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**REVIEW**

# Privileged heterocycles: bioactivity and synthesis of 1,9-diazaspiro[5.5]undecane-containing compounds

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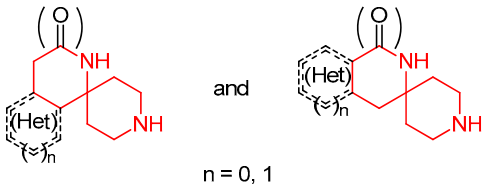


This review discusses the biological activity and synthesis of 1,9-diazaspiro[5.5]undecanes, including those ring-fused with arenes and heteroarenes and/or containing a carbonyl group at position 2. These compounds could be used for the treatment of obesity, pain, as well as various immune system, cell signaling, cardiovascular, and psychotic disorders.

**Keywords**: 1,9-diazaspiro[5.5]undecane, 1,9-diazaspiro[5.5]undecan-2-one, spiro dipiperidines, obesity, pain treatment.

1,9-Diazaspiro[5.5]undecanes are dipiperidines spiro-fused at position 2 of one piperidine ring and at position 4 of the other (Fig. 1). To the best of our knowledge, this is the first review on this compound class and covers the literature up until February 2017. The biological activity of these compounds, arranged by the type of disorder treated, is outlined in the first part of this review. Firstly, compounds based on the 1,9-diazaspiro[5.5]undecane scaffold are presented (Fig. 2) and, secondly, compounds with this scaffold as derivative of other scaffolds are discussed (Section 1.6. Miscellaneous).

The majority of the compounds studied include an arene ring commonly fused at positions 4 and 5 of the diazaspiro core. In addition to arene-fused structures, the presence of a carbonyl at position 2 is a common feature. Bioactive compounds that contain the 1,9-diazaspiro[5.5]undecane core always have substituents at position 9 and sometimes at position 1. Accordingly, when these diazaspiro compounds are used as substituents on other heterocycles they are almost always attached through position 9.

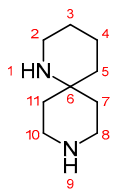


**Figure 1**. 1,9-Diazaspiro[5.5]undecane (systematic numbering).

The second part of this review highlights syntheses of the 1,9-diazaspiro[5.5]undecane cores, with each type of arene fusion having its own preferable synthesis strategy. Substitution options at position 9 and/or 1 are specific for each compound and mostly concern the last step of the synthesis. Some of these substitution options are exemplified.

## 1. BIOLOGICAL ACTIVITY

This review presents the biological activities of several 1,9-diazaspiro[5.5]undecanes arranged by the type of disorder that was treated and proposed biochemical mechanism. For example, in Section 1.1, the treatment of obesity may be based on various biological activities of 1,9-diazaspiro[5.5]undecanes, such as inhibition of acetyl CoA carboxylase, antagonism against neuropeptide Y, and inhibition of 11β-hydroxysteroid dehydrogenase type 1. The pharmacological data are presented (e.g., $IC_{50}$, $EC_{50}$, AUC, etc.) when reported in the primary sources.

### 1.1. Treatment of obesity

Obesity is a major concern amongst Western civilizations worldwide. According to the World Health Organization (WHO), 1.9 billion adults suffered from overweight in 2014, of which 600 million were obese.[1] Obesity was the

