumption. The maximum concentration in the blood plasma is reached after about 4 hours. The half-life of citalopram is estimated to be approximately 35 hours. In the body, citalopram is metabolized to: demethylcitalopram by CYP2C19 and CYP3A4, didemethylcitalopram by CYP2D6 and citalopram *N*-oxide by monoamine oxidase enzymes and aldehyde oxidase[103].

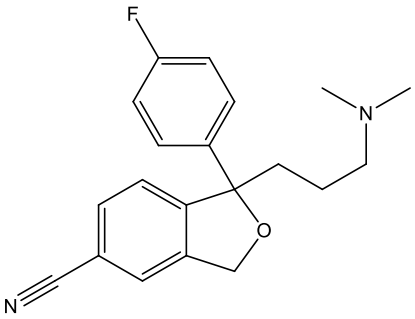


Figure 5 Citalopram

1.2.2 Escitalopram

Escitalopram is the S-enantiomer of citalopram introduced into medicine in 2001 by the Danish company H. Lundbeck under the name Cipralex (*Figure 6*)[99]. In 2018, it was ranked 3rd among the most popular antidepressants on the US market (38 million prescriptions)[100]. It can be successfully used not only in the treatment of depression, but also in a whole range of anxiety disorders (neuroses). The approved indications for escitalopram are the treatment of panic disorder with or without agoraphobia[104].

Escitalopram is the most selective inhibitor of the serotonin transporter (in relation to the norepinephrine transporter). The inhibitory potency of escitalopram on the serotonin transporter is twice as large compared to citalopram (in the absence of a difference in the effect on the norepinephrine transporter). S-enantiomer of citalopram does not have significant affinity for more than 140 receptors and binding sites[104].

Escitalopram is considered an allosteric serotonin reuptake inhibitor. This means that in addition to binding to the orthosteric (primary) binding site on the serotonin transporter (all SSRIs), it also binds to a secondary allosteric site on the SERT molecule to more strongly inhibit 5-HT reuptake. The combination of orthosteric and allosteric activity on SERT allows for higher levels of extracellular 5-HT, faster onset of action and greater efficacy compared to other SSRIs[105].

Escitalopram has relatively low protein binding of about 55-56%. The bioavailability of the drug is about 80%. The maximum concentration in the blood plasma is reached after about 4-5 hours. The half-life of escitalopram is estimated to be around 27-32 hours. It is metabolized in the same way as citalopram[105].

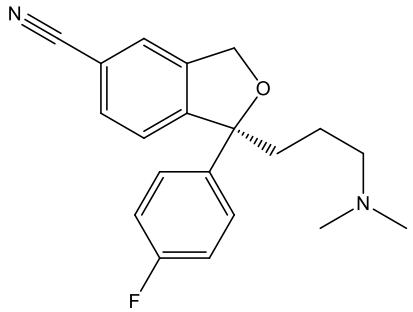


Figure 6 Escitalopram

1.2.3 Fluoxetine

Fluoxetine is an SSRI drug that was introduced to the US market in 1987 by the pharmaceutical company Eli Lilly under the trade name *Prozac* (*Figure 7*)[106]. In 2018, Prozac was ranked 7th among the most popular antidepressants on the US market (31 million prescriptions)[100]. Fluoxetine is used to treat depression, obsessive compulsive disorder, bulimia nervosa, and panic disorder[107].

Fluoxetine is the least selective serotonin transporter inhibitor (in relation to the noradrenaline transporter) - 70 times less selective than citalopram[104]. It also has little or no affinity for dopaminergic, serotonergic (5-HT_1, 5-HT_2), adrenergic (α_1, α_2, β), opioid, γ-aminobutyric acid, muscarinic and histamine (H_1) receptors[108].

Fluoxetine shows very high protein binding at the level of about 94%. The oral bioavailability of fluoxetine is <90%. The maximum concentration in the blood plasma is reached after about 6-8 hours. The half-life time of fluoxetine is 1-3 days after a single administration and 4-6 days during chronic use. Moreover, half-life time of norfluoxetine (fluoxetine active metabolite) is 4-16 days[107,108]. Fluoxetine is metabolised to norfluoxetine by CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5. Although all these enzymes contribute to the *N*-demethylation of fluoxetine, CYP2D6, CYP2C9 and CYP3A4 appear to be the main enzymes contributing to first metabolism phase. In addition, there is sugestive evidence that CYP2C19 and CYP3A4 mediate in the *O*-dealkylation of fluoxetine and norfluoxetine with formation of *p*-trifluoromethylphenol which is then metabolised to hippuric acid. Both fluoxetine and norfluoxetine undergo glucuronidation to facilitate excretion[106,109,110].

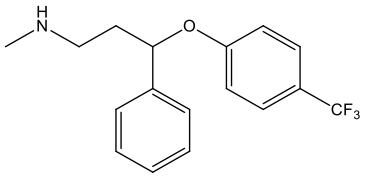


Figure 7 Fluoxetine

1.2.4 Fluvoxamine

Fluvoxamine was synthesized in Duphar's laboratories in 1971. The drug was first registered in Switzerland in 1983 by the Solvay concern. While in the United States, fluvoxamine was first authorized a few years later in 1987. It follows that fluvoxamine is currently the longest-used drug from the group of selective serotonin reuptake inhibitors[111]. Unlike other SSRIs, it is monocyclic molecules and the only one that does not have a chiral carbon atom (*Figure 8*). Although it belongs to the same class of drugs as the other SSRIs, it is most commonly used to treat obsessive-compulsive disorder[112].

Fluvoxamine is one of the least selective inhibitors of the serotonin transporter (in relation to the noradrenaline transporter) - 8 times less selective than citalopram[113]. Besides, apart from binding to the σ_1 receptor, it has a low affinity for the following receptors: serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_2), adrenergic (α_1, α_2, β), dopaminergic, cholinergic, benzodiazepine, GABA and histaminergic[111,114].

Fluvoxamine shows high plasma protein binding - about 77%. Due to the hepatic first-pass metabolism, the bioavailability of the drug is estimated at approximately 50%. The maximum serum concentration is reached after about 1.5-8 hours and this time is independant of the type of food consumed. The half-life time of this drug is 17-22 hours. Fluvoxamine is metabolized in the liver by cytochrome P450 isoenzymes, and 9 identified metabolites are pharmacologically inactive substances which are excreted in the urine[111].

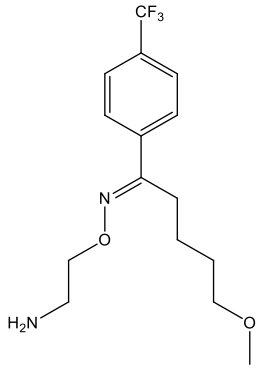


Figure 8 Fluvoxamine

1.2.5 Paroxetine

Paroxetine is sold as a phenylpiperidine hydrochloride as an antidepressant drug (*Figure 9*). It was introduced to the pharmaceutical market in 1991 under the trade name *Seroxat* by the British concern SmithKline Beecham (currently GlaxoSmithKline)[115]. In 2018, *Paxil* was ranked 17th in the most popular antidepressant drugs on the US market (13 million prescriptions)[100]. Paroxetine is used to treat depressive disorders, anxiety disorders, obsessive-compulsive disorders, post-traumatic stress disorder, panic disorders and social phobia[116].

Paroxetine is one of the least selective inhibitors of the serotonin transporter (in relation to the noradrenaline transporter) - 8 times less selective than citalopram[113]. In addition to high affinity for the serotonin transporter, it has low affinity for the following receptors: dopaminergic (D_2), serotonergic (5-HT_1, 5-HT_2), adrenergic (α_1, α_2, β), muscarinic, and histamine receptors[117].

Paroxetine shows high plasma protein binding of approximately 95%. Due to the hepatic first-pass metabolism, the bioavailability of the drug is estimated at 30-60%. The maximum serum concentration is reached after about 5 hours. The half-life time of the drug is 21 hours. Paroxetine is metabolised in the liver mainly by the CYP2D6 to inactive glucuronide and sulphate metabolites[118].

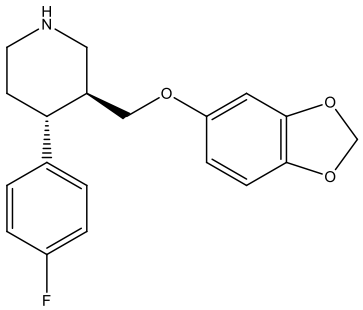


Figure 9 Paroxetine

1.2.6 Sertraline

Sertraline is an SSRI drug that was introduced to the pharmaceutical market in 1991 by the pharmaceutical company Pfizer under the trade name Zoloft (*Figure 10*)[119]. In 2018, Zoloft took the first place among the most popular antidepressants on the US market (49 million prescriptions)[100]. Sertraline is used to treat depression, obsessive-compulsive disorder, social anxiety disorder, post-traumatic anxiety disorder and panic disorder[120].

Sertraline is one of the less selective inhibitors of the serotonin transporter (in relation to the noradrenaline transporter) - 5 times less selective than citalopram[113]. Moreover, apart from binding to the σ1 receptor, it has little or no affinity for the following receptors: dopaminergic, serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_2), adrenergic (α_1, α_2, β), cholinergic, GABA, histaminergic, benzodiazepine[121,122].

Sertraline is slowly absorbed after oral administration, the maximum plasma concentration is reached after 4-8 hours. The bioavailability of the drug has been estimated at more than 44%. Sertraline shows high plasma protein binding at the level of approx. 98.5%. The half-life time of the drug is 24 hours. Sertraline is extensively metabolised by the liver by a number of enzymes from the cytochrome P450 family: CYP2B6, CYP2D6, CYP2C19 and also CYP3A4. Its main metabolite is norsertraline, which is formed by the *N*-demethylation of sertraline. This metabolite only in 5-10% inhibits serotonin reuptake, therefore its contribution to the action of sertraline is insignificant. Besides *N*-demethylation, the metabolism of sertraline includes *N*-hydroxylation, oxidative deamination and glucuronidation[122,123].

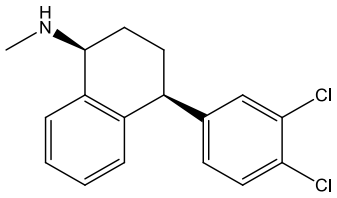


Figure 10 Sertraline

1.3 Tetrahydrocarbazole derivatives in the treatment of mental disorders

Pharmacological treatment of mental illnesses, such as mood disorders and anxiety disorders, is mainly associated with the manipulation of serotonin levels in the central nervous system. Thus, the design and synthesis of compounds targeting serotonin receptors and/or serotonin transporters continues to be in the spotlight. The invention and marketing of selective serotonin reuptake inhibitors has proved invaluable in the treatment of mental disorders in the vast majority of patients. Unfortunately, there is still a large group of patients suffering from drug-resistant depression[124]. Moreover, most antidepressants in use today are not completely devoid of side effects. Examples of less dangerous side effects include sleep disorders, dermatological problems, and sexual dysfunction. The most disturbing side effect is the suicidal tendency in the initial stage of therapy in the age group under 25[125,126]. Therefore, the search for new substances that modulate serotonin levels in the CNS, especially those that can selectively bind to a specific receptor subtype (receptor-specific agonists and antagonists) is still a subject

of research interest. Carbazole derivatives play an important role among the various groups of chemical compounds showing affinity for serotonin receptors or transporters.

One of the examples of potential antidepressants based on the carbazole structure are 6-arylsulfonyltetrahydro- and hexahydrocarbazoles **10** (*Figure 11*), which were patented in 2004 by the pharmaceutical concern Pharmacia & Upjohn (currently belongs to Pfizer). They are ligands for the 5-HT_6 serotonin receptor and may be useful in the treatment of disorders such as: anxiety disorders, depression, schizophrenia, Alzheimer's disease, stress-related diseases, panic disorders, phobia, obsessive-compulsive disorders, obesity, post-traumatic stress disorder, epilepsy and other CNS diseases in humans and animals[127].

A similar example are *N*-arylsulfonyltetrahydrocarbazoles **11** (*Figure 11*), which were patented in 2012 by the Indian pharmaceutical company Suven Life Sciences. These compounds, like 6-arylsulfonyltetrahydro- and hexahydrocarbazoles **10**, have an affinity for the 5-HT_6 receptor and can be used as effective therapeutic agents in the treatment of CNS diseases[128].

An interesting example of 5-HT_6 receptor antagonists are *N,N*-dimethyl-[9- (arylsulfonyl) -2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]amines. The tested compounds showed antagonistic activity by inhibiting the accumulation of serotonin. Additionally, in studies on selectivity against closely related receptors: adrenergic α_{1B}, serotonergic (5-HT_{1A}, 5-HT_{2A}), dopaminergic D_2, histamine (H_3, H_4) and the SERT and DAT transporters, the selectivity of the tested compounds was confirmed. The most promising compounds in the series were profiled for their CYP450 inhibitory potential. The two most attractive compounds were tested *in vitro* for metabolic stability in rat and human liver microsomes. Based on the conducted research, one compound with the most favorable attributes was selected - 6-methoxy-*N,N*-dimethyl-9- (phenylsulfonyl) -2,3,4,9-tetrahydro-1*H*-carbazol-3-amine **12** (*Figure 11*) and its pharmacokinetic profile and potential utility in the treatment of cognitive disorders was investigated. The Novel Object Recognition Test (NORT) carried out on rats proved the efficacy of the tested compound, which confirms its potential usefulness in the treatment of mental and neurological disorders with cognitive impairment[129].

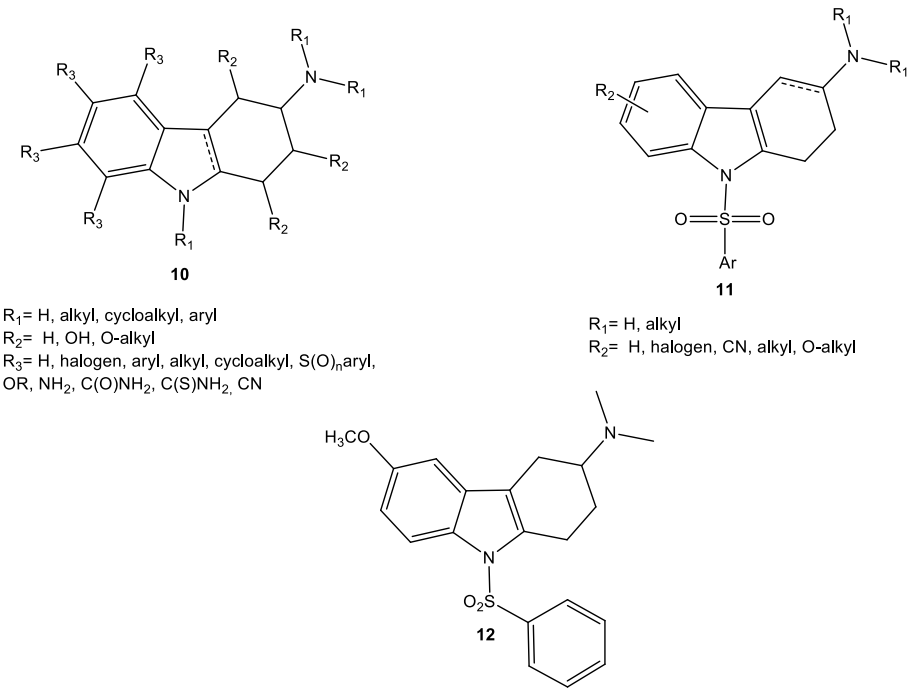


Figure 11 5-HT_6 receptor ligands

In 2000, Loza and coworkers[130] developed a method for the synthesis of new carbazole derivatives - 2-aminomethyltetrahydrocarbazolones, which show affinity for the dopaminergic D_2 receptor and serotonergic 5-HT_2 receptors (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) and are potential atypical antipsychotic drugs. The most promising derivative 2-((4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl) methyl)-2,3-dihydro-1*H*-carbazol-4(9H)-one (*Figure 12*) has a high affinity for both the D_2 receptor and the 5-HT_{2A} receptor with a simultaneous high Meltzer's ratio.

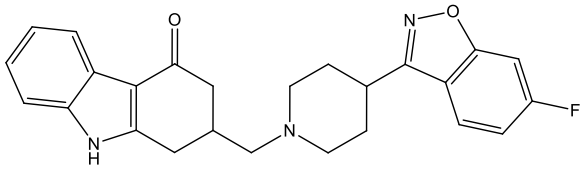


Figure 12 D_2 i 5-HT_2 receptors ligand

2. Carbazole derivatives in cancer therapy

Non-communicable diseases are currently responsible for the majority of deaths worldwide. Whereas, cancer is likely to become the leading cause of death and the most important barrier to increasing life expectancy in any country in the world in the 21st century[131]. According to a World Health Organization (WHO) estimates from 2015, cancer is the first or second most common cause of death before the age 70 years in 91 of 172 countries, and it

ranks third or fourth in an additional 22 countries. The number of cancer patients is growing rapidly around the world. The worldwide estimates by GLOBOCAN (a database prepared by IARC Global Cancer Observatory) states that in 2018 the number of new cases increased to 18.1 million, and deaths to 9.6 million. The main reasons for the continuous increase in morbidity are: population growth, aging and socioeconomic development[22].

There are many ways to fight cancer, including surgery, chemotherapy and radiation therapy[132]. Unfortunately, they are not always effective. Moreover, most of them cause irreversible changes in the human body, which may contribute to the relapse or the appearance of another disease. Therefore, the greatest challenge of today's medicine is the search for targeted therapies. These therapies are directed only to cancer cells without causing any changes or death of healthy cells.

Since the discovery of telomerase and the subsequent discovery of its activity mainly in cancer cells, telomerase has become an important target of anticancer therapies. Reducing its activity is a great way to fight cancer and an example of targeted therapy. The use of telomerase inhibitors in anticancer therapy is a fairly new solution that gives a wide range of possibilities in designing new inhibitors, which are currently the target of many scientists[133,134]. An example of such a solution is the use of carbazole derivatives as telomerase inhibitors. Carbazoles are a key structural motif of many biologically active compounds, both natural and synthetic, including anticancer drugs. They play an important role in all existing anticancer drugs because they are found in many different types of organisms including bacteria, fungi, plants and animals[15].

2.1 Telomeres, telomerase - structure and functions

Telomeres (Greek: Telos- end and meros- part) are short tandem repeats of DNA sequences that are found at the ends of a chromosome[135]. The human telomere sequence contains double-stranded guanine-rich tandem repeats (5′-TTAGGG-3′) varying in length from 5 to 10 kb in somatic cells and 10-20 kb in germ cells. Telomere length in somatic cells decreases with each cell division, with a loss of approximately 50-200 bp during each division[136].

Hexanucleotide tandem repeats in combination with specific telomerase binding proteins (TBP) form a "cap" structure that protects the ends of the chromosomes from degradation (*Figure 13*)[137]. The telomere with the binding proteins TRF1 and TRF2, forms a shelterin complex and a 3'-overhang loop (T-loop) within the double stranded telomer (D-loop). This complex protects the ends of the chromosomes from inducing DNA damage response (DDR)[136,138]. The shelterin complex consists of six proteins:

- POT1 (protection of telomeres 1) - regulates the length of telomeres and participates in the formation of the T-loop

- TRF1 (telomeric repeat binding factor 1) - negative regulator of telomere length, prevents telomerase from binding to the RNA matrix; can form a dimer with the TRF2 protein; binds to the double-stranded telomer fragment through the domain Myb

- TRF2 (telomeric repeat binding factor 2) - prevents fusion of telomere ends and facilitates the formation of a T-loop

- TIN2 (TRF1 interacting nuclear factor 2) - regulates telomerase access to telomers and allows TPP1 and POT1 proteins to bind to a double-stranded fragment of telomere

- TPP1 (tripeptidyl peptidase 1) - enables interaction between POT1 and TIN2 proteins

- RAP1 (repressor - activator protein 1) - regulates the length of telomere and prevents fusion of the telomere ends[139]

The activity of binding DNA to TRF1 and TRF2 is regulated by poly(ADP-ribose) polymerases (PARPs). PARP1 and PARP2 bind to TRF2 and promote its post-translational modification that blocks the ability of DNA binding by TRF2. TRF1 can also be modified by PARP enzymes (tankyrase 1 and tankyrase 2), losing the ability to bind DNA. In cancer cells, overexpression of TNKS1 (tankyrase 1) reduces the level of TRF1 at the telomere, thereby giving telomerase increased access to telomeres causing their gradual elongation. Thus, inhibition of PARP results in the maintenance of telomere length[140].

The G-quadruplex is another higher-order structure formed by the stacking of several guanosine tetrads including the 16-nucleotide sequence d(GGGTTAGGGTTAGGGT) and the 6-nucleotide sequence d(TAGGGT) of the telomeric 3'-overhang stabilized by hydrogen bonding (*Figure 13*). The G-quadruplex protects the telomeric 3'-overhang against telomerase access. Stabilization of the G-quadruplex with small molecule ligands can block the 3'-overhang and telomerase access to telomeres[141,142,143].

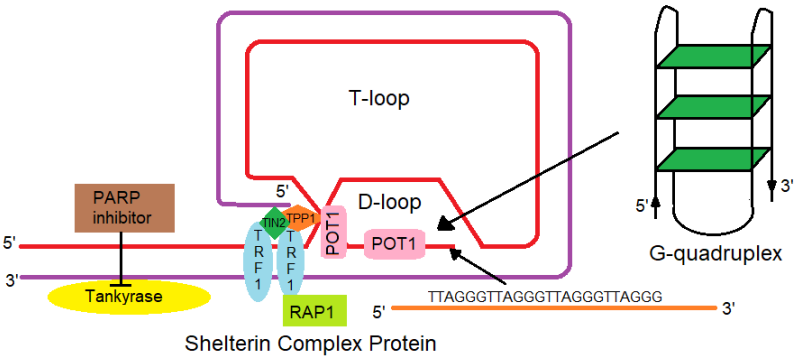


Figure 13 Telomere structure (modyfication according to [143])

Telomeres play an important role in a variety of cellular processes. Human telomeres have a single-stranded fragment at the 3'end of DNA - 3'-overhang, which limits replication causing telomere shortening. Valid cells have a certain number of divisions. When telomere length is reduced to the critical point, the cell undergoes senescence. The phenomenon of senescence normal human cells is called the "Hayflick limit" (approximately 60 divisions) [144,145]. On the other hand, cancer cells have higher telomerase activity, which prevents telomere shortening and inhibits cell senescence. Therefore, the development of telomerase inhibitors is a potential approach in anticancer therapy. Another important function of telomeres is to prevent chromosome end fusion, thereby maintaining chromosome stability and genomic integrity[136]. Additionally, telomeres protect chromosomes from degradation by exonuclease and support pairing and recombination of homologous chromosomes. Appropriate telomere length is crucial for homologous recombination and chromosome segregation during meiosis[146]. Too short telomeres cause a reduction in recombination rate, segregation abnormalities and meiosis nondisjunction, which can lead to apoptosis or the generation of aneuploid gametes[147].

Telomerase is a reverse transcriptase responsible for telomere elongation. It works by transcribing a short RNA template sequence into DNA. Unlike retroviral or viral revertases, telomerase specializes in the synthesis of multiple short tandem repeats at the ends of chromosomes[148]. RNA-dependent DNA polymerase consists of the protein component TERT (telomerase reverse transcriptase) and the component TERC (telomerase RNA component) (*Figure 14*). Based on the current data, it is assumed that the TERT protein consists of three domains: the N-terminal domain containing the RNA-DNA binding motif, the central domain with catalytic activity, and the C-terminal domain. The function of TERTis the synthesis of single DNA strands on RNA template. The protein uses the (3'-CAAUCCCAAUC-5') TERC region, and adds TTAGGG repeats to extend the single-stranded fragment at the 3' end of the telomer. The

TERC subunit consists of a central domain, a binding site for proteins responsible for the maturation and stabilization of the domain, and a TERT binding site. The hTERC gene consists of 445 nucleotides with a 5'-(CUAACCCUAAC)-3' repeating nucleotide sequence complementary to the telomere sequence (TTAGGG)[137,139].

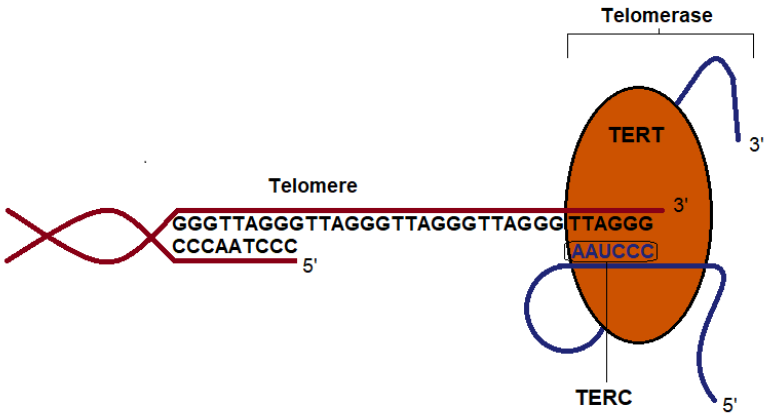


Figure 14 Telomer/telomerase complex (modyfication according to [149])

The mechanism of the telomerase reaction can be described in three steps. The first step is to align the telomerase RNA template with the short telomeric sequence at the 3'end of the chromosome. This is followed by strand elongation during which the TERT subunit uses the RNA fragment (3'-CAAUCCCAAUC-5') as a template and adds TTAGGG repeats thereby creating a new telomere termination. The last stage is translocation, during which the telomerase moves to the new 3'end of the chromosome and adds another repeat or dissociation (leaving the telomere region) (*Figure 15*)[139].

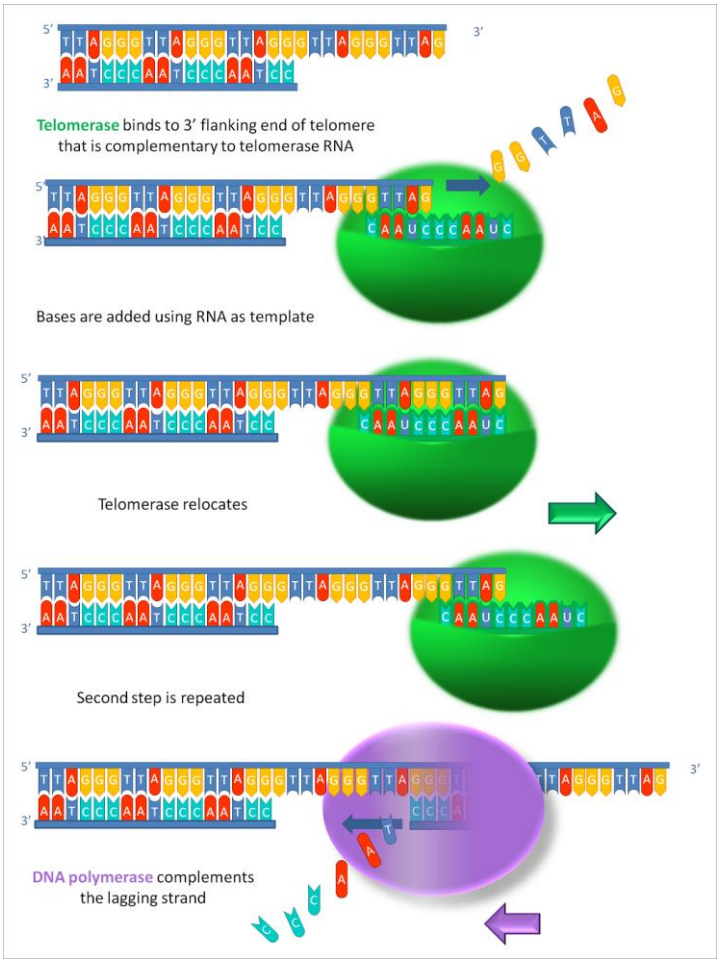


Figure 15 Mechanism of the telomerase reaction („Working principle of telomerase" by Fatma Uzbas licensed under CC BY-SA 3.0)

2.2 Telomerase inhibition strategies as a target of anticancer therapy

The relationship between telomerase activity and neoplastic transformation is obvious. Telomerase works by lengthening the ends of telomeres, which promotes unlimited cell division and is one of the features of neoplastic cells. While the absence of telomerase activity results in telomere shortening and consequently cell apoptosis. Most of human somatic cells do not show telomerase activity, which results in their limited viability. On the other hand, cancer cells are characterized by high activity of this enzyme, which leads to their unlimited proliferation, thus ensuring their immortality. Current data show that telomerase is expressed in approximately 90% of human cancers[139]. Based on the information about telomeres and telomerase, it can be seen that there are many different strategies for inhibiting telomerase activity. In this chapter, I will briefly describe only those that are most important.

2.2.1 G-quarduplex stabilizers

The G-quadruplex is a sequence of polynucleotides that forms the specific structure of guanidine tetrads stabilized by Hoogsteen hydrogen bonds. This structure can be formed in guanine-rich nucleic acids including telomeres. The function of the G-quadruplex is probably protection the telomere ends from nuclease attack. These protective structures are recognized and partially unfolded by the telomerase at the 3'end. These protective structures are recognized and partially unfolded by the telomerase at the 3'end. Therefore, the strategy of inhibiting telomerase activity in this case is the use of so-called "stabilizers" which effectively "block" the telomeres in the quadruplex configuration and prevent telomere elongation by telomerase or ALT (alternative lengthening of telomeres). G-quadruplex stabilizers accelerate telomere shortening and subsequent cell death. An additional function of these compounds is disturbing the spatial structure of telomeres (uncapping)[135]. Examples of G-quadruplex stabilizers are: RHPS4[150-152], BRACO-19[153], and telomestatin[154] (*Figure 16*). These compounds are still at an early stage of development and have not yet been subjected to clinical trials.

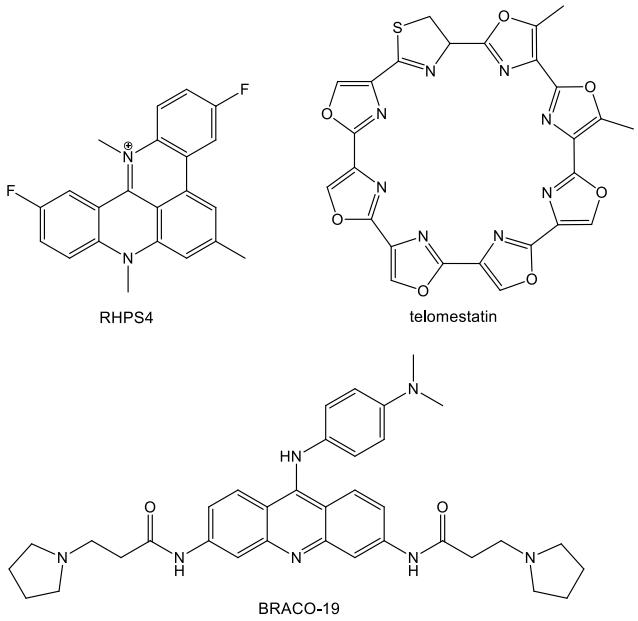


Figure16 G-quarduplex stabilizers

2.2.2 Oligonucleotide inhibitors

Oligonucleotide inhibitors we are called antisense oligonucleotides and chemically modified nucleic acids. They act by inhibiting telomerase and inducing telomere shortening, leading to cell senescence and apoptosis. Oligonucleotide inhibitors can act directly or indirectly on the RNA template, the hTERT protein and related proteins[155]. One of the most important

oligonucleotide inhibitors is imetelstat (GRN163L). It is a 13-mer thiophosphoramidate deoxyribo-oligonucleotide that inhibits telomerase activity by binding directly to the telomerase RNA (hTR) template. The sequence complementary to hTR is 5'-palmitate-TAGGGTTAGACAA-NH_2-3'. The palmitoyl group is bound to the 5'-phosphorothioate group, which makes the molecule hydrophobic, improving the retention of the drug in biological membranes and thus increases the telomerase inhibition. So far, GRN163L is the most clinically tested telomerase inhibitor. This inhibitor showed significant inhibition of telomerase in many tumor cell lines, i.e. pancreas, bladder, liver, breast and prostate[156,157]. Another promising oligonucleotides are *T-oligos*, which are guanine rich deoxyribo-oligonucleotides homologous to the telomere 3' overhang. *T-oligo* targets incorrect signaling pathways in cancer cells, including DDR (DNA damage responses). After accumulation in the cell nucleus, *T-oligos* induce strong DNA damage reactions, i.e. cell cycle arrest and apoptosis[135]. *T-oligos* have shown antitumor activity in many *in vitro* tumor cell lines, i.e. melanoma[158,159], lymphoma[160] or lung cancer[161].

2.2.3 Gene therapy

Gene therapy is based on the use of the hTERT promoter-driven expression of oncolytic adenoviruses and/or suicide genes only in tumor cells. This leads to the selective killing of cancer cells and leaving healthy cells intact[135,162]. An example of oncolytic virus therapy is the use of telomelysin (OBP-301) - an attenuated adenovirus vector type 5, which has the hTERT promoter in genome that directs the expression of the E1A and E1B genes. In this way, viral-mediated lysis of tumor cells is induced after virus propagation in TERT-overexpressing cells. In normal cells there is no production of viral proteins due to the lack of activation of the hTERT promoter. The drug is in phase I/II of clinical trials on liver and esophageal tumors[163]. Another approach involves therapy with suicide genes which encode enzymes that make it possible to convert an inactive chemical compound into a toxic substance that causes cancer cell death. An example is the pro-drug CB1954, in which the regulatory sequences of the hTERT and hTR genes were used to regulate the expression of the nitroreductase enzyme. As a result of the activity of telomerase promoter sequences the production of nitroreductase increases in cells, which leads to an increase in the metabolism of the pro-drug CB1954 and the formation of its active form toxic for cells. This form does not occur in normal cells that are unable to metabolize pro-drug[164].

2.2.4 Small-molecule telomerase inhibitors

Small-molecule telomerase inhibitors are designed based on screening of chemical libraries or structures of naturally occurring telomerase inhibitors[165-169]. The best known small-molecule telomerase inhibitor is BIBR1532 ((2E)-3-naphthalen-2-yl-but-2-enoylaminobenzoic

acid) (*Figure 17*). It is a non-competitive inhibitor of TERT and hTR which acts *in vitro* by shortening telomere and inhibiting cell proliferation causing cell senescence. Although BIBR1532 has shown good results in preclinical studies in breast, prostate and fibrosarcoma cell lines, no further progress or entry into clinical trials has been reported[170]. In recent years, BIBR1532 has been used as a telomerase inhibition tool showing that it lowers the expression of alpha-fetoprotein (AFP)[171], and that glucose restriction increases the activity of this inhibitor[172].

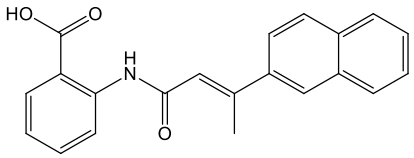


Figure 17 BIBR1532 structure

2.2.5 Immunotherapy

Telomerase-targeted immunotherapy uses the relatively high expression of telomerase in tumor cells as a neoantigen (tumor antigen). In cancer cells, peptides derived from the telomerase protein component (TERT) are processed and presented on the cell surface by the major histocompatibility complex (MHC I), making these cells the target of activated immune cells. Considerable efforts have been made to prove that TERT is a tumor-associated antigen (TAA) capable of inducing CD8+ cytotoxic T lymphocyte response in many types of cancer. There are two approaches used in immunotherapy: direct *in vivo* immune activation or *ex vivo* activation and expansion of immune cells. Vaccines that are promising in anti-cancer therapy, acting by direct immune activation *in vivo*, are: GV1001, Vx-001 and GX-301. Whereas, an important vaccine that works by *ex vivo* activation and expansion of immune cells is GRNVAC1. GV1001 vaccine consists of 16 amino acids (p611-EARPALLTSRLRFIPK-p626) and is recognized by both MHC class I and class II, allowing the induction of both CD8+ and CD4+ responses[135]. GV1001 has been used in clinical trials in non-small cell lung cancer (NSCLC) [173], pancreatic cancer[174], hepatocellular carcinoma[175] and malignant melanoma[176]. Another promising vaccine is Vx-001. It consists of two peptides: a native cryptic peptide (TERT-572) and an optimized variant (TERT-572Y). The first vaccination with immunogenic TERT-572Y initiates an anti-tumor immune response, and the subsequent vaccination with native non-immunogenic TERT-572 is performed to select highly specific cytotoxic T cells against the TERT 572 peptide presented by tumor cells[135]. Currently, studies on the use of Vx-001 in the treatment of NSCLC are underway and are in the phase II of clinical trials[177]. The next one vaccine that acts by *in vivo* direct immune activation is GX-301. It consists of four peptides derived from the TERT subunit: p540-548, p611-626, p672-686 and p766-780, which activate T

lymphocyte and release cytokines[135]. There are ongoing studies on the use of GX-301 in the treatment of prostate and kidney cancer[178]. An example of a promising vaccine acting by *ex vivo* activation and expansion of immune cells is GRNVAC1. In this vaccination, patient-derived dendritic cells are isolated, transfected ex-vivo with mRNA encoding a chimeric protein, and then injected intradermally into patients inducing a TERT specific CD4+ and CD8+ T lymphocyte response[135]. Studies on the use of GRNVAC1 (now AST-VAC1) in the treatment of acute myeloid leukemia (AML) have been carried out. TERT-specific T cell responses were observed in 11 out of 19 patients in phase II clinical trials[179].

2.3 Carbazoles used in cancer treatment

The beginning of interest in the antitumor activity of carbazoles is attributed to the isolation of ellipticin from the leaves of the tropical tree *Ochrosia elliptica Labill* in 1959[180]. Since that time, three anticancer drugs which are carbazole derivatives have been introduced to the pharmaceutical market: celiptium, alecansa and rydapt[15].

The first synthesized ellipticin analogue to be approved as an anticancer drug is Celiptium (*N*-methyl-9-hydroxyelipticin acetate) (*Figure 18*). It works by stabilizing the topoisomerase II complex and inducing DNA breaks, which leads to inhibition of DNA and RNA replication and protein synthesis[181]. Reports on Celiptium anticancer effect date back to the 1970s. Since then, it has been extensively studied and has proved to be useful in the treatment of metastatic breast cancer[182,183]. The low haematological toxicity of Celiptum made it a promising ingredient in combination therapy in the treatment of breast cancer, mainly in combination with vinblastine[184].

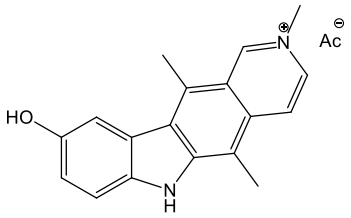


Figure18 Chemical structure of Celiptium

The second carbazole derivative that has been approved for treatment is alectinib (commercially available under the name Alecensa) based on the 5*H*-benzo[b]carbazol-11(6*H*)-one core (*Figure 19*). Alectinib was approved in 2015 by the FDA (American Food and Drug Administration)[185] and then in 2017 by the EMA (European Medicines Agency)[186]. It is used to treat advanced ALK-positive (ALK-anaplastic lymphoma kinase) non-small cell lung cancer (NSCLC). Alecensa works by blocking the action of an enzyme called ”ALK tyrosine kinase”.

The abnormal forms of this enzyme, resulting from a defective version of the gene producing it, promote the growth of cancer cells. Alecensa may slow or stop the growth of the tumor. It can also reduce its size[186]. Alectinib has a very high protein binding of about 99%. Oral bioavailability of alecensa is 37%. The maximum concentration in the blood plasma is reached after about 4-6 hours. Its half-life is 32.5 hours. Alectinib is metabolised mainly by CYP3A4, another cytochrome P450 enzymes and aldehyde dehydrogenases playing only a minor role[187].