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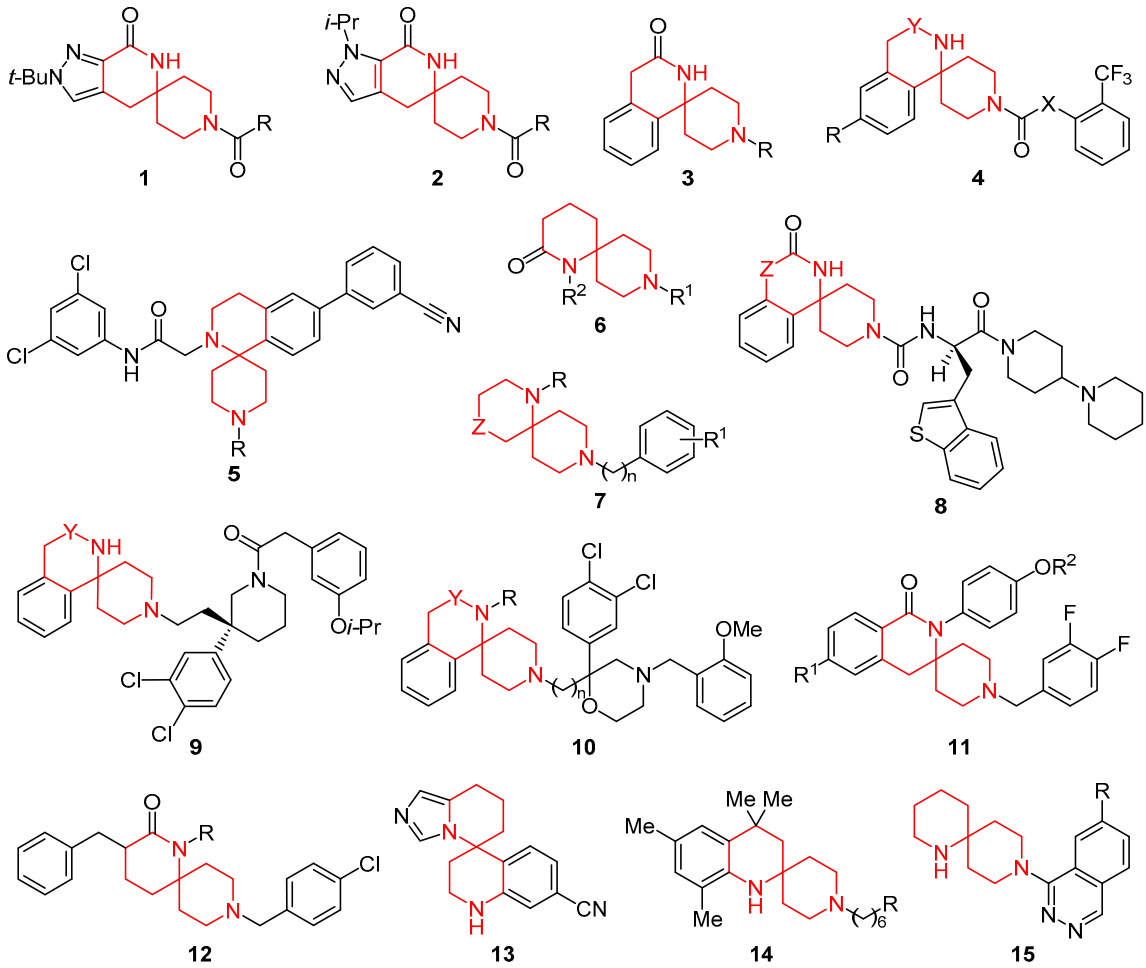


**Figure 2**. Bioactive 1,9-diazaspiro[5.5]undecane derivatives **1**–**15** used in drug development studies as main scaffolds (Y = $CH_2$, CO; X = $CH_2$, $CH_2CH_2$, CH=CH). Some hetera analogs will be included for comparison in the discussion (Z = N, O).

global leading cause of death in 2012, and it is associated with cancer (e.g., breast, endometrial, ovarian, prostate, liver, gallbladder, kidney, and colon cancer), cardiovascular diseases (e.g., stroke, congestive heart failure, heart arrhythmias, and coronary heart disease), osteoarthritis, type 2 diabetes mellitus, insulin resistance, hyperlipidemia, and increased premature and sudden death.[1,2] The data of the WHO show[3] that the prevalence of obesity in Europe is more than 15% in almost every country (see a graphical representation in Fig. 3).

With cardiovascular diseases being the main cause of death worldwide, putting a stop to obesity would save many lives. Although obesity itself is preventable without drugs, developing medicines would partially assist in bringing down the number of obese adults.

**Inhibition of acetyl-CoA carboxylase**. A biological target with regard to the treatment of obesity is the inhibition of acetyl coenzyme A carboxylase (ACC). ACC is responsible for converting acetyl-CoA into malonyl-CoA, a step that is vital in fatty acid synthesis. Two isoforms of ACC, ACC1 and ACC2, have been identified in mammals. Acetyl-CoA is metabolized *via* the citric acid cycle if it is not converted into malonyl-CoA. ACC1 and ACC2 are highly expressed in the liver where fatty acid