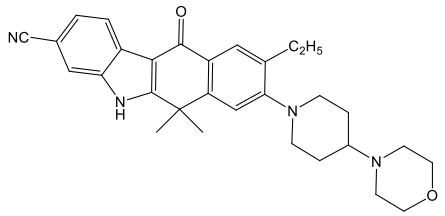


Figure 19 Chemical structure of Alectinib

A third carbazole derivative recently (2017) approved by the FDA[188] and EMA[189] is midostaurin (trade name Rydapt) (*Figure 20*). It is used to treat acute myeloid leukemia (AML) with FLT3 gene mutation, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) or mast cell leukemia (MCL). The action of midostaurin is based on the inhibition of numerous receptors with the activity of tyrosine kinases, including FLT3 and KIT kinase. Midostaurin inhibits the FLT3 receptor signaling pathway and induces cell cycle arrest and apoptosis in leukemic cells expressing mutant FLT3 ITD or TKD receptors or overexpressing wild-type FLT3 receptors. In addition, it has the ability to inhibit KIT signaling, blocks the multiplication and survival of mast cells and the release of histamine. Midostaurin also inhibits several other receptors with tyrosine kinase activity, such as PDGFR (platelet-derived growth factor receptor) or VEGFR2 (vascular endothelial growth factor receptor 2), as well as members of the PKC (protein kinase C) family that belong to the serine-threonine kinases. It binds to the catalytic domain of these kinases and inhibits the mitogenic signals of the appropriate growth factors in cells, causing growth arrest. Rydapt shows very high protein binding of over 98%. Its oral bioavailability is unknown. The maximum concentration in the blood plasma is reached after about 1-3 hours. The half-life of rydapt is approximately 20.9 hours. Midostaurin is metabolised by CYP3A4 mainly by oxidative processes. Its most important active metabolites are CGP62221 (formed by *O*-demethylation) and CGP52421 (formed by hydroxylation)[190].

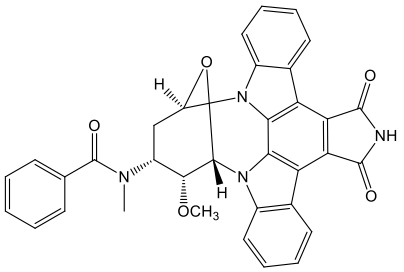


Figure 20 Chemical structure of Midostaurin

2.4 Carbazoles derivatives as telomerase inhibitors

Currently, cancers are one of the most problematic diseases that humanity has to deal with. The number of new cases and deaths is increasing every year[22]. There is still no single universal method of fighting cancer. Each type of cancer requires a different treatment. Unfortunately, despite many methods of treating neoplastic diseases, such as surgery, chemotherapy or radiotherapy[132], the fight against this disease is always long and exhausting for the body. Very often, the disease relapses or another one appears as a result of previous treatment. The search for new ways to deal with cancer continues to be the focus of many scientists[133,134]. Telomerase is an important target of modern cancer therapies. One example of telomerase inhibitors are carbazoles. So far, many alkaloids have been isolated and tested for biological activity[191]. The beginning of interest in the antitumor activity of carbazoles dates back to the 1960s, when ellipticin was isolated[180]. Since then, a huge number of carbazole derivatives with anticancer potential have been synthesized[14,192].

An example of a carbazole telomerase inhibitor is 3,6-bis(1-methyl-4-vinylpyridinium)-carbazole diiodide (BMVC) (*Figure 21*). It works by suppressing the activity of telomerase to cause the cancer cells senescence leading to tumor destruction. Most of the research is based on the use of BMVC as a G-quadruplex ligand, which interacts with nucleic acids in various forms and stabilizes the G-quadruplex structure[15]. During the research on human cancer cell lines of lung cancer H129 and oral cancer Ca9-22, BMVC did not cause acute cytotoxicity, but only minimal damage to healthy fibroblast cell lines in the lung (MRC5) and skin (Detroit-551)[193]. Unlike other telomerase inhibitors, tumor cells treated with BMVC showed a high rate of telomere shortening and a growth retardation before entering the aging phase. Moreover, BMVC suppressed the neoplastic properties of cancer cells, such as cell migration, colony formation, and anchorage-independent growth[192].

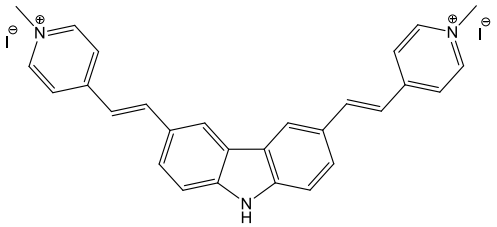


Figure 21 Chemical structure of BMVC

In 2014, Bhattacharya and coworkers[194] described four carbazole-benzimidazole conjugates (CMP, CHP, CBM, and CBhoe), which are G-quadruplex selective ligands that inhibit telomerase activity (*Figure 22*). The mono-(bis-benzimidazole) derivatives CMP, CHP and CBM showed a 500 times higher preference toward the G-quadruplex over double-stranded DNA than the di-(bis-benzimidazole) ligand - CBhoe. Additionally, during *in vitro* research on telomerase derived from A549 human lung cancer cell lines, CMP and CHP ligands were found to be most effective in inhibiting telomerase activity (IC_{50} below 1 μM). The low concentration of ligand needed to inhibit the activity of telomerase and the selective attack on tumor cells means that carbazole-benzimidazole conjugates may be useful as anticancer drugs in the future.

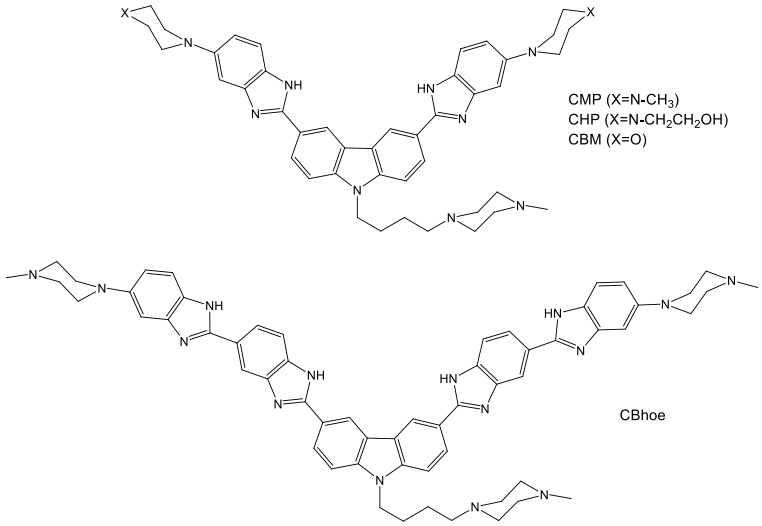


Figure 22 Chemical structures of carbazole-benzimidazole conjugates

In 2018, Rubiś et al.[195] described a carbazole derivative containing a benzothiazole moiety, which is a G-quadruplex stabilizer (*Figure 23*). The stabilization of the G-quadruplex by the described ligand was checked using UV-VIS techniques, fluorescence and circular dichroism spectroscopy. Based on the research, it was determined that the formation of the ligand/G-quadruplex complex takes place in two stages. On the other hand, clear changes in the UV-Vis spectra indicated strong interactions between the ligand and external G-tetrads,

which is also confirmed by the results obtained with the CD. It was also observed that the free ligand has a low fluorescence, which rises after the addition of G-quadruplex. Additionally, during the research on breast cancer cell lines, carbazole derivative has shown significant cytotoxicity.

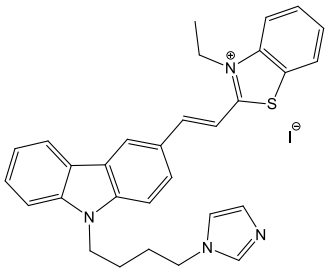


Figure 23 Chemical structure of a carbazole derivative containing a benzothiazole moiety

3. Selected methods of synthesis of tetrahydrocarbazolone derivatives

Tetrahydrocarbazolones are carbazole derivatives that consist of an indole scaffold and a cyclic ketone (usually six or five-membered), very often found in natural products. Moreover, substituted carbazolones are key intermediates in the synthesis of alkaloids and carbazolone drugs. For example, murrayquinone A (HIV integrase inhibitor), ondansetron, and alosetron (selective 5-HT_3 serotonin receptor antagonists) are carbazolone derivatives[196]. Therefore, many different methods have been developed to synthesize the carbazolone core. The most conventional method of synthesizing these compounds is the Fischer indole synthesis using cyclohexane-1,3-dione and phenylhydrazine as a substrates. Heck-type coupling reaction, which is transition metal catalyzed intracellular cyclization of *o*-halo aryl enaminions, is also frequently used. Additionally, reductive *N*-heterocyclization of substituted 2-(2-nitrophenyl)cyclohexanones and direct oxidative coupling of aryl enaminions to form a C-C bond are used in the synthesis of tetrahydrocarbazolones. Other methods are based on the synthesis of carbazolones from indole derivatives using metals or Lewis acids[196,197].

3.1 Fischer indolization

Fischer indolization is an extremely useful method of creating an indole ring. It was discovered in 1883 by Emil Fischer[198]. The use of phenylhydrazine **13** and cyclohexane-1,3-dione **14** as substrates leads to the preparation of tetrahydrocarbazol-4-one **15**. The first step of the reaction mechanism involves the condensation of phenylhydrazine **13** with cyclohexane-1,3-dione **14**. The obtained arylhydrazone **16** is then converted in an acidic environment to intermediate **17**. In the next step, as a result of the [3,3]-sigmatropic rearrangement, intermediate **18** is formed, which by protonation and nucleophilic addition (**19**) leads to the

tricyclic compound **20**. The last step is the elimination of ammonia to obtain tetrahydrocarbazole-4-one **15** (*Figure 24*)[197].

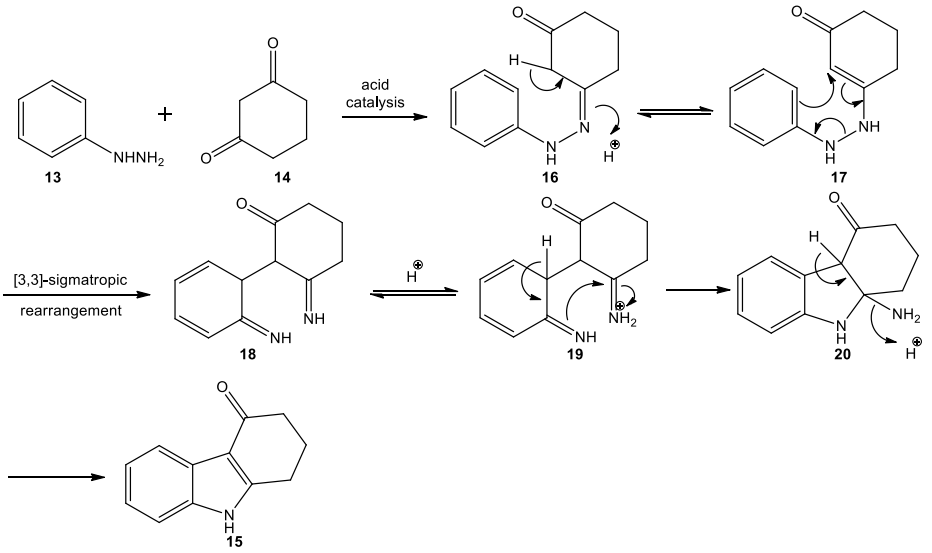


Figure 24 Fischer indolization mechanism

In 2005, Wheeler and Czeskis[199] used Fischer indolization in the synthesis of tetrahydrocarbazol-4-one, which is an intermediate of LY377604 (β_3 adrenergic receptor agonist). Hydrazone **16** was obtained in reaction of phenylhydrazine hydrochloride **21** with cyclohexane-1,3-dione **14**. The received phenylhydrazone **16** was then cyclized in the presence of zinc chloride in acetic acid to obtain tetrahydrocarbazol-4-one **15** in 52% yield (*Figure 25a*).

Another example is Vince and Li[200] research from 2006 about the application of carbazolone-containing α,γ-diketoacids acids as potential HIV integrase inhibitors. They also used the Fischer indolization to synthesize the carbazolone core. The first step of the synthesis was carried out in the same way as in the previous case. However, they used TFA for the cyclization of the phenylhydrazone (*Figure 25b*). The corresponding tetrahydrocarbazolone **22** was obtained in 40% yield.

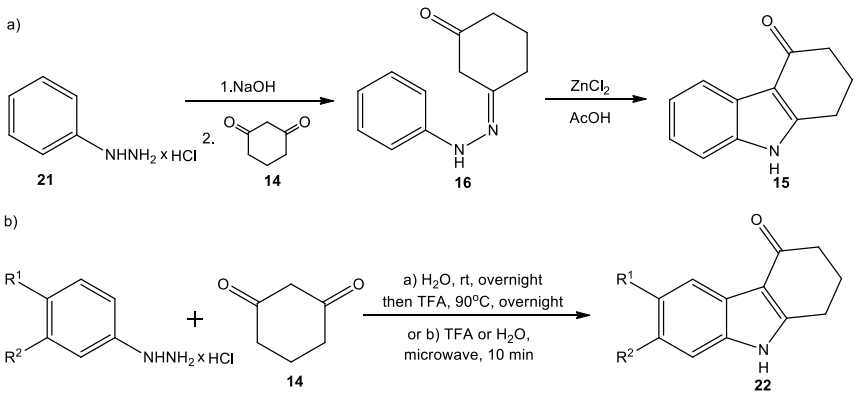


Figure 25 Synthesis of tetrahydrocarbazol-4-ones

Fischer indolization in the synthesis of tetrahydrocarbazolones was also used by Hu and coworkers[201] to obtain 1-oxo-1,2,3,4-tetrahydrocarbazoles **25**. The reaction was performed in a single step (so-called "one pot reaction") using as substrates phenylhydrazine hydrochloride **23** and 2-aminocyclohexanone hydrochloride **24** mixed in a ratio of 1:1.2 (*Figure 26*). The yield of the synthesis in certain cases reached up to 94%.

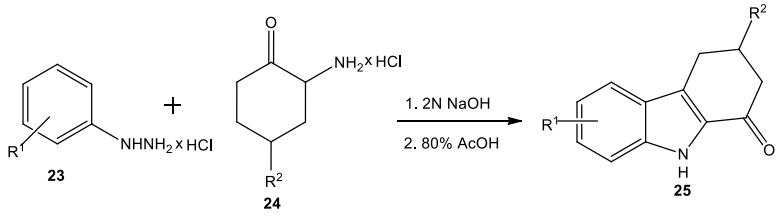


Figure 26 Synthesis of 1-oxo-1,2,3,4-tetrahydrocarbazoles

An interesting use of Fischer indolization to obtain tetrahydrocarbazolones is synthesis catalyzed by SO_3H-functionalized ionic liquids (ILs) **26**, which was developed by Xu et al.[202] in 2009 (*Figure 27a*). They synthesized a series of ILs **26** containing two alkyl sulfonic groups attached to the imidazolium cation, which improved the synthesis efficiency over the use of sulfuric acid as a catalyst (yield up to 93%). These catalysts can be regenerated using the cation exchange resin Dowex-50 *(Figure 27b*). It is also worth noting that the products obtained by this synthesis can be easily separated from the reaction mixture by simple filtration.

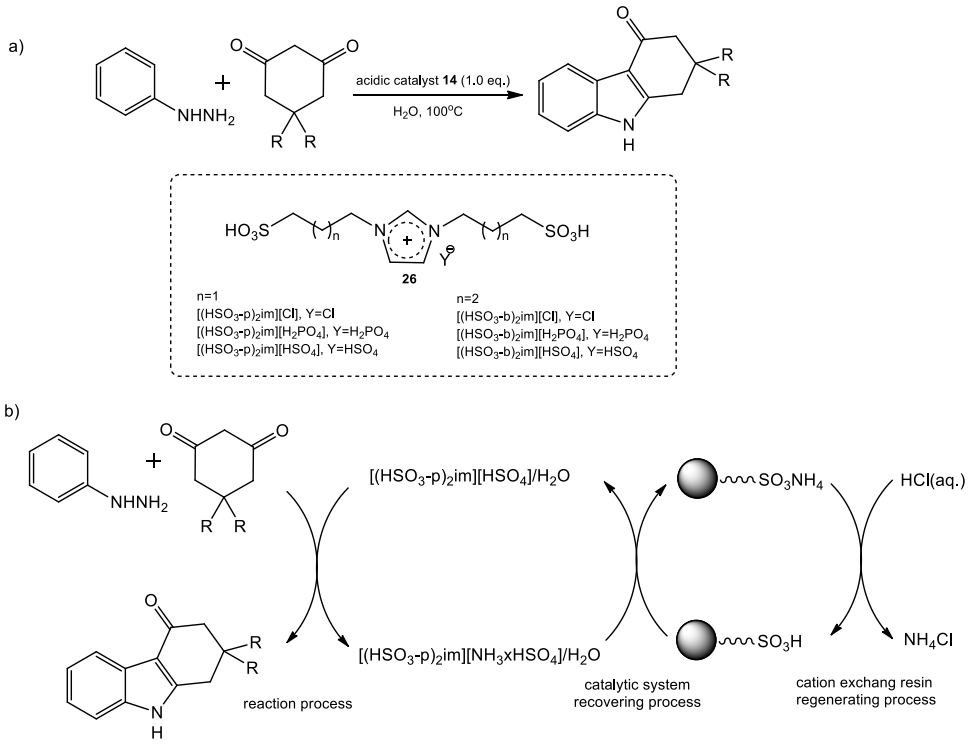


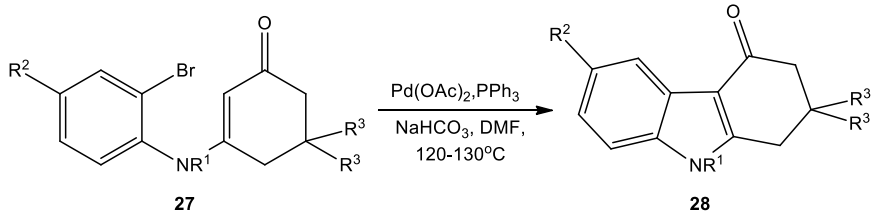
Figure 27 ILs catalyzed synthesis of tetrahydrocarbazolones

3.2 Heck reaction

Another important method of obtaining the carbazolone core is the Heck reaction. It involves the attachment of unsaturated organic compound (halide) to an alkene with a new carbon-carbon bond formation. This reaction takes place under basic conditions and requires organometallic catalysis. The most common catalysts are palladium and rhodium[203] complexes. The name comes from the surname of the discoverer, the American chemist Richard Heck, who first described this reaction in 1972[204].

As early as 1980, Kibayashi and coworkers[205] used the Heck reaction in the synthesis of tetrahydrocarbazol-4-one derivatives **28**. The appropriate bromo enaminone **27** was treated with palladium acetate and triphenylphosphine in the presence of sodium bicarbonate to obtain carbazolone **28**. The reaction was carried out in DMF at 120-130°C for 20-35 h. Unfortunately, the yield of the reaction, depending on the derivative, was only 9-36%. Scientists in their work also proposed a reaction mechanism (*Figure 28*). In the first reaction step, palladium (II) acetate is reduced by triphenylphosphine to palladium (0). The next step is oxidative addition, during which the palladium atom is introduced in place of the previous carbon-bromine bond. Then a π-complex is formed between the palladium atom and the double bond present in the enone ring. In the fourth step, the π complex is transformed into the σ-complex, which results in the

formation of a new carbon-carbon bond. The V step is β-hydride elimination with the formation of a carbon-carbon double bond and the release of the free palladium (II) complex, which in step VI undergoes reductive elimination, resulting in the regeneration of the catalytically active palladium (0) complex[206].



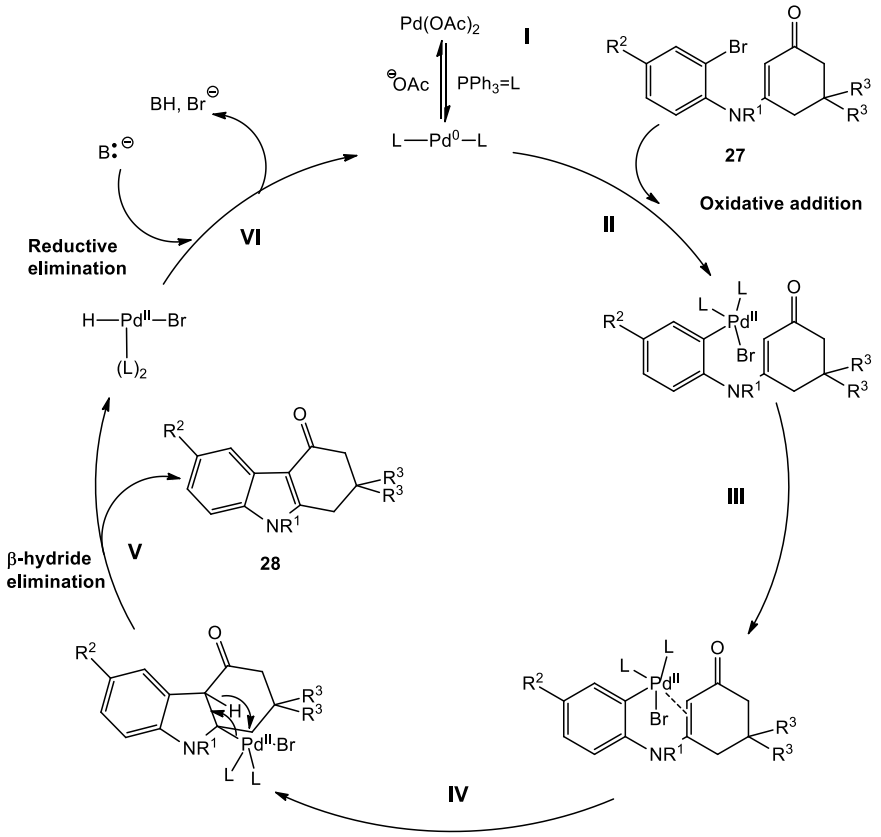


Figure 28 Heck reaction mechanism

Another example is the Pombo-Villar and Sørensen[207] study from 2004. They used the Heck reaction to synthesize cyclopenta[*b*]indol-1-ones and carbazol-4-ones. In order to obtain 2,3-dihydrocyclopenta[*b*]indol-1(4*H*)-one **32**, they used the *o*-halo aryl enaminion **31**, which they obtained by condensation of *o*-bromoaniline **29** with 1,3-cyclopentanedione **30**. The prepared compound **31** underwent the palladium catalyzed cyclization in the presence of $Pd(OAc)_2$, and

tri(*o*-tolyl)phosphine. The reaction was carried out in DMF under microwave heating (100°C) for 5 min (*Figure 29a*). However, in order to obtain tetrahydrocarbazol-4-one **15**, they cyclized cyclohex-2-enone **34**, formed by the condensation of *o*-iodoaniline **33** and cyclohexane-1,3-dione **14**. In this case, they also used a complex prepared from palladium acetate and tri(*o*-tolyl)phosphine as catalyst, but the reaction was carried out in the presence of tetrabutylammonium chloride and sodium acetate in DMF at 120°C for 16 h (*Figure 29b*). The yields of both the first and the second synthesis reached 95-99%.

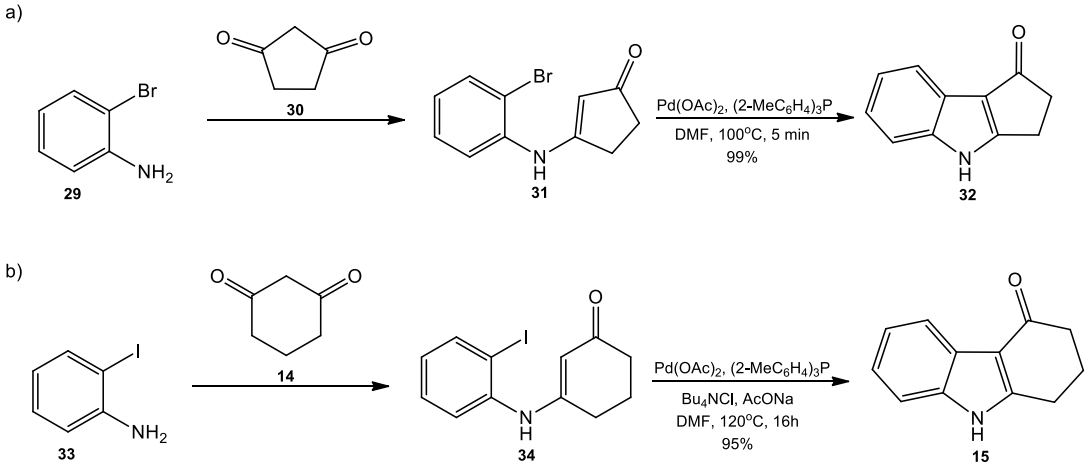


Figure 29 Synthesis of cyclopenta[*b*]indol-1-ones and carbazol-4-ones

3.3 Reductive cyclization

Alternative method for the synthesis of carbazolones is reductive cyclization. Söderberg et al.[208] developed a palladium catalyzed reductive *N*-hetero-annulation of 2-(2-nitrophenyl)-2-cycloalkenones **35** using CO as a reducing agent. In the reaction, they used a ternary catalyst system which consists of $Pd(dba)_2$, 1,3-bis(diphenylphosphino)propane (dppp) and 1,10-phenanthroline. The applied catalytic system effectively catalyzed the annulation process leading to the desired tetrahydrocarbazolones **36** (*Figure 30*). They used the developed method in subsequent studies to synthesize the alkaloid murrayaquinone A[209].

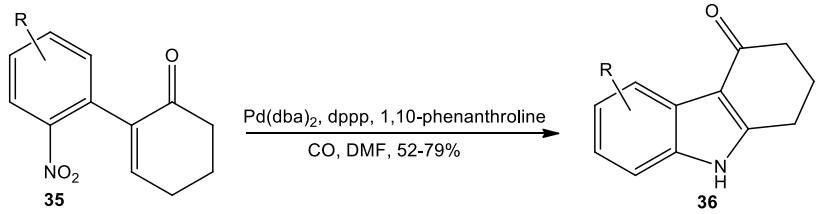


Figure 30 Palladium catalyzed reductive cyclization

Another example of the use of reductive cyclization in the synthesis of tetrahydrocarbazolones **38** is the cyclization of 3-hydroxy-2-(2-nitrophenyl)-2-cyclohexanones **37** with Fe/AcOH, which was reported by Yao group[210]. The reaction was performed in boiling acetic acid for 1-2.5 h (*Figure 31*). This method was applied to a wide group of substrates, and the yields of the synthesis of carbazolone derivatives were high, in the range 75-93%. It is also worth noting that this method is limited to 3-hydroxy substituted substrates.

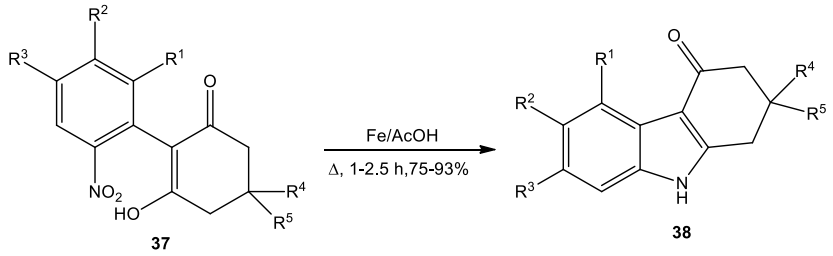


Figure 31 Cyclization promoted by Fe/AcOH

Zhu and coworkers[211] reported the use of $TiCl_3$ in the reductive cyclization of α-substituted 2-nitrophenylcyclohexanone **39**. The product of this reaction is the tetrahydrocarbazole derivative **40**, which is a key intermediate in aspidospermidine and other aspidosperm-type alkaloids. The reaction undergoes in mild conditions, i.e. the substrate **39** is treated with $TiCl_3$ and NH_4OAc in acetone at room temperature (*Figure 32*). The yield of this reaction is 70%.

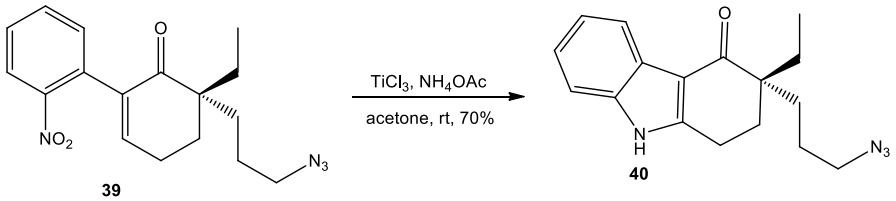


Figure 32 Cyclization promoted by $TiCl_3$

In 2018, Sagar group[212] described a molybdenum-catalyzed reductive cyclization reaction, which they successfully used in the synthesis of polysubstituted chirally enriched tetrahydrocarbazolones **44**. The substrate **43** was obtained by palladium catalyzed Ulmann coupling of the corresponding α-iodo cyclohexanones **41** and *o*-bromo nitroarenes **42**. The catalyst was $MoO_2Cl_2(dmf)_2$, and the green reducer was pinacol (after the reaction it generates only acetone and water). The reaction was carried out in toluene or DMA (dimethylacetamide) in microwave heating at 130°C (*Figure 33*). However, in all cases the yields are rather moderate, in the range 50-70%.

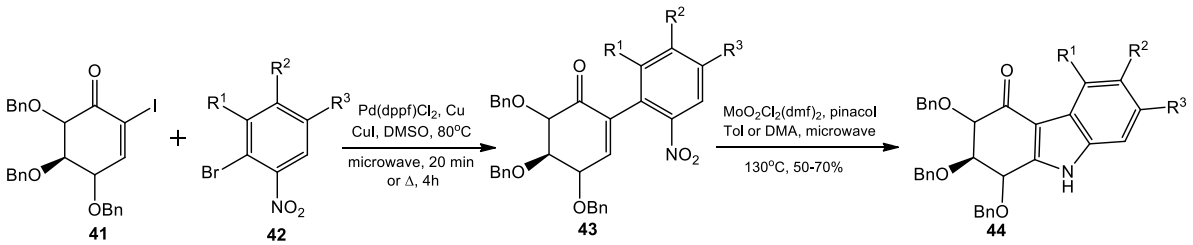


Figure 33 Molybdenum catalyzed reductive cyclization

3.4 Oxidative cyclization

Next key method for the synthesis of the carbazolone scaffold is oxidative cyclization. In the era of modern synthetic chemistry, the direct oxidative cyclization reaction is a frequently used synthetic strategy. This applies in particular to the very popular direct oxidative coupling of two C-H bonds with sp^2 hybridization catalyzed by palladium, which is widely used in homo-[213], cross-[214] and intramolecular coupling[215].

Based on these reports, in 2010, Li and coworkers[216] developed an effective method for the synthesis of carbazolone derivatives by palladium-catalyzed intramolecular oxidative cyclization of arylenaminones. They carried out a series of experiments and, in a high yield (83%) 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **15** was obtained from *N*-phenylenaminone **45** by intramolecular oxidative cyclization catalyzed with palladium acetate and copper acetate in ethanol (*Figure 34a*). The proposed mechanism of this reaction involves three steps: (a) the electrophilic attack of palladium acetate at the *N*-phenylenaminone; (b) activation CH group in *ortho* position to form a six membered ring containing a palladium atom; (c) reductive elimination leading to the formation of carbazolone and active palladium (0) complex, which in the presence of $Cu(OAc)_2 \times H_2O$ and oxygen is oxidized to palladium (II) (*Figure 34b*).

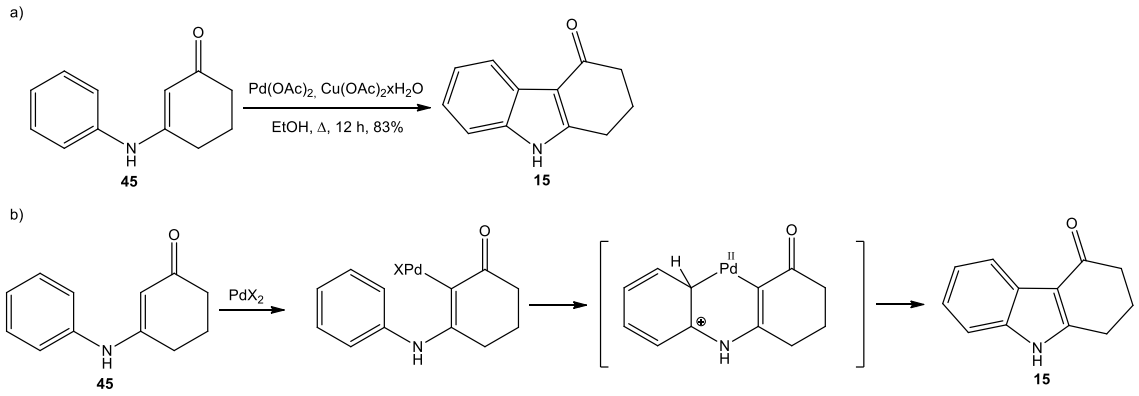


Figure 34 Oxidative cyclization of arylenaminones promoted by $Pd(OAc)_2$ in the presence of $Cu(OAc)_2 \times H_2O$

In the same year, the work of Du and Huang group[217] about palladium acetate catalyzed synthesis of *N*-alkylcarbazolone derivatives **47** was published. The reaction was limited only to *N*-methyl and *N*-benzyl substituted arylenaminiones **46**. Palladium acetate was also used as a catalyst in this process. The reaction was carried out in acetic acid at 100°C under an oxygen atmosphere (*Figure 35*). Scientists proposed a reaction mechanism identical to that presented in the work of Li et al.[216] However, in this case, the palladium (0) complex is oxidized to palladium (II) by oxygen.

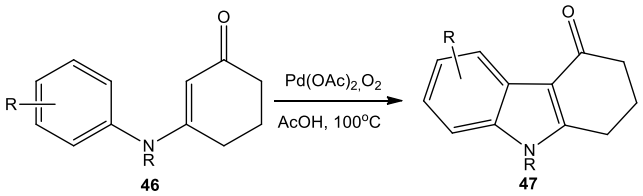


Figure 35 $Pd(OAc)_2$ catalyzed oxidative cyclization of *N*-alkylarylenaminiones under an oxygen atmosphere

Palladium-catalyzed cyclization was also used by Qiu and Yang[218] as a key step in the enantioselective synthesis of (-) aspidophytine. The corresponding *N*-arylenaminone **50** was obtained from 2,3-dimethoxyaniline **48** and enantioenriched cyclohexane-1,3-dione **49**. The obtained compound **50** underwent oxidative cyclization catalyzed by palladium acetate to enantioenriched tetrahydrocarbazolone **51**, which was further used in the synthesis of (-) aspidophytine (*Figure 36*).

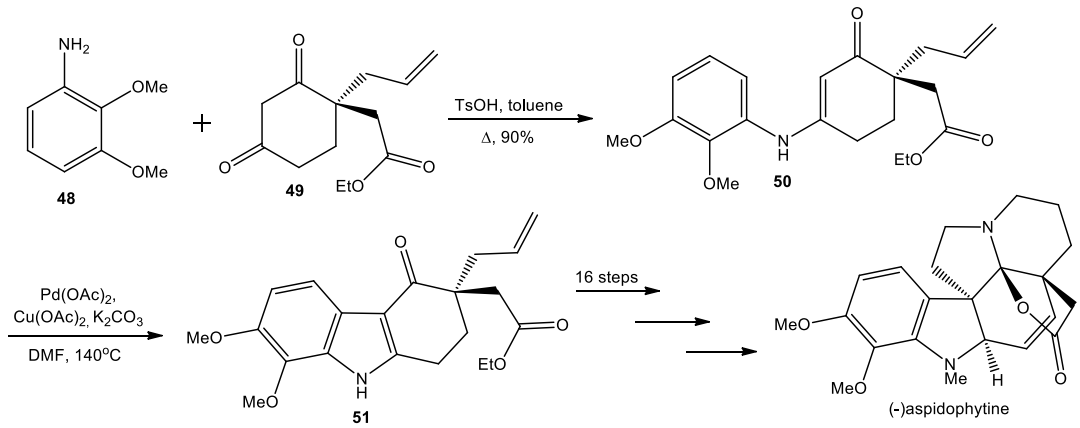


Figure 36 Synthesis of enantioenriched tetrahydrocarbazole

3.5 Cyclization promoted by Mn, Rh, Ru

Over the past 30 years, there has been a growing interest in radical reactions in organic synthesis. Manganese compounds received a great deal of attention. They were also used in the synthesis of carbazolone derivatives. In 1994, Chuang and Wang[219] described free radical oxidation reaction between 3-substituted *N*-benzoylindole **51** and dimethyl malonate **52** initiated by manganese (III) acetate in acetic acid at 80°C (*Figure 37*).

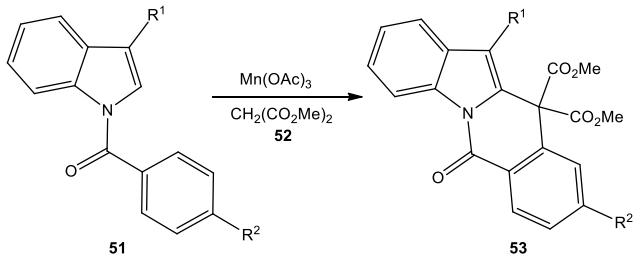


Figure 37 Free radical oxidation reaction promoted by manganese (III) acetate

It was not until 2005 that Chuang and coworkers[220] proposed a mechanism for the above reaction. In the first step, the oxidation of dimethyl malonate **52** by manganese (III) leads to the formation of the malonate radical **54**. Then, the radical **54** reacts with the compound **51** in position 2, another oxidation takes place, and the compound **55** is formed. In the last step, the malonic radical **56** formed by the oxidation of the malonate **55** is cyclized. The prepared resonance-stabilized radical **57** can undergo further oxidation to carbocation **58** and then aromatization to form compound **53** (*Figure 38*).

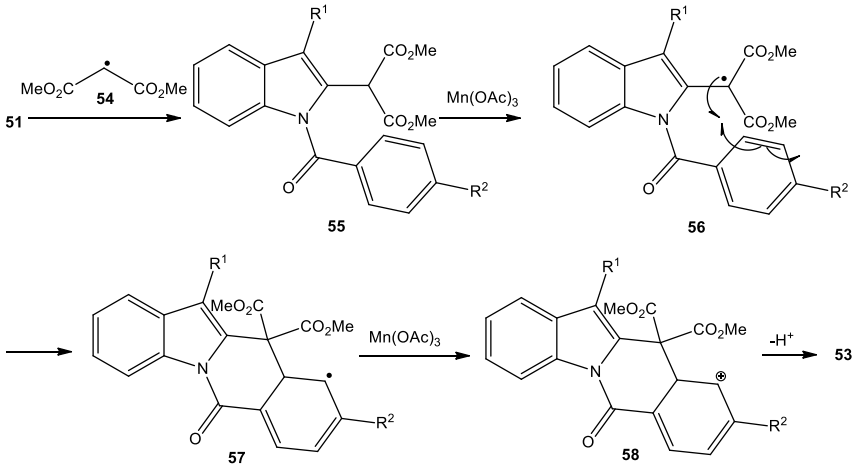


Figure 38 Mechanism of free radical oxidation reaction promoted by Mn

In 2013, Kanai and coworkers[221] used manganese-catalyzed cyclization in the synthesis of dimethyl 3,4-dihydro-1*H*-carbazole-1,1(2*H*,9*H*)-dicarboxylate **60**. For this purpose, substrate **59** underwent an intramolecular radical cyclization reaction using $Mn(acac)_3$ as a catalyst. The reaction was carried out in xylene at 130°C using air and CaCl2 tube as oxidant (*Figure 39*). The reaction yield was 84%. The mechanism of this reaction is identical to that proposed by Chuang group[220].

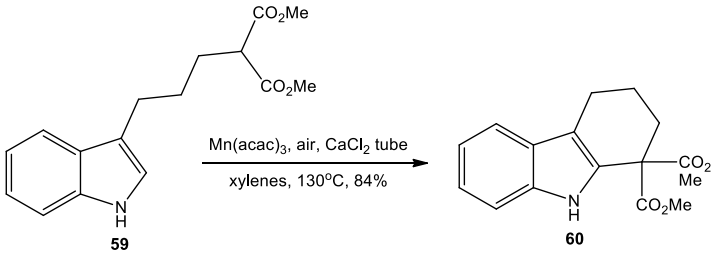


Figure 39 Synthesis of dimethyl 3,4-dihydro-1*H*-carbazole-1,1(2*H*,9*H*)-dicarboxylate **60** catalyzed by $Mn(acac)_3$

Another metal that has been used in the synthesis of carbazolone derivatives is Rh (II). The first reports of the use of rhodium (II) as a catalyst in the synthesis of polycyclic systems date back to 1986, when the Jefford group[222] extensively studied the Rh (II) catalyzed process, using α-diazoketones as carbenoid precursors for the synthesis of several naturally occurring indolysine derivatives. Dirodium (II) tetraacetate catalysis was used for intramolecular cyclization of α-diazoketone **61** to indolizinone **62**. The process turned out to be highly efficient, adding 1-2 mol% $Rh_2(OAc)_4$ was enough to obtain product **62** with a yield reaching 75-89%. The reaction was carried out in methylene chloride for 30 minutes at room temperature (*Figure 40*).