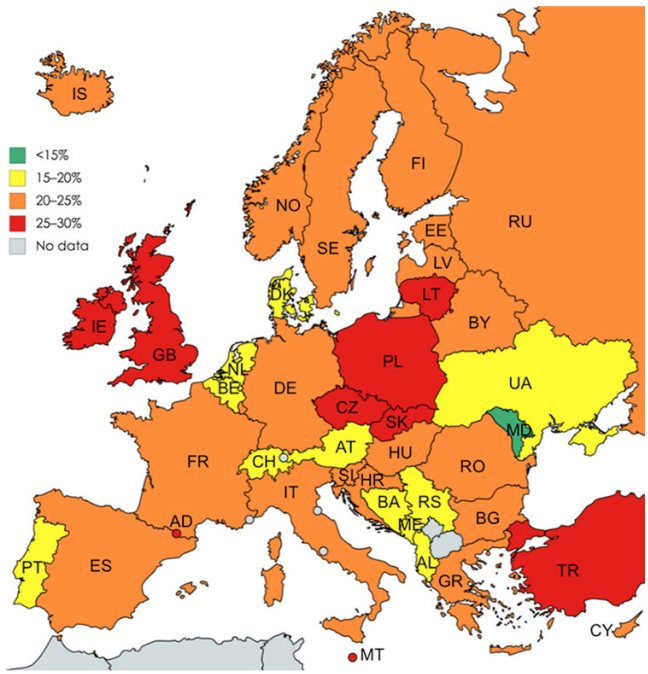



**Figure 3**. Obesity of adults in Europe in 2015. Obesity incidence: green <15%, yellow 15–20%, orange 20–25%, red 25–30%.

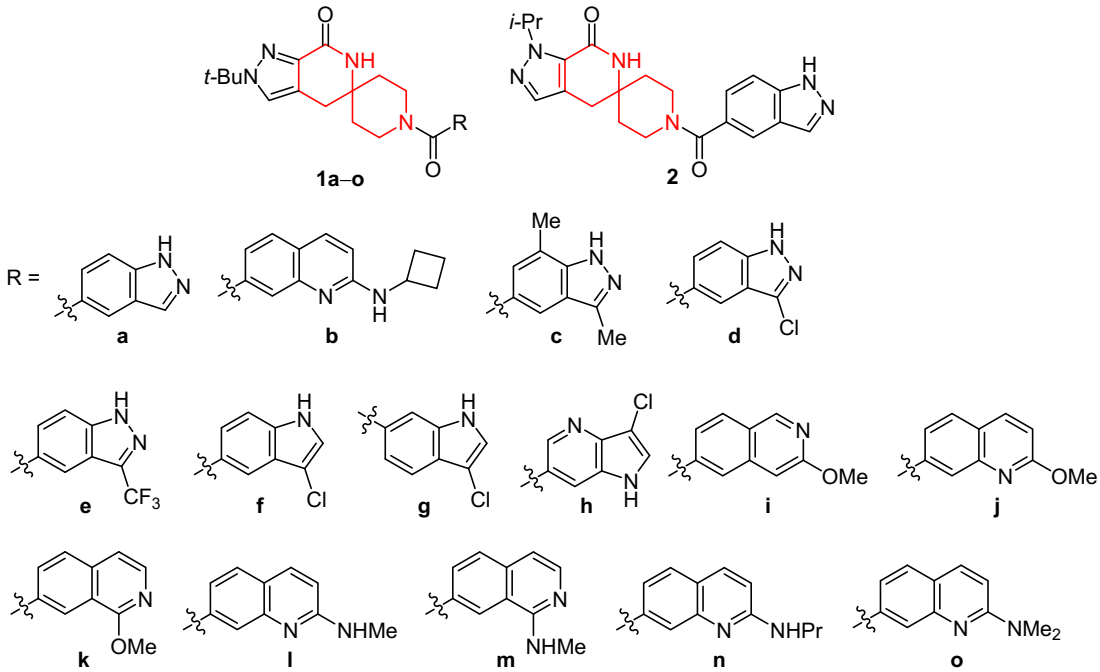



**Figure 4**. Compounds used for studying the SAR for ACC inhibition with respect to the substitution at position 9 of the 1,9-diazaspiro-[5.5]undecane ring system.

synthesis and oxidation are important. ACC2, the isoform predominantly present in heart and skeletal tissues, regulates the amount of fatty acid used in β-oxidation by inhibiting carnitine palmitoyl transferase. Inhibition of both isoforms would decrease the synthesis of new fatty acids and deplete the use of fatty acids stored, thereby resulting in weight loss.[4] Additionally, ACC inhibitors may be used to treat type 2 diabetes mellitus.[5] ACC inhibition is expected to impact both skeletal muscle and hepatic insulin sensitivity by rebalancing lipid metabolism associated with insulin resistance pathogenesis. Menhaji-Klotz and coworkers at Pfizer Inc. synthesized many 1,9-diazaspiro[5.5]undecan-2-ones containing a pyrazole ring fused to positions 3 and 4 in two different ways to achieve this ACC inhibition.[5] $IC_{50}$ values for ACC inhibition of 67 and 174 nM were measured for compounds **1a** and **2**, respectively (Fig. 4). Part of the same group synthesized a library of 125 3,4-pyrazole-fused 1,9-diazaspiro[5.5]undecan-2-ones (compounds **1b**–**o** as representative examples) and tested them for $IC_{50}$ values on human recombinant ACC1 and ACC2. The smallest $IC_{50}$ for ACC1 and ACC2 found were 3.4 and 1.0 nM, respectively, both exhibited by compound **1b** (Fig. 4).[4]