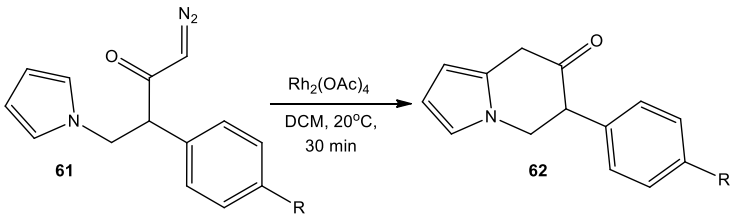


Figure 40 Synthesis of indolizinone **62** - an intermediate in the synthesis of indolizine derivatives

In 2001, Jung et al.[223] as a result of the same intramolecular cyclization of α-diazoketoester **63**, catalyzed with dirodium (II) tetraacetate, obtained the tetrahydrocarbazole derivative **67** in 72% yield. In their work, they proposed tentative reaction mechanism (*Figure 41*). The probable path of obtaining compound **67** from α-diazoketoester **63** involves the initial formation of rhodium carbenoid **64**, which then undergoes cyclization to cyclopropane **65**.

Although, simple indole adducts containing cyclopropane rings are known, e.g. adduct of ethyl diazoacetate and *N*-carbomethoxyindole, compound **65** cannot be expected to be stable. The last step involves opening the cyclopropane ring and forming a stabilized zwitterion **66**, which after deprotonation gives product **67**.

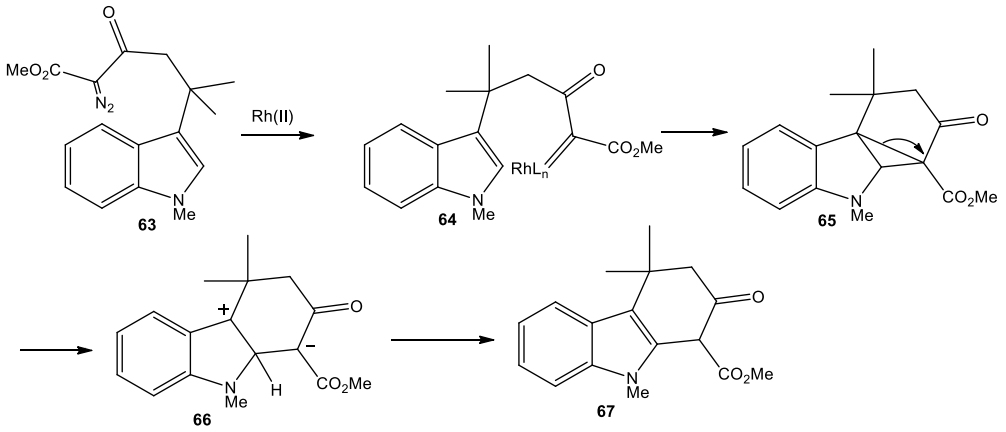


Figure 41 Reaction mechanism catalyzed by dirodium (II) tetraacetate

Since the pioneering work of Nishiyama and coworkers[224,225] about ruthenium-catalyzed alkene cyclopropanation reactions from 1994 and 1995, Ru-catalyzed cyclization has become the subject of research by many scientists. In 2010, a very interesting work by Stephenson group[226] was created. It concerned the use of tris(bipyridine)ruthenium (II) dichloride as a photo-redox catalyst in the synthesis of carbazolone derivatives. The course of the reaction consisted of treating the indole derivative **68** with triethylamine and tris(bipyridine)ruthenium (II) dichloride in DMF at room temperature and irradiation with visible light to obtain the cyclization product **72**. The yield of the reaction was 60%. Scientists in their work proposed the mechanism of the described reaction (*Figure 42*). When the reaction mixture is exposed to visible light, the charge is transferred from the metal to the ligand (metal-to-ligand charge-transfer: MLCT) and excited Ru (II)* is formed, which is then reduced by triethylamine to generate an electron-rich ruthenium complex (I) and the triethylammonium radical cation. The Ru (I) acts as a single-electron transporter and provides selective reduction of the activated C-Br bond, generating an electron deficient alkyl radical **69** and regenerating the $Ru(bpy)_3^{2+}$ catalyst. The product of the radical intramolecular cyclization is compound **70**. The resulting radical **70** is probably oxidized by excited Ru (II)* or by bromomalonate **68** to intermediate **71a** or **71b**. Elimination of a proton in the case of **71a** or the elimination of hydrogen bromide in the case of **71b** produces the end product **72**.

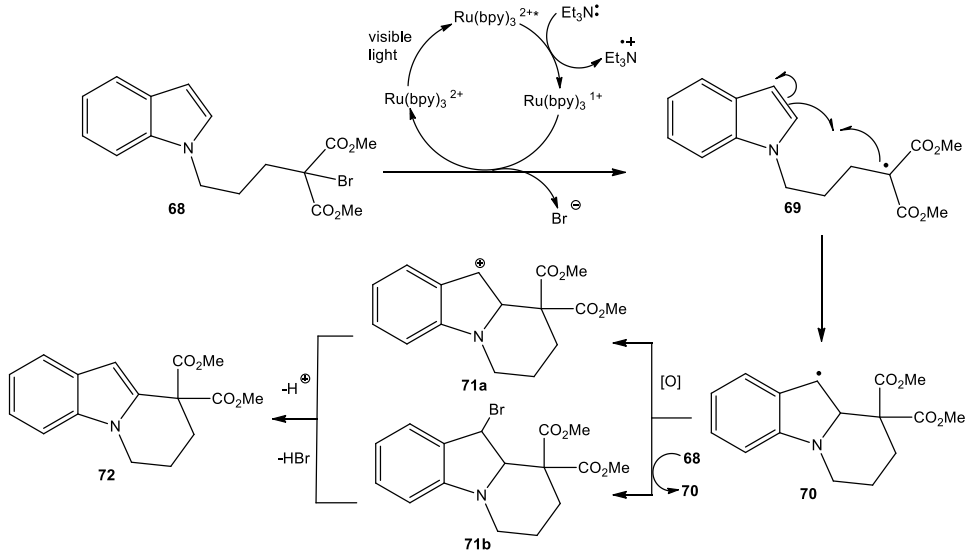


Figure 42 Mechanism of radical cyclization catalyzed by $Ru(bpy)_3Cl_2$

3.6 Cyclization promoted by Lewis acid

An interesting approach in the synthesis of carbazole derivatives is the use of Lewis acids. In 2003, Shimada and coworkers[227] described the intramolecular Friedel-Crafts reaction of 4-arylbutyric acids catalyzed by Lewis acid in the synthesis of 1-tetralones. When they were used 4-(1*H*-indol-3-yl)butanoic acid **73** as a substrat, they obtained 1-oxotetrahydrocarbazole **74** (*Figure 43*). $Bi(NTf_2)_3$ was used as the Lewis acid. The reaction was carried out in refluxing p-xylene for 7 h. The yield was 81%.

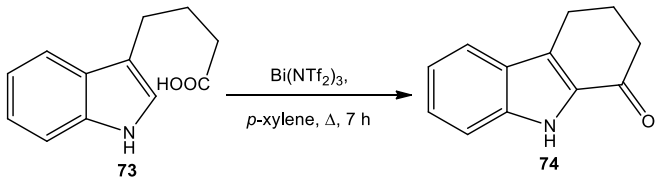


Figure 43 $Bi(NTf_2)_3$ catalyzed synthesis of 2,3,4,9-tetrahydro-1*H*-carbazol-1-one **74**

In 2011 another paper[228] was published, describing the intramolecular cyclization reaction of methyl 1-(1*H*-indolcarbonyl)-1-cyclopropanecarboxylate **75** with acid catalysis. The developed conditions allowed the synthesis of functionalized hydropyrido[1,2-*a*]indole-6(7*H*)-ones **76** in 99% yield. The core of the hydropyrido[1,2-*a*]indole is found in many naturally occurring indole alkaloids such as tronocarpine, mersicarpine, vincamine. *Figure 44* shows the synthesis path of compound **76** - the reaction was conduced in the presence of $In(OTf)_3$ in dichloromethane at room temperature.

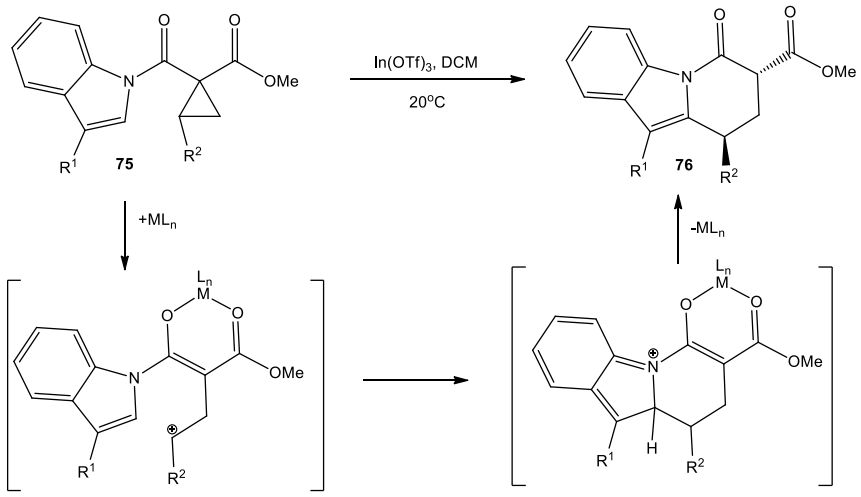


Figure 44 Synthesis of funcjonalized hydropyrido hydropyrido[1,2-*a*]indole-6(7*H*)-ones **76** promoted by $In(OTf)_3$

Recently, Sakthivel and Balamurugan[229] conducted research on the use of the $Sc(OTf)_3/Rh_2(OAc)_4$ catalitic system in the synthesis of tetrahydrocarbazoles **79**. Indole **78**, which is a good substrate for the Michael addition, was reacted with compound **77** in the presence of Lewis acid, followed by cyclization catalyzed by $Rh_2(OAc)_4$ (*Figure 45a*). The reaction conditions allowed to obtain tetrahydrocarbazole **79** in 80% yield, along with less than 2% of the corresponding aromatized product **80**. Product **79** occured only in the enol form. The role of Lewis acid, in this case $Sc(OTf)_3$, is crucial both in the initial intermolecular reaction between indole **78** and diazo compound **77** and in the subsequent Rh(II)-catalyzed intramolecular annulation. In order to prove the role of $Sc(OTf)_3$, the cyclization reaction of indolyl α-diazo acetate **81** was performed only in the presence of $Rh_2(OAc)_4$. As a, trace amounts of product **79** were obtained. On the other hand, the use of the $Sc(OTf)_3/Rh_2(OAc)_4$ system give compound **79** with 79% yield (*Figure 45b*).

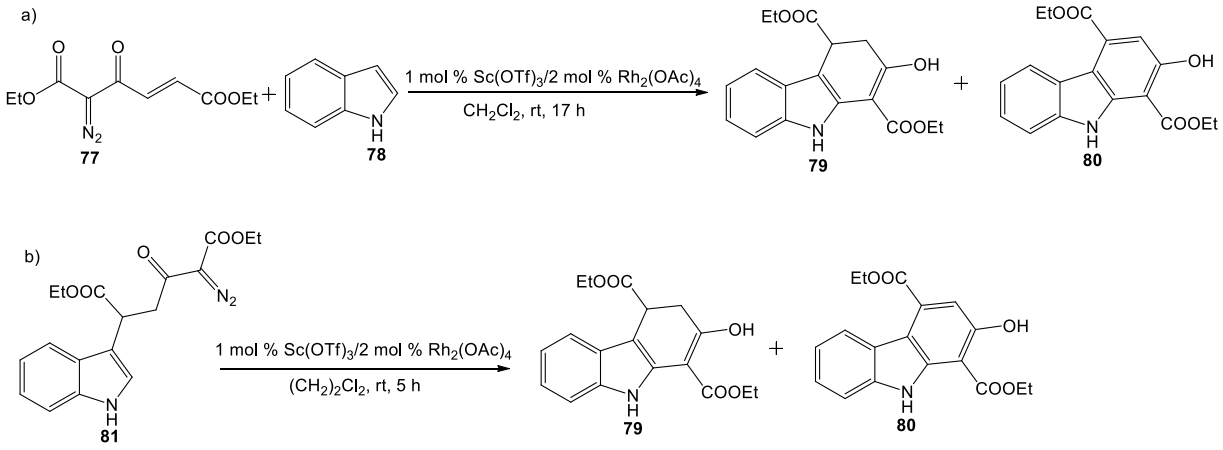


Figure 45 Synthesis of tetrahydrocarbazoles catalyzed by $Sc(OTf)_3/Rh_2(OAc)_4$

4. Selected methods of synthesis of carbazole derivatives

Due to the great interest in carbazoles, many synthetic strategies for synthesizing this scaffold have been described in the literature. These reactions are divided into two types: the formation of the A or C ring from substituted indole derivatives and the formation of the B ring from benzene derivatives. Traditional methods of synthesis of carbazole derivatives, such as Fischer indolization, nitrene insertion or Plieninger indolization, are quite well described in the literature. However, recently, scientists attention is focused mainly on methods such as cycloaddition or cyclization promoted by iodine, transition metals and Lewis acids. Many of these strategies are constantly innovating to solve the regioselectivity and efficiency problems. In this chapter, I will describe only selected methods of synthesis of carbazole derivatives.

4.1 Formation of A (benzen) ring

4.1.1 Cyclization catalyzed by Rh, Mn, Pd

Metal-catalyzed cyclization is widely used in the formation of carbon-carbon and carbon-heteroatom bonds including the synthesis of carbazole derivatives. In this subsection, I will present only one example of applications in carbazole synthesis for each metal - Rh, Mn and Pd.

In 2015, Yi and coworkers[230] described the intermolecular annulation of indoles **82** with terminal alkynes **83** catalyzed by Rh(III) (*Figure 46a*). The designed synthesis pathway using as a catalyst $[Cp^*Rh(MeCN)_3][SbF_6]_2$, running in oxygen atmosphere allowed to obtain carbazoles **84** in good yield with excellent tolerance of various functional groups. Scientists proposed a plausible reaction mechanism (*Figure 46b*).

First, coordination of the rhodium catalyst to the C2-position of *N*-2-pyrimidylindole **82** is a key step for regioselective cleavage of the C2-H indole bond to form a five-membered intermediate **85**. The next step is coordination of compound **85** with one equivalent of terminal alkyne **83** and formation of adduct **86**. Then insertion of alkyne **83** into the C2-Rh bond to form a seven-membered compound **87,** followed by one more coordination and insertion of second alkyne equivalent **83** to give compound **88** and **89**. The penultimate step consists of subsequent coordination of Rh to the C3-position of indole and formation of adduct **90**, which in the last step undergoes reductive elimination to give the desired carbazole **84** and active Rh (III) catalyst.

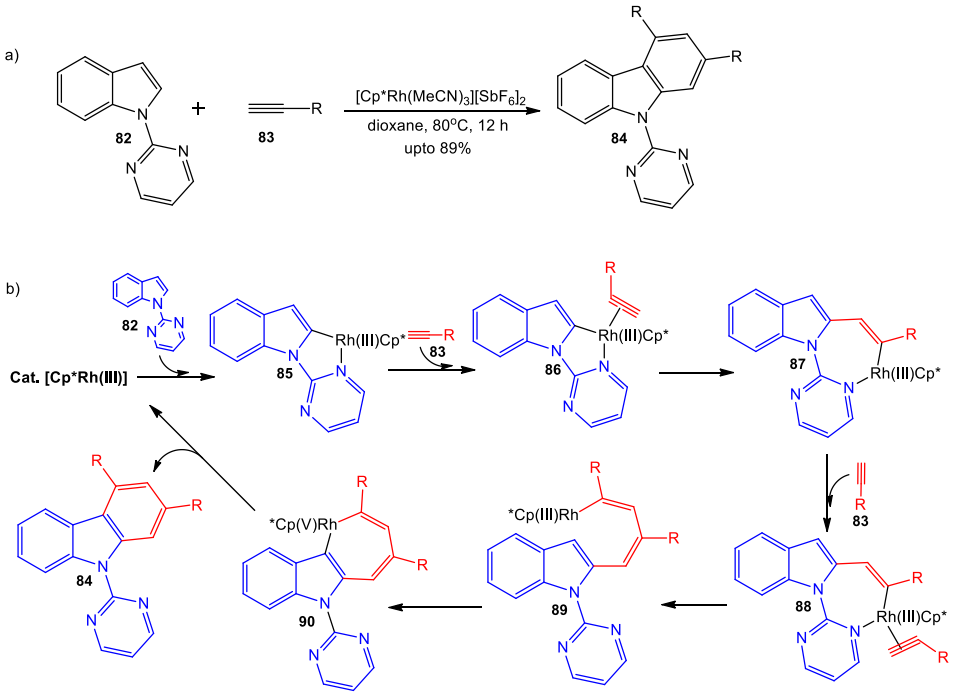


Figure 46 Plausible $[Cp^*Rh(MeCN)_3][SbF_6]_2$-catalyzed reaction mechanism

An alternative to using the expensive Rh-catalyst is the study by Li and colleagues[231] who designed $MnBr(CO)_5$-catalyzed C-H functionalization of indole **91** by alkynes **92** (*Figure 47*). Without the addition of acid, the reaction proceeds via [2+2+2] cyclization to give carbazoles **93** in lower yields. However, when catalytic amounts of acid were used for this reaction, bis/trisubstituted indolyl alkenes were obtained in good yield. The *N*-protecting pyrimidyl group can be easily removed under basic conditions, leading to NH-carbazoles **94**.

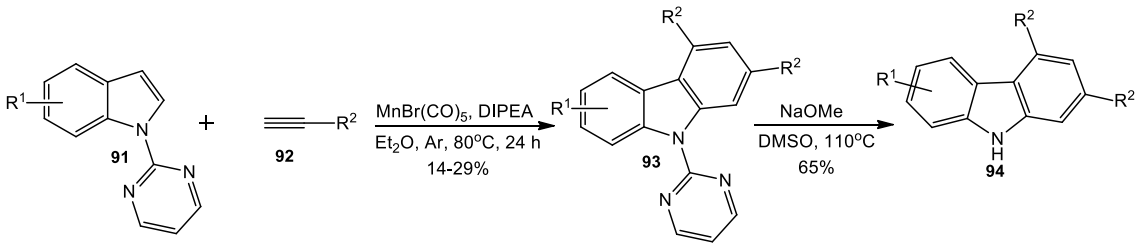
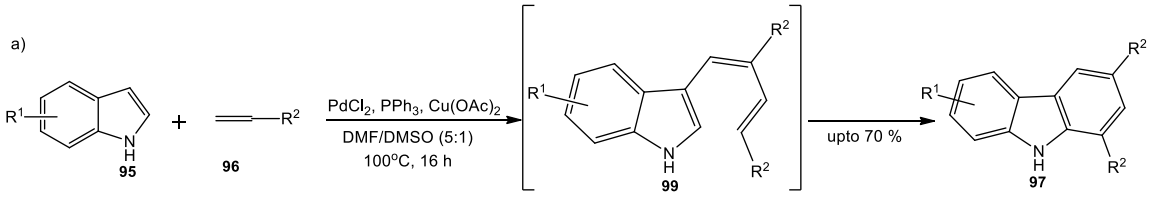


Figure 47 $MnBr(CO)_5$-catalyzed synthesis of carbazole derivatives

Pd catalysis is often used in the synthesis of carbazoles. One example is the Verma group[232] study on the use of $PdCl_2$ in the direct conversion of indoles **95** to carbazoles **97** using alkenes **96** with good yields (*Figure 48a*). The presented experiment describes a triple oxidative Heck reaction at the C3-position of the indole with subsequent cyclization. Interestingly, indoles without a protecting group on the nitrogen atom were used in this reaction. Based on the evidence from the control experiments, scientists proposed a probable reaction path (*Figure 48b*). First oxidative Heck reaction involves the coupling of indole **95** with alkene **96** which proceeds through: regioselective coordination of palladium to carbon C3 (I), alkene insertion (II-III), and β-hydrogen elimination. The another regioselective coordination of palladium takes place on intermediate **98** at the α-position of R^2 (IV), proceeds through the formation of palladium complexes (steps V and VI) and completes the second oxidative Heck cycle with the formation of intermediate **99**. The third intramolecular oxidative Heck reaction proceeds by coordination of palladium to carbon C2 of adduct **99** (VII), generation of palladium complexes (steps VIII and IX) and ends with the formation of carbazole **97**.



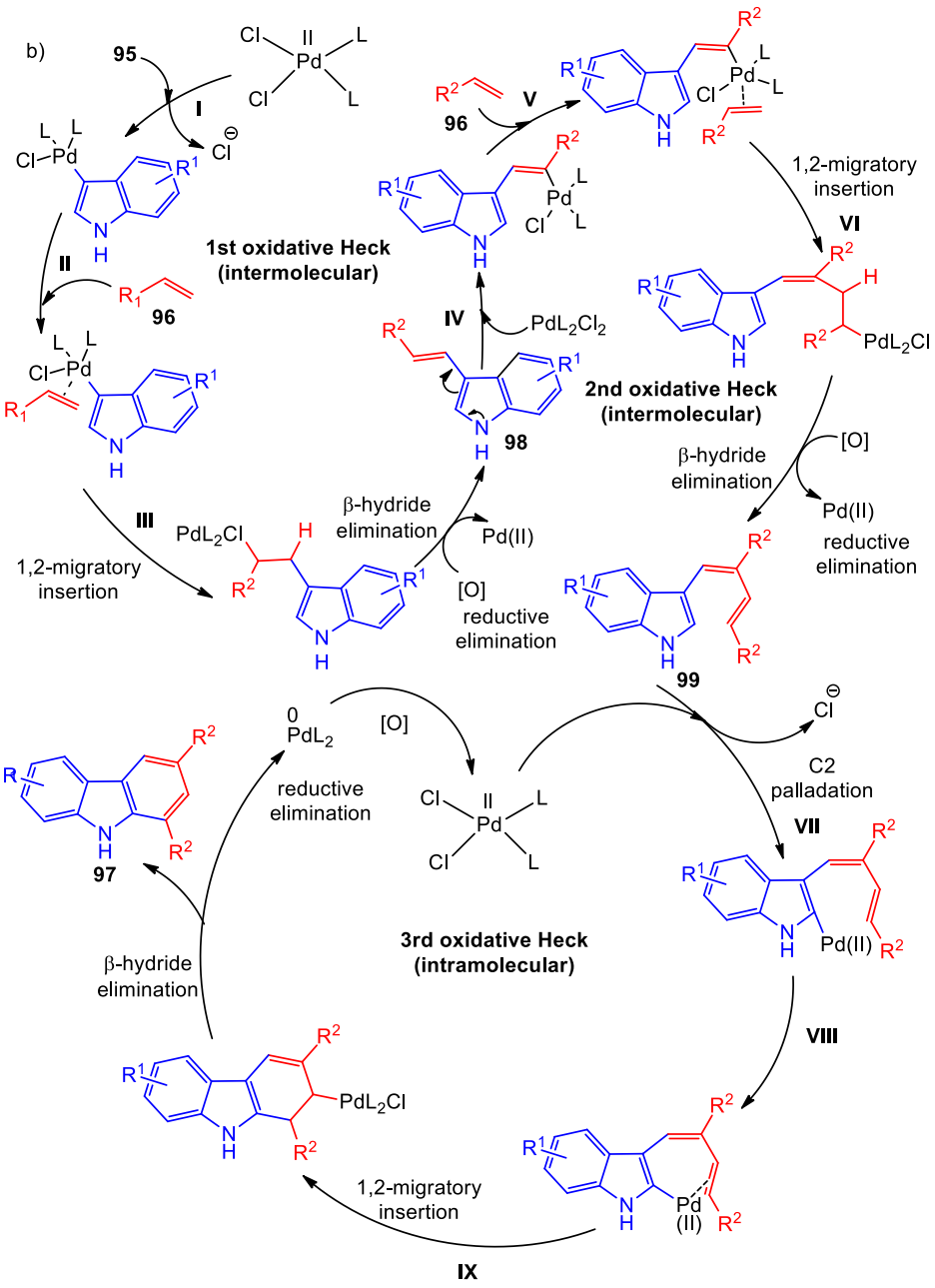


Figure 48 Synthesis of carbazole derivatives catalyzed by $PdCl_2$

4.1.2 Cyclization promoted by Lewis acid

Recently, cyclization with the use of Lewis acids has attracted a lot of attention from scientists, which can be successfully used in the synthesis of carbazoles. This method is readily used because of the easy availability of Lewis acids and the mild reaction conditions. In 2017, Wang et al.[233] described the synthesis of aryl-substituted carbazoles **90** in the presence of $BF_3 \times OEt_2$ (*Figure 49a*). The reaction takes place between tryptophol **100** and propargyl alcohol

101 at 60°C and gives the product **102** in good yield. Based on the obtained results, scientists proposed a mechanism for this reaction (*Figure 49b*). In the first step, propargyl alcohol **101** activated by BF_3 to improve electrophilicity is attacked by the electronrich tryptophol **100** and forms the imine **103**. In the next step, the 1,2-migration of allene takes place with the formation of carbocation **10**4, followed by the β-hydrogen elimination and the formation of compound **105**. In the final step, the following occurs: BF_3-catalyzed 6-exo-tet intramolecular cyclization of compound **106**, formation of carbocation **107**, loss of hydrogen and formation of product **102**.

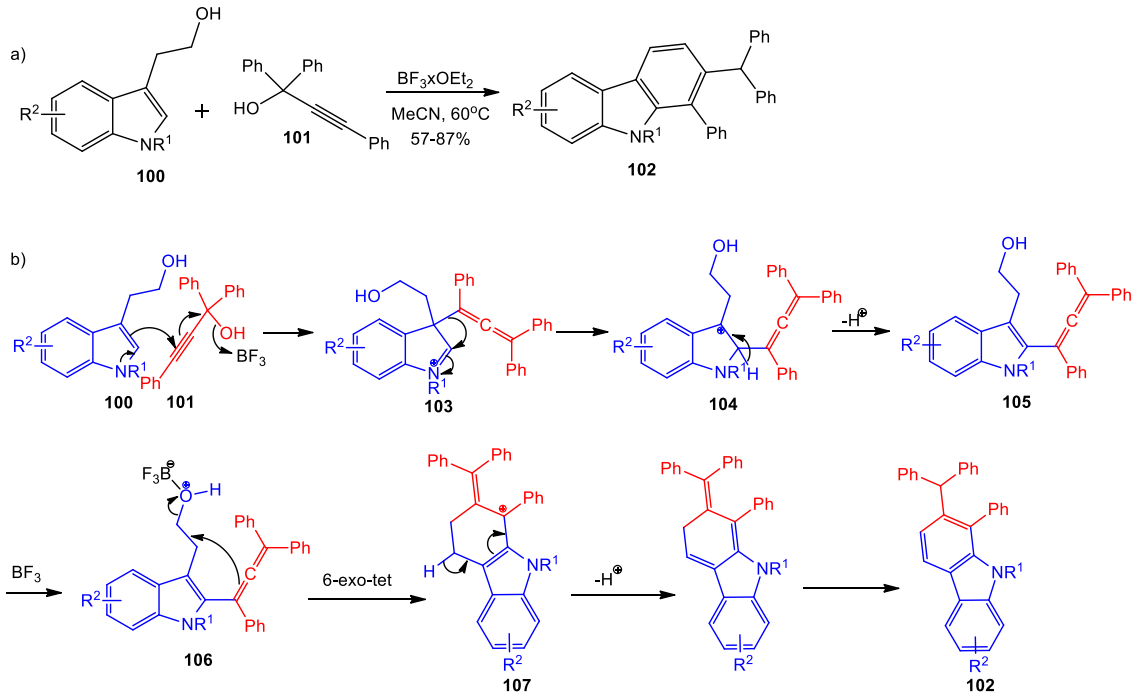


Figure 49 BF_3×OEt_2 promoted carbazole synthesis

Another example is the use of $BiCl_3$ in the synthesis of benzo[*a*]carbazoles **110** by Gu group[234]. The product **110** was obtained as a result of $BiCl_3$-catalyzed reaction of 2-phenylindole **108** with α-bromoacetal **109** (*Figure 50a*). The reaction was carried out at 80°C in acetonitrile for 3h. The reaction yield was 70-90%. In the paper, authors proposed the following reaction mechanism: (a) Friedel-Crafts alkylation, which proceeded through activation of **109** by $BiCl_3$ and nucleophile (**108**) attack on the formed carbocation **111**; (b) formation of intermediate **112**; (c) restoration of indole aromaticity via HBr release; (c) deacetylation of **113** under acidic conditions and generation of compound **114**; (d) HBr catalyzed intramolecular cyclization (**115**), dehydration and preparation of product **110** (*Figure 50b*).

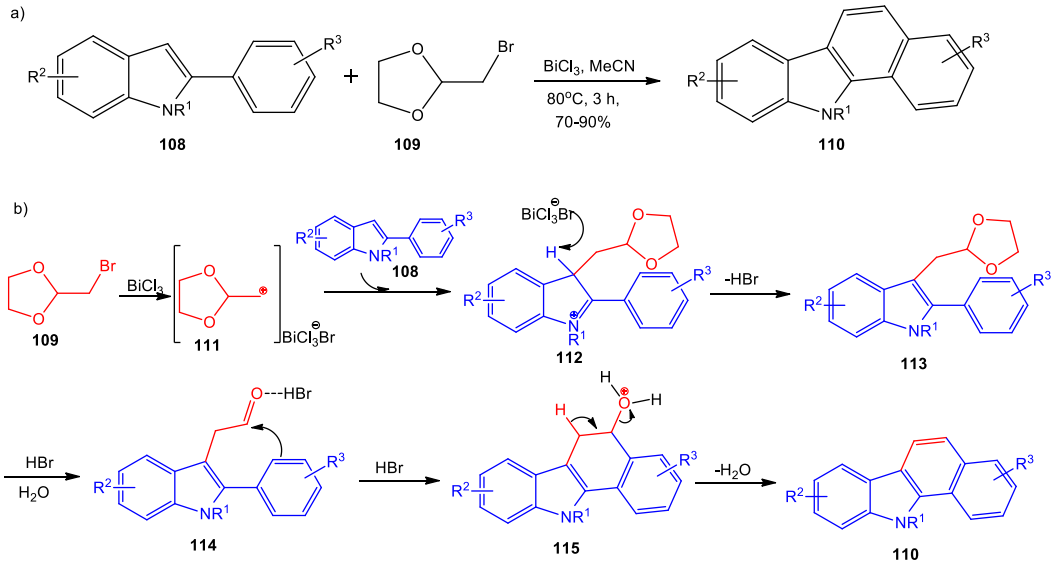


Figure 50 Synthesis of benzo[*a*]carbazoles promoted by $BiCl_3$

Recently, Banerjee and coworkers[235] reported indium chloride catalyzed synthesis of carbazoles (*Figure 51*). The reaction took place between alcohol **116** and donor-acceptor cyclopropanes (DACs) **117** via [3+3] annulation. This methodology tolerates a wide range of functional groups and results in the preparation of tetrahydrocarbazoles **118** in good yields. The resulting tetrahydrocarbazoles **118** undergo aromatization by removal of the ester group, leading to the formation of the corresponding carbazoles **119**.

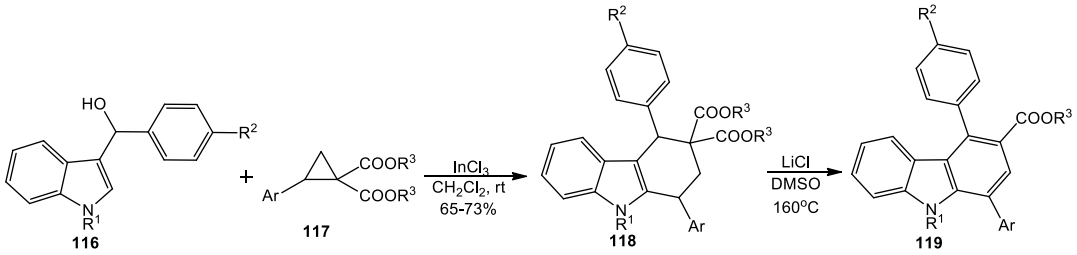


Figure 51 Synthesis of carbazoles promoted by $InCl_3$

4.1.3 Cyclization mediated by iodine

Among various methods of carbazole core synthesis, cyclization mediated by iodine deserves attention. It enables the synthesis of iodine-substituted carbazoles, which can be used as intermediates in the synthesis of natural products. In 2011, Wu and colleagues[236] used iodocyclization in the synthesis of benzo[*a*]carbazoles **121**. In order to obtain product **121**, the substituted *N,N*-dimethyl 2-[2-(2-ethynylphenyl)-ethynyl]anilines **120** was treated with iodine in dichloromethane at room temperature (*Figure 52*). The iodinated carbazoles **121** were obtained

in a satisfactory yield, reaching 95%. Based on the experimental results, the following reaction mechanism was proposed: (a) cyclization **120** into iodoindole **122** mediated by iodine; (b) coordination excess of iodine to a second triple bond and promoting subsequent cyclization leads to the formation of intermediate **123**; (c) attack of the iodide anion on the resulting compound **123** and obtaining carbazole **121** and regenerated iodine which enables the continuation of the catalytic cycle (*Figure 52*).

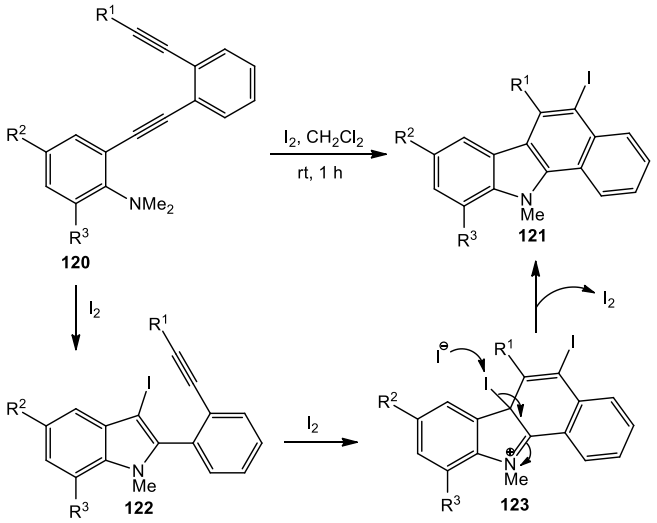


Figure 52 Synthesis of carbazole derivatives promoted by I_2

Another strategy for the synthesis of iodocarbazoles **125** by iodocyclization with 1,2-migration and aromatization has been described by the Liang group[237]. This reaction was performed on the indole derivatives **124** at room temperature in the presence of iodine chloride (*Figure 53a*). Scientists in their work proposed a reaction mechanism (*Figure 53b*). First, the iodide cation activates the alkyne moiety to form adduct **126**, which is then attacked by the highly nucleophilic 3-position of the indole ring to generate cation **127**. The next step is the 1,2-migration of the bond from 3- to 2-positon of the indole and formation of intermediate **128**. The last step is the rearomatization of the indole into compound **129** which then undergo aromatization by dehydration to give the desired carbazole **125**.

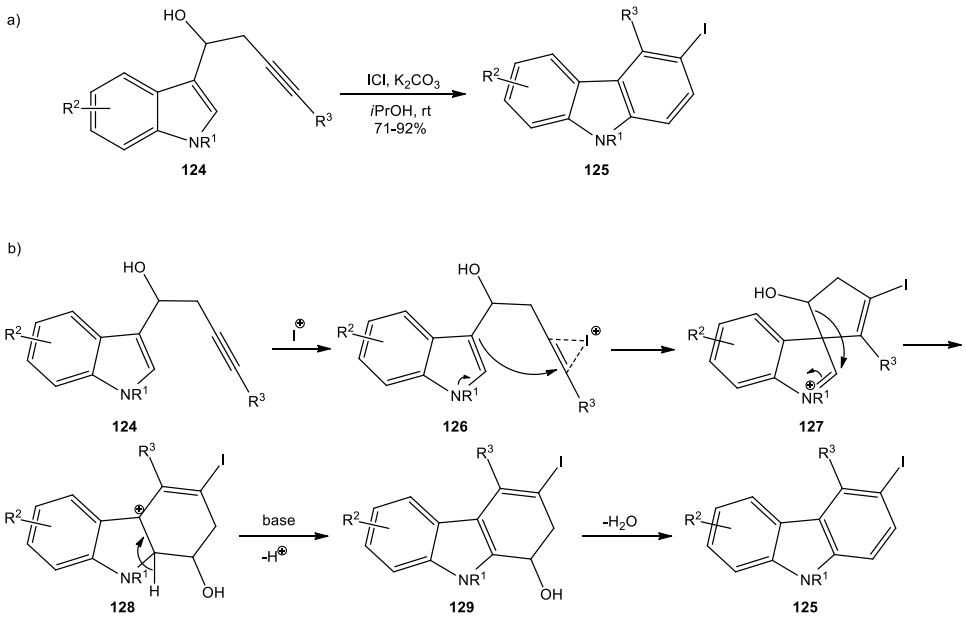


Figure 53 Synthesis of iodocarbazoles mediated by ICl

In 2018, Yaragorla et al.[238], inspired by the work of Liang group, described the cyclization of alcohols **130** in the presence of molecular iodine, which resulted in obtaining iodine substituted carbazoles **131** with yield up to 70% (*Figure 54*). The reaction was conduced in ethyl acetate at room temperature for 1 h. The reaction mechanism that they presented in their work is the same as that proposed by the Liang group.

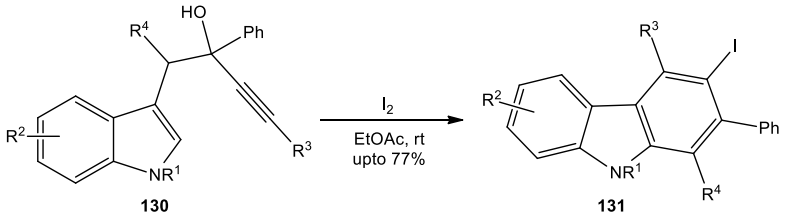


Figure 54 Synthesis of substituted carbazoles in the presence of I_2

4.1.4 Cycloaddition

Another noteworthy method of carbazoles synthesis is cycloaddition. It was used by Wu and coworkers[239] to synthesize benzo[*c*]carbazoles **134**, which are an important structural motif in medicine and materials science rarely found in nature. These compounds were prepared from 2-alkenylindole **132** and 2-(trimethylsilyl)phenyl triflate **133**. The reaction was conduced in the presence of CsF and Cs_2CO_3 in MeCN and toluene at 100°C under an oxygen atmosphere for 36 h (*Figure 55*). The result of this reaction was the preparation of the product **134** in a yield reaching to 95%.

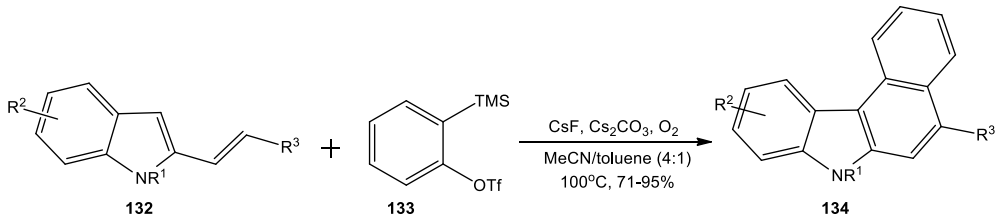


Figure 55 Synthesis of benzocarbazoles in an alkaline environment

Another example of the use of cycloaddition in the synthesis of carbazoles is the work of the Koth group[240] from 2017. They used an environmentally friendly approach to synthesize carbazole derivatives using a eutectic mixture of L-tartaric acid (TA) and *N,N*-dimethylurea (DMU) mixed in a ratio of 70:30. The reaction mechanism includes: (a) condensation of indole **135** and carbonyl compound **136**; (b) elimination of water from the resulting alcohol **137**; (c) Diels-Alder reaction between the intermediate **138** and dienophile **139**; (d) oxidation of the obtained adduct **140** and preparation of the carbazole derivative **141** (*Figure 56*).

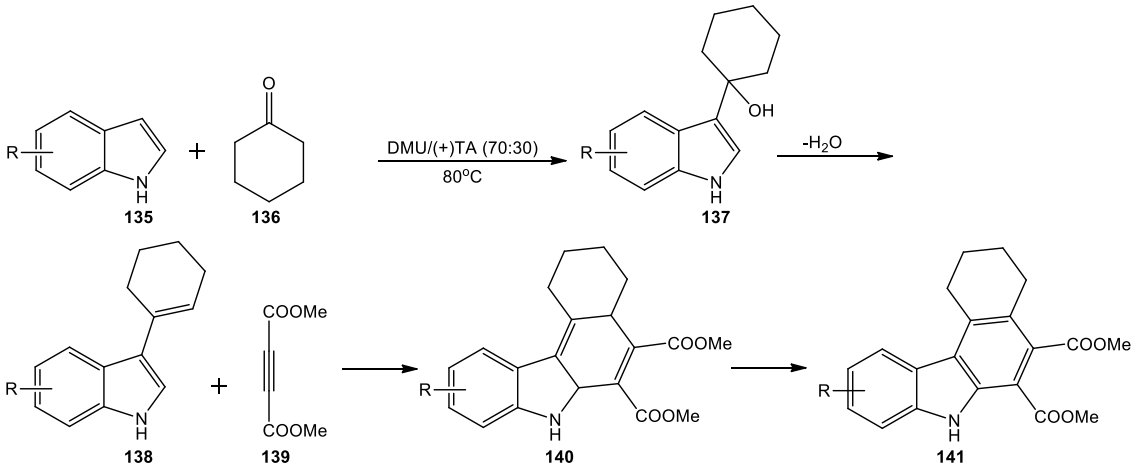


Figure 56 Synthesis of carbazoles in the presence of eutectic mixture

4.2 Formation of B (pyrrole) ring

4.2.1 Knölker carbazole synthesis

The Knölker group developed a basically new method of synthesis of carbazole alkaloids based on arylation via the iron-arene complex and the formation of a C-N bond. The first alkaloid that they synthesized in 1989 using this method was carbazomycin A[241]. The method of preparation of this alkaloid is presented at *Figure 57*. The necessary iron complex **143** was obtained from 1,3-cyclohexadiene **142** and $Fe(CO)_5$ by treatment with a triphenylcarbenium tetrafluoroborate. The next step was the reaction between cation **143** and

amine **144**, which resulted in the formation of compound **145**. Subsequently, oxidative cyclization of **145** in the presence of manganese dioxide resulted in iron-complexed dihydrocarbazol-3-one **146**. Removal of the metal complex from **146** in the presence of trimethylamine *N*-oxide provided carbazole **147**, which was then methylated to afford carbazomycin A **148**.

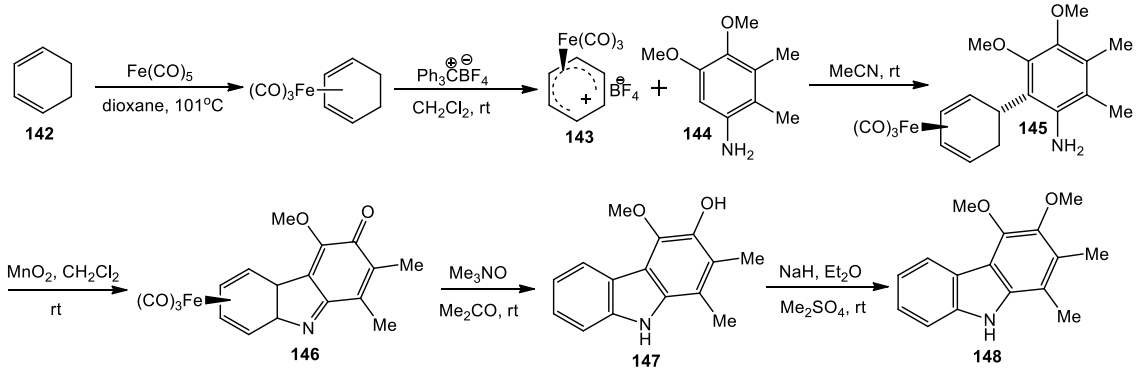


Figure 57 Knölker synthesis of carbazomycin A

Other alkaloids obtained by Knölker[242] via iron complex mediated oxidative cyclization are (-)- neocarazostatin B and carquinostatin A. The synthesis pathway for these alkaloids was as follows: (a) reaction of salt **143** with arylamine **149** and generation of adduct **150**; (b) aromatization and removing the metal complex in the presence of NBS and a base; (c) reaction of bromocarbazole **151** with a nickel complex prepared in situ and synthesis of di(*O*-acetyl)neocarazostatin B **152**; (d) removing the acetyl group from compound **152** in the presence of $LiAlH_4$; (e) oxidation of (-)-neocarazostatin B **153** to carquinostatin A **154** by CAN (ceric (IV) ammonium nitrate) (*Figure 58*).

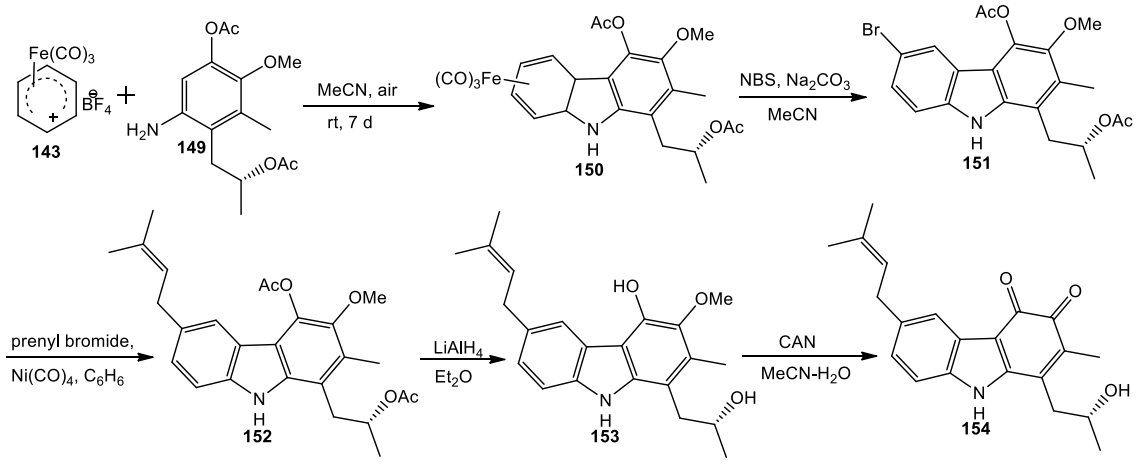
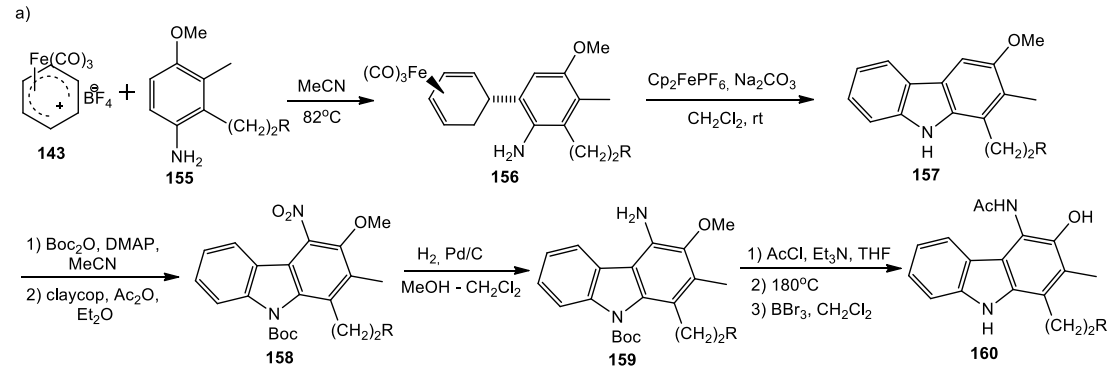
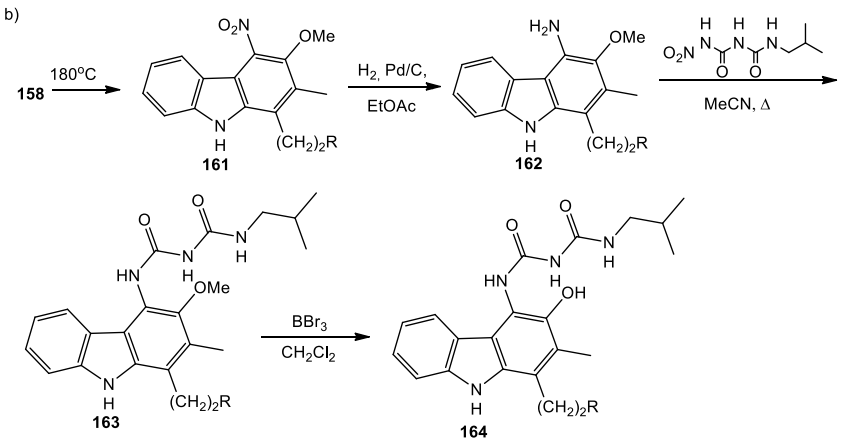


Figure 58 Synthesis of (-)-neocarazostatin B and carquinostatin A

The Knölker carbazole synthesis for the first time made it possible to synthesize antiostatins A and B[243]. In order to obtain antiostatins A in the first step the iron complex salt **143** was reacted with arylamine **155**. The obtained complex **156** was then subjected to oxidative cyclization by excess of ferrocene hexafluorophosphate in the presence of sodium carbonate to give carbazole **157**. After converting compound **157** into corresponding tert-butyl carbamate by nitration with claycop (clay-supported copper nitrate), 4-nitrocarbazole **158** was obtained. Then, the nitro group (**158**) was reduced to the amino group (**159**) by catalytic hydrogenation. In the last step, the obtained amine **159** was converted into antiostatins A **160** in three steps (*Figure 59a*). The antiostatins B series was synthesized from **158** in four steps. After removal of Boc group from **158**, the nitrocarbazoles **161** were reduced to aminocarbazoles **162** by catalytic hydrogenation with H_2/Pd. Subsequently, reaction of compounds **162** with 5-isobutyl-1-nitrobiuret in refluxing acetonitrile gave compound **163**. The last step was removal of the methyl group from **163** to give antiostatins B **164** (*Figure 59*b).



A_1: R=$(CH_2)_4$Me; A_2: R=$(CH_2)_2$CH(Me)CH_2Me; A_3: R= $(CH_2)_4$CH$(Me)_2$; A_4: R=$(CH_2)_6$Me



B_2: R=$(CH_2)_5$Me; B_3: R=$(CH_2)_4$CH$(Me)_2$; B_4: R=$(CH_2)_6$Me; B_5: R=$(CH_2)_5$CH$(Me)_2$

Figure 59 Synthesis of antiostatins A and B

4.2.2 Cyclization catalyzed by Rh, Pd

Metal-catalyzed cyclization plays an important role not only in the synthesis of carbazoles by the formation of benzene ring, but also in the synthesis of carbazole by the formation of central (pyrrole) ring. In this case, the metals that deserve the greatest attention are palladium and rhodium.

In 2009, Driver and coworkers[244] used Rh-catalyzed cyclization in the synthesis of carbazole regioisomers **166** and **167**. They performed the reaction on azides **165** at 60°C using as the Rh-catalyst: $Rh_2(O_2CC_3F_7)_4$ or $Rh_2(O_2CC_7H_{15})_4$ (*Figure 60a*). Scientists in their work proposed a mechanism for the developed synthesis (*Figure 60b*). The first step is the formation of a rhodium-azide complex **168**, from which the N_2 molecule is then removed to form quinoid **169**. Compound **169** is resonance stabilized into structure **170** and undergoes an electrocyclization reaction to form compound **171**. The last step involves aromatization of compound **171** to form a carbazole **166**.

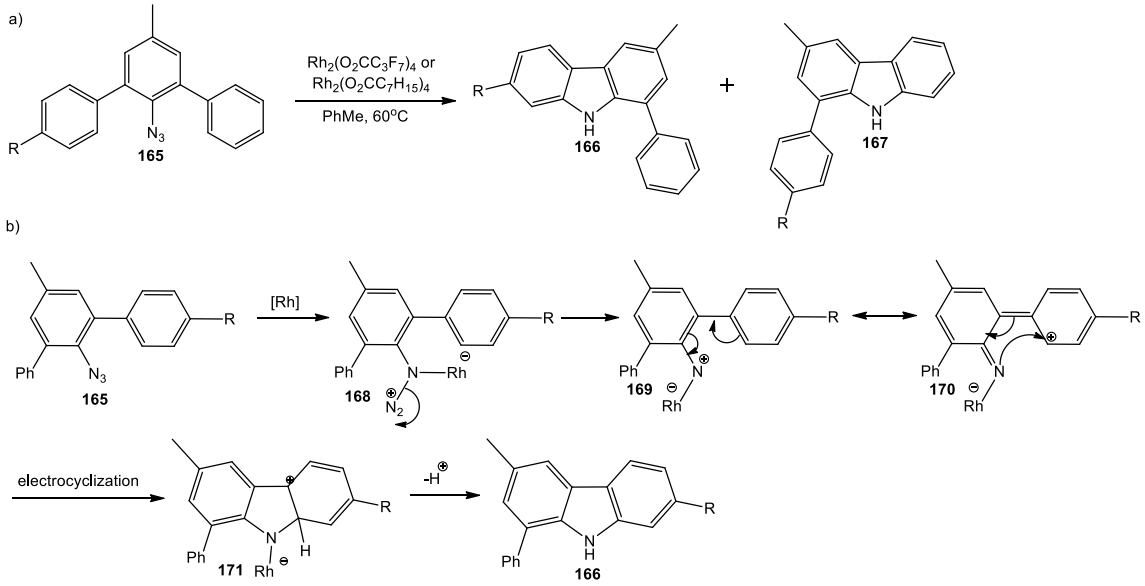


Figure 60 Synthesis of carbazoles catalyzed by $Rh_2(O_2CC_3F_7)_4$/$Rh_2(O_2CC_7H_{15})_4$

In the same year, the Ackermann group[245] developed the synthesis of functionalized carbazoles **174** involving the annulation of aniline **172** and dihalobenzene **173** derivatives in the presence of a palladium catalyst (*Figure 61*). The key steps in the synthesis were intermolecular amination and intramolecular direct arylation. Palladium (II) acetate was used as the catalyst. The highest yields were obtained by conduced the reaction in the presence of PCy_3 (tricyclohexylphosphine), using NaO*t*-Bu or K_3PO_4 as the base. When NaO*t*-Bu was used,

toluene proved to be the best solvent, while K_3PO_4 was used, *N*-methyl-2-pyrrolidone (NMP) was the best solvent.

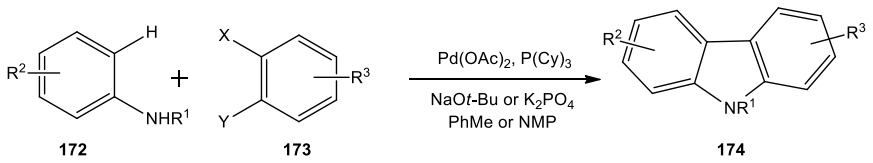


Figure 61 Pd(II)-catalyzed annulation

Another example of the use of a palladium catalyst in the synthesis of the central carbazole ring is the work of Youn et al.[246] They developed a $Pd(OAc)_2$ catalyzed cyclization of *N*-Ts-2-arylaniline **175** at room temperature using oxone as an inexpensive and safe oxidant (*Figure 62*). This reaction proceeds smoothly through C-H activation followed by oxidation of the C-C bond at the C2'-position. Oxone promotes the oxidation of adduct **176** to intermediate **177**, which then undergoes reductive elimination with simultaneous C-N bond formation, yielding carbazole **178**.

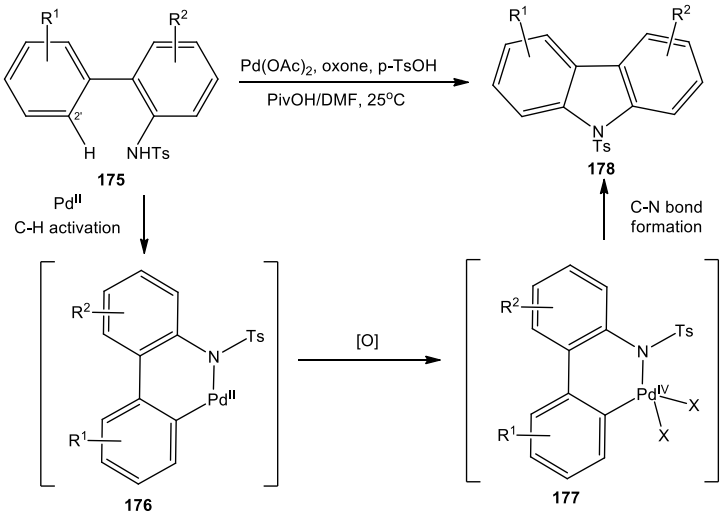


Figure 62 $Pd(OAc)_2$ catalyzed cyclization of *N*-Ts-2-arylaniline **175**

4.2.3 Cyclization promoted by iodine

The central (pyrrole) ring can also be formed by using an electrochemically generated hypervalent iodine oxidant. In 2010, the Kajiyama group[247] successfully synthesized glycozoline - carbazole with antibacterial and antifungal properties present in the roots of *Glycosmis pentaphylla*. The first two steps involved bromination of *p*-toluidine **179** followed by *N*-acetylation to give acetanilide **180**. The next step was the Suzuki-Miyaura coupling of the obtained acetanilide **180** with the appropriate borate **181** to give diaryl **182** in 78% yield. The

last two steps were oxidative cyclization **182** by electrochemically generated $PhI(OCH_2CF_3)_2$ and basic *N*-deacetylation to give glycozoline **183** in a total yield of 50% (*Figure 63a*). Scientists assumed that the reaction mechanism was through intermediate **184**, which undergoes cyclization to carbazole **185** (*Figure 63b*).

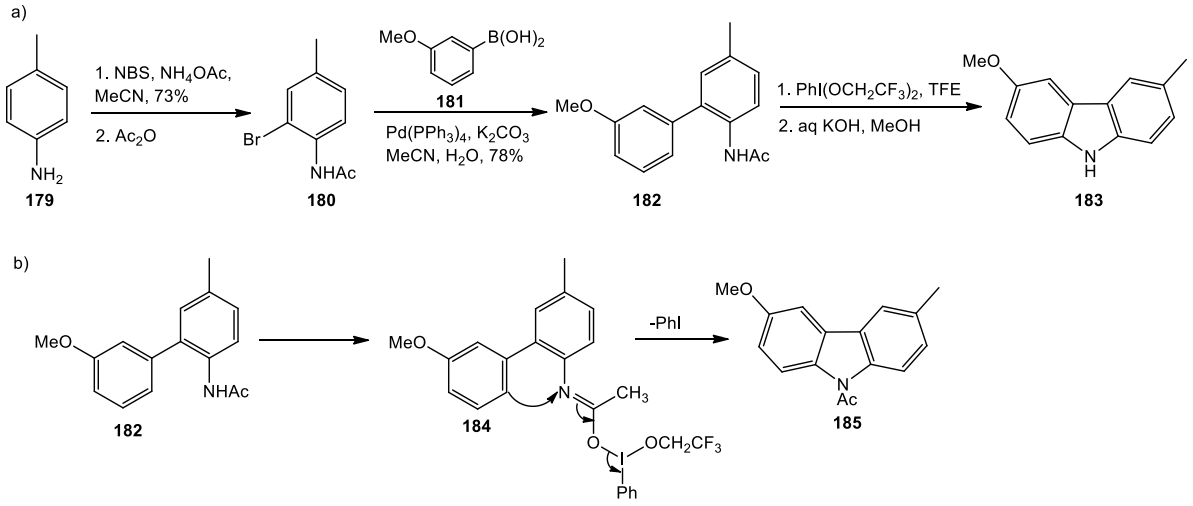


Figure 63 Synthesis of glycozoline mediated by $PhI(OCH_2CF_3)_2$

In 2011, Antonchick and coworkers[248] developed the $PhI(OAc)_2$ mediated C-N bond formation method in the synthesis of carbazoles **187**, without any additional reagents such as bases, acids and transition metal compounds at room temperature (*Figure 64*). The substrate for the reaction was 2-acetaminobiphenyl **186**. The highest yields were obtained when they used HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) as a solvent. The mechanism proposed in paper consists in: (a) the reaction of (diacetoxy)iodobenzene with amide **186**, resulting in the formation of intermediate **188**; (b) converting adduct **188** to nitrenium ion **189** through an oxidation; (c) the nucleophilic attack of the arene on the electron-deficient nitrenium ion to give the desired product **187** (*Figure 64*).

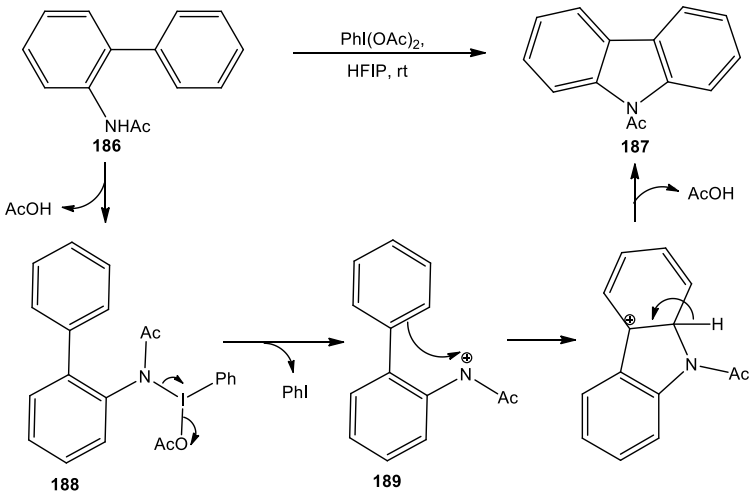


Figure 64 $PhI(OAc)_2$ promoted carbazole synthesis

II. RESEARCH AIM

Working in the dr hab. Sławomir Makowiec research team at the Department of Organic Chemistry, Gdańsk University of Technology, as part of my doctoral thesis, I was verified the possibility of using 3-(1H-indol-3-yl)-3-propionic acids and tryptophan in the synthesis of tetrahydrocarbazole and carbazole derivatives with biological potential. In order to perform these tasks, the following goals had to be achieved:

1) Develop synthesis conditions of the 1,2,3,4-tetrahydrocyclopenta[*b*]indole substituted in 1 and 3 positions

2) Molecular docking of new 5-HT reuptake inhibitors based on modified 1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one scaffold

3) Develop synthesis conditions of a 1,2,4-trisubstituted carbazole core from 5-(1*H*-indol-3-yl)-3-oxopentanoic acid esters or amides based on transition metal-promoted oxidative cyclization

4) Carry out research on the possibility of using the developed transition-metal-promoted oxidative cyclization in the synthesis of carbazole derivatives with antitumor potential from tryptophan

5) Perform biological research on the antitumor properties of synthesized 1,2,3-trisubstituted carbazole derivatives

III. RESULTS AND DISCUSSION

1. Synthesis and molecular docking of 1,2,3,4-tetrahydrocyclopenta[*b*]indole substituted in 1 and 3 positions

In the first stage of my research, I focused my efforts on developing conditions for the synthesis of tetrahydrocyclopenta[*b*]indole derivatives, which are ligands for the human serotonin transporter. The structure of these compounds is based on a tricyclic ring containing as a substituent amino **190** or imino group **191** and an aryl group at the chiral center (*Figure 65*).

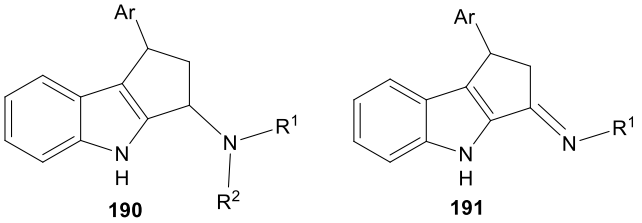


Figure 65 Ligands for human serotonin transporter

After the literature studies, I found out that compounds containing indole moiety connected to an aliphatic ring can be prepared in several different ways, some of which have described in chapter entitled „Selected methods of synthesis of tetrahydrocarbazolone derivatives". I decided to obtain the desired amines/imines from the corresponding 1-aryl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-ones **192**, which can be easily synthesized by intramolecular Friedel-Crafts acylation. In order to obtain compounds **192**, I developed a three-step synthesis pathway, which is presented in *Figure 66*.

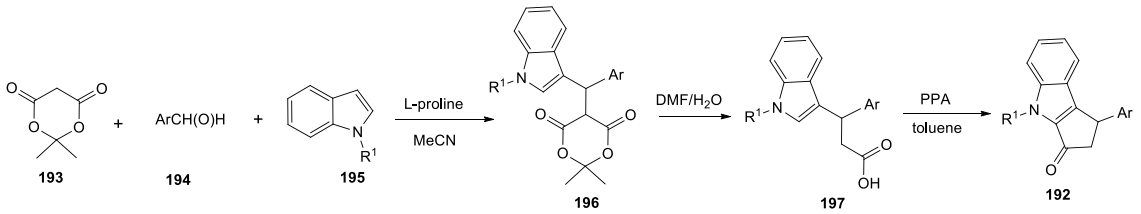
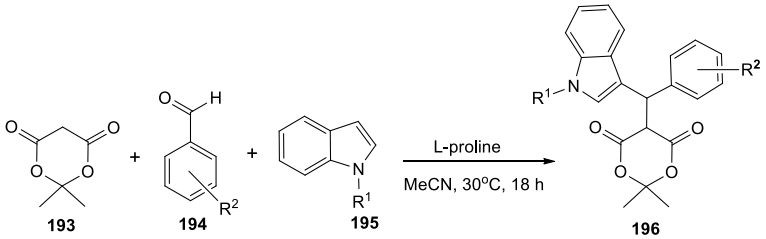


Figure 66 Preparation of 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4*H*)-ones

First, it was necessary to develop a method for the synthesis of 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones **196**. In this case, one-pot type reaction of Oikawa-Yonemitsu[249] involving the simultaneous condensation of Meldrum's acid **193**, arylaldehyde **194** and the corresponding indole **195** mixed in a 1:1:1 ratio in acetonitrile in the presence of L-proline, proved to be excellent. The yields of obtained **196a-d** are presented in

Table 1. Compound **196** has a chiral center, but as the addition of L-proline does not affect the enantiomeric excess, prepared 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones **196** were racemic.

Table 1. Synthesis of 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones **196a-d**

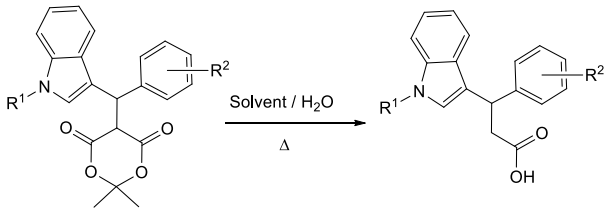


193 194 195 196

Entry	R^1	R^2	196	Yield [%]
1	H	H	**a**	48
2	CH_3	H	**b**	50
3	H	4-CF_3	**c**	56
4	H	3-Cl	**d**	60

In the second step, based on the procedure described in the literature[250], the prepared 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones **196** had to be hydrolyzed in a mixture of DMF/H_2O solvents to form the corresponding 3-(1*H*-indol-3-yl)-3-arylpropanoic acids **197**. However, as the use of DMF as a solvent was associated with problematic removal from the reaction mixture due to the high boiling point, I decided to test two other solvents: THF and acetone. Unfortunately, carrying out the reaction in tetrahydrofuran resulted in the appearance of butanediol in the reaction mixture from the decomposition of THF. As a result, despite the purification in the proton NMR spectrum, I observed signals from butanediol. On the other hand, the use of acetone resulted in extended reaction time and lower yields at the same time. The synthesis yields **197** are presented in *Table 2*.

Table 2. Hydrolysis of 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones **196a-d**



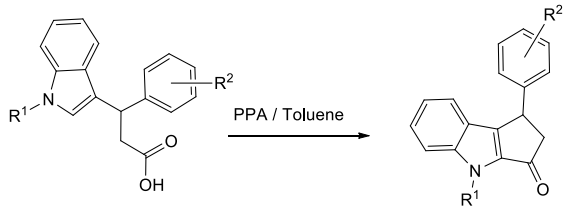
196 197

Entry	R^1	R^2	196, 197	Hydrolysis Conditions			Yield of 197 [%]
				Solvent	Time [h]	Temp. [°C]	
1	H	H	**a**	DMF	4	100	45
2	H	H	**a**	Acetone	24	56	31
3	CH_3	H	**b**	DMF	4	100	60
4	H	4-CF_3	**c**	DMF	4	100	60
5	H	3-Cl	**d**	DMF	4	100	58
6	H	3-Cl	**d**	THF	23	66	58
7	H	3-Cl	**d**	Acetone	24	56	23

During isolation of acids **197** by extraction, I encountered a problem related to their migration from the organic layer to the water layer, which resulted in the loss of some product and reduced insolation efficiency. In order to improve the purification efficiency, I decided to use flash chromatography. Unfortunately, in this case, I was unable to isolate any of the products. The attempt to use crystallization as a method of purification was also unsuccessful.

In the next step, compound **197** had to be converted into 1-aryl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-ones **192**. For this purpose, I used Friedel-Crafts acylation of acids **197**, which I treated with PPA in toluene[251]. The use of PPA, although successful, had several disadvantages. The problem was with the phase transfer of the reagents and with the efficient mixing of the reaction mixture. On the micro scale, the effect was negligible, but on the macro scale I noticed a significant decrease in efficiency (the results presented in *Table 3* correspond to the macro scale).

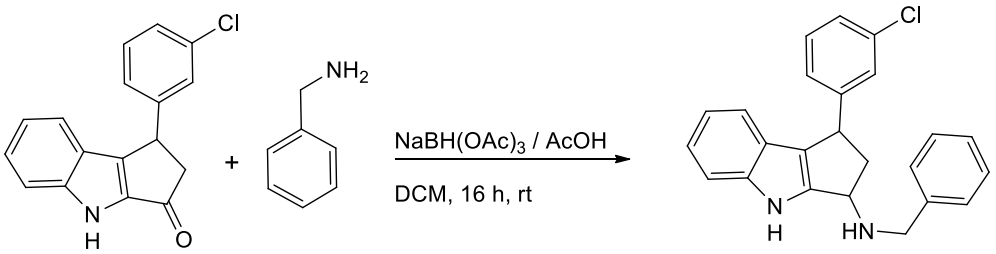
Table 3. Cyclization of acids **197a-d** to 1-aryl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-ones **192**



197 192

Entry	R^1	R^2	192	Yield [%]
1	H	H	**a**	38
2	CH_3	H	**b**	33
3	H	4-CF_3	**c**	25
4	H	3-Cl	**d**	15

The final step of amine **190** synthesis seemed to by very simple. I expected to follow via typical one-pot reductive amination reaction with in situ generation of imine and reduction to amine with sodium triacetoxyborohydride. Unfortunately, using this method, I was able to synthesize only *N*-benzyl-1-(3-chlorophenyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-amine **190cc** (*Figure 67*).



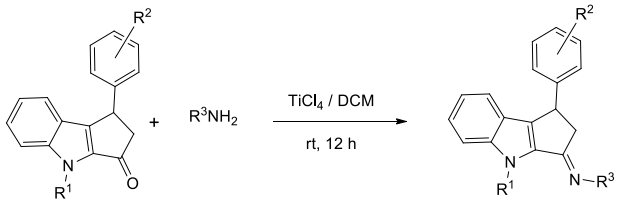
192d 190cc

Figure 67 Reductive amination of 1-(3-chlorophenyl)-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one

Application of above procedure for the amination of the others 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ones **192a-c** was unsuccessful. In another attempt, I decided to replace sodium triacetoxyborohydride with a stronger reducing agent, which is sodium cyanoborohydride. Unfortunately, replacing the reductant did not bring the expected results, preventing the synthesis of the desired amines. Because sodium cyanoborohydride is practically insoluble in DCM in the next two approaches, I decided to change the reaction conditions so that the solubility of all components was not objectionable. Therefore, in the next approach, the reduction with $NaBH_3CN$ was conducted in THF with the addition of acetic acid at room temperature[252] or in boiling methanol with the addition of sodium acetate[253]. Unfortunately,

both of these approaches failed to obtain the desired amines. I also tried to synthesize the amine **190** using a two-step approach with the in situ preparation of the imine under azeotropic conditions and then reduction with $NaBH_3CN$[254], which also did not give the expected results. Finally, the method of synthesis of imines **191** in the presence of $TiCl_4$[255] turned out to be effective, which resulted in obtaining two models: with 2-phenylethylamine and with cyclohexylamine. Unluckily, attempts to reduce the imines with $LiBH_4$, $NaBH_4$, $NaBH(OAc)_3$ or $LiAlH_4$ failed to obtain the desired amines **190**. However, the prepared imines turned out to be very stable, which can be explained by the conjugation of the imino group with the electron-rich indole ring. In addition, molecular docking studies showed a high affinity of imines for the used model of serotonin transporter, even higher than for amines. The stability of imines, their high affinity for the serotonin transporter and the already developed method of their synthesis made me decide to obtain a number of these compounds. I summarized the results in *Table 4*. To my surprise, the obtained imines **191** turned out to be sufficiently stable to allow purification by flash chromatography.

Table 4. Synthesis of *N*-(1-aryl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-ylidene)alkylamines **191aaa-acb**



192 191

Entry	R^1	R^2	R^3	191	Yield [%]
1	H	H	$PhCH_2CH_2$	**aaa**	29
2	H	H	c-Hex	**aab**	65
3	CH_3	H	$PhCH_2CH_2$	**baa**	85
4	CH_3	H	c-Hex	**bab**	90
5	H	4-CF_3	$PhCH_2CH_2$	**aba**	73
6	H	4-CF_3	c-Hex	**abb**	77
7	H	3-Cl	$PhCH_2CH_2$	**aca**	55
8	H	3-Cl	c-Hex	**acb**	58

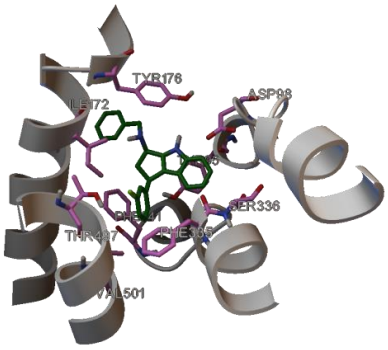
1.1 Molecular docking

The designed compounds were subjected to molecular docking with AutoDock Tools software[256]. For this purpose, the crystallographic structures of the necessary proteins, i.e. human serotonin TS3 transporter[257], human dopamine D3 receptor[258] and Drosophila dopamine transporter[259] were obtained from the PDB database. The energy of ligand molecules was minimized using an MM2 force field.

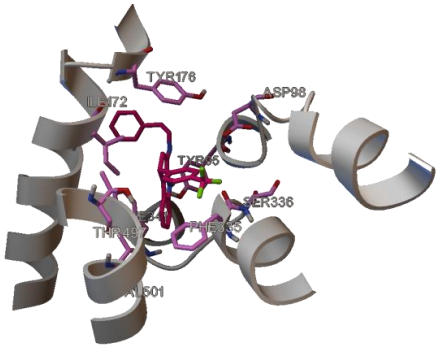
1.1.1 Docking study

As mentioned above, selection of molecules for synthesis that bind to the serotonin transporter was made using the AutoDock Tools software[256]. As the used crystallographic structure of the human serotonin transporter TS3[257] initially contained paroxetine in its structure, in the first step we checked whether the removed paroxetine would dock in the same place during our procedure. As a result, we were able to get the same structure with paroxetine docked in the right place. Moreover, serotonin docked similarly - with indole ring near TYR 176 and ILE 172 and with amine residue oriented to the side chain COOH of ASP98. The obtained results convinced us that the applied procedure is correct, therefore, in the next step, we could start molecular docking on the compounds we designed. First, we performed calculations for amines **190aa-ed**. In the case of our ligands, we obtained a different way of docking : the region of TYR176 and ILE 172 was occupied with an alkylamino side chain of ligand, while the indole moiety was placed in the middle of the pocket (*Figure 68a*).

a)



b)



c) d)

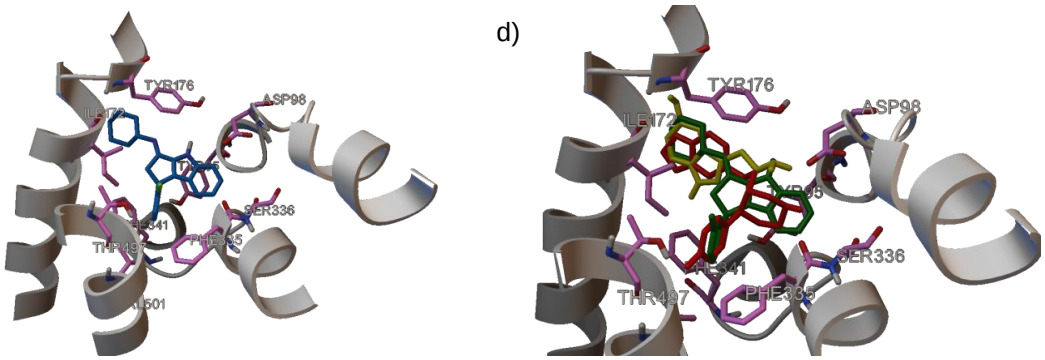
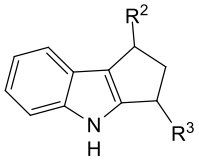


Figure 68 Binding modes on TS3 transporter active site a) amine **190cc** (1*R*, 3*R*), b) imine **191aba** (*R*), c) imine **191acb** (*R*) d) binding comparison of **191acb** (*R*) (green), paroxetine (red) and serotonin (yellow).

The value of free energy binding for four stereoisomers of amine types ligands are presented in *Table 5*.

Table 5. Binding energy of amines **190aa-ed** to human serotonin transporter TS3



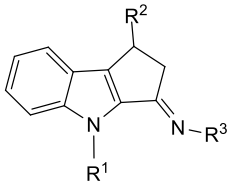
190

Entry	R^2	R^3	190	Binding Energy [kcal/mol]			
				(1*R*, 3*R*)	(1*R*, 3*S*)	(1*S*, 3*R*)	(1*S*, 3*S*)
1	Ph	$PhCH_2CH_2NH$	**aa**	-10.4	-10.1	-11.2	-10.8
2	Ph	c-HexNH	**ab**	-11.6	-11.8	-10.5	-11.0
3	Ph	$PhCH_2NH$	**ac**	-11.9	-11.9	-11.1	-10.5
4	Ph	$(Et)_2NH$	**ad**	-9.2	-9.3	-9.8	-9.3
5	4-$CF_3(C_6H_4)$	$PhCH_2CH_2NH$	**ba**	-12.1	-11.3	-11.3	-10.4
6	4-$CF_3(C_6H_4)$	c-HexNH	**bb**	-11.3	-11.5	-11.7	-11.4
7	4-$CF_3(C_6H_4)$	$PhCH_2NH$	**bc**	-11.9	-11.9	-11.9	-10.9
8	4-$CF_3(C_6H_4)$	$(Et)_2NH$	**bd**	-10.4	-9.9	-10.7	-10.2
9	3-$Cl(C_6H_4)$	$PhCH_2CH_2NH$	**ca**	-10.5	-10.6	-11.5	-11.0
10	3-$Cl(C_6H_4)$	c-HexNH	**cb**	-11.9	-12.2	-11.0	-11.1
11	3-$Cl(C_6H_4)$	$PhCH_2NH$	**cc**	-12.3	-12.2	-11.7	-10.2
12	3-$Cl(C_6H_4)$	$(Et)_2NH$	**cd**	-9.6	-9.5	-9.9	-9.2
13	4-F(C_6H_4)	$PhCH_2CH_2NH$	**da**	-10.2	-10.4	-11.5	-10.9
14	4-F(C_6H_4)	c-HexNH	**db**	-11.6	-11.5	-10.8	-10.8
15	4-F(C_6H_4)	$PhCH_2NH$	**dc**	-11.4	-12.0	-11.4	-10.7
16	4-F(C_6H_4)	$(Et)_2NH$	**dd**	-9.5	-9.4	-10.1	-9.5
17	t-Bu	$PhCH_2CH_2NH$	**ea**	-10.6	-10.3	-10.6	-10.0
18	t-Bu	c-HexNH	**eb**	-9.9	-10.6	-10.5	-9.1
19	t-Bu	$PhCH_2NH$	**ec**	-10.2	-10.1	-10.5	-9.9
20	t-Bu	$(Et)_2NH$	**ed**	-8.4	-8.4	-8.5	-8.3

Next, we performed molecular docking for imin **191aaa-bcc**. In this case, we observed the same location of the alkylamine side chain and the indole moiety. Additionally, in the case of imine **191aba** (*R*) the indole moiety interacted with PHE 341 (*Figure 68b*), and for imine **191acb** (*R*) with TYR 95 (*Figure 68c*). Moreover, in many cases, the affinity for the imines was even higher than that for the amines **190** (*Table 6*). This can be explained by the better fitting of planar imine side chain compared to amines alkylamino group located on the sp^3 chiral carbon. The last figure compares the binding of paroxetine, serotonin and **191acb** (*R*) to the serotonin transporter TS3 (*Figure 68d*). Summarizing, for proper binding mode of our designed ligand

190aa-ed and **191aaa-bcc**, the crucial components are: primary or secondary alkyl amino side chain with aromatic or cycloaliphatic ring, introducing a secondary noncyclic amine moiety significantly decrees the affinity of molecule (Entry: 4, 8, 12, 16, 20; *Table 5*). The second side chain should be aromatic, but the type of substitution is not a critical factor as it interact with PHE 335. Introducing the tert-butyl alkyl group disturbs the interaction of ligand with transporter (Entry: 17-20; *Table 5*).