A general trend in dual ACC1/ACC2 inhibition was often encountered among the 125 compounds tested: good ACC1 inhibition was linked to good ACC2 inhibition.[4] The same group elaborated on this study by examining the structure–activity relationship (SAR) for the pyrazole part and the substitution at position 9 of the 1,9-diazaspiro[5.5]-undecane. In this study, additional pharmacokinetics were studied along with the $IC_{50}$ values for ACC1 and ACC2, such as the lipophilic ligand efficiency (LipE), measured lipophilicity (ElogD), human liver microsomal incubation (HLM), and passive permeability (Papp) in Ralph Russ canine kidney cells.[6] 1,9-Diazaspiro[5.5]undecan-2-one **1c** (Fig. 4) was selected for a SAR study of the effects of modifying the 3,4-pyrazole-fused moiety. Herein it was found that decreasing the bulk of the substituent at N-2 atom of the pyrazole ring (with respect to *t*-Bu group) similarly decreased ACC1/ACC2 inhibition. Increasing the bulkiness of this group (*tert*-pentyl) improved the $IC_{50}$ values for both ACC1 and ACC2, but also resulted in an increase in HLM by a factor of 4, which outweighed the small inhibitory advantage. Introducing substitution at the N-1 atom did improve the Papp values, but resulted in too much loss of ACC inhibition. Therefore, the *tert*-butyl-substituted pyrazole-fused core was used for the further studies.

The SAR with regard to substitution at position 9 of the 1,9-diazaspiro[5.5]undecane core was determined for aroyl substituents containing a bicyclic fused heteroaryl group. Comparisons were made with compound **1c**. Compounds **1d**,**e** showed similar ACC inhibition, HLM clearance, and LipE, but only modest improvement of Papp. Compounds **1f**,**g** showed improved Papp, and good ACC inhibition, but LipE values lowered along with higher HLM clearance. The very good ACC1 and ACC2 $IC_{50}$ values of compound **1g** (7 and 3 nM, respectively) were matched by compound **1h** (11 and 5 nM, respectively). Compound **1h** was designed on results obtained from compounds **1f**,**g** in the hope of showing a better LipE value, which it did. The downside was the poor Papp value obtained for compound **1h** when compared to compound **1g**. Compound **1i** showed reasonable LipE values and diminished ACC inhibition (74 and 29 nM for ACC1 and ACC2, respectively), but a greatly increased Papp value of 9.7 ($\times 10^{-6}$ cm/s) *vs* 0.8 for compound **1h**. Based on these results, a further SAR study was performed by using isoquinolines and quinolines as

substituents (compounds **1j**–**o**). The development of amino-substituted species **1l**–**o** did result in improved thermodynamic solubility at pH 1.2 with a factor up to 10 when compared to compounds **1j**,**k**. The Papp values of compounds **1l**,**m** were as bad as those of compound **1h**. Efforts to improve Papp by increasing the alkylation on the amine led to compounds **1n**,**o** exhibiting better Papp than compounds **1l**,**m**. The Papp values of compounds **1n**,**o** were still lower than those obtained for compounds **1j**,**k** and, in addition, HLM clearance significantly worsened. Compounds **1j**,**k** were chosen for *in vivo* examination of their pharmacological properties. Compound **1j** showed the best pharmacokinetics with an oral bioavailability of 71%, $c_{max}$ 403 ng/ml, AUC 2070 ng·h/l when administered to rats at 5 mg/kg. An intravenous dose of 1 mg/kg in rats demonstrated a moderate systemic clearance of 29 ml/(min·kg) and volume of distribution of 1.7 l/kg. Similarly, compound **1k** showed lower bioavailability and better clearance and volume of distribution than compound **1j**. Different oral dosages of compound **1j** were administered to rats in combination with $^{14}$C-labeled acetate precursors of lipids. The conversion of these acetate precursors into their respective lipid products for different dosages is shown in Figure 5.[6] It became clear from these results that compound **1j** could be very effective in decreasing new fatty acid synthesis and, therefore, in treatment of obesity and type 2 diabetes mellitus.