Table 6. Binding energy of imines **191aaa-bcc** to human serotonin transporter TS3



191

Entry	R^1	R^2	R^3	191	Binding Energy [kcal/mol]	
					(*R*)	(*S*)
1	H	Ph	$PhCH_2CH_2$	**aaa**	-11.6	-11.8
2	H	Ph	c-HexNH	**aab**	-11.7	-10.8
3	H	Ph	$PhCH_2$	**aac**	-11.7	-11.2
4	H	4-$CF_3(C_6H_4)$	$PhCH_2CH_2$	**aba**	-11.7	-11.4
5	H	4-$CF_3(C_6H_4)$	c-HexNH	**abb**	-11.3	-11.2
6	H	4-$CF_3(C_6H_4)$	$PhCH_2$	**abc**	-11.8	-12.0
7	H	3-$Cl(C_6H_4)$	$PhCH_2CH_2$	**aca**	-11.3	-11.6
8	H	3-$Cl(C_6H_4)$	c-HexNH	**acb**	-12.4	-10.8
9	H	3-$Cl(C_6H_4)$	$PhCH_2$	**acc**	-11.9	-11.5
10	CH_3	Ph	$PhCH_2CH_2$	**baa**	-11.2	-10.9
11	CH_3	Ph	c-HexNH	**bab**	-11.3	-10.7
12	CH_3	Ph	$PhCH_2$	**bac**	-11.2	-11.1
13	CH_3	4-$CF_3(C_6H_4)$	$PhCH_2CH_2$	**bba**	-11.2	-11.8
14	CH_3	4-$CF_3(C_6H_4)$	c-HexNH	**bbb**	-11.9	-11.6
15	CH_3	4-$CF_3(C_6H_4)$	$PhCH_2$	**bbc**	-11.4	-11.7
16	CH_3	3-$Cl(C_6H_4)$	$PhCH_2CH_2$	**bca**	-10.1	-11.0
17	CH_3	3-$Cl(C_6H_4)$	c-HexNH	**bcb**	-11.6	-11.0
18	CH_3	3-$Cl(C_6H_4)$	$PhCH_2$	**bcc**	-11.4	-11.4

Additionally, we tried docking our imine ligands into human dopamine D3 receptor[260] and Drosophila dopamine transporter[261]. In the case of D3 dopamine receptor, we did not observed good binding modes of our ligands. Some docking results suggest steric hindrance

caused by TYR365, which blocks entering of ligand inside of receptor pocket (*Figure 69*). Alkylamino side chain R3 tried to penetrate the binding site of the receptor, but the aryl side chain was hindered with a tyrosine ring.

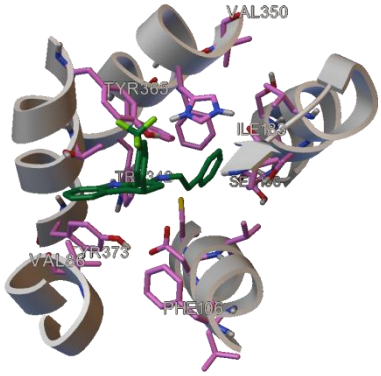
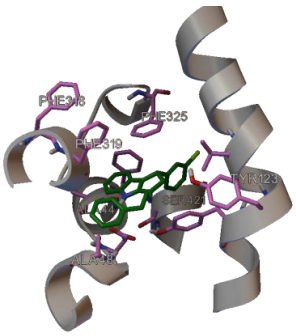


Figure 69 Unsuccessful fitting of **191aba** (*S*) in the active site of Dopamine D3 receptor

For dopamine transporter binding, the modes of our ligands were not perfect as they were for TS3 transporter, however, analysis of affinity energy exhibited a better interaction with enantiomeric forms. We observed moderately good interaction of **191acb** (*S*) (*Figure 70a*) and **191aba** (*S*) (*Figure 70b*). The side chain of the aromatic ring of our ligand fit at an angle to a place normally occupied by the aromatic ring of dopamine or RTI-55.

a)



b)

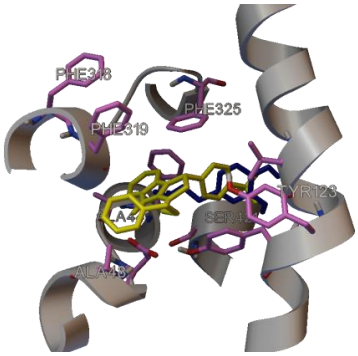


Figure 70 Binding modes on Dopamine Transporter active site a) **191acb** (*S*) b) binding comparison of **191aba** (*S*) (yellow) and dopamine (blue)

1.2 Conclusions

As a result of the research, four 1,2-dihydrocyclopenta[b]indol-3(4*H*)-one derivatives were synthesized based on a three-step synthesis path including the formation of arylidene derivatives of Meldrum's acid, hydrolysis to 3-substituted propionic acids and intramolecular cyclization by Friedel-Crafts acylation. Attempts were made to convert the obtained carbazolone derivatives into the corresponding amines, which ended in a fiasco. Therefore, the research was

stopped at the stage of imine synthesis, which surprisingly turned out to be very stable. The binding energy of these ligands to the human serotonin TS3 transporter as well as selectivity for the human dopamine D3 receptor and the dopamine transporter were tested *in silico* using docking software. During docking, the prepared imines showed a high affinity to serotonin transporter and a very similar active site placement compared to serotonin and paroxetine.

The results presented in the chapter „Synthesis, and molecular docking of 1,2,3,4-tetrahydrocyclopenta[*b*]indole substituted in 1 and 3 positions" were included in the scientific publication: Szewczyk, M.; Punda, P.; Janikowska, K.; Makowiec, S. (**2019**) Design, synthesis, and molecular docking of new 5-HT reuptake inhibitors based on modified 1,2-dihydrocyclopenta[b]indol-3(4H)-one scaffold. *J. Chem. Sci., 131,* DOI 10.1007/s12039-019-1621-x.

2. Synthesis of 1,2,4-trisubstituted carbazole derivatives from 5-(1*H*-indol-3-yl)-3-oxopentanoic acid esters or amides promoted by metal compounds

According to the literature studies on the construction of the carbazole scaffold, which I described in the chapter entitled "Selected methods of synthesis of carbazole derivatives", there are many ways to obtain this core, from traditional methods such as Fisher indolization to modern approaches based on cyclization promoted by iodine, transition metals or Lewis acids. After the literature studies, as part of the next step of my research, I focused my efforts on developing a new approach to the synthesis of carbazole and tetrahydrocarbazole derivatives containing substituents in 1,2,4 positions. For this purpose, I decided to use the cyclization of 5-(1*H*-indol-3-yl)-5-aryl-3-oxopentanoic acid derivatives **199aa-db** and 5-(1*H*-indol-3-yl)-3-oxopentanoic acid derivatives **199ea ed**. However, first, it was necessary to develop a method of obtaining these compounds. I developed the synthesis path which is presented in *Figure 71*.

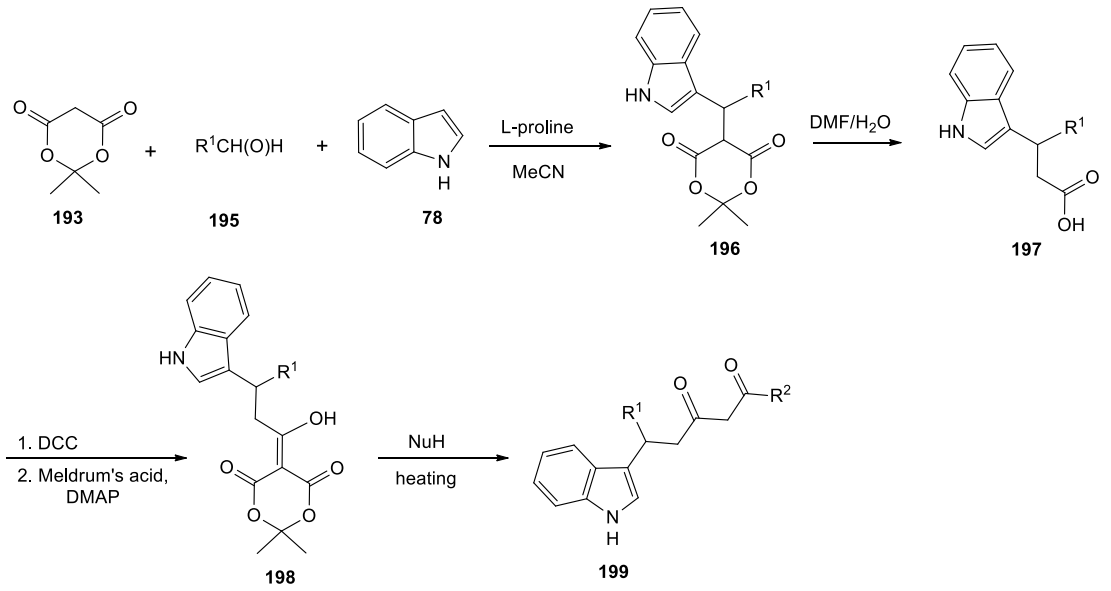
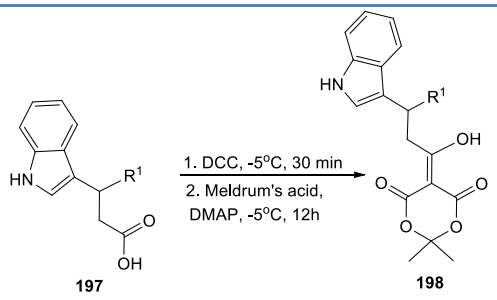


Figure 71 Synthesis of intermediates for cyclization

In the case of synthesis of 5-(1*H*-indol-3-yl)-5-aryl-3-oxopentanoic acid derivatives **199aa-db**, I used compounds **197a** and **197d**, which were prepared according to the method described in the chapter "Synthesis and molecular docking of 1, 2,3,4-tetrahydrocyclopenta[*b*]indole substituted in 1 and 3 positions". In order to prepare of 5-(1*H*-indol-3-yl)-3-oxopentanoic acid derivatives **199ea-ed** (R^1=H), the synthesis was started from commercially available 3-(1*H*-indol-3-yl)propionic acid **197e**. Then, from compounds **197a-e** via condensation with Meldrum's acid **193** in the presence of DCC and DMAP, I obtained acyl Meldrum's acid derivatives **198a-e**[262] with yields shown in *Table 7*.

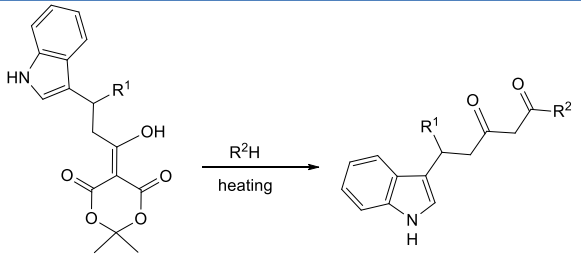
Table 7. Synthesis of acyl Meldrum's acids **198a-e**



Entry	R^1	198	m.p. [°C]	Yield [%]
1	Ph	**a**	55-57	64
2	3-ClC_6H_4	**d**	107-109	73
3	H	**e**	88-90	87

In the next step, compounds **198a-e** were subjected to a nucleophilic substitution reaction with appropriate alcohol (ethanol, methanol)[263] or amine (morpholine, p-toluidine)[264,265], which resulted in obtaining compounds **199aa-ed**. The alcoholysis was performed in boiling alcohol for 24h. The use of amines as nucleophiles required different reaction conditions. When I used morpholine it was necessary to add TMSCl to speed up the reaction because of high basicity of this amine. The reaction was carried out in boiling benzene for 3 h. As *p*-toluidine is an aromatic amine much less basic than morpholine, the addition of TMSCl in this case was unnecessary. The reaction was conduced in toluene at 70°C for 18 hours. The obtained results are summarized in *Table 8*.

Table 8. Preparation of 3-oxoamides and 3-oxoesters **199aa–ed**



198 199

Entry	R^1	R^2	199	Yield [%]
1	Ph	OMe	**aa**	71
2	Ph	OEt	**ab**	67
3	Ph	$O(CH_2CH_2)N$	**ac**	70
4	Ph	4-MeC_6H_4NH	**ad**	75
5	3-ClC_6H_4	OMe	**da**	66
6	3-ClC_6H_4	OEt	**db**	57
7	H	OMe	**ea**	96
8	H	OEt	**eb**	75
9	H	$O(CH_2CH_2)N$	**ec**	98
10	H	4-MeC_6H_4NH	**ed**	88

Taking into account the fact that compounds containing the 1,3-dicarbonyl system are very easily oxidized to the radicals with manganese (III) acetate[266], first I decided to check whether the prepared 3-oxoesters **199aa-eb** and 3-oxoamides **199ad**, **199ec** and **199ed** will cyclize in the presence of $Mn(OAc)_3$ in acetic acid (*Figure 72*). We assumed that electrophilic radical generated on 1,3-dicarbonyl moiety would easily attack an electron rich indole π-system, which after subsequent oxidation with Mn(III) and abstraction of proton should lead to the recovery of the aromatic system.

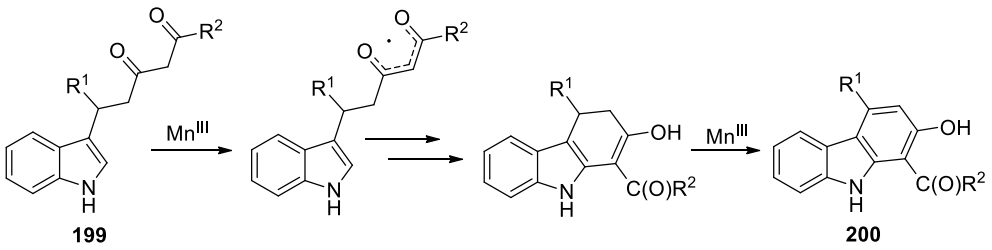
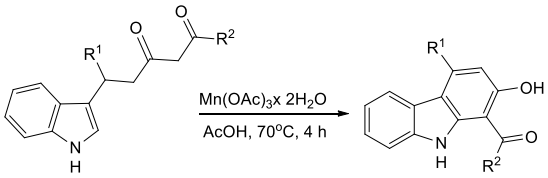


Figure 72 Key step of cyclization promoted by manganese (III) acetate

As a result of using this method, I was able to obtain a series of **200aa-eb** derivatives which are products of cyclization of **199aa-eb** esters. Unfortunately, this approach did not work in the case of amide cyclization (**199ad**, **199ec**, **199ed**), in all cases I obtained a complicated mixture of oxidation products. Taking into account the reaction mechanism, we expected that for the entire cyclization and aromatization process up to 4 equivalents of $Mn(OAc)_3$ may be needed. In order to determine the optimal amount of oxidant, I conducted a series of experiments (*Table 9*). In most cases, the highest yields of **200aa-eb** were obtained with 2.5 equivalents of $Mn(OAc)_3$, a further increase in the amount of oxidant led to a decrease in yield.

Table 9. Oxidative cyclization of 3-oxoesters **199aa–eb** with $Mn(OAc)_3$



Entry	199	R^1	R^2	Yield of 200 [%] $Mn(OAc)_3$		
				1,6 eq	2,5 eq	3,2 eq
1	**aa**	Ph	OMe	29	32	12
2	**ab**	Ph	OEt	18	72	27
3	**da**	3-ClC_6H_4	OMe	52	51	35
4	**db**	3-ClC_6H_4	OEt	59	61	60
5	**ea**	H	OMe	33	31	31
6	**eb**	H	OEt	19	26	20

Unfortunately, this approach did not solve my problems with β-ketoamides cyclization. Moreover, replacing $Mn(OAc)_3$ with another oxidizer, i.e. CAN, also did not work. In another attempt, according to the research by Sleiter and coworkers[267] who generate radicals from α-iodoesters/nitriles in the presence of H_2O_2/DMSO/Fe^{2+} to introduce an ester or nitrile group in the 2-position of pyrrole, I decided to transform the ester **199ea** into the α-iodoester using NIS in DMSO[268], and then prepared α-iodinated ester in the presence of H_2O_2/DMSO/Fe^{2+} system convert into desired carbazole derivatives **200**. This attempt also ended in failure. In the course

of further research, I came across the work of Cheung and coworkers[269] who described the intramolecular cyclopropanation reaction of β-ketoesters containing unsaturated moiety in the presence of I_2/Lewis acid/Et_3N. Despite the far analogy to the designed compounds, I decided to check whether (1*H*-indoyl)-3-oxocarboxylic acids derivatives **199aa-ed** react with iodine in the presence of Lewis acid. I conducted the first experiment on the 3-oxoester **199ea**, to which I added 1 eq $Sc(OTf)_3$ in the presence of 2.5 eq Et_3N and 1.5 eq I_2. I carried out the reaction in DCM at room temperature. I assumed that the reaction product would be compound **202**, but to my surprise I isolated methyl 2-hydroxy-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate **201ea** from the reaction mixture in 43% yield (*Figure 73*).

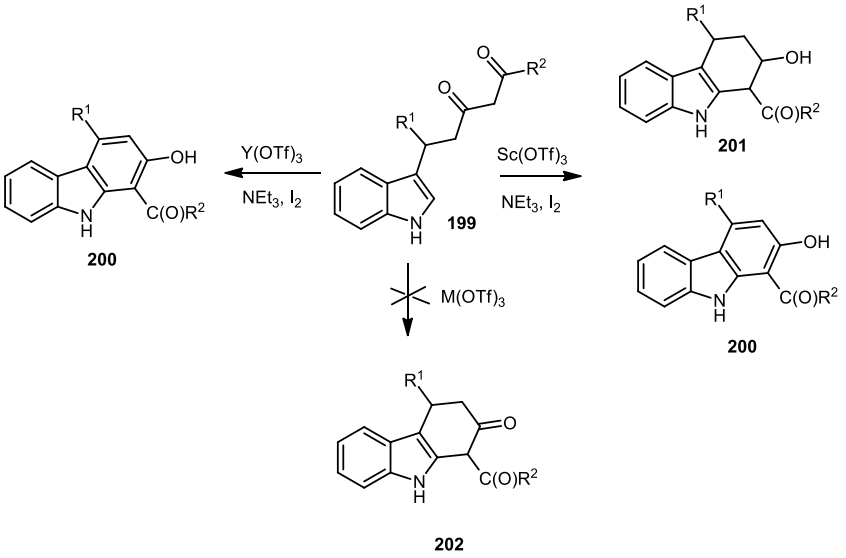
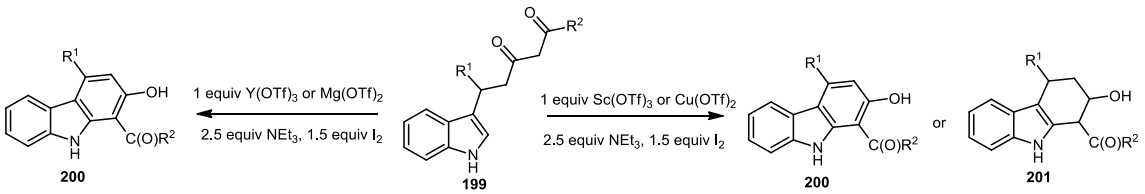


Figure 73 Cyclization of 3-oxoesters and 3-oxoamides with transition-metal triflates

Then I decided to test three more Lewis acids on the β-ketoester **199ea**: $Y(OTf)_3$, $Cu(OTf)_2$ and $Mg(OTf)_2$ (*Table 10*). Depending on the triflate used, I received two different products. When I used $Cu(OTf)_2$, I obtained compound **201ea**, identical as in the case of using $Sc(OTf)_3$, which is composed of two aromatic rings and one aliphatic ring, the so-called tetrahydrocarbazole. However, when I used $Y(OTf)_3$ or $Mg(OTf)_2$ for the reaction, I received a carbazole derivative **200**. In further research, I decided to use only $Sc(OTf)_3$ and $Y(OTf)_3$ because of the higher reaction yield than in the case of $Cu(OTf)_2$ and $Mg(OTf)_2$.

Table 10. Cyclization of 3-oxoesters and 3-oxoamides **199aa-eb** with metal triflates $M(OTf)_x$



Entry	199	$M(OTf)_x$	R^1	R^2	Yield [%]	
					200	201
1	**aa**	$Sc(OTf)_3$	Ph	OMe	45	-
2	**aa**	$Y(OTf)_3$	Ph	OMe	37	-
3	**ab**	$Y(OTf)_3$	Ph	OEt	12	-
4	**ac**	$Y(OTf)_3$	Ph	$O(CH_2CH_2)_2NH$	40	-
5	**ad**	$Y(OTf)_3$	Ph	$4\text{-}MeC_6H_4NH$	42	-
6	**da**	$Sc(OTf)_3$	$3\text{-}ClC_6H_4$	OMe	16	-
7	**da**	$Y(OTf)_3$	$3\text{-}ClC_6H_4$	OMe	23	-
8	**db**	$Y(OTf)_3$	$3\text{-}ClC_6H_4$	OEt	11	-
9	**ea**	$Sc(OTf)_3$	H	OMe	-	43
10	**ea**	$Cu(OTf)_2$	H	OMe	-	14
11	**ea**	$Y(OTf)_3$	H	OMe	41	-
12	**ea**	$Mg(OTf)_2$	H	OMe	27	-
13	**eb**	$Sc(OTf)_3$	H	OEt	28	-
14	**eb**	$Y(OTf)_3$	H	OEt	21	-
15	**ed**	$Y(OTf)_3$	H	$4\text{-}MeC_6H_4NH$	42	-

As can be seen from the results in *Table 10*, for the rest of the derivatives **199aa-ed**, I was able to isolate only product **200**, even though I observed traces of alcohol **201** in the crude mixture. Therefore, I put forward hypothesis that compound **200** was formed by the oxidation of compound **201**. In order to prove the hypothesis, I conducted a series of experiments on the compound **201ea**, which I treated with various oxidants (*Figure 74*). The reaction was carried out in dichloromethane at room temperature. I monitored the reaction mixture by TLC. I observed oxidation to the product **200ea** in two cases: (a) when I used iodine as the oxidant, then I observed the gradual formation of **200ea**, which after 7 days was about 50% (*Figure 74a*); (b) in the case of using the complete composition of the reactants, then I observed fast and complete oxidation of **201ea** to **200ea** within one day (*Figure 74d*).

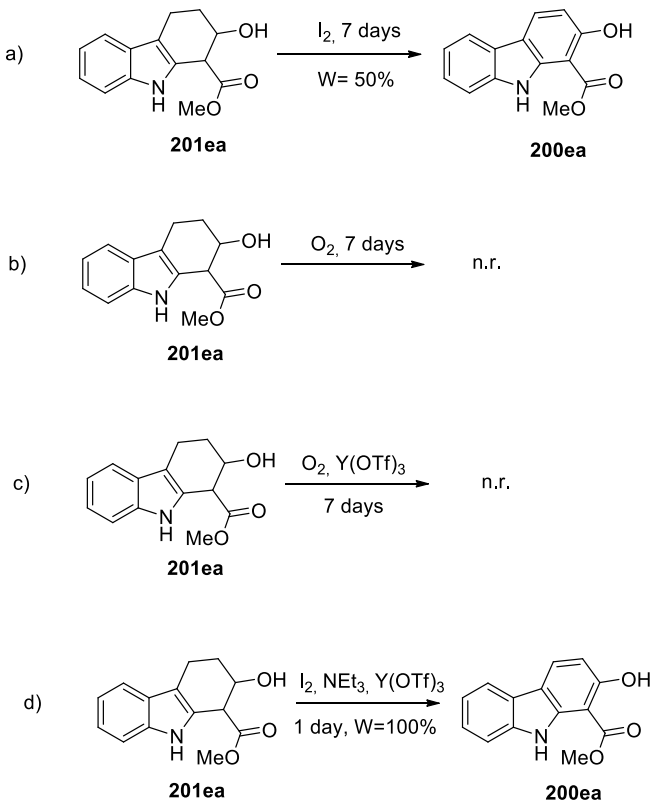


Figure 74 2-hydroxy-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylic acid **201ea** stability checking

The application of the described reaction conditions allowed me to obtain not only the products of cyclization of β-ketoesters **199aa-eb**, but as can be seen from the results summarized in *Table 10*, it also solved the problem with the cyclization of β-ketoamides (**199ac**, **199ad**, **199ed**).

Encouraged by the obtained results, in the next step I decided to synthesize carbazole derivatives with a smaller C ring, i.e. with 1,2,3,4-tetrahydrocyclopenta[*b*]indole **203** and 2,3-dihydro-1*H*-cyclobut[b]indole **204** cores (*Figure 75*). However, when trying to synthesize **203** and **204**, I was not able to isolate the pure acylation products of Meldrum's acid **193** with 2-(1*H*-indol-3-yl)acetic acid **205** and 1*H*-indole-3-carboxylic acid **206**. Moreover, even crude 5-[1-hydroxy-2-(1*H*-indol-3-yl)ethylidene]-2,2-dimethyl-1,3-dioxa-4,6-dione **207** or 5-[hydroxy(1*H*-indol-3-yl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-dione **208** treated with methanol did not produce β-ketoester (**209**,**210**), suggesting decomposition of initially formed compound **207** or **208** (*Figure 76*).

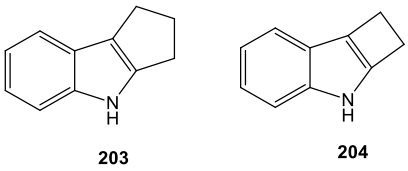


Figure 75 1,2,3,4-tetrahydrocyclopenta[*b*]indole **203** and 2,3-dihydro-1*H*-cyclobuta[*b*]indole **204** scaffolds

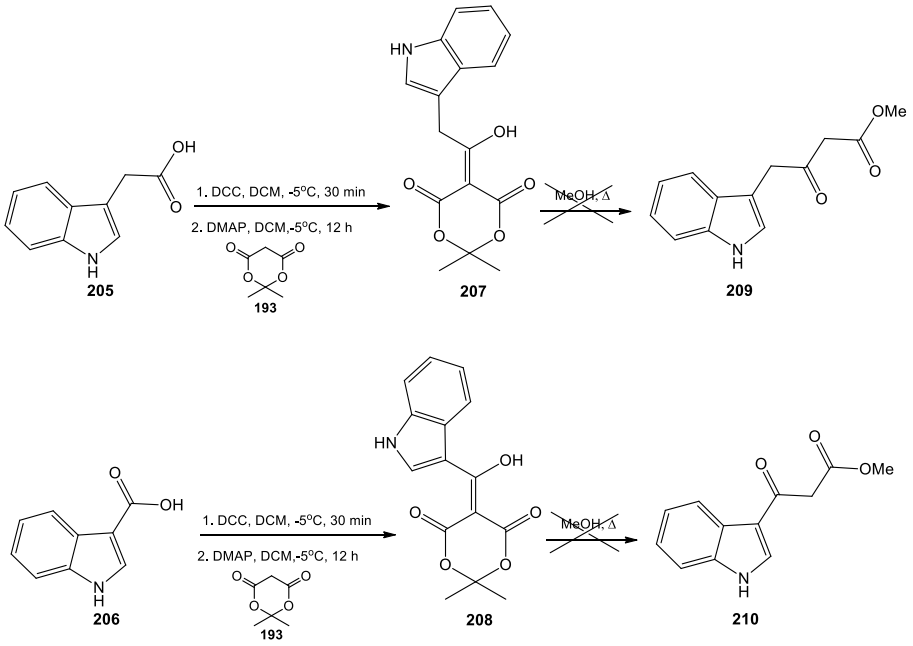


Figure 76 Attempts to synthesize β-ketoesters **209** and **210**

I have also tried to prepare core **204** via 1*H*-indole-2-carboxylic acid derivatives. For this purpose, I conducted reaction of methyl 3-(1*H*-indol-2-yl)-3-oxopropionate **211** with I_2 in the presence of $Sc(OTf)_3$ and Et_3N in DCM at room temperature. From the reaction mixture, I isolated methyl 3-(3-iodo-1*H*-indol-2-yl)-3-oxopropanoate **212** (*Figure 77*). The results may confirm the hypothesis that Wheland type iodonium cation is formed, which can react with chelated β-keto to form a cyclization product, and after the elimination of HI it leads to the recovery of the indole aromatic system. In the case of 2-substituted indole the cyclization of iodonium cation was not possible. However we observed the formation of iodination product **212** with 52% yield.

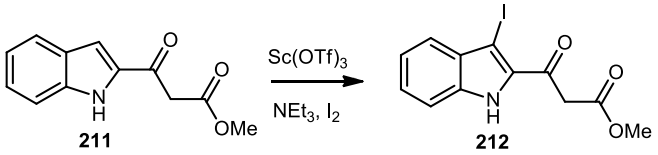


Figure 77 Attempts to cyclize methyl 3-(1*H*-indol-2-yl)-3-oxopropanoate

2.1 Considerations on the reaction mechanism

Based on the collected material and literature review, we decided to propose a preliminary mechanism of the studied cyclization process with the use of iodine and $M(OTf)_3$ (*Figure 78*). Regardless of the substitution of the indole derivative at position 2 or 3, the first two steps were as follows: coordination to Lewis acid (Sc^{3+}, Y^{3+} etc.) and addition of iodine with formation of the iodonium cation **213a**, **b**. Then the formed cation **213a** is cyclized to form enol **214**, which we assume is then isomerized to compound **215**. In the next step, the obtained allyl alcohol **215** during the attack of the iodide anion should undergo reductive elimination to form compound **201**, which in the last step is oxidized with iodine in the presence of $M(OTf)_3$ to carbazole **200**. In the case of **213b**, cyclization would lead to a non-aromatic spiro product, which was obviously not observed.

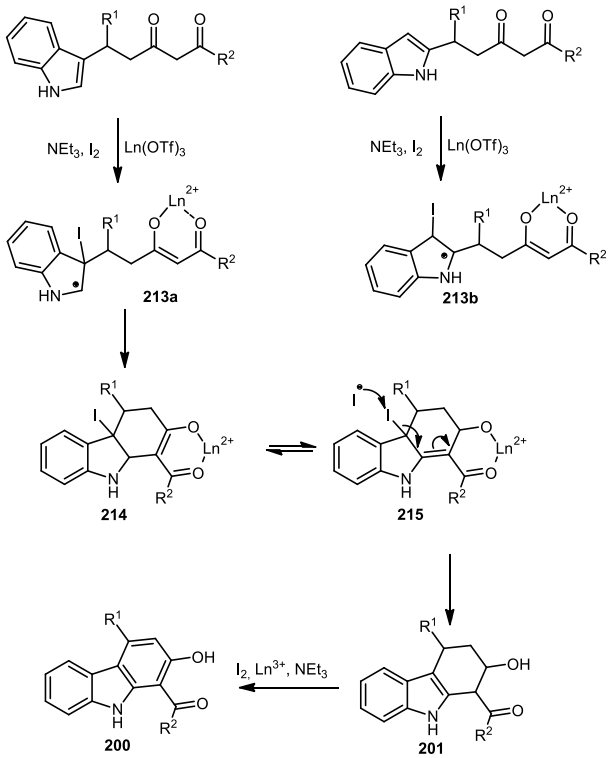


Figure 78 Tentative reaction mechanism for the cyclization of 5-(1*H*-indol-3-yl)-3-oxopentanoic acids

In order to confirm the hypothesis about the reductive elimination reaction, evidence of iodine regeneration had to be found. That's why I conducted an experiment with iodine deficiency. Compound **199ea** (1 eq) was reacted with 0.1 eq I_2 in the presence of 2 eq $Y(OTf)_3$ and 2.5 eq Et_3N. The reaction was carried out in dichloromethane at room temperature for 12 hours. From the reaction mixture, I isolated the compound **200ea** with 18% yield, which

indicated the regeneration of iodine, as for the reaction to proceed with such a yield, 0.54 eq of iodine would be needed (*Figure 79a*). I obtained similar results in the case of the compound **199aa** (*Figure 79b*). In order to exclude the possibility of oxidation of the iodide anion to molecular iodine in the presence of oxygen, despite carrying out the reaction under argon atmosphere, I conducted an experiment in which to 1 eq of β-ketoester **199ea** I added 1 eq $Y(OTf)_3$, 2.5 eq Et_3N and 1.5 eq NEt_3CH_3I in dichloromethane. I did not observe the formation of the cyclization product and the color characteristic for the reactions carried out with the use of molecular iodine (*Figure 79c*). In this way, I also excluded the possibility of the formation of reduced alcohol in the reaction of the 3-oxoester **199ea** with the iodide anion in the presence of $Y(OTf)_3$. Additionally, I performed a similar experiment on methyl 2-benzyl-3-oxobutanate **216**. In this case, I also did not observe oxidation of the iodide anion or reduction of the β-ketoester (*Figure 79d*).

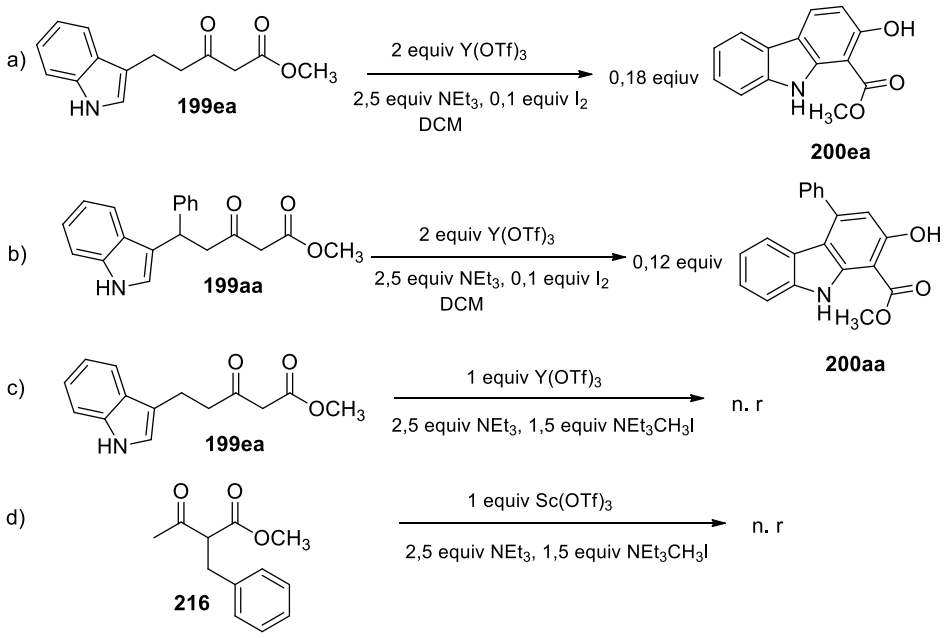


Figure 79 Control experiments for the elucidation of reaction mechanism

2.2 Conclusions

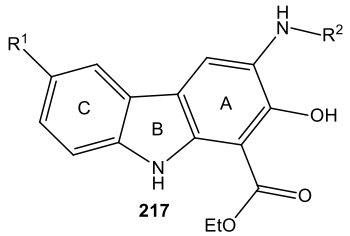
As a result of the conducted research, successfully developed a new method for the synthesis of functionalized carbazoles and tetrahydrocarbazoles using esters and amides of (5-(1*H*-indol-3-yl)-5-aryl-3-oxopentanoic acids and (5-(1*H*-indole)-3-)yl)-3- oxopentanoic acids. The following reaction conditions were used to achieve this goal: cyclization promoted with manganese (III) acetate in acetic acid, which worked perfectly for the cyclization of (5-(1*H*-indol-3-yl)-5-aryl-3-oxopentanoic acids and (5-(1*H*-indol-3-)yl)-3-oxopentanoic acids esters and

cyclization in the presence of I_2/Lewis acid/Et_3N, which enabled the synthesis of both ester and amide derivatives of carbazole/tetrahydrocarbazole. On the basis of the collected material and the literature review, the tentative mechanism of cyclization of β-oxoesters and β-oxoamides in the presence of I_2/Lewis acid/Et_3N was proposed and verified.

The results presented in the chapter „Synthesis of 1,2,4-trisubstituted carbazole derivatives from 5-(1*H*-indol-3-yl)-3-oxopentanoic acid esters or amides promoted by metal compounds" were included in the scientific publication: Szewczyk, M.; Ryczkowska, M.; Makowiec, S. (**2019**) Transition-Metal-Promoted Oxidative Cyclization To Give 1,2,4-Trisubstituted Carbazole Scaffolds. *Synthesis, 51,* 4625-4634*.* DOI 10.1055/s-0039-1690681.

3. Synthesis of 1,2,3,6-tetrasubstituted carbazole derivatives with anticancer potencial

In the last stage of my research, I decided to develop conditions for the synthesis of carbazole derivatives showing anticancer activity. These compounds are consisted of three aromatic rings: two benzene (A, C) and one pyrrole (B). Additionally, ring A has three substituents: an ester group, a hydroxyl group, and an amide/urethane group. Some derivatives additionally contain a amide/urethane or acetoxy group at 6-position on the ring C (*Figure 80*).



217

Figure 80 Structure of compounds with anticancer activity

Encouraged by the results obtained during previous research, I decided to prepare the desired carbazoles **217** from ethyl 5-(1*H*-indol-3-yl)-3-oxopentanoate derivatives **220** as a result of the developed method of oxidative cyclization promoted by $Mn(OAc)_3$ or I_2/Lewis acid/Et_3N . However, first it was necessary to design a synthetic pathway to obtain compounds **220**. For this purpose, I used the methodology presented in *Figure 81*.

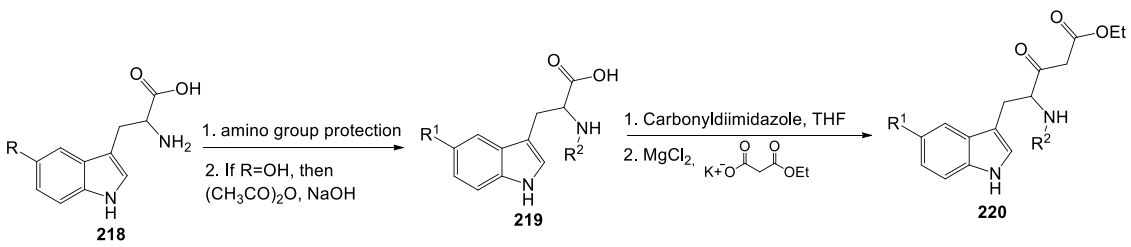


Figure 81 Synthesis of intermediates 3-oxoesters **220**

First, the *N*-terminus of tryptophan **218a** had to be protected. For this purpose, I used the following reagents: di-tert-butyl dicarbonate[270], ethyl chloroformate[271], acetic anhydride[272], benzyl chloroformate[273] and phthalic anhydride[274] (*Figure 82*). In the case of 5-hydroxytryptophan, after protecting the amino group, in the next step it was necessary to protect the hydroxyl group at the 5-position of the indole ring. I used the standard reacion with acetic anhydride in an alkaline medium (*Figure 82*)[275]. The obtained results are presented in *Table 11*.

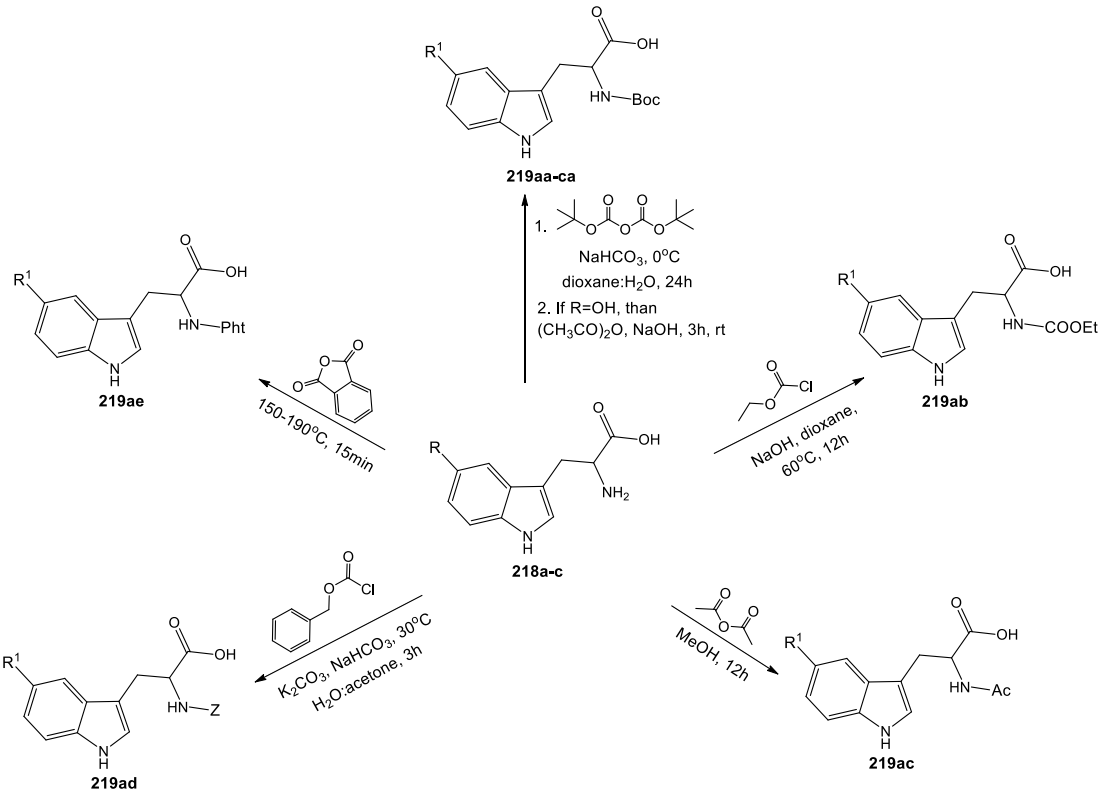
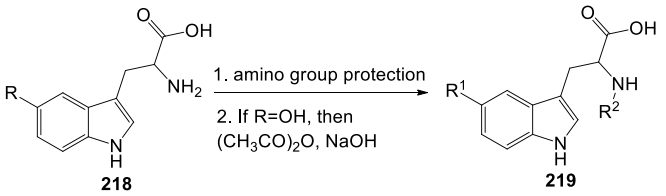


Figure 82 Protection of the tryptophan amino group

Table 11. Synthesis of *N*-protected tryptophan **219aa-ca**

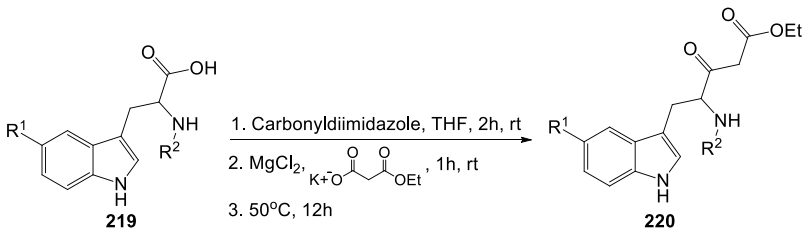


218 219

Entry	218	R	R^1	R^2	219	Yield [%]
1	**a**	H	H	Boc	**aa**	98
2	**a**	H	H	COOEt	**ab**	31
3	**a**	H	H	Ac	**ac**	98
4	**a**	H	H	Z	**ad**	70
5	**a**	H	H	Pht	**ae**	98
6	**b**	NH_2	NHBoc	Boc	**ba**	98
7	**c**	OH	OAc	Boc	**ca**	60

Then, appropriate derivatives of ethyl 5-(1*H*-indol-3-yl)-3-oxopentanoate **220** had to be synthesized. First, I tried to use the previously described acylation of Meldrum's acid **193** with *N*-Boc-tryptophan **219aa** or *N*-Pht-tryptophan **219ae**, and then esterification reaction with methanol. Unfortunately, I was unable to isolate clean acylation products. Moreover, even crude [1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-(1*H*-indol-3-yl)propan-2-yl]tert-butyl carbamate or 2-[1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3(1*H*-indol-3-yl)propan-2-yl]isoindoline-1,3-dione treated with methanol did not lead to the formation of the β-oxoester (**220aa**, **220ae**), suggesting self-decomposition of the initially formed acyl derivative of Meldrum's acid. After an unsuccessful attempt, in order to obtain β-ketoesters **220**, I decided to use the reaction involving the coupling of *N*-protected tryptophan **219** with 1,1′-carbonyldiimidazole, which is then replaced with monoethyl malonate[276]. The results are summarized in *Table 12*.

Table 12. Synthesis of ethyl 5-(1*H*-indol-3-yl) -3-oxopentanoate derivatives **220**



219 **220**

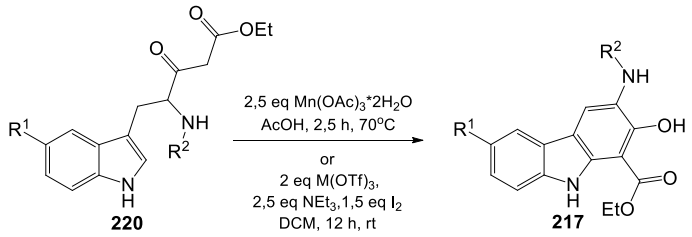
Entry	R^1	R^2	220	Yield [%]
1	H	Boc	**aa**	44
2	H	COOEt	**ab**	16
3	H	Ac	**ac**	46
4	H	Z	**ad**	28
5	H	Pht	**ae**	25
6	NHBoc	Boc	**ba**	43
7	OAc	Boc	**ca**	49

Having at my disposal, a new method for the synthesis of carbazole derivatives promoted by $Mn(OAc)_3$ or I_2/Lewis acid/Et_3N, prepared in previous studies, which I described in the chapter entitled „Synthesis of 1,2,4-trisubstituted carbazole derivatives from 5-(1*H*-indol-3-yl)-3-oxopentanoic acid esters or amides promoted by metal compounds", in the next step I proceeded to the synthesis of 1,2,3,6-tetrasubstituted carbazole derivatives **217** using the corresponding ethyl 5-(1*H*-indol-3-yl)-3-oxopentanoate derivatives **220** as starting materials. The first experiments were performed on compound **220aa** with the following results:

- when I ran the reaction with I_2/$Y(OTf)_3$/Et_3N, I obtained the product **217aa** with 12% yield;
- changing the Lewis acid to $Sc(OTf)_3$ did not improve the reaction yield, and even made it impossible to obtain the product;
- the use of manganese (III) acetate led to an increase in efficiency to 67%

I also conducted the same experiments on compound **220ae**. However, the use of the mentioned reaction conditions did not in any case lead to the formation of the desired product. Therefore, for the cyclization of the other compounds **220ab-ca**, I used $Mn(OAc)_3$. The results are presented in *Table 13*.

Table 13. Synthesis of 1,2,3,6-tetrasubstituted carbazole derivatives **217aa-ae**

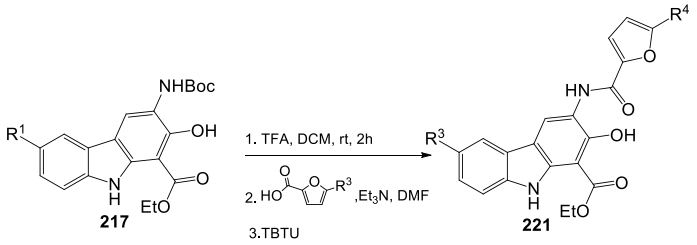


Entry	220	MX_3	R^1	R^2	Yield of 217 [%]
1	**aa**	$Y(OTf)_3$	H	Boc	12
2	**aa**	$Sc(OTf)_3$	H	Boc	-
3	**aa**	$Mn(OAc)_3$	H	Boc	67
4	**ab**	$Mn(OAc)_3$	H	COOEt	28
5	**ac**	$Mn(OAc)_3$	H	Ac	29
6	**ad**	$Mn(OAc)_3$	H	Z	-
7	**ae**	$Y(OTf)_3$	H	Pht	-
8	**ae**	$Sc(OTf)_3$	H	Pht	-
9	**ae**	$Mn(OAc)_3$	H	Pht	-
10	**ba**	$Mn(OAc)_3$	NHBoc	Boc	36
11	**ca**	$Mn(OAc)_3$	OAc	Boc	25

As can be seen from the results summarized in *Table 13*, as a result of the experiments I was able to obtain 5 derivatives **217aa-ca**, which were then submitted for research in order to determine their antitumor activity consisting in inhibiting the activity of telomerase, which will be presented in more detail in the chapter entitled "Biological evaluation".

The research obtained by the molecular docking method carried out by the Professor Maciej Bagiński group showed that the activity of telomerase is most inhibited by the amino group at the 3-position of the carbazole ring substituted with furan-2-carboxylic acid derivatives. As the protecting group for the amine function of derivatives **217aa** and **217ba** was tert-butyloxycarbonyl (Boc), these compounds could be easily modified to obtain the desired products **221aaa-baa**. For this purpose, the Boc protecting group was removed with TFA, and the obtained compounds were acylated with furan-2-carboxylic acid derivatives in the presence of Et_3N and TBTU. The results are presented in *Table 14*.

Table 14. Synthesis of ethyl 3-(5-alkylfuran-2-carboxamido)-2-hydroxy-9*H*-carbazole-1-carboxylate derivatives **221aaa-baa**.



Entry	217	R^1	R^3	R^4	221	Yield[%]
1	**aa**	H	H	Me	**aaa**	15
2	**aa**	H	H	Et	**aab**	31
3	**ba**	NHBoc	5-methylfuran-2-carboxamide	Me	**baa**	54

Unfortunately, none of prepared compounds showed activity against telomerase. Therefore, the obtained derivatives were additionally tested for antibacterial, antifungal and antitumor activity, which was described in the chapter entitled "Biological evaluation". On the basis of the conducted research, it turned out that the compound **217aa** shows promising antitumor activity. In the next step of research, I decided to modify the compound **217aa** in order to obtain even better biological activity. For this purpose, compound **217aa** was subjected to basic hydrolysis of the ester group to afford compound **222** with 99% yield (*Figure 83*)[277]. As we assumed, the conversion of **217aa** to the acid **222** improved its anticancer activity.

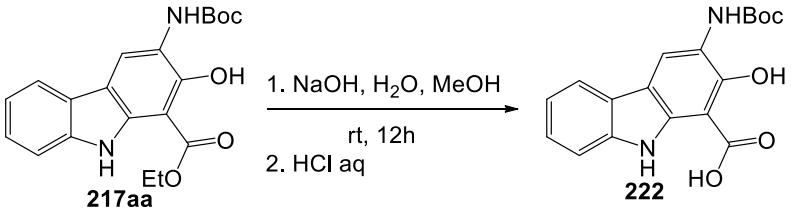


Figure 83 Synthesis of 3-((tert-butoxycarbonyl)amino)-2-hydroxy-9*H*-carbazole-1-carboxylic acid

3.1 Biological evaluation

The compounds submitted for research were tested by the MSc Natalia Maciejewska for *in vitro* anticancer activity by using colorimetric MTT assay on six tumor lines: A-549 (non-small cell lung adenocarcinoma), HCT-116 (human colon cancer), MCF-7 (human breast carcinoma), U-2 OS (human bone osteosarcoma), Hep-G2 (human liver cancer) and HEK-293 (human embryonic kidney cell line). The results are summarized in *Table 15*.

Table 15. *In vitro* anticancer activity of carbazole derivatives

Compound	MTT IC50 (μM)					
	HCT-116	A-549	MCF-7	U-2 OS	Hep-G2	HEK-293
200eb	28.82± 1.43	>50	>50	43.17±2.07	>50	>50
217aa	10.73± 0.61	16.94± 0.75	>50	15.65 ±1.50	>50	>50
217ab	>50	>50	>50	>50	>50	>50
217ac	>50	>50	>50	>50	>50	>50
217ba	>50	>50	>50	>50	>50	>50
217ca	46.43± 3.253	>50	>50	37.50±2.13	>50	>50
220aa	>50	>50	>50	>50	>50	>50
221aaa	>50	>50	>50	>50	>50	>50
221aab	>50	>50	>50	>50	>50	>50
221baa	>50	>50	>50	>50	>50	>50
222	3.75±0.49	11.50 ± 1.23	>50	2.35±0.24	>50	>50

200eb: Ethyl 2-hydroxy-9*H*-carbazole-1-carboxylate

Anticancer activity was demonstrated by four out of eleven tested compounds. Derivatives **200eb** and **217ca** exhibited moderate activity against human colon cancer and human bone osteosarcoma. While compounds **217aa** and **222** showed potent anti-proliferation activity at submicromolar concentrations after 72 h treatment in HCT-116, A-549 and U-2 OS cell lines. Compound **222** showed much higher activity than **217aa**. Half maximal inhibitory concentration of **222** for HCT-116 and U-2 OS was 3.75±0.49 μM and 2.35±0.24 μM, respectively. Further studies on the biological activities of carbazole derivatives were performed on the most cytotoxic compounds **217aa** and **222**.

From the conducted studies, we know that the compound induces the following effects in cancer cells:

a) increase in the number of polyploid cells, micronucleation, cell arrest in the G2/M phase and apoptosis, as confirmed by flow cytometry and immunofluorescence

b) induction of DNA double strand breaks (*Figure 84*) which was confirmed by immunofluorescence and then quantified by flow cytometry

a) b)

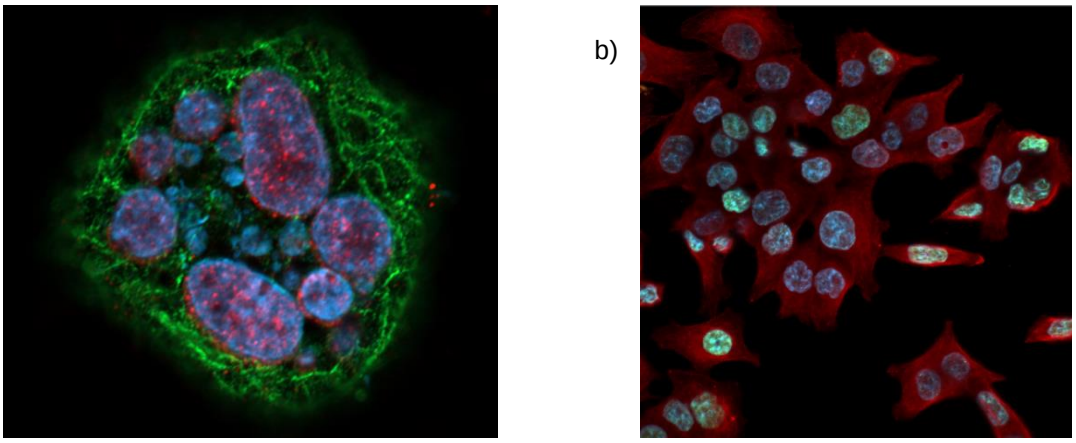


Figure 84 Microscopic image of HCT-116 cells after treatment with: a) compound **217aa** for 24 h: blue – cell nuclei stained with DAPI, red – DNA breaks (h2AX), green – tubulin b) compound **222** for 72 h: blue – cell nuclei stained with DAPI, green – DNA breaks (h2AX), red – tubulin

c) causes the effects of oxidative stress in the cell-after treatment with the compound **217aa** and **222**, a significantly increased level of production of reactive oxygen species (ROS) is observed on HCT-116 and U-2 OS cell lines

3.2 Conclusions

As part of the research, a new method for the synthesis of 1,2,3,6-tetrasubstituted carbazole derivatives was developed. The desired carbazoles were successfully obtained from ethyl 5-(1*H*-indol-3-yl)-3-oxopentanoate derivatives **220** as a result of the oxidative cyclization method promoted by $Mn(OAc)_3$ developed in earlier studies. The synthesized 1,2,3,6-tetrasubstituted carbazole derivatives were submitted for research in order to determine their antitumor activity. According to the conducted research, the highest antitumor activity was shown by compounds **217aa** and **222**. This derivatives induces the following effects in cancer cells: increase in the number of polyploid cells, micronucleation, cell arrest in the G2/M phase, apoptosis, induction of DNA double strand breaks and causes the effects of oxidative stress in the cell.

The results presented in the chapter „Synthesis of 1,2,3,6-tetrasubstituted carbazole derivatives with anticancer potencial" constitute the content of another publication, which is currently at the editing stage.

4. Summary

As part of my doctoral studies at the Gdańsk University of Technology, I investigated the possibility of using 3-(1*H*-indol-3-yl)-3-propionic acids and tryptophan in the synthesis of tetrahydrocarbazole and carbazole derivatives with biological potential. The most important goals I have accomplished include:

1) Designing the structure of compounds binding to the serotonin transporter TS3 and their verification by molecular modeling method using AutoDock Tools software.

2) Development of a method for the synthesis of tetrahydrocyclopenta[*b*]indole derivatives, ligands for the human serotonin transporter, as a result of which I obtained 9 new compounds showing high affinity for the serotonin transporter with a very similar placement in the active site compared to serotonin and paroxetine.

3) Preparation of new conditions for the synthesis of 1,2,4-trisubstituted carbazoles with the use of esters and amides of (5-(1*H*-indol-3-)yl)-3-oxopentanoic acids as substrates. To achieve this aim, I used the following reaction conditions: cyclization promoted by manganese (III) acetate in acetic acid and cyclization in the presence of I_2/Lewis acid/Et_3N.

4) Explanation on the basis of the collected research material and literature review the tentative mechanism of cyclization of β-oxoesters and β-oxoamides in the presence of I_2/Lewis acid/Et_3N.

5) Synthesis of 1,2,3,6-tetrasubstituted carbazole derivatives with anticancer potential using the oxidative cyclization method promoted by $Mn(OAc)_3$, developed in earlier studies. In this way, I obtained 9 new compounds, which I then submitted for biological research to determine their anticancer activity. Two compounds showed significant antitumor activity on HCT116 and U-2 OS cancer cell lines.

5. Scientific achievements

1. Papers in Journals from JCR list (concerning PhD studies)

   a) M. Szewczyk, P. Punda, K. Janikowska, S. Makowiec, „Design, synthesis, and molecular docking of new 5-HT reuptake inhibitors based on modified 1,2-dihydrocyclopenta[b]indol-3(4H)-one scaffold", J. Chem. Sci., 2019, 131, DOI 10.1007/s12039-019-1621-x

   b) M. Szewczyk, M. Ryczkowska, S. Makowiec, „Transition-Metal-Promoted Oxidative Cyclization To Give 1,2,4-Trisubstituted Carbazole Scaffolds", Synthesis, 2019, 51, 4625-4634, DOI 10.1055/s-0039-1690681

2. Conferences

   a) M. Szewczyk, S. Makowiec, „Design and synthesis of novel SSRI based on *N*-alkyl-1-aryl-1,2,3,4- tetrahydrocyclopent[b]indole-3-amine scaffold", 19th International Symposium "Advances in the Chemistry of Heteroorganic Compounds", Łódź 25.11.16, poster

   b) M. Szewczyk, S. Makowiec, „Synteza nowoczesnych SSRI opartych na strukturze *N*-alkilo-1-arylo-1,2-dihydrocyklopenta[b]indolo-3(4*H*)- ylidenoamin", 60 Zjazd Naukowy Polskiego Towarzystwa Chemicznego, Wrocław 17-21.09.17, poster

   c) M. Szewczyk, S. Makowiec, „Otrzymywanie nowoczesnych selektywnych inhibitorów wychwytu zwrotnego serotoniny opartych na rdzeniu układu karbazolonowego", II Ogólnopolskie Sympozjum Chemii Bioorganicznej, Organicznej i Biomateriałów, Poznań 2.12.17, poster

   d) M. Szewczyk, S. Makowiec, „Synteza pochodnych karbazolu-intermediatów dla związków biologicznie czynnych", IX Kongres Technologii Chemicznej, Gdańsk 3.09-7.09.18, poster

   e) M. Szewczyk, S. Makowiec, „Cyklizacja estrów kwasu 5-(1*H*-indolo-3-yl)-3-oksopentanowego katalizowana triflatami metali przejściowych", 61 Zjazd Naukowy Polskiego Towarzystwa Chemicznego, Kraków 17-21.09.18, poster

   f) M. Szewczyk, S. Makowiec, „Synteza i aspekty mechanistyczne otrzymywania pochodnych karbazolu przy wykorzystaniu katalizy metalami przejściowymi", BioMed Session, Gdańsk 7.12.18, poster

g) M. Szewczyk, M. Ryczkowska, S. Makowiec, „Cyclization of 5-(1*H*-indol-3-yl)-3-oxopentanoic acid esters/amids promoted with transition metal triflates", 21st European Symposium on Organic Chemistry, Vienna 14-18.07.19, poster

h) M. Szewczyk, S. Makowiec, „New approach to the construction of carbazoles derivatives with high application potencial", International Symposium on Synthesis and Catalysis, Evora 3-6.09.19, poster

i) M. Witkowska, S. Makowiec, „Design and synthesis of novel potential telomerase inhibitors based on 1,2,4-trisubstituted carbazole scaffold", XXII International Symposium "Advances in the Chemistry of Heteroorganic Compounds", Łódź 22.11.19, poster

j) M. Witkowska, S. Makowiec, „Synthesis of 1,2,4-trisubstituted carbazole derivatives with anticancer potential", RSC Chemical Biology and Bio-organic Group Forum 2020, Leicester 10.01.20, poster

k) M. Witkowska, S. Makowiec, „Synthesis of 1,2,4-trisubstituted carbazole derivatives-new compounds with anticancer potential", Florida Heterocyclic and Synthetic Conference 2020, Gainesville 1-4.03.20, poster

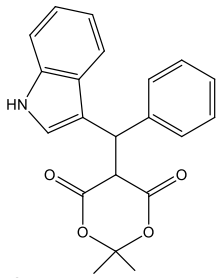
IV. EXPERIMENTAL

Commercially available reagents were purchased from Sigma-Aldrich or Acros. Toluene, benzene and THF were distilled from potassium under argon and stored over molecular sieves. DCM was distilled over P_4O_{10} and stored over molecular sieves. Analytical TLC was performed on aluminum sheets of UV-254 Merck silica gel. Flash chromatography was performed using 40–63 micron Zeochem silica gel. The ^1H, ^{13}C were recorded on Bruker Avance III HD 400 MHz, Varian Gemini 200 and Varian Unity Plus 500, chemical shifts (δ) in ppm relative to internal Me_4Si; coupling constants *J* in Hz. High-resolution (HRMS) was recorded on Agilent 6540 Q-TOF. Melting points were determined with Warsztat Elektromechaniczny W-wa apparatus and are not corrected.

1. General procedure for preparation of 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (196a-d)

According to original procedure.[250] To a stirred mixture of Meldrum's acid 1.44 g (10 mmol), appropriate aryl aldehyde (10 mmol) and indole 1.17 g (10 mmol) in acetonitrile 50 ml was added L-proline 57 mg (0.5 mmol) was added. Mixture was stirred for 18 h at 30°C. After completion of the reaction, solvent was removed under reduced pressure and the residue was purified with flash chromatography as specified below.

*5-((1H-Indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**196a**)*[250]



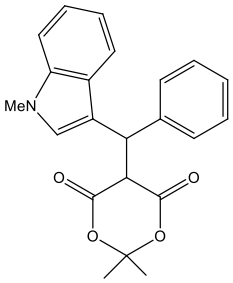
Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 48%; yellow oil.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H), 7.44-7.35 (m, 5 H), 7.30-7.17 (m, 4 H), 7.08-7.05 (m, 1 H), 5.65 (d, 1 H, *J* = 2.0), 4.31 (d, 1 H, *J* = 2.4), 1.71 (s, 3 H), 1.42 *(*s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8; 164.9, 140.0, 136.0, 129.3, 128.6, 127.4, 127.2, 124.4, 122.5, 119.9, 119.3, 115.2, 111.4, 105.4, 52.1, 41.9, 28.3, 28.2.

*5-((1-Methyl-1H-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**196b**)*[278]



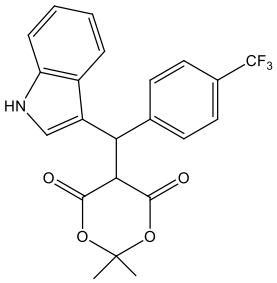
Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 50%; yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49-7.43 (m, 3 H), 7.34-7.22 (m, 6 H), 7.10-7.07 (m, 1 H), 5.67 (d, 1 H, *J* = 2.4), 4.31 (d, 1 H, *J* = 2.4), 3.81 (s, 3 H), 1.74 (s, 3 H), 1.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.5, 164.7, 140.09, 136.6, 128.9, 128.9, 128.4, 127.5, 127.1, 121.8, 119.2, 119.0, 113.3, 109.2, 105.1, 52.1, 41.5, 32.9, 28.1, 27.9.

*5-((1H-Indol-3-yl)(4-(trifluoromethyl)phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**196c**)*



Purification by flash column chromatography (EtOAc/Hex, 1:2).

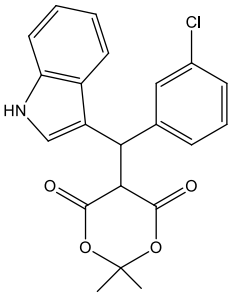
Yield: 56%; yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.22 (s, 1 H), 7.55 (s, 4 H), 7.44-7.39 (m, 3 H), 7.25-7.121 (m, 1 H), 7.12-7.08 (m, 1 H), 5.73 (d, 1 H, *J* = 2.2), 4.33 (d, 1 H, *J* = 2.2), 1.78 (s, 3 H), 1.57 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 165.1, 164.3, 144.0, 135.8, 129.4 129.2 (q, J^{C-F} = 32.1), 126.8, 125.1 (q, J^{C-F} = 3.7), 124.1 (q, J^{C-F} = 270.3), 122.6, 119.9, 118.8, 114.1, 111.2, 105.2, 51.9, 40.5, 28.1, 27.6.

HRMS (ESI-): *m*/*z* $[M - H]^-$ calcd for $C_{22}H_{17}F_3NO_4$: 416.1109; found: 416.1094.

*5-((3-Chlorophenyl)(1H-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**196d**)*[279]



Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 60%; yellow oil.

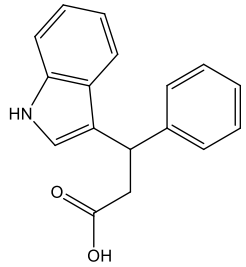
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.23 (s, 1 H), 7.47-7.44 (m, 2 H), 7.40-7.37 (m, 2 H), 7.33-7.29 (m, 1 H), 7.24-7.19 (m, 3 H), 7.12-7.08 (m, 1 H), 5.66 (d, 1 H, *J* = 2.3), 4.31 (d, 1 H, *J* = 2.3), 1.76 (s, 3 H), 1.54 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.2, 164.4, 142.1, 135.7, 134.2, 129.5, 129.2, 127.4, 127.3, 126.8, 124.2, 122.5, 119.9, 118.8, 114.2, 111.2, 105.2, 51.9, 40.6, 28.2, 27.7.

2. General procedure for preparation of 3-(1*H*-indol-3-yl)-3-arylpropanoic acids (197a-d)

5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**196a-d**) (1 mmol) was dissolved in mixture of DMF (10 ml) and water (1ml). Resulted solution was stirred and heated in oil bath at 100°C for 4 h. After completion of the reaction, solvent was removed under reduced pressure and the residue was dissolved in ethyl ether and extracted with $NaHCO_3$ (2x10 ml, sat. aq). Water layer was acidified with conc. aq. HCl. Resulted suspension was extracted with DCM (4x10 ml). Organic extract was dried with $MgSO_4$, filtered and solvents was removed under reduced pressure to give acid **197a-d**.

*3-(1H-Indol-3-yl)-3-phenylpropanoic acid (**197a**)*[280]



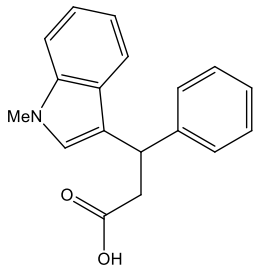
Yield: 45%; yellow oil.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 10.1 (s, 1 H), 7.98 (s, 1 H); 7.44-7.33 (m, 5 H), 7.28-7.24 (m, 2 H), 7.17-7.13 (m, 1 H), 7.08-7.04 (m, 1 H), 6.94-6.90 (m, 1 H), 4.80 (t, 1 H, J = 7.6), 3.20 (dd, 1 H, J^2 = 15.5, J^3 = 7.6), 3.06 (dd, 1 H, J^2 = 15.5, J^3 = 7.6).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 172.7, 145.1, 137.3, 128.4, 128.0, 126.3, 121.8, 121.7, 121.6, 119.2, 118.8, 111.5, 111.4, 40.9, 39.4.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}NO_2$: 266.1180; found: 266.1139.

*3-(1-Methyl-1H-indol-3-yl)-3-phenylpropanoic acid (**197b**)*



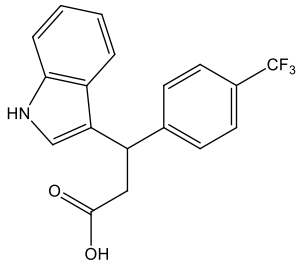
Yield: 60%; yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.2 (s, 1 H), 7.47-7.44 (m, 1 H), 7.38-7.34 (m, 2 H), 7.33-7.28 (m, 3 H), 7.25-7.19 (m, 2 H), 7.08-7.03 (m, 1 H), 6.93-6.91 (m, 1 H), 4.83 (t, 1 H, J = 7.8), 3.77(s, 3 H), 3.22 (dd, 1 H, J^2 = 15.7, J^3 = 7.8), 3.09 (dd, 1 H, J^2 = 15.7, J^3 = 7.8).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 178.1, 143.6, 137.3, 128.5, 127.7, 126.9, 126.5, 125.9, 121.8, 119.5, 118.9, 116.9, 109.2, 41.2, 38.9, 32.8.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{18}H_{18}NO_2$: 280.1337; found: 280.1295.

*3-(1H-Indol-3-yl)-3-(4-(trifluoromethyl)phenyl)propanoic acid (**197c**)*



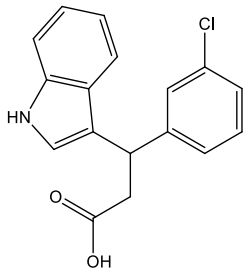
Yield: 60%; yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07 (s, 1 H), 7.56-7.53 (m, 2 H), 7.47-7.44 (m, 2 H), 7.39-7.36 (m, 2 H), 7.22-7.19 (m, 1 H), 7.10-7.04 (m, 2 H), 4.87 (t, 3 H, *J* = 7.6), 3.23 (dd, 1 H, J^2 = 15.8, J^3 = 7.7), 3.08 (dd, 1 H, J^2 = 15.8, J^3 = 7.7).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 176.9, 147.5, 136.5, 128.8 (q, J^{C-F} = 32.1), 128.1, 126.2, 125.5 (q, J^{C-F} = 3.7), 124.2 (q, J^{C-F} = 270.0), 122.5, 121.2, 119.7, 119.1, 117.6, 111.3, 40.6, 38.7.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{15}F_3NO_2$: 334.1055; found: 334.1003.

*3-(3-Chlorophenyl)-3-(1H-indol-3-yl)propanoic acid (**197d**)*



Yield: 58%; yellow oil.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 10,21 (s, 1 H), 8.01 (s, 1 H), 7.51-7.39 (m, 5 H), 7.35-7.31 (m, 1 H), 7.31-7.27 (m, 1 H), 7.20-7.18 (m, 1 H), 7.10-7.06 (m, 1 H), 6.97-6.93 (m, 1 H), 4.81 (t, 1 H, *J* = 7.8), 3.21 (dd, 1 H, J^2 = 15.6, J^3 = 7.3), 3.10 (dd, 1 H, J^2 = 15.6, J^3 = 7.3).

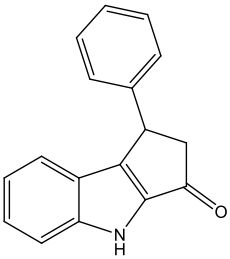
^{13}C NMR (acetone-d_6, 100 MHz): δ= 172.1, 147.5, 136.9, 133.5, 129.8, 127.8, 126.6, 126.4, 126.2, 121.6, 121.5, 118.8, 118.7, 117.3, 111.3, 40.3, 38.8.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}ClNO_2$: 300.0790; found: 300.0746.

3. General procedure for preparation of 1-aryl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-ones (192a-d)

Solution of 3-(1*H*-indol-3-yl)-3-arylpropanoic acid (**197a-d**) (5 mmol) in toluene (125 ml) and polyphosphoric acid (7.5 g) was stirred and mixed at 60°C for the time selected in the *Table 2*. After completion of the reaction, solvent was removed under reduced pressure and the residue was dissolved in water (150 ml) and extracted with DCM 3x50 ml. Organic layer was dried with $MgSO_4$, filtered and solvents was removed under reduced pressure. Residue was purified with flash chromatography.

*1-Phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**192a**)*[281]



Purification by flash column chromatography (EtOAc/Hex, 1:3).

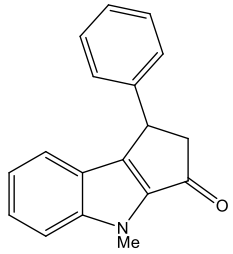
Yield: 38%; white amorphous solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.83 (s, 1 H), 7.48-7.46 (m, 1 H), 7.34-7.20 (m, 7 H), 7.03-6.99 (m, 1 H), 4.72 (dd, 1 H, J^3 = 2.1, J^3 = 6.6), 3.58 (dd, 1 H, J^2 = 18.3, J^3 = 6.6), 2.95 (dd, 1 H, J^2 = 18.3, J^3 = 2.1).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 193.1, 147.3, 144.3, 143.6, 139.2, 129.1, 127.5, 127.1, 127.0, 122.8, 121.7, 120.6, 114.3, 51.4, 39.0.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{14}NO$: 248.1074; found: 248.1065.

*4-methyl-1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**192b**)*[281]



Purification by flash column chromatography (EtOAc/Hex, 1:3).

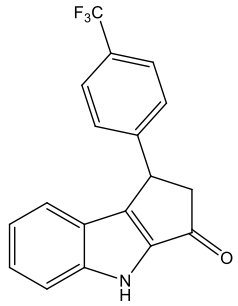
Yield: 33%; white amorphous solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44-7.42 (m, 2 H), 7.41-7.38 (m, 1 H), 7.36-7.31 (m, 2 H), 7.29-7.24 (m, 3 H), 7.13-7.08 (m, 1 H), 4.67 (dd, 1 H, J^3 = 6.8, J^3 = 2.4), 4.01 (s, 3 H), 3.54 (dd, 1 H, J^2 = 18.4, J^3 = 6.8), 2.92 (dd, 1 H, J^2 = 18.4, J^3 = 2.4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 193.8, 146.4, 145.1, 142.9, 138.9, 128.8, 127.2, 126.8, 122.7, 122.2, 120.5, 111.0, 52.1, 39.0, 30.2.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{16}NO$: 262.1232; found: 262.1248.

*1-(4-(trifluoromethyl)phenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**192c**)*



Purification by flash column chromatography (EtOAc/Hex, 1:3).

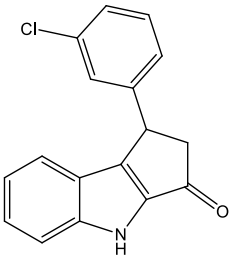
Yield: 25%; white amorphous solid.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 10.93 (s, 1 H), 7.71-7.68 (m, 2 H), 7.63-7.59 (m, 1 H), 7.55-7.53 (m, 2 H), 7.42-7.31 (m, 2 H), 7.13-7.05 (m, 1 H), 4.91 (dd, 1 H, J^3 = 7.2, J^3 = 2.4), 3.55 (dd, 1 H, J^2 = 18.4, J^3 = 7.2), 2.79 (dd, 1 H, J^2 = 18.4, J^3 = 2.4).

^{13}C NMR (acetone-d_6, 100 MHz): δ= 191.4, 148.3, 145.9, 144.1, 139.3, 128.3 (q, J^{C-F} = 31.8), 127.9, 126.7, 125.6 (q, J^{C-F} = 3.8), 124.5 (q, J^{C-F} = 269.4), 122.9, 121.2, 120.5, 113.7, 50.8, 38.8.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{18}H_{13}F_3NO$: 316.0948; found: 316.0951.

*1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**192d**)*



Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 15%; white amorphous solid.

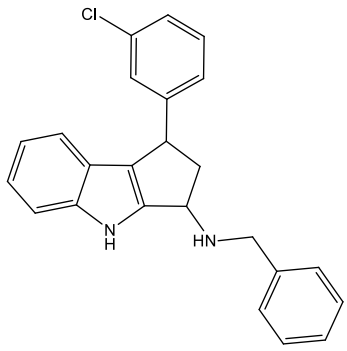
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.87 (s, 1 H), 7.52-7.46 (m, 1 H), 7.37-7.25 (m, 5 H), 7.22-7.18 (m, 1 H), 7.07-7.02 (m, 1 H), 4.76 (dd, 1 H, J^3 = 6.8, J^3 = 2.4), 3.48 (dd, 1 H, J^2 = 18.3, J^3 = 6.8), 2.74 (dd, 1 H, J^2 = 18.3, J^3 = 2.4).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 192.7, 146.4, 146.3, 144.3, 139.4, 133.7, 131.0, 127.4, 127.1, 127.0, 126.3, 122.7, 121.6, 120.8, 114.4, 51.1, 38.6.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{17}H_{13}ClNO$: 282.0686; found: 282.0679.

4. Procedure for preparation of *N*-benzyl-1-(3-chlorophenyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-amine (190cc)

To a solution of 1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**192d**) 147 mg (0.52 mmol) in DCM (5 ml); $NaBH(OAc)_3$ 170 mg (0.80 mmol) was added followed by acetic acid 46 µl (0.80 mmol) and benzylamine 0.087 µl (0.80 mmol). Mixture was stirred at room temperature trough 24 h. Saturated aqueus $NaHCO_3$ (5 ml) and EtOAc (5 ml) was added and stirred for 30 min. Layers was separated, water phase was washed with EtOAc (2x5 ml). Organic solution was dried with anh. $MgSO_4$, filtered and solvents was removed under reduced pressure. Residue was purified with flash column chromatography on silica gel.



Purification by flash column chromatography (EtOAc/Hex, 1:2, NEt_3 0.5%).

Yield: 64%; yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.22 (brs, 1 H), 7.40-7.29 (m, 7 H), 7.26-7.14 (m, 5 H), 7.05-7.01 (m, 1 H), 4.48 (1H, dt, *J* = 1.1, *J* = 6.2), 4.35 (t, 1 H, *J* = 6.8), 3.99 (d, 1 H, *J* = 13.0), 3.86 (d, 1 H, *J* = 13. 0), 3.42 (ddd, 1 H, *J* = 6.8, *J* = 6.2, *J* = 13), 2.18 (brs, 1 H), 2.13-2.07 (m, 1 H).