In a different study performed by Pfizer Inc., ACC inhibitors were explored to treat acne vulgaris.[7] Acne vulgaris is a skin disease caused by increased sebum secretion and manifests when hair follicles become clogged with oil and dead skin cells.[8] Increased production of sebum is linked to both the onset and severity of acne.[9] In addition, 80% of sebum content is made through *de novo* fatty acid synthesis, which is greatly dependent on ACC.[10] Treatment of humans with an ACC inhibitor may reduce sebum triglyceride content by 66%.[7] In the study carried out by Pfizer Inc., compound **1k** showed ACC inhibitor activity. For this compound, human ACC1/ACC2 (hACC1/hACC2) and sebocyte inhibition were measured in a transcreener assay and ACC1/ACC2 inhibition was also determined in a radiometric assay. $IC_{50}$ values for the transcreener assay were 14 and 3 nM for hACC1 and hACC2, respectively, and 94 nM for C9302E sebocytes. Only 2 out of 24 compounds from the same study showed better $IC_{50}$ values than compound **1k** for hACC1/hACC2 inhibition and only one of these also improved on the $IC_{50}$ value for the sebocytes. These two compounds had a 4-azaspiro[5.5]-undecane core structure (similar to that of 1,9-diazaspiro[5.5]-undecane with the nitrogen at position 1 replaced by carbon). For the radiometric assay of compound **1k**, the $IC_{50}$ values obtained were 11 and 4 nM for hACC-1/hACC-2, respectively; values that were in the highest order along with six other compounds.[7] Further *in vivo* testing was not performed with compound **1k**, but its effectiveness as ACC1/ACC2 dual inhibitor is apparent.

**Neuropeptide Y antagonism**. Another study, developed by Poindexter et al., showed that 4,5-benzene-fused 1,9-diazaspiro[5.5]undecanes **3a**–**n** (Fig. 6) presented antagonistic activity against neuropeptide Y (NPY).[11]

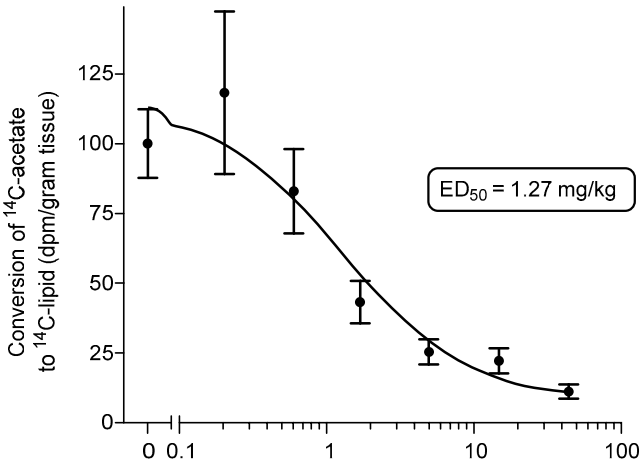
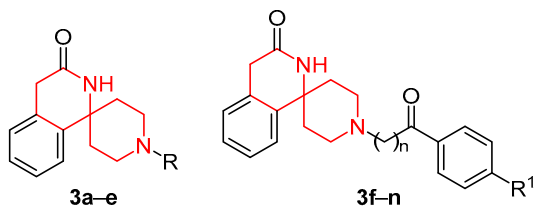



**Figure 5**. Conversion percentage of $^{14}$C-labeled acetate precursors into their lipid products *vs* mg/kg of compound **1j** administered in rats.[6] Reprinted (adapted) with permission. Copyright 2013 American Chemical Society.

NPY is a 36-amino acid neuropeptide that was found to be one of the most important regulators of feeding behavior and energy homeostasis. NPY is most abundant in the brain and has a high expression in the hypothalamus.[12] Furthermore, NPY is expressed in the spinal cord and most sympathetic nerve fibers, especially around blood vessels. Antagonism of the NPY receptors (NPY $Y_1$–$Y_5$) has been related to reduced food-intake in mammals,[11] making NDY antagonists drug candidates for the treatment of obesity. Various studies with mice have shown that especially the NPY $Y_1$ and NPY $Y_5$ are important targets for treating obesity.[13] The treatment of obesity by NPY $Y_5$ antagonism works in two ways. Firstly, it was found that food consumption was lowered by 10% in diet-induced obese mice. Secondly, the chronic treatment with NPY $Y_5$ antagonists inhibited the reduction of the metabolic rate. This indicated that NPY $Y_5$ antagonists could be used to prevent decrease in energy expenditure due to dieting or other anti-obesity treatments.[2] It was also shown that the combination of food restriction and administration of an NPY $Y_5$ antagonist was more successful in giving weight loss than either treatment alone.[2]

In developing an approach to treat obesity, it was herein suggested that combination of an NPY $Y_5$ antagonist and

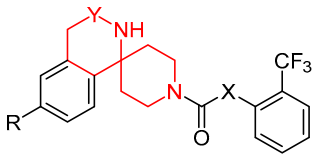



**3 a** R = $C_9H_{19}$, **b** R = $C_{10}H_{21}$, **c** R = $CH_2CH{=}CH_2$,
**d** R = $CH_2CH(OMe)_2$, **e** R = $(CH_2)_4N(CH_2Ph)_2$,
**f**–**h** n = 1, **i**–**k** n = 2, **i**–**n** n = 3,
**f**,**i**,**l** $R^1$ = Ph, **g**,**j**,**m** $R^1$ = Br, **h**,**k**,**n** $R^1$ = OPh

**Figure 6**. Compounds **3a**–**n** tested for NPY antagonism.

an anti-obesity drug would be effective in treating humans.[2] Furthermore NPY $Y_5$ antagonism was demonstrated by compounds containing the 1,9-diazaspiro[5.5]undecane structural moiety.[2] Characterization of the bioactivity was performed by employing insect cells (BRI-TN-5BI-4) infected with NPY $Y_5$-recombinant Baculovirus. The radioligand used was iodine-125 labeled PYY ligand. Herein the $IC_{50}$ values of compounds **3a**–**n** were less than 10 μM, with compounds having an $IC_{50}$ of less than 500 nM or less than 100 nM.[11] The results of this binding assay showed that these compounds may be used in treatment of disorders that are characterized by an excess of NPY, including cardiovascular diseases, renal system disorders, cerebral diseases, conditions of pain or nociception, abnormal food intake disorders, inflammation disorders, sleep disturbance, and diabetes. When it comes to the treatment of obesity, compounds **3a**–**n** are expected to have an effective dose in the range of 0.05–1 mg/kg bodyweight if administered parenterally, and of 1–20 mg/kg bodyweight if administered orally.

**Inhibition of 11β-hydroxysteroid dehydrogenase type 1**. Inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) by compounds with the diazaspiro moiety may also combat obesity amongst other diseases. This was the conclusion drawn after a study performed by Claremon and coworkers on compounds **4a**–**d** (Fig. 7) that presented significant 11β-HSD1 inhibitory activity ($IC_{50}$ < 100 nM).[14]



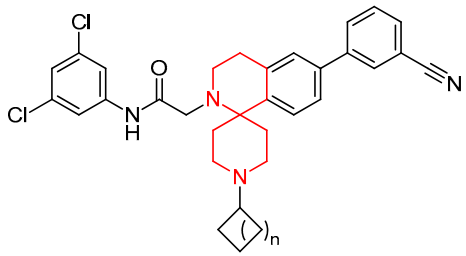

**4 a** R = H, Y = CO, X = (*E*)-CH=CH
**b** R = OMe, Y = $CH_2$, X = (*E*)-CH=CH
**c** R = OMe, Y = $CH_2$, X = $CH_2$
**d** R = OMe, Y = $CH_2$, X = $CH_2CH_2$

**Figure 7**. 11β-HSD1 inhibitors **4a**–**d**.

11β-Hydroxysteroid dehydrogenase pre-receptor control enzymes that modulate activation of the glucocorticoid receptor and the mineralocorticoid receptor *via* regulation of glucocorticoid hormones.[15–17] Glucocorticoids (e.g., cortisol) are steroid hormones that regulate fat metabolism, function, and distribution, as well as carbohydrate and protein metabolism. Therefore, inhibition of 11β-HSD1 may prove useful in treating multiple glucocorticoid-related disorders and/or aspects of the metabolic syndrome. Examples include combatting obesity, glucose intolerance, insulin resistance, hyperglycemia, hypertension, and hyperlipidemia.[14]

**Melanin-concentrating hormone antagonism**. Another way in which compounds containing 1,9-diazaspiro[5.5]undecane moiety may treat obesity is by exhibiting antagonizing activity toward melanin-concentrating hormone receptor 1 (MCH-R1).[18] MCH-R1 is a member of the G protein-coupled receptors and binds MCH, a hypothalamic cyclopeptide. Targeting MCH-R1 is mentioned as having a major potential for treatment of obesity.[19–22] Since it was found that the MCH-R1 was highly conserved between rodents and humans, the results obtained in rodents concerning MCH and MCH-R1 antagonism could serve as a model for assessment of MCH-R1 antagonism in humans. MCH mRNA was overexpressed in the hypothalamus of diet-induced obese rats and mice, as well as in leptin-deficient ob/ob mice, fasting leptin-deficient ob/ob mice and their control mice, and in leptin-resistant fa/fa Zucker rats.[21] In addition, MCH-R1-knockout mice are lean, hypophagic, hyperactive, have increased metabolic rate and reduced fat mass, and are resistant to diet-induced obesity.[23] MCH also increases the release of NPY, a contributor to feeding behavior as mentioned earlier.[21] This means that inhibition of MCH production or of its MCH-R1 receptor could have direct and indirect effects resulting in treatment of obesity.

4,5-Benzene-fused 1,9-diazaspiro[5.5]undecane derivatives **5a**–**c** (Fig. 8) presented the good binding affinities of 13, 16, and 11 nM, respectively, for MCH-R1. In this study, the SAR of related compounds was also examined. It was found that substitutions at position 9 of the 1,9-diazaspiro[5.5]undecane core other than alkyl groups (e.g., sulfonyl, acyl, carbamoyl groups) significantly reduced the MCH-R1 binding affinity of such compounds.[23] Following this trend, it was concluded that having the basic nitrogen on position 9 of the diazaspiro moiety was an important condition for binding MCH-R1. A pharmacokinetics study of compound **5b** showed an AUC of 332 ng·h/ml in rats.[23]




**5a**–**c**
**a** n = 1, **b** n = 2, **c** n = 4

**Figure 8**. MCH antagonists **5a**–**c**.

### 1.2. Treatment of central nervous system disorders

**Orexin antagonism**. The family of diazaspiro[5.5]undecanes, including the 1,9-diazaspiroundecanes, was also used to develop orexin antagonists. Orexins A and B, also known as hypocretins, are small neuropeptides that are produced in discrete neurons of the lateral hypothalamus and that bind to G-protein-coupled receptors. Orexins are recognized as important targets for treating sleep disorders[24] (e.g., narcolepsy and insomnia) and are also considered vital in regulating feeding, metabolism, and energy homeostasis.[25] Orexins may also be involved in psychiatric/neurological disorders like Parkinson disease, Huntington disease, Tourette syndrome, and epilepsy, as well as involvement in cardiovascular diseases, heart and lung diseases, and multiple sorts of pain.[26]

In the treatment of sleep disorders, antagonists for both orexin receptors ($OX_1R$ and $OX_2R$) were developed based on the 1,9- and 2,9-diazaspiro[5.5]undecane cores.[27] The aim of this research performed by Hoyer and coworkers was to develop a dual antagonist against $OX_1R$ and $OX_2R$, as well as a selective $OX_2R$ antagonist to distinguish the effects of both receptors on sleep behavior. The SAR was studied for a number of structures **6a**–**f** with respect to both substitution at positions 1 and 9 (Fig. 9).

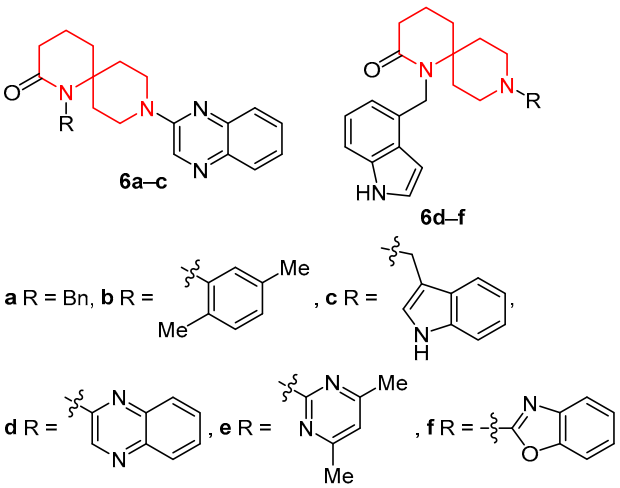



**Figure 9**. 1,9-Diazaspiro[5.5]undecan-2-ones **6a**–**f** tested for dual $OX_1R/OX_2R$ antagonism and selective $OX_2R$ antagonism.

Compound **6a** was taken as a starting point. Introduction of small substituents (e.g., methyl groups) on the benzyl group led to compound **6b**, which exhibited a more than tenfold increase in inhibition of both $OX_1R$ and $OX_2R$. The lipophilicity of compound **6b** was, however, too high and substitution with monoaryl groups (e.g., pyridines) resulted in loss of inhibition potency. The introduction of bicyclic-fused aryl substituents led to compounds **6c**,**d**, which showed a similar increase in inhibition for both $OX_1R$ and $OX_2R$, whilst also favorably reducing the lipophilicity. The SAR study was then carried out for substitution at position 9. When testing compounds **6d**–**f**, it was observed that $OX_2R$ inhibition was maintained in a high range, whereas $OX_1R$ values greatly varied, leading to more selective $OX_2R$ antagonists like compound **6e**. For compound **6d**, an excellent subnanomolar $K_i$ was obtained for $OX_2R$ ($pK_i$ 9.34). When examined *in vivo* such compounds, containing the 1,9-diazaspiro[5.5]undecane core, were found ineffective. A high blood clearance and volume distribution were found (188 ml/(min·kg) and 3.1 l/kg, respectively), along with poor $c_{max}$ (18 nM), AUC (31 nM·h) and oral bioavailability (5%). The 2,9-diazaspiro[5.5]undecane performed much better in *in vivo* testing and it was suggested that poor *in vivo* performance is directly related to the 1,9-diazaspiro[5.5]undecane core.[27]