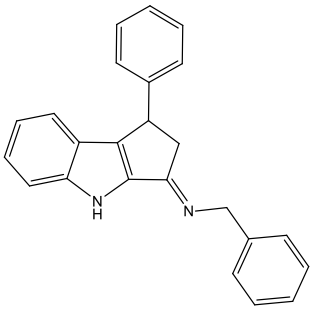
^{13}C NMR ($CDCl_3$, 100 MHz): δ= 147.5, 144.3, 141.1, 139.3, 134.4, 129.8, 128.7, 128.5, 127.6, 127.5, 126.5, 125.6, 123.7, 121.7, 121.2, 119.8, 119.2, 111.9, 57.0, 51.3, 48.4, 42.5.

HRMS (ESI-): *m/z* [M - H]$^-$ calcd for $C_{24}H_{20}ClN_2$: 371.1315; found: 371.1256.

6. General procedure for preparation *N*-(1-aryl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-ylidene)amines (191aaa-acb)

To a cooled solution of 1-aryl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-ones (**192a-d**) (0.5 mmol) in DCM (2 ml) 2-phenylethylamine or cyclohexylamine (2.5 mmol) was added. Followed by dropwise addition of $TiCl_4$ solution in DCM (0.33 mmol, 1M) through 30 min. Resulted mixture was allowed to warm to ambient temperature and stirred for 12 h. Reaction was quenched with aqueous NaOH solution (10 ml, 0.5 M) and extracted with DCM (2x20 ml). Organic layer was dried with $MgSO_4$, filtered and solvents was removed under reduced pressure. Residue was purified with flash chromatography.

*2-phenyl-N-(1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)ethanamine (**191aaa**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

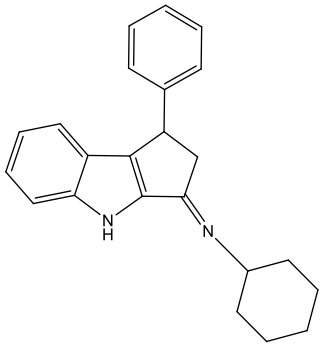
Yield: 29%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.78 (brs, 1 H), 7.45-7.43 (m, 1 H), 7.37-7.22 (m, 1 H), 7.32-7.22 (m, 9 H), 7.06-7.02 (m, 1 H), 4.58 (dd, 1 H, J^3 = 7.1, J^3 = 2.4), 3.75 (td, 2 H, J^3 = 7.4, J^3 = 2.4), 3.50 (dd, 1 H, J^2 = 17.5, J^3 = 7.1), 3.07 (t, 2 H, J = 7.4), 2.74 (dd, 1 H, J^2 = 17.5, J^3 = 2.4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 165.6, 143.6, 142.9, 140.5, 139.9, 138.0, 128.9, 128.7, 128.4, 127.2, 126.7, 126.2, 125.1, 123.5, 120.7, 120.2, 112.9, 54.6, 44.3, 41.2, 37.2.

HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{25}H_{23}N_2$: 351.1860; found: 351.1873.

*N-(1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)cyclohexanamine (**191aab**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

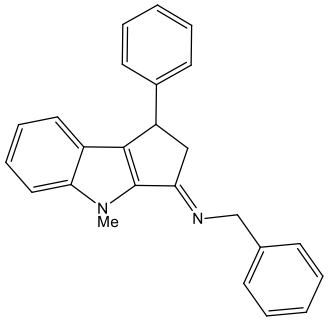
Yield: 65%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.07 (brs, 1 H), 7.58-7.53 (m, 1 H), 7.37-7.27 (m, 5 H), 7.19-7.16 (m, 2 H), 7.09-7.05 (m, 1 H), 4.83 (dd, 1 H, J^3 = 6.0, J^3 = 1.4), 4.02 (dd, 1 H, J^2= 18.8, J^3= 6.0), 3.57-3.48 (m, 1 H, C-20), 3.24 (dd, 1 H, J^2 = 18.8, J^3 = 1.4), 2.10-2.00 (m, 2 H), 1.98-1.82 (m, 4 H), 1.71-1.65 (m, 1 H), 1.38-1.23 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 167.8, 149.3, 146.5, 140.2, 133.4, 129.7, 129.2, 127.8, 127.0, 122.2, 122.1, 121.5, 114.6, 58.8, 45.2, 41.7, 32.0, 31.9, 24.5, 24.5, 24.4.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2$: 329.2018; found: 329.2191.

*N-(4-methyl-1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)-2-phenylethanamine (**191baa**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

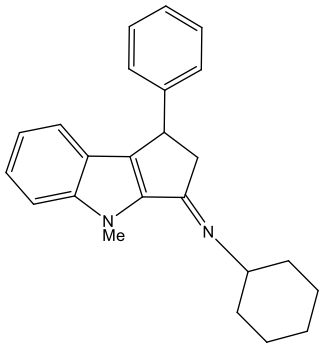
Yield: 85%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43-7.39 (m, 1 H), 7.36-7.28 (m, 8 H), 7.27-7.17 (m, 4 H), 7.09-7.03 (m, 1 H), 4.54 (dd, 1 H, J^3 = 7.3, J^3 = 2.8), 4.13 (s, 3 H), 3.76-3.67 (t, 2 H, J^3 = 7.1), 3.49 (dd, 1 H, J^2 = 17.3, J^3 = 7.3), 3.09 (t, 2 H, J^3 = 7.1), 2.75 (dd, 1 H, J^2 = 17.3, J^3 = 2.8).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 165.3, 144.3, 144.2, 140.7, 129.0, 128.8, 128.6, 128.3, 127.2, 126.8, 126.5, 126.0, 124.1, 123.2, 120.7, 119.7, 110.3, 55.4, 44.5, 40.7, 37.7, 30.5.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2$: 365.2018; found: 365.2021.

*N-(4-methyl-1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)cyclohexanamine (**191bab**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

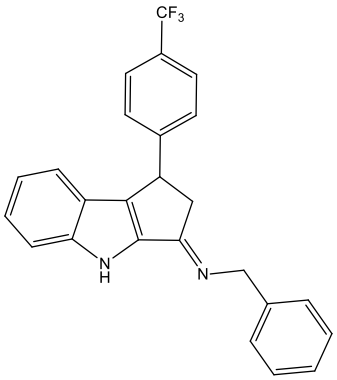
Yield: 90%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42-7.36 (m, 1 H), 7.35-7.21 (m, 7 H), 7.09-7.01 (m, 1 H), 4.67-4.57 (m, 1 H), 4.11 (s, 3 H), 3.66 (dd, 1 H, J^2 = 16.4, J^3 = 6.4), 3.36-3.22 (m, 1 H), 2.91-2.85 (m, 1 H), 1.94-1.64 (m, 5 H), 1.62-1.48 (m, 2 H), 1.45-1.28 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 161.7, 144.8, 143.9, 142.0, 133.6, 128.6, 127.2, 126.4, 123.6, 123.2, 120.5, 119.5, 110.2, 61.8, 43.8, 40.7, 34.0, 33.9, 30.3, 25.9, 24.8.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{27}N_2$: 343.2173; found: 343.2247.

*2-phenyl-N-(1-(4-(trifluoromethyl)phenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)ethanamine (**191aba**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

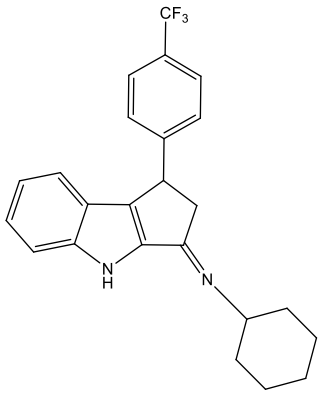
Yield: 73%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.41 (brs, 1 H), 7.58-7.53 (m, 2 H), 7.48-7.44 (m, 1 H), 7.36-7.30 (m, 8 H), 7.26-7.22 (m, 7 H), 7.20-7.14 (m, 1 H), 7.09-7.05 (m, 1 H), 4.63 (dd, 1 H, J^3 = 7.1, J^3 = 2.4), 3.88-3.73 (m, 2 H), 3.51 (dd, 1 H, J^2 = 17.7, J^3 = 7.0), 3.09 (t, 2 H, J = 7.2), 2.62 (dd, 1 H, J^2 = 17.7, J^3 = 2.4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 165.7, 147.3, 143.5, 139.7, 139.5, 138.4, 129.2 (q, J^{C-F} = 32.2), 129.0, 128.5, 127.5, 126.4, 125.9, 125.7 (q, J^{C-F} = 3.7), 124.1 (q, J^{C-F} = 270.2), 123.1, 120.7, 120.6, 113.3, 54.2, 44.1, 40.9, 36.8.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}F_3N_2$: 419.1734; found: 419.1878.

*N-(1-(4-(trifluoromethyl)phenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)cyclohexanamine (**191abb**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

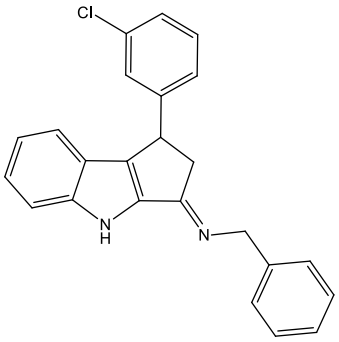
Yield: 77%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.42 (brs, 1 H), 7.60-7.55 (m, 2 H), 7.44-7.40 (m, 1 H), 7.39-7.34 (m, 2 H), 7.31-7.25 (m, 2 H), 7.09-7.03 (m, 1 H), 4.72 (dd, 1 H, J^3 = 7.3, J^3 = 2.6), 3.73 (dd, J^2 = 17.4, J^3 = 7.3), 3.34-3.22 (m, 1 H), 2.90 (dd, 1 H, J^2 = 17.4, J^3 = 2.6), 1.85-1.62 (m, 4H), 1.59-1.47 (m, 2 H), 1.43-1.2 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 161.7, 148.1, 142.6, 141.1, 135.8, 129.1 (q, J^{C-F} = 32.2), 127.5, 125.7 (q, J^{C-F} = 3.7), 125.0, 124.2 (q, J^{C-F} = 270.2), 123.3, 120.4, 113.0, 61.6, 43.5, 41.0, 33.8, 33.7, 25.5, 24.9, 24.8.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{24}H_{24}F_3N_2$: 397.1891; found: 397.2385.

*N-(1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)-2-phenylethanamine (**191aca**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

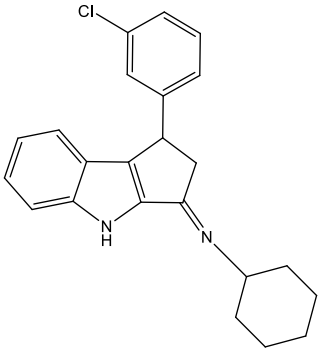
Yield: 55%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.39 (brs, 1 H); 7.49-7.44 (m, 1 H), 7.37-7.31 (m, 1 H), 7.30-7.29 (m, 1 H), 7.27-7.22 (m, 6 H), 7.20-7.13 (m, 2 H), 7.10-7.04 (m, 2 H), 4.54 (dd, 1 H, J^3 = 7.8, J^3 = 2.4), 3.87-3.71 (m, 2 H), 3.47 (dd, 1 H, J^2 = 17.6, J^3 = 7.8), 3.09 (t, 2 H, J^3 = 7.2), 2.62 (dd, 1 H, J^2 = 17.6, J^3 = 2.4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 165.9, 145.3, 143.5, 139.7, 139.5, 138.6, 134.6, 130.0, 129.0, 128.5, 127.3, 127.1, 126.4, 125.8, 125.4, 123.2, 120.7, 120.5, 113.3, 54.2, 44.3, 40.9, 36.9.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{22}ClN_2$: 385.1470; found: 385.1551.

*N-(1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)cyclohexanamine (**191acb**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

Yield: 58%; colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.45-7.40 (m, 1 H), 7.31-7.26 (m, 2 H), 7.25-7.22 (m, 3 H), 7.14-7.10 (m, 1 H), 7.09-7.04 (m, 1 H), 4.64 (dd, 1 H, J^3 = 7.2, J^3 = 2.6), 3.71 (dd, 1 H, J^2= 17.5, J^3 = 7.2), 3.33-3.25 (m, 1 H), 2.92 (dd, 1 H, J^2 = 17.5, J^3 = 2.6), 1.90-1.76 (m, 4 H), 1.72-1.65 (m, 1 H), 1.60-1.50 (m, 2 H), 1.40-1.22 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 162.1, 145.9, 142.7, 140.6, 136.6, 134.6, 130.1, 127.4, 127.0, 125.3, 125.2, 123.2, 120.5, 120.4, 113.0, 61.5, 43.7, 40.9, 33.7, 33.6, 25.5, 24.9, 24.8.

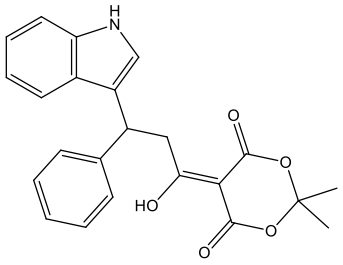
HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{24}ClN_2$: 363.1627; found: 363.1660.

7. General procedure for preparation 5-acyl-2,2-dimethyl-1,3-dioxane-4,6-diones (198a-f)

According to typical DCC mediated acylation of Meldrum's acid[262]. To a cooled (-10°C) solution of 3-(1*H*-indol-3-yl)-propanoic acid (**197a**-**e**) or 1*H*-indole-2-carboxylic acid (**197f**) (3 mmol) in DCM (5 ml), solution of DCC (0.74 g, 3.6 mmol) in 5 ml DCM was added. After 30 min Meldrum's acid (0.43 g ,3 mmol) followed by solution of DMAP (0.55 g, 4.5 mmol) in DCM (2 ml) were added. Reaction mixture was allowed to reach room temperature and stirring was

continued through 12 h. Precipitated DCU was filtered, resulted solution was washed with aq 10% $KHSO_4$ (10 ml), water (10 ml) and brine (10 ml). Organic layer was dried with anh. $MgSO_4$, filtered and solvents was removed under reduced pressure. Residue was crystalized from ethyl ether.

*5-(1-Hydroxy-3-(1H-indol-3-yl)-3-phenylpropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**198a**)*



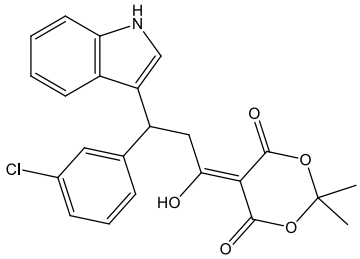
Yield: 64%; yellow crystalline solid; mp = 55-57°C.

^{1}H NMR(DMSO, 400 MHz): δ= 10.95 (s,1 H), 7.40-7.22 (m, 7 H), 7.19-7.12 (m, 1 H), 7.07- 7.00 (m, 1 H), 6.93-6.87 (m, 1 H), 4.77 (t, J= 8.0 Hz, 1 H), 3.98-3.82 (m, 2 H), 1.52 (s, 6 H).

^{13}C NMR(DMSO, 100 MHz): δ= 199.62, 148.8, 141.6, 133.5, 133.3, 132.8, 132.7, 131.5, 131.3, 127.2, 126.3, 123.8, 123.6, 121.9, 116.7, 109.7, 97.9, 35.9, 35.3, 31.1.

HRMS (ESI-): m/z [M - H]- calcd for $C_{23}H_{20}NO_5$: 390.1341; found: 390.1314.

*5-(3-(3-Chlorophenyl)-1-hydroxy-3-(1H-indol-3-yl)propylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**198d**)*



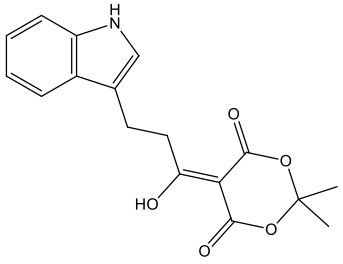
Yield: 73%; yellow crystalline solid; mp = 107-109°C.

^{1}H NMR(DMSO-d_6, 400 MHz): δ= 11.00 (s, 1H), 7.41-7.27 (m, 6 H), 7.26-7.19 (m, 1 H), 7.09-7.00 (m, 1 H), 6.96-6.87(m, 1H), 4.80 (t, *J* = 8.0 Hz, 1 H), 3.95 (dd, *J* = 8.0 Hz, *J* = 14.4 Hz, 1 H), 3.85 (dd, *J* = 8.0 Hz, *J* = 14.4 Hz, 1 H), 1.56 (s, 6 H).

^{13}C NMR(DMSO-d_6, 100 MHz): δ= 177.2, 169.3, 161.8, 151.6, 141.6, 138.1, 135.4, 132.6, 131.6, 131.2, 127.5, 126.5, 123.8, 123.7, 121.2, 116.8, 109.7, 97.8, 38.6, 35.9, 31.1.

HRMS (ESI-): *m/z* [M - H]$^-$ calcd for $C_{23}H_{19}ClNO_5$: 424.0952; found: 424.0914.

*5-(1-Hydroxy-3-(1H-indol-3-yl)propylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**198e**)*



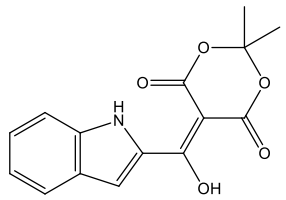
Yield: 87%; yellow crystalline solid; mp = 88-90°C.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 15.33 (s, 1 H), 8.05 (s,1 H), 7.75-7.70 (m, 1 H), 7.38-7.34 (m, 1 H), 7.24-7.18 (m, 1 H), 7.18-7.13 (m, 1 H), 7.10-7.07 (m, 1 H), 3.56-3.48 (m, 2 H), 3.26-3.18 (m, 2H), 1.65 (s, 6 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 197.1, 170.4, 160.3, 136.2, 127.1, 122.2, 121.9, 119.6, 118.8, 114.2, 111.1, 104.8, 91.8, 36.6, 26.7, 21.9.

HRMS (ESI-): *m*/*z* [M - H]$^-$ calcd for $C_{17}H_{16}NO_5$: 314.1028; found: 314.1022.

*5-(Hydroxy(1H-indol-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**198f**)*



Yield: 66%; yellow crystalline solid; mp = 111-113°C.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 16.03 (s, 1 H), 12.21 (s, 1 H), 7.87-7.82 (m, 1 H), 7.77-7.71 (m, 1 H), 7.52-7.47 (m, 1 H), 7.44-7.38 (m, 1 H), 7.21-7.16 (m, 1 H), 1.83 (s, 6 H).

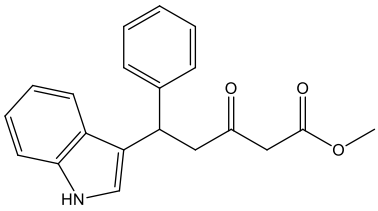
^{13}C NMR($CDCl_3$, 100 MHz): δ= 176.7, 171.8, 162.9, 139.1, 129.5, 127.8, 126.92, 123.0, 121.6, 116.1, 113.0, 104.9, 88.4, 26.5.

HRMS (ESI-): *m*/*z* [M - H]$^-$ calcd for $C_{15}H_{12}NO_5$: 286.0715; found: 286.0716.

8. General procedure for preparation of 5-(1*H*-indol-3-yl)-3-oxo-5-arylpentanoates (199aa-db), 5-(1*H*-indol-3-yl)-3-oxopentanoates (199ea-eb) and methyl 3-(1*H*-indol-2-yl)-3-oxopropanoate (211)

5-(1-hydroxy-3-(1H-indol-3-yl)-(3-phenyl)-propylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**198a, 198d**), 5-(1-hydroxy-3-(1H-indol-3-yl)-propylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**198e**) or 5-(hydroxy(1H-indol-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**198f**) (1 mmol) was dissolved in methanol or ethanol (10 ml). Resulted solution was refluxed for 24 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified with flash chromatography as specified below.

*Methyl 5-(1H-indol-3-yl)-3-oxo-5-phenylpentanoate (**199aa**)*



Purification by flash column chromatography (EtOAc/Hex, 1:4).

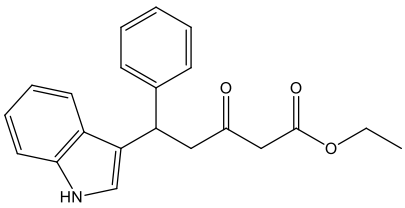
Yield: 71%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.09 (s, 1H), 7.45-7.43 (m, 1 H), 7.35-7.27 (m, 5 H), 7.23-7.16 (m, 2 H), 7.07-7.00 (m, 2 H), 4.88 (t, *J* =7.4 Hz, 1H), 3.68 (s, 3H), 3.45-3.28 (m, 4H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 201.4, 167.5, 143.6, 136.6, 128.5, 127.7, 126.5, 126.4, 122.2, 121.5, 119.5, 119.4, 118.4, 111.2, 52.3, 49.5, 49.4, 38.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}NO_3$: 322.1433; found: 322.1424.

*Ethyl 5-(1H-indol-3-yl)-3-oxo-5-phenylpentanoate (**199ab**)*



Purification by flash column chromatography (EtOAc/Hex, 1:4).

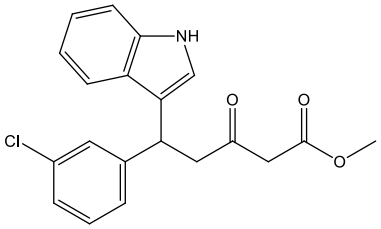
Yield: 67%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.05 (s, 1H), 7.46-7.42 (m, 1 H), 7.36-7.27 (m, 5 H), 7.22-7.15 (m, 2 H), 7.07-7.01 (m, 2 H), 4.87 (dd, *J* = 14.4; 7.2 Hz, 1H), 4.15 (q, 7.2 Hz, 2 H), 3.46-3.25 (m, 4H), 1.24 (t, *J* =7.1 Hz, 3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 201.4, 167.1, 143.6, 136.6, 128.5, 127.7, 126.5, 126.4, 122.2, 121.5, 119.5, 119.4, 118.5, 111.2, 61.4, 49.6, 49.5, 38.1, 14.1.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_3$: 336.1599; found: 336.1595.

*Methyl 5-(3-chlorophenyl)-5-(1H-indol-3-yl)-3-oxopentanoate (**199da**)*



Purification by flash column chromatography (EtOAc/Hex, 1:4).

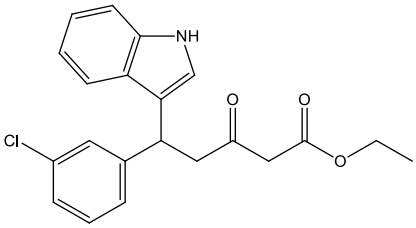
Yield: 66%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.12 (s, 1H), 7.43-7.41 (m, 1 H), 7.36-7.34 (m, 1 H), 7.30-7.28 (m, 1 H), 7.24-7.16 (m, 4 H), 7.08-7.01 (m, 1H), 7.04-6.99 (m, 1H), 4.86 (t, *J* =7.4 Hz, 1H), 3.69 (s, 3H), 3.45-3.26 (m, 4H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 200.8, 167.4, 145.8, 136.6, 134.3, 129.8, 127.8, 126.7, 126.2, 126.1, 122.4, 121.5, 119.6, 119.2, 117.7, 111.3, 52.4, 49.3, 49.2, 37.6.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{19}ClNO_3$: 356.1053; found: 356.1034.

*Ethyl 5-(3-chlorophenyl)-5-(1H-indol-3-yl)-3-oxopentanoate (**199db**)*



Purification by flash column chromatography (EtOAc/Hex, 1:4).

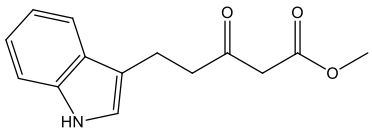
Yield: 57%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.09 (s, 1H), 7.44-7.41 (m, 1 H), 7.39-7.32 (m, 1 H), 7.32-7.27 (m, 1 H), 7.27-7.14 (m, 4 H), 7.10-6.99 (m, 2H), 4.86 (dd, *J* = 14.4; 7.2 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.45-3.14 (m, 4 H), 1.25 (t, *J* =7.1 Hz, 3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 200.9, 167.0, 145.9, 136.6, 134.3, 129.8, 127.8, 126.7, 126.6, 126.1, 122.4, 121.5, 119.6, 119.2, 117.8, 111.2, 61.5, 49.6, 49.2, 37.6, 14.1.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{21}ClN_2O_3$: 370.1210; found: 370.1182.

*Methyl 5-(1H-indol-3-yl)-3-oxopentanoate (**199ea**)*



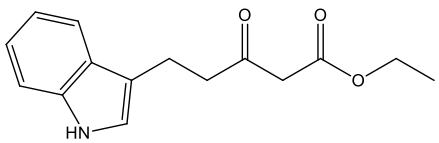
Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 96%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.04 (s, 1 H), 7.64-7.57 (m, 1 H), 7.43-7.35 (m, 1 H), 7.27-7.19 (m, 1 H), 7.19-7.11 (m, 1 H), 7.04-6.97 (m, 1 H), 3.72 (s, 3H), 3.46 (s, 2H), 3.15-3.05 (m, 2H), 3.02-2.93 (m, 2H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 202.5, 167.6, 136.3, 127.1, 122.1, 121.7, 119.4, 118.6, 114.6, 111.2, 52.3, 49.2, 43.5, 19.1.

*Ethyl 5-(1H-indol-3-yl)-3-oxopentanoate (**199eb**)*[282]



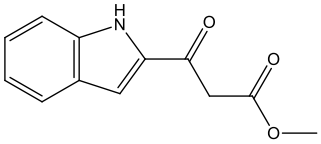
Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 85%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.06 (s, 1 H), 7.62-7.60 (m, 1 H), 7.38-7.36 (m, 1 H), 7.24-7.20 (m, 1 H), 7.17-7.13 (m, 1 H), 7.02-6.97 (m, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 3.45 (s, 2 H), 3.12-3.09 (m, 2H), 2.99-2.96 (m, 2H), 1.27 (t, *J* =7.2 Hz, 3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 202.7, 167.2, 136.3, 127.1, 122.1, 121.7, 119.3, 118.6, 114.7, 111.2, 61.4, 49.4, 43.5, 19.1, 14.1.

*Methyl 3-(1H-indol-2-yl)-3-oxopropanoate (**211**)*[283]



Purification by flash column chromatography (EtOAc/Hex, 1:5).

Yield: 75%; yellow oil.

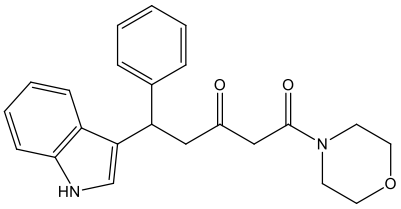
^{1}H NMR($CDCl_3$, 400 MHz): δ= 9.41 (s, 1 H), 7.77-7.69 (m, 1H) 7.51-7.44 (m, 1 H), 7.42-7.36 (m, 1 H), 7.31-7.26 (m, 1 H), 7.22-7.15 (m, 1 H), 4.02 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 184.4, 167.7, 137.9, 134.3, 127.4, 127.01, 123.3, 121.2, 112.4, 111.09, 52.6, 45.2.

9. General procedure for preparation of morpholides 199ac, ec and 199f

198a-f (0.66 mmol) was dissolved in benzene (5 ml). To a resulted solution morpholine (113 mg, 1.3 mmol) and trimethylsilyl chloride (108 mg, 1 mmol) were added. Mixture was refluxed under argon for 4 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified with flash chromatography as specified below.

*5-(1H-Indol-3-yl)-1-morpholino-5-phenylpentane-1,3-dione (**199ac**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

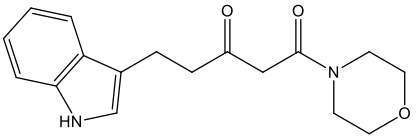
Yield: 70%; yellow oil.

^{1}H NMR(DMSO-d_6, 400 MHz): δ= 10.89 (s, 1 H), 7.42-7.40 (m, 1 H), 7.36-7.29 (m, 4 H), 7.26-7.22 (m, 2 H), 7.15-7.10 (m, 1 H), 7.05-7.01 (m, 1 H), 6.92-6.88 (m, 1 H), 4.70 (t, *J* = 7.6 Hz, 1H), 3.69 (d, *J* = 16.7 Hz, 1 H), 3.68 (d, *J* = 16.7 Hz, 1 H), 3.58-3.50 (m, 1 H), 3.48-3.37 (m, 5 H), 3.31-3.22 (m, 3 H), 2.99-2.97 (m, 1 H).

^{13}C NMR(DMSO-d_6, 100 MHz): δ= 203.9, 165.8, 145.3, 136.8, 128.6, 128.0, 126.7, 126.4, 122.4, 121.5, 119.1, 118.7, 117.9, 11.8, 66.4, 66.3, 49.2, 48.9, 46.3, 41.9, 37.7.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_3$: 377.1865; found: 377.1875.

*5-(1H-Indol-3-yl)-1-morpholinopentane-1,3-dione (**199ec**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

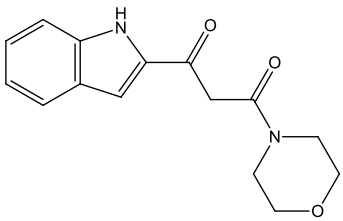
Yield: 98%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.13 (s, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 7.37 (dt, *J* = 8.0 Hz, *J* = 0.8 Hz, 1 H), 7.23-7.20 (m, 1 H), 7.16-7.12 (m, 1 H), 7.01 (s, 1 H), 3.65-3.47 (m, 8 H), 3.29-3.18 (m, 2H), 3.12-3.06 (m, 2 H), 3.06-2.93 (m, 2 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 204.1, 163.2, 136.3, 127.1, 122.1, 121.7, 119.4, 118.6, 111.2, 66.6, 66.5, 49.3, 46.7, 43.3, 42.2, 19.3.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_3$: 301.1552; found: 301.1539.

*1-(1H-Indol-2-yl)-3-morpholinopropane-1,3-dione (**199f**)*



Purification by flash column chromatography (DCM/MeOH, 60:1).

Yield: 75%; yellow oil.

^{1}H NMR(DMSO-d_6, 400 MHz): δ= 11.80 (s, 1H), 7.72-7.69 (m, 1 H), 7.46-7.41 (m, 2 H), 7.32-7.27 (m, 1 H), 7.11-7.05 (m, 1 H), 4.18 (s, 2 H), 3.62-3.56 (m, 4 H), 3.49-3.47 (m, 4 H).

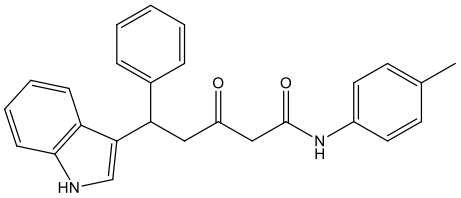
^{13}C NMR(DMSO-d_6, 100 MHz): δ= 187.3, 166.2, 138.4, 135.6, 127.3, 126.1, 123.2, 120.8, 113.2, 110.8, 66.6, 66.5, 46.7, 44.7, 42.1.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1239; found: 273.1225.

10. General procedure for preparation of 5-(1*H*-indol-3-yl)-3-oxo-5-aryl-*N*-(*p*-tolyl)pentanamide (199ad) and 5-(1*H*-indol-3-yl)-3-oxo-*N*-(*p*-tolyl)pentanamide (199ed)

198a or **198e** (1 mmol) was dissolved in toluene (10 ml). To a resulted solution p-toluidine (107 mg, 1.3 mmol) was added. Mixture was stirred at 70°C 18 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified with flash chromatography as specified below.

*5-(1H-Indol-3-yl)-3-oxo-5-phenyl-N-(p-tolyl)pentanamide (**199ad**)*



Purification by flash column chromatography (EtOAc/Hex/AcOH, 1:2:0,01).

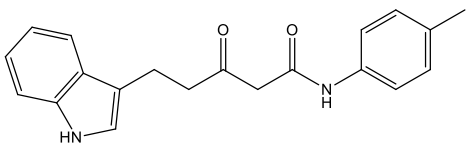
Yield: 75%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.79 (s, 1 H), 8.10 (s, 1H), 7.46-7.44 (m, 1 H), 7.35-7.24 (m, 7 H), 7.21-7.16 (m, 2 H), 7.14-7.08 (m, 2 H), 7.08-7.02 (m, 1H), 7.01-6.96 (m, 1 H), 4.88 (t, *J* =7.6 Hz, 1H), 3.56-3.38 (m, 3 H), 3.34-3.24 (m, 1 H), 2.33 (s, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 206.1, 143.3, 136.5, 134.8, 134.2, 129.4, 128.6,127.6, 126.7, 126.4, 122.4, 121.3, 120.3, 119.6, 119.3, 118.2, 111.3, 50.4, 49.7, 38.1, 20.9.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_2$: 397.1916; found: 397.1889.

*5-(1H-Indol-3-yl)-3-oxo-N-(p-tolyl)pentanamide (**199ed**)*



Purification by flash column chromatography (EtOAc/Hex/AcOH, 1:2:0,01).

Yield: 88%; yellow oil.

^{1}H NMR(DMSO-d_6, 400 MHz): δ= 10.8 (s, 1H), 10.0 (s, 1 H), 7.55-7.49 (m, 1 H), 7.49-7.44 (m, 2 H), 7.36-7.31 (m, 1 H), 7.15-7.03 (m, 4 H), 7.01-6.94 (m, 1 H), 3.58 (s, 2 H), 2.99-2.90 (m, 4 H), 2.26 (s, 3 H).

^{13}C NMR(DMSO-d_6, 100 MHz): δ= 204.9, 165.3, 136.9, 136.7, 132.8, 129.6, 127.4, 122.7, 121.4, 119.6, 118.7, 118.6, 113.8, 111.8, 51.9, 43.5, 20.9, 19.2.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_2$: 321.1603; found: 321.1617.

11. Oxidative cyclization of 3-oxoesters and 3-oxoamides (199aa-ed, 199f, 220aa-ca)

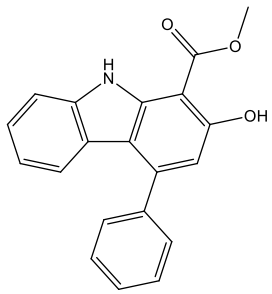
*General procedure for oxidative cyclization of 3-oxoesters **199aa-eb** and **220aa-ca** with $Mn(OAc)_3$*2 H_2O*

Ester **199aa-eb** or **220aa-ca** (0.1 mmol) was dissolved in AcOH (2 ml). To a resulted solution amount of $Mn(OAc)_3$*2 H_2O specified in the *Table 9* was added. Mixture was heated for 4 h/2.5 h at 70°C. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified with flash chromatography as specified below.

*General procedure for oxidative cyclization of 3-oxoesters and 3-oxoamides **199aa**-**ed**, **199f**, **220aa** and **220ae** with transition metal triflates*

Ester or amide **199aa-ed**, **199f**, **220aa** or **220ae** (0.2 mmol) was dissolved in anhydrous DCM (4 ml). To a resulted solution (0.2mmol) of triflate specified in the table 3 was added, followed by I_2 (0.3 mmol) and NEt_3 (0.5 mmol, 69 µl). Mixture was stirred for 12 h at rt. After completion of the reaction, residue was dissolved in DCM (30 ml) and washed with aqueous sat. Na_2SO_3. Organic layer was dried with $MgSO_4$, solvent was removed under vacuum, and the residue was purified with flash chromatography as specified below.

*Methyl 2-hydroxy-4-phenyl-9H-carbazole-1-carboxylate (**200aa**)*



Purification by flash column chromatography (DCM/Hex, 1:3).

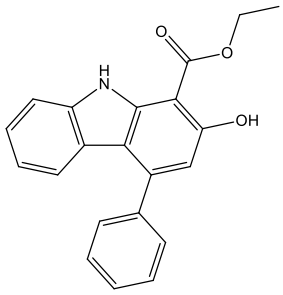
Yield: 45%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 11.03 (s, 1H), 9.45 (s, 1H), 7.64-7.60 (m, 2H), 7.58-7.53 (m,3H), 7.49-7.44 (m, 1 H), 7.35-7.31 (m, 2 H), 7.03-6.99 (m, 1 H), 6.78 (s, 1H), 4.21 (s, 3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.4, 161.2, 145.5, 139.9, 139.5, 138.9, 128.7, 128.5, 128.3, 124.6, 122.7, 121.3, 119.9, 114.2, 110.9, 110.6, 95.4, 52.6.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{20}H_{16}NO_3$: 318.1130; found: 318.1144.

*Ethyl 2-hydroxy-4-phenyl-9H-carbazole-1-carboxylate (**200ab**)*



Purification by flash column chromatography (DCM/Hex, 1:2-1:1).

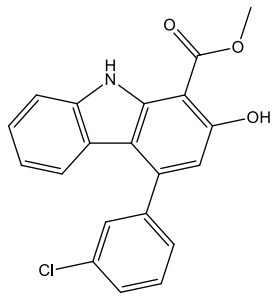
Yield: 72%; white amorphous solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 11.05 (s, 1H), 9.48 (s, 1H), 7.65-7.59 (m, 2H), 7.58-7.51 (m,3H), 7.48-7.44 (m, 1 H), 7.34-7.30 (m, 2 H), 7.02-6.98 (m, 1 H), 6.78 (s, 1H), 4.69 (q, *J* = 7.1 Hz, 2 H), 1.63 (t, *J* =7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 169.6, 161.2, 145.3, 139.9, 139.7, 138.9, 128.7, 128.5, 128.3, 124.6, 122.7, 121.3, 119.9, 114.2, 110.9, 110.6, 95.6, 61.9, 14.7.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}NO_3$: 332.1287; found: 332.1295.

*Methyl 4-(3-chlorophenyl)-2-hydroxy-9H-carbazole-1-carboxylate (**200da**)*



Purification by flash column chromatography (DCM/Hex, 1:3).

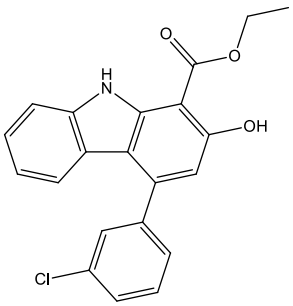
Yield: 52%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 11.02 (s, 1H), 9.46 (s, 1H), 7.65-7.60 (m, 1H), 7.54-7.46 (m,4H), 7.38-7.29 (m, 2 H), 7.08-7.01 (m, 1 H), 6.75 (s, 1H), 4.21 (s, 3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.3, 161.2, 143.6, 141.6, 139.5, 139.0, 134.4, 129.8, 128.8, 128.4, 126.9, 124.8, 122.4, 121.1, 120.1, 114.1, 110.8, 110.7, 95.7, 52.7.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}ClNO_3$: 352.0740; found: 352.0748.

*Ethyl 4-(3-chlorophenyl)-2-hydroxy-9H-carbazole-1-carboxylate (**200db**)*



Purification by flash column chromatography (DCM/Hex, 1:3).

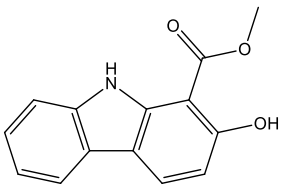
Yield: 61%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 11.05 (s, 1 H), 9.49 (s, 1 H), 7.66-7.59 (m, 1 H), 7.56-7.45 (m, 4 H), 7.37-7.29 (m, 2 H), 7.10-7.01 (m, 1 H), 6.75 (s, 1 H), 4.69 (q, *J* = 7.1 Hz, 2 H), 1.63 (t, *J* =7.1 Hz, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 169.8, 161.2, 143.4, 141.7, 139.7, 138.9, 134.4, 129.8, 128.8, 128.4, 127.0, 124.8, 122.4, 121.1, 120.1, 114.0, 110.8, 110.7, 95.9, 62.0, 14.7.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{17}ClNO_3$: 366.0897; found: 366.0905.

*Methyl 2-hydroxy-9H-carbazole-1-carboxylate (**200ea**)*



Purification by flash column chromatography (DCM/Hex, 1:3).

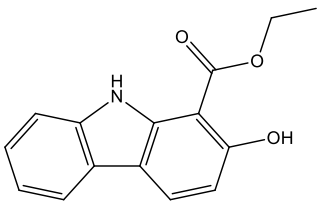
Yield: 41%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 11.00 (s, 1H), 9.25 (s, 1H), 8.16-8.12 (m, 1H), 8.01-7.97 (m,1H), 7.52-7.47 (m, 1 H), 7.43-7.37 (m, 1 H), 7.31-7.24 (m, 1 H), 6.91-6.85 (m, 1 H), 4.19 (s, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.5, 161.8, 138.9, 138.7, 127.9, 124.8, 123.0, 120.3, 119.2, 116.4, 110.7, 109.3, 96.5, 52.5.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}NO_3$: 242.0817; found: 242.0823.