**σ, μ, and D2 receptors**. The treatment of pain in general has always been important because one out of five adults suffer from pain and one out of ten are diagnosed with chronic pain each year.[28] The incidence of pain is only increasing due to population ageing and is often related to comorbidities like depression, anxiety, and insomnia. Existing pain therapies, which use nonsteroidal anti-inflammatory drugs, opioid agents, calcium channel blockers, and antidepressants, exhibit limited efficacy and a range of side effects, limiting their usefulness in chronic pain treatment. In addition, pain is often multimodal, making the use of monomodal treatment not able to relieve all of the pain. The multimodal activity of the compounds containing the 1,9-diazaspiro[5.5]undecane core against multiple receptors associated with pain or side effects related to pain could make this class of compounds of high interest in new treatments of pain.

The most effective compounds in suppressing pain are the opioids (e.g., morphine), mainly through their activation of the μ opioid receptor. The side effects associated with the use of opioids are also the most severe and can include derangement, hallucination, nausea, constipation, respiratory depression, and addiction.[29,30] In addition, opioids have not proven useful in the treatment of chronic pain, as demonstrated by morphine. Morphine has only a limited effectiveness against chronic pain of neuropathic or inflammatory origin, opposed to greatly diminishing acute pain. Furthermore a tolerance for morphine is built up in the body, which leads to an increase of dosage to maintain the same pain-suppressing effects. Weaker opioid analgesics, like pentazocine, are less effective at suppressing strong pain and display the same side effects, albeit less intense.[31] Some of the mentioned side effects are associated with an activation of the dopamine D2 receptors.[32] Antagonistic activity against the dopamine D2 receptor has also been linked to reducing the addictive effect of opioid analgetics.[32] Therefore, the possible combination of μ opioid and dopamine D2 antagonistic activity may lead to development of new pain-control agents with reduced or suppressed side effects.[32] Studies with mice have also shown that $\sigma_1$ receptor antagonism may also relieve neuropathic pain and address some comorbidities (e.g., anhedonia, a core symptom in depression) related to pain states.[30]

The $K_i$ values, for both the $\sigma_1$ and μ receptors, were determined for compounds **7a**–**d** in a study developed by Virgili-Bernado et al.[33] (Fig. 10). Compounds **7b**–**d** showed good dual $\sigma_1/\mu$ inhibition with $K_i$ for both receptors between 100 and 500 nM. Of the compounds with a core of closely related 4-oxa-1,9-diazaspiro[5.5]undecanes, 48 derivatives were tested of which only compounds **7e**–**g** performed better than compounds **7b**–**d** with $K_i$ values for both receptors lower than 100 nM.

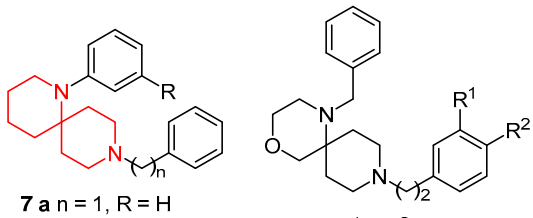
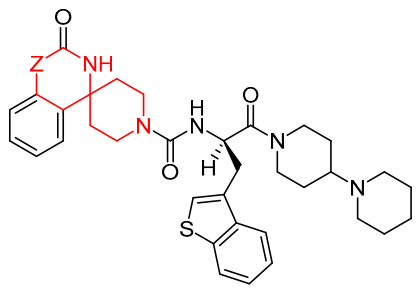



**Figure 10.** Dual $\sigma_1/\mu$ inhibitors **7a**–**g**.

**Calcitonin gene-related peptide antagonism**. The calcitonin gene-related peptide (CGRP) is a neuropeptide that has two forms in humans: α-CGRP and β-CGRP. α-CGRP plays a central role in migraine pathology, migraine being a disease that affects 12% of the population.[34] CGRP and its receptor are widely expressed in both the central and peripheral nervous system by multiple cell types which are involved in the regulation of inflammatory and nociceptive response.[34,35] Although the compounds developed with the aim of inhibiting CGRP do not exclusively contain the 1,9-diazaspiro[5.5]undecane core, even some measure of CGRP inhibition could be useful. This usefulness might be expressed in a multimodal activity against the CGRP among others, possibly giving rise to the improved effectiveness of the diazaspiro compounds when treating, for example, obesity or (chronic) pain. The usefulness of combining compounds that may inhibit