*Ethyl 2-hydroxy-9H-carbazole-1-carboxylate (**200eb**)*[282]



Purification by flash column chromatography (DCM/Hex, 1:3).

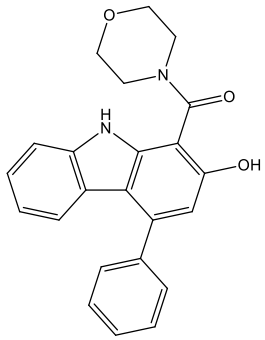
Yield: 28%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 11.06 (s, 1 H), 9.25 (s, 1 H), 8.15-8.09 (m, 1H), 8.01-7.96 (m, 1 H), 7.51-7.45 (m, 1 H), 7.43-7.37 (m, 1 H), 7.31-7.23 (m, 1 H), 6.89-6.85 (m, 1 H), 4.66 (q, *J* = 7.1 Hz, 2 H), 1.61 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.0, 161.8, 139.1, 138.7, 127.8, 124.7, 123.1, 120.3, 119.2, 116.4, 110.7, 109.3, 96.7, 61.9, 14.7.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}NO_3$: 256.0974; found: 256.0978.

*(2-hydroxy-4-phenyl-9H-carbazol-1-yl)(morpholino)methanone (**200ac**)*



Purification by flash column chromatography (EtOAc/Hex, 1:1).

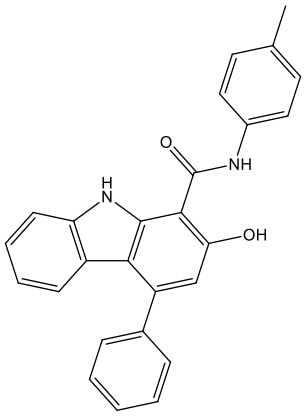
Yield: 40%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.75 (s, 1 H), 7.54-7.46 (m, 6 H), 7.36-7.22 (m, 3 H), 6.96-6.92 (m, 1 H), 6.61 (s, 1 H), 3.83-3.73 (m, 6 H), 7.71-7.59 (m, 2 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 169.4, 154.6, 141.7, 139.9, 139.6, 138.5, 128.8, 128.4, 128.0, 124.8, 122.9, 121.3, 119.7, 114.9, 111.0, 110.5, 101.4, 67.1, 46.2.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_3$: 373.1552; found: 373.1536.

*2-hydroxy-4-phenyl-N-(p-tolyl)-9H-carbazole-1-carboxamide (**200ad**)*



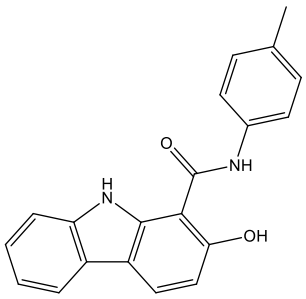
Purification by flash column chromatography (EtOAc/Hex, 1:6). Yield: 42%; yellow amorphous solid.

^{1}H NMR(acetone-d_6, 400 MHz): δ= 11.54 (s, 1H), 10.79 (s, 1 H), 10.57 (s, 1 H), 7.77-7.72 (m, 3 H), 7.65-7.54 (m, 5 H), 7.33-7.29 (m, 2 H), 7.23-7.21 (m, 2 H), 6.96-6.91 (m, 1 H), 6.85 (s, 1 H), 2.34 (s, 3 H).

^{13}C NMR(acetone-d_6, 100 MHz): δ= 165.3, 154.2, 142.2, 141.8, 140.3, 136.6, 132.9, 129.3, 128.7, 128.6, 128.2, 124.6, 121.9, 120.8, 120.1, 120.0, 118.9, 115.2, 111.5, 109.5, 101.3, 20.90.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_2$: 393.1603; found: 393.1590.

*2-hydroxy-N-(p-tolyl)-9H-carbazole-1-carboxamide (**200ed**)*



Purification by flash column chromatography (EtOAc/Hex, 1:3).

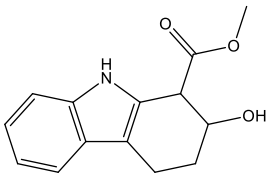
Yield:42%; white amorphous solid.

^{1}H NMR(DMSO-d_6, 400 MHz): δ= 11.55 (s, 1 H), 11.48 (s, 1 H), 10.58 (s, 1 H), 8.12-8.10 (m, 1 H), 8.01-7.99 (m, 1 H), 7.70-7.67 (m, 3 H), 7.32-7.27 (m, 1 H), 7.21-7.19 (m, 2 H), 7.16-7.12 (m, 1 H), 6.90-6.88 (m, 1 H), 2.31 (s, 3 H).

^{13}C NMR(DMSO-d_6, 100 MHz): δ= 165.2, 155.3, 141.1, 140.2, 136.7, 133.0, 129.7, 124.9, 124.7, 122.4, 120.4, 119.5, 119.4, 117.1, 112.3, 108.6, 103.2, 20.9.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_2O_2$: 317.1290; found: 317.1280.

*Methyl 2-hydroxy-2,3,4,9-tetrahydro-1H-carbazole-1-carboxylate (**201ea**)*



Purification by flash column chromatography (EtOAc/Hex, 1:5).

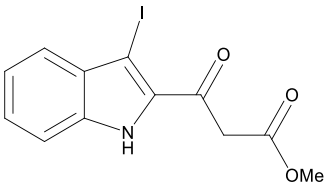
Yield: 43%; colorless oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 12.33 (s, 1 H), 7.14-7.05 (m, 2 H), 6.81-6.76 (m, 1 H), 6.74-6.70 (m, 1 H), 4.62 (d, *J* = 7.6 Hz, 1 H), 3.88 (s, 3 H), 3.53-3.28 (m, 1 H), 2.46-2.36 (m, 2 H), 2.03-1.87 (m, 2 H), 1.28 (brs, 1 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 175.6, 172.7, 131.8, 128.5, 128.0, 123.6, 119.4, 110.4, 98.4, 56.8, 51.8, 40.3, 28.0, 23.7.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{14}H_{16}NO_3$: 246.1130; found: 246.1129.

*Methyl 3-(3-iodo-1H-indol-2-yl)-3-oxopropanoate (**212**)*

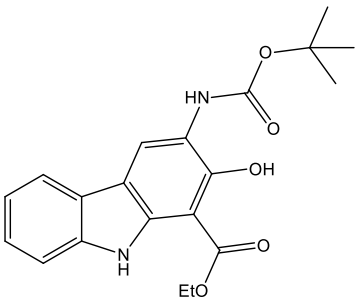


Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 52%; yellow amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 9.60 (s, 1 H), 7.60-7.58 (m, 1 H), 7.46-7.39 (m, 2 H), 7.28-7.24 (m, 1 H), 4.35 (s, 2 H), 3.82 (s, 3 H).

*Ethyl 3-((tert-butoxycarbonyl)amino)-2-hydroxy-9H-carbazole-1-carboxylate (**217aa**)*



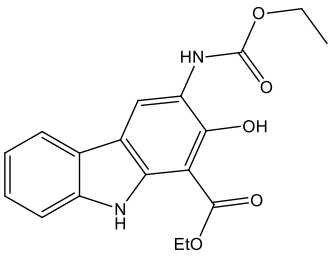
Purification by flash column chromatography (EtOAc/Hex, 1:5).

Yield: 67%; yellow amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 11.60 (s, 1 H), 9.01 (s, 1 H), 8.97 (s, 1 H), 8.02 (d, *J* = 7.6 Hz, 1 H), 7.46-7.44 (m, 1 H), 7.40-7.36 (m, 1 H), 7.27-7.23 (m, 1 H), 7.14 (ds, 1 H), 4.66 (q, *J* = 7.2 Hz, 2 H), 1.61 (t, *J* = 7.2 Hz, 3 H), 1.60 (s, 9 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.5, 153.3, 150.8, 138.6, 133.9, 124.7, 123.3, 120.7, 120.0, 119.7, 116.9, 115.4, 110.6, 96.2, 80.3, 62.2, 28.5, 14.6.

*Ethyl 3-((ethoxycarbonyl)amino)-2-hydroxy-9H-carbazole-1-carboxylate (**217ab**)*



Purification by flash column chromatography (EtOAc/Hex, 1:5).

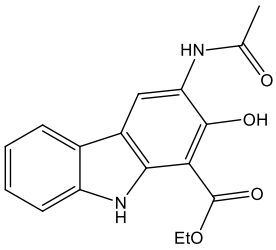
Yield: 28%; yellow amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 11.56 (s, 1 H), 8.96 (s, 1 H), 8.92 (s, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.44-7.42 (m, 1 H), 7.40-7.36

(m, 1 H), 7.26-7.20 (m, 2 H), 4.63 (q, *J* = 7.2 Hz, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 1.59 (t, *J* = 7.2 Hz, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.4, 154.1, 150.9, 138.7, 134.1, 124.8, 123.2, 120.2, 120.1, 119.6, 117.0, 115.4, 110.6, 96.2, 62.2, 61.2, 14.7, 14.6.

*Ethyl 3-acetamido-2-hydroxy-9H-carbazole-1-carboxylate (**217ac**)*



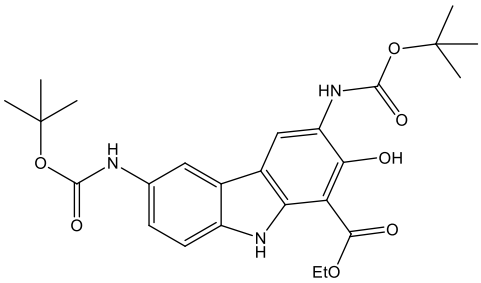
Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 29%; yellow amorphous solid.

^{1}HNMR($CDCl_3$, 400 MHz): δ = 11.65 (s, 1 H), 9.19 (s, 1 H), 9.01 (s, 1 H), 8.00 (d, *J* = 7.6 Hz, 1 H), 7.80 (s, 1 H), 7.45-7.43 (m, 1 H), 7.40-7.36 (m, 1 H), 7.27-7.24 (m, 1 H), 4.64 (q, *J* = 7.2 Hz, 2 H), 2.29 (s, 3 H), 1.60 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.5, 168.3, 151.0, 138.7, 134.5, 124.9, 123.2, 120.2, 119.8, 118.6, 115.4, 110.6, 96.1, 62.3, 24.8, 14.6.

*Ethyl 3,6-bis((tert-butoxycarbonyl)amino)-2-hydroxy-9H-carbazole-1-carboxylate (**217ba**)*



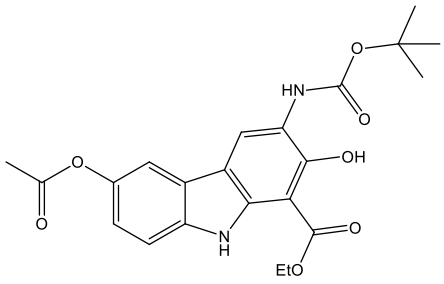
Purification by flash column chromatography (EtOAc/Hex, 1:4).

Yield: 36%; colorless oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 11.61 (s, 1 H), 8.91 (s, 1 H), 8.87 (s, 1 H), 7.97 (s, 1 H), 7.35 (s, 2 H), 7.09 (s, 1 H), 6.56 (s, 1 H), 4.65 (q, *J* = 7.2 Hz, 2 H), 1.60 (t, *J* = 7.2 Hz, 3 H), 1.60 (s, 9 H), 1.58 (s, 9 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.5, 166.7, 153.2, 151.1, 135.3, 134.5, 131.2, 123.6, 120.5, 117.3, 115.3, 110.6, 96.1, 80.3, 80.2, 62.2, 28.5, 14.6.

*Ethyl 6-acetoxy-3-((tert-butoxycarbonyl)amino)-2-hydroxy-9H-carbazole-1-carboxylate (**217ca**)*



Purification by flash column chromatography (EtOAc/Hex, 1:4).

Yield: (25%); white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 11.63 (s, 1 H), 9.00 (s, 1 H), 8.91 (s, 1 H), 7.72-7.71 (m, 1 H), 7.41-7.39 (m, 1 H), 7.13-7.07 (m, 2 H), 4.67 (q, *J* = 7.2 Hz, 2 H), 2.37 (s, 3 H), 1.61 (t, *J* = 7.2 Hz, 3 H), 1.59 (s, 9 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.4, 170.3, 153.2, 151.2, 144.4, 136.4, 134.6, 123.8, 120.9, 118.4, 116.9, 115.2, 112.4, 110.9, 96.3, 80.4, 62.3, 28.4, 21.2, 14.6.

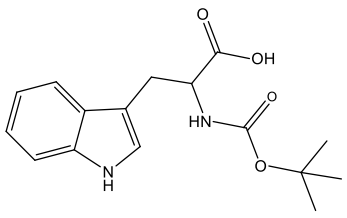
12. General procedure for preparation of tryptophan derivatives with Boc-protected amino group (219aa, 219ba, 219ca)

To a solution of **218a-c** (9.8 mmol) and $NaHCO_3$ (1.64 g, 19 mmol) in a dioxane:water 1:1 mixture (20 ml) at 0°C di-tert-butyl dicarbonate (3.37 ml, 15 mmol) was added in one portion. Reaction mixture was stirred 13 h at room temperaturę and than concentrated in vacuum. Residue was washed with AcOEt (2 x 15 ml) and discarded. Water layer was acidified to pH = 3 with 5% aqueous HCl and extracted with AcOEt (2 x 15 ml), organic extract was dried with $MgSO_4$ filtered and evaporated to dryness under reduced pressure. The crude products was used without additional purification.

In the case of 5-hydroksytryptophane **218**c, crude product was subject to additional O-acetylation with following procedurę:

Crude *N*-Boc-5-hydroksytryptophane (100 mg, 0.31 mmol) was dissolved in 1N NaOH (0.7 ml) and acetic anhydride was added (63 µl, 0.67 mmol). Reaction mixture was stirred for 3 h at R. T. under argon. Solution was acidified with 5% citric acid and extracted with AcOEt (3 x 5 ml), organic extract was washed with brine (5 ml), dried with $MgSO_4$ filtered and evaporated to dryness under reduced pressure. The crude products was used without additional purification.

*2-((tert-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoic acid (**219aa**)*[270]



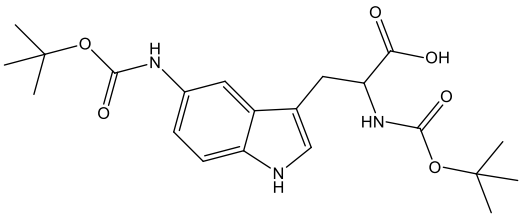
Yield: 98%; white solid; mp = 136°C.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.1 (s, 1 H), 7.60 (d, *J*= 7.6 Hz, 1 H), 7.36 (d, *J* = 8 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.02 (s, 1 H), 5.04 (d, *J* = 6.8 Hz, 1 H), 4.65 (s, 1 H), 3.33 (bs, 2 H), 1.5-1.2 (s, 9 H).

^{13}C NMR($CDCl_3$, 125 MHz): δ= 176.3, 155.8, 136.3, 127.9, 123.2, 122.3, 119.8, 118.9, 111.4, 110.1, 80.4, 54.4, 28.5, 27.7.

HRMS (ESI+): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{20}N_2O_4Na$: 327.1321; found: 327.1310.

*2-((tert-butoxycarbonyl)amino)-3-(5-((tert-butoxycarbonyl)amino)-1H-indol-3-yl)propanoic acid (**219ba**)*



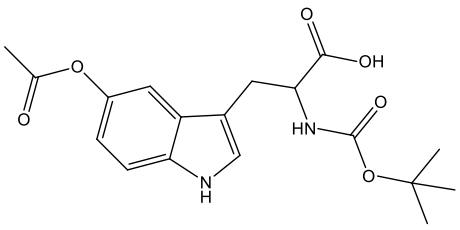
Purification by flash column chromatography (EtOAc/Hex, 1:1).

Yield: 98%; colorless oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.54 (bs, 1 H), 7.54 (bs, 1 H), 7.13-7.05 (m, 2 H), 6.88 (s, 1 H), 6.76-6.69 (m, 1 H), 5.23-5.11 (m, 1 H), 4.62-4.60 (m, 1 H), 3.20-3.04 (m, 2 H), 1.55 (s, 9 H), 1.43 (s, 9 H).

^{13}C NMR($CDCl_3$, 125 MHz): δ= 175.6, 171.3, 155.6, 133.3, 130.1, 127.8, 124.2, 116.5, 111.4, 110.6, 109.6, 80.0, 53.9, 28.5, 28.4.

*3-(5-acetoxy-1H-indol-3-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid (**219ca**)*



Purification by flash column chromatography (DCM/MeOH/AcOH, 1:1:0,01).

Yield: 39%; white oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ= 8.46 (s, 1 H), 7.29-7.25 (m, 2 H), 6.92-6.87 (m, 2 H, 5.17-5.15 (m, 1 H), 4.64-4.63 (m, 1 H), 3.31-3.18 (m, 2 H), 2.33 (s, 3H), 1.46 (s, 9 H).

^{13}C NMR($CDCl_3$, 125 MHz): δ= 8.46 (s, 1 H), 7.29-7.25 (m, 2 H), 6.92-6.87 (m, 2 H, 5.17-5.15 (m, 1 H), 4.64-4.63 (m, 1 H), 3.31-3.18 (m, 2 H), 2.33 (s, 3H), 1.46 (s, 9 H).

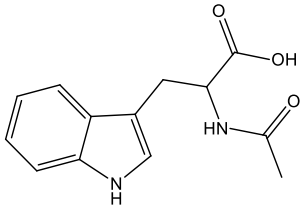
13. Procedure for preparation of 2-((ethoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoic acid (*219*ab)

To a solution of **218a** (2.0 g, 9.8 mmol) in 1,4-dioxane (60 ml) was slowly added 2N NaOH (5 ml). Then, ethyl chloroformate (1.4 ml, 14.7 mmol) was added dropwise over 5 minutes. After completion of the dropwise addition, the reaction was then stirred at 60^{o}C overnight. After completion of the reaction, the mixture was cooled to room temperature and washed three times with diethyl ether (3 × 15 ml). The resulting organic layer was discarded and the aqueous portion was acidified with 2M HCl to pH = 3. The aqueous solution was extracted three times with diethyl ether (3 × 15ml). The combined organic layers were washed with a saturated NaCl solution, dried over $MgSO_4$ and evaporated under reduced pressure. Product **219ab** was obtained as a white solid (31%) which was used for the next step without purification.

14. Procedure for preparation of 2-acetamido-3-(1*H*-indol-3-yl)propanoic acid (219ac)

Trp-OH **218a** (1 g, 4.9 mmol) was suspended in methanol (20 ml). To the mixture was added acetic anhydride (0.926 ml, 9.8 mmol) dropwise. The resulting solution was stirred for 12 h at room temperature. After completion of the reaction, methanol was evaporated under reduced pressure. The precipitate was purified by column chromatography.

*2-acetamido-3-(1H-indol-3-yl)propanoic acid (**219ac**)*[284]



Purification by flash column chromatography (EtOAc/Hex/AcOH, 3:1:0,001).

Yield: 98%; white amorphous solid.

^{1}H NMR (DMSO, 500 MHz): δ= 12.63 (s, 1H), 10.85 (s, 1H), 8.18 (d, 1H, *J* = 7.5), 7.55 (d, 1H, *J* = 8.0), 7.34 (d, 1H, *J* = 8.0), 7.16 (s, 1H), 7.04 (m, 2H), 4.50 (m, 1H), 3.19 (dd, 1H, *J* = 4.5, 14.5), 3.02 (dd, 1H, *J* = 9.0, 14.5), 1.83 (s, 3H).

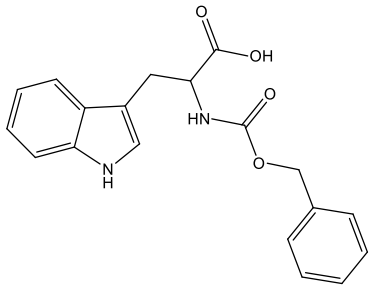
^{13}C NMR (DMSO, 125 MHz): δ= 173.7, 169.4, 136.2, 127.3, 123.6, 121.0, 118.5, 118.2, 111.5, 110.0, 53.1, 27.2, 22.5.

HRMS (ESI): *m/*z $[M+H]^+$ calculated for $C_{13}H_{15}O_3N_2$: 247.1077; found: 247.1076.

15. Procedure for preparation of 2-(((benzyloxy)carbonyl)amino)-3-(1*H*-indol-3-yl)propanoic acid (219ad)

Trp-OH **218a** (5 g, 25 mmol) was suspended in water (150 ml). To the mixture K_2CO_3 (6.75 g, 49 mmol) and $NaHCO_3$ (2.05 g, 25 mmol) were added. Then acetone (20 ml) was added to obtain a homogeneous solution. In the next step, benzyl chloroformate (4.3 ml, 30 mmol) was slowly added to the solution placed in an ice bath. The resulting solution was heated to 30°C and stirred for 3 h. After completion of the reaction, the solution was washed with diethyl ether (25 ml). The aqueous layer was acidified with 2M HCl to pH = 2 and washed three times with ethyl acetate (3 × 25 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The resulting oil was dissolved in dichloromethane (25 ml) and evaporated under reduced pressure. The obtained product **219ad** was used for the next step without purification.

*2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanoic acid (**219ad**)*[285]



Yield: 98%; white solid; mp = 132-134°C.

^{1}H NMR (DMSO): δ= 7.57-7.53 (m, 2H), 7.35-7.22 (m, 6H), 7.16-7.15 (m, 1H), 7.09-7.04 (m, 1H) 7.00-6.95 (m, 1H), 5.02-4.92 (m, 2H), 4.28-4.21 (m, 1H), 3.22-3.16 (m, 1H), 3. 04-2.96 (m, 1H).

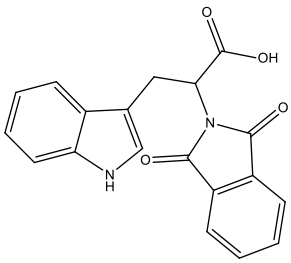
^{13}C NMR (DMSO): δ= 174.2, 156.5, 137.4, 136.6, 128.8, 128.2, 128.0, 127.6, 124.2, 121.4, 118.8, 118.6, 111.9, 110.5, 65.8, 55.5, 27.4.

LRMS (ESI):): *m/*z $[M+H]^+$ calculated for $C_{19}H_{19}N_2O_4$: 339.13; found: 339.35.

16. Procedure for preparation of 2-(1,3-dioxoisoindolin-2-yl)-3-(1*H*-indol-3-yl)propanoic acid (219ae)

Trp-OH **218a** (1 g, 4.9 mmol) and phthalic anhydride (0.722 g, 4.9 mmol) were placed in the flask. Then the resulting mixture was melted at the temperature of 150-190°C for 15 minutes. After cooling, the solidified mass was placed on the oil pump to get rid of the water formed. The product was an orange solid which was used for the next step without purification.

*2-(1,3-dioxoisoindolin-2-yl)-3-(1H-indol-3-yl)propanoic acid (**219ae**)*[286]



Yield: 98%; orange solid; mp= 179-183°C.

^{1}H NMR(DMSO, 400 MHz): δ= 13.37 (brs, 1 H), 10.77 (s, 1 H), 7.75-7.83 (m, 4 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 7.28 (d, *J* = 7.9Hz, 1 H), 7.06 (d, *J* = 1.9 Hz, 1 H), 7.02 (t, *J* = 7.9 Hz, 1 H), 6.92 (t, *J* = 7.9 Hz, 1 H), 5.16 (m, *J* = 9.2, 6.6 Hz, 1 H), 3.57-3.58 (m, 2 H).

^{13}C NMR(DMSO, 75 MHz): δ= 170.5, 167.3, 136.1, 134.8, 131.0, 127.0, 123.5, 123.4, 121.1, 118.5, 118.0, 111.5, 109.8, 52.7, 24.2.

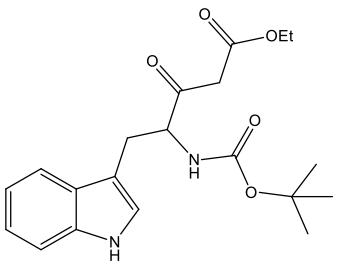
HRMS (ESI+): *m/z* $[M + Na]^+$ calculated for $C_{19}H_{14}N_2O_4Na$: 357.0851; found: 357.0845.

17. General procedure for preparation of ethyl 5-(1*H*-indol-3-yl) -3-oxopentanoate derivatives (220aa-ca)

To a solution of *N*-protected Trp **219aa-cb** (0.59 mmol) in dry THF (12 ml) carbonyldiimidazole (106 mg, 0.65 mmol) was added. Resulting mixture was stirred for 2 h at R.T under argon. Then $MgCl_2$ (56 mg, 0.59 mmol) was added following by ethyl potassium malonate (100 mg, 0.59 mmol). Resulting reaction mixture was stirred for 1 h at room temperature under argon and then was heated to 40-45°C stirred for additional 12 h. After

completion of the reaction, the mixture was filtered and concentrated in vacuum. Residue was purified with flash chromatography as specified below.

*Ethyl 4-((tert-butoxycarbonyl)amino)-5-(1H-indol-3-yl)-3-oxopentanoate (**220aa**)*



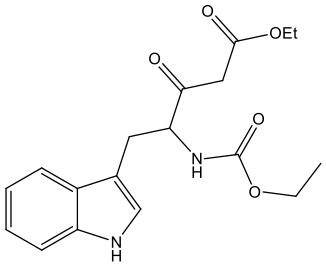
Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 44%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 8.23 (s, 1 H), 7.65-7.63 (m, 1 H), 7.40-7.37 (m, 1 H), 7.25-7.22 (m, 1 H), 7.20-7.12 (m, 1 H), 7.04-7.03 (m, 1 H), 5.18-5.16 (m, 1 H), 4.74-4.69 (m, 1 H), 4.18-4.13 (m, 2 H), 3.51 (d, *J* = 16.0 Hz, 1 H), 3.44 (d, *J* = 16.0 Hz, 1 H), 3.34-3.22 (m, 2H), 1.44 (s, 9 H), 1.26 (t, *J* = 8.0 Hz, 3 H)..

^{13}C NMR($CDCl_3$, 100 MHz): δ= 202.7, 167.0, 155.4, 136.2, 127.5, 123.0, 122.3, 119.8, 118.8, 111.2, 110.0, 80.1, 61.4, 59.9, 47.0, 28.3, 26.9, 14.0.

*Ethyl 4-((ethoxycarbonyl)amino)-5-(1H-indol-3-yl)-3-oxopentanoate (**220ab**)*



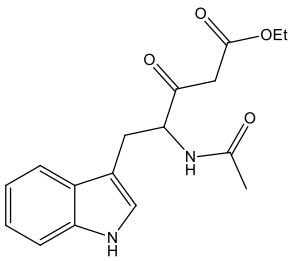
Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 16%; colorless oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 8.27 (s, 1 H), 7.66-7.64 (m, 1 H), 7.39-7.36 (m, 1 H), 7.25-7.20 (m, 1 H), 7.20-7.13 (m, 1 H), 7.03 (s, 1 H), 5.36 (d, *J* = 7.2 Hz, 1 H), 4.81-4.76 (m, 1 H),4.18-4.10 (m, 4 H), 3.50 (d, *J* = 16.0 Hz, 1 H), 3.44 (d, *J* = 16.0 Hz, 1 H), 3.34-3.25 (m, 2 H), 1.27-1.22 (m, 6 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 202.4, 166.9, 156.2, 136.2, 127.4, 123.1, 122.4, 119.9, 118.7, 111.3, 109.8, 61.5, 60.1, 47.2, 27.1, 14.0.

*Ethyl 4-acetamido-5-(1H-indol-3-yl)-3-oxopentanoate (**220ac**)*



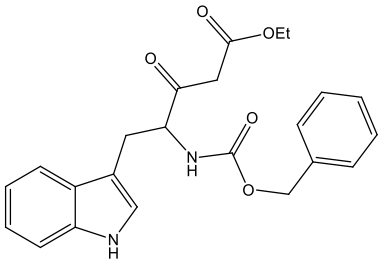
Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 46%; yellow amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 8.53 (s, 1 H), 7.62-7.60 (m, 1 H), 7.38-7.36 (m, 1 H), 7.23-7.19 (m, 1 H), 7.16-7.13 (m, 1 H), 7.01 (s, 1 H), 6.38 (d, *J* = 7.2 Hz, 1 H), 5.06-5.00 (m, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.50 (d, *J* = 16.0 Hz, 1 H), 3.45 (d, *J* = 16.0 Hz, 1 H), 3.34-3.22 (m, 2 H), 1.94 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 201.9, 170.5, 166.9, 136.2, 127.5, 123.1, 122.3, 119.8, 118.5, 111.5, 109.5, 61.6, 58.9, 47.2, 26.6, 22.9, 14.0.

*Ethyl 4-(((benzyloxy)carbonyl)amino)-5-(1H-indol-3-yl)-3-oxopentanoate (**220ad**)*

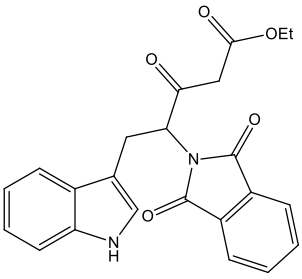


Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 28%; white amorphous solid.

^{1}HNMR($CDCl_3$, 400 MHz): δ = 8.19 (s,1 H), 7.63 (d, *J* = 7.6 Hz, 1 H), 7.42-7.30 (m, 6 H), 7.26-7.20 (m, 1 H), 7.17-7.12 (m, 1 H), 7.01-6.95 (m, 1 H), 5.48 (d, *J* = 7.6 Hz, 1 H), 5.12 (s, 2 H), 4.82 (dd, *J* = 13.6 Hz, *J* = 6.4 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.50 (d, *J* = 16.0 Hz, 1 H), 3.44 (d, *J* = 16.0 Hz, 1 H), 3.56-3.40 (m, 2 H), 3.35-3.25 (m, 2H), 1.24 (t, *J* = 6.8 Hz, 3 H).

*Ethyl 4-(1,3-dioxoisoindolin-2-yl)-5-(1H-indol-3-yl)-3-oxopentanoate (**220ae**)*

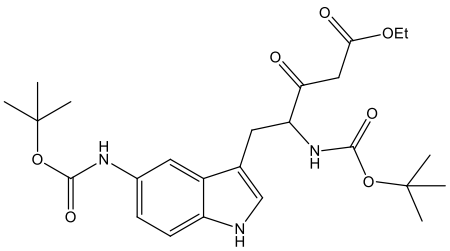


Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 25%; yellow amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 7.98 (bs, 1 H), 7.79-7.75 (m, 2 H), 7.69-7.65 (m, 2 H), 7.64-7.62 (m, 1 H), 7.29-7.27 (m, 1 H), 7.17-7.12 (m, 1 H), 7.10-7.05 (m, 1 H), 7.03 (d, *J* = 2 Hz, 1 H), 5.30 (dd, *J* = 10.0 Hz, *J* = 6.0 Hz, 1 H), 4.22-4.16 (m, 2 H), 3.84-3.73 (m, 2 H), 1.72-1.64 (m, 2 H), 0.92 (t, *J* = 7.6 Hz, 3 H).

*Ethyl 4-((tert-butoxycarbonyl)amino)-5-(5-((tert-butoxycarbonyl)amino)-1H-indol-3-yl)-3-oxopentanoate (**220ba**)*



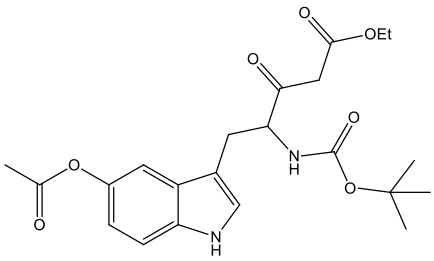
Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 43%; colorless oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 8.36 (s, 1 H), 7.53 (s, 1 H), 7.27-7.23 (m, 1 H), 7.23-7.19 (m, 1 H), 6.97 (s, 1 H), 6.59 (s, 1 H), 5.17 (d, *J* = 7.6 Hz, 1 H), 4.67-4.62 (m, 1 H),4.18-4.13 (m, 2 H), 3.50 (d, *J* = 16.0 Hz, 1 H), 3.43 (d, *J* = 16.0 Hz, 1 H), 3.25-3.14 (m, 2 H), 1.55 (s, 9 H), 1.42 (s, 9 H), 1.30-1.23 (m, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 202.8, 167.0, 155.4, 153.7, 133.2, 130.9, 127.6, 124.0, 116.4, 111.5, 109.8, 109.5, 80.1, 61.4, 59.8, 47.0, 28.4, 26.9, 14.1.

*Ethyl 5-(5-acetoxy-1H-indol-3-yl)-4-((tert-butoxycarbonyl)amino)-3-oxopentanoate (**220ca**)*



Purification by flash column chromatography (EtOAc/Hex, 1:2).

Yield: 49%; colorless oil.

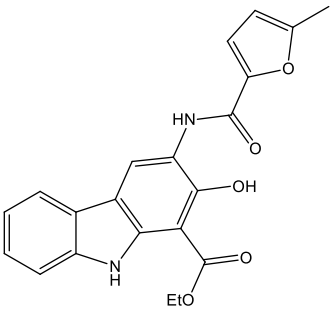
^{1}H NMR($CDCl_3$, 400 MHz): δ = 8.38 (s, 1 H), 7.53-7.31 (m, 2 H), 7.01 (s, 1 H), 6.94-6.91 (m, 1 H), 5.16 (d, *J* = 7.2 Hz, 1 H), 4.68-4.63 (m, 1 H),4.19-4.12 (m, 2 H), 3.52 (d, *J* = 16.0 Hz, 1 H), 3.45 (d, *J* = 16.0 Hz, 1 H), 3.28-3.15 (m, 2 H), 2.34 (s, 3 H), 1.44 (s, 9 H), 1.30-1.24 (m, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 202.4, 170.5, 167.0, 155.3, 144.4, 134.0, 127.9, 124.5, 116.5, 111.8, 110.8, 110.3, 80.0, 61.5, 59.9, 46.9, 28.3, 26.7, 21.2, 14.1.

18. General procedure for preparation of ethyl 3-(5-alkylfuran-2-carboxamido)-2-hydroxy-9*H*-carbazole-1-carboxylate derivatives (221aaa-baa).

Compound **217aa** or **217ba** (0.135 mmol) was dissolved in dry DCM (1 ml) and TFA 0.5 ml was added. Reaction mixture was stirred and monitored with TLC until the substrate disappears. Then solvents were removed under reduced pressure, and the residue was evaporated three times with 3 ml of toluene. Residue was dissolved in DMF (2 ml), and 5-metylfuran-2-carboxylic acid or 5-ethylfuran-carboxylic acid (0.135 mmol) was added followed by NEt_3 (225 µL, 1.63 mmol) and TBTU (53 mg, 0.163 mmol). Reaction mixture was stirred for 18 h at R. T. Solvent was removed under reduced pressure, residue was purified with flash chromatography as specified below.

*Ethyl 2-hydroxy-3-(5-methylfuran-2-carboxamido)-9H-carbazole-1-carboxylate (**221aaa**)*



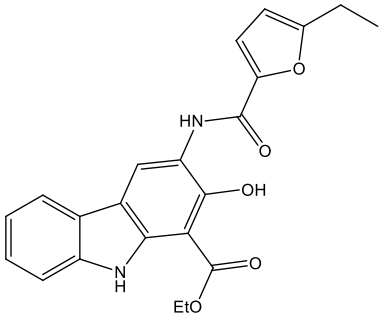
Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 15%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 10.04 (s, 1 H), 9.28 (s,1 H), 8.38 (s, 1 H), 8.12 (d, *J* = 7.6 Hz, 1 H), 7.52-7.46 (m, 3 H), 7.31-7.27 (m, 1 H), 7.15-7.14 (d, *J* = 3.6 Hz, 1 H), 6.16-6.15 (m, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 2.51 (s, 3 H), 1.17 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 165.8, 158.9, 156.3, 154.7, 146.2, 142.1, 140.3, 127.0, 123.4, 122.4, 121.7, 120.8, 120.2, 118.8, 116.4, 111.1, 109.4, 105.9, 61.5, 14.2, 13.7.

*Ethyl 3-(5-ethylfuran-2-carboxamido)-2-hydroxy-9H-carbazole-1-carboxylate (**221aab**)*



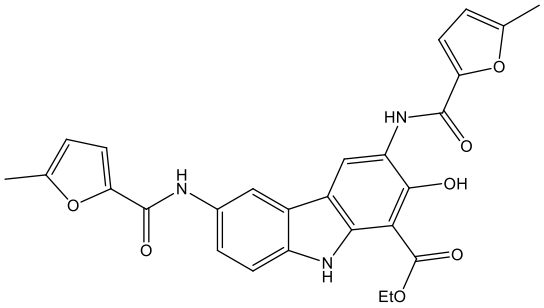
Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 31%; yellow oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 10.05 (s, 1H), 9.34 (s, 1 H), 8.40 (s, 1 H), 8.13 (d, *J* = 7.6 Hz, 1 H), 7.53-7.52 (m, 1 H), 7.50-7.46 (m, 1 H), 7.32-7.28 (m, 2 H), 7.17-7.16 (m, 1 H), 6.16-6.15 (m, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 2.85 (q, *J* = 7.2 Hz, 2 H), 1.14 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 165.8, 164.5, 160.1, 156.4, 146.1, 141.9, 140.3, 126.7, 123.5, 122.5, 121.6, 120.8, 120.2, 118.5, 116.2, 111.1, 107.6, 105.8, 61.5, 21.5, 13.7, 11.7.

*Ethyl 2-hydroxy-3,6-bis(5-methylfuran-2-carboxamido)-9H-carbazole-1-carboxylate (**221baa**)*



Purification by flash column chromatography (EtOAc/Hex, 1:3).

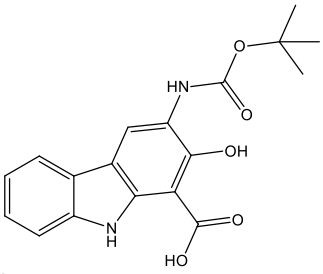
Yield: 54%; colorless oil.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 9.97 (s, 1 H), 9.10 (s,1 H), 8.33 (s, 1 H), 8.23-8.21 (m, 2 H), 7.82-7.80 (m, 1 H), 7.51-7.50 (m, 1 H), 7.45-7.43 (m, 1 H), 7.19-7.18 (m, 1 H), 7.14-7.13 (m, 1 H), 6.19-6.18 (m, 1 H), 6.15-6.14 (m, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 2.51 (s, 3 H), 2.44 (s, 3 H), 1.17 (t, *J* = 7.2 Hz, 3 H).

19. Procedure for preparation of 3-((tert-butoxycarbonyl)amino)-2-hydroxy-9*H*-carbazole-1-carboxylic acid (222)

Compound **217aa** (20 mg, 0.054 mmol) was dissolved in 0.5 M solution of NaOH (H2O:MeOH 1:1) (2 ml) and stirred for 12 h at R. T. Solution was acidified with 2 M HCl to pH = 3, and extracted with DCM (3 x 5ml). Organic layers was washed with water (5ml) brine (5ml) and dried with MgSO4. Solvent was removed under reduced pressure and the residue was purified with flash chromatography. (EtOAc/Hex, 1:3). White amorphous solid; yield 99%;

*3-((tert-butoxycarbonyl)amino)-2-hydroxy-9H-carbazole-1-carboxylic acid (**222**)*



Purification by flash column chromatography (EtOAc/Hex, 1:3).

Yield: 99%; white amorphous solid.

^{1}H NMR($CDCl_3$, 400 MHz): δ = 11.52 (s, 1 H), 9.00 (s, 1 H), 8.96 (s, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.46-7.44 (m, 1 H), 7.40-7.36 (m, 1 H), 7.26-7.22 (m, 1 H), 7.13 (s, 1 H, 1.61 (s, 9 H).

^{13}C NMR($CDCl_3$, 100 MHz): δ= 170.9, 153.3, 150.8, 138.7, 133.8, 124.8, 123.3, 120.6, 120.0, 119.7, 117.1, 115.5, 110.6, 96.0, 80.4, 28.5.

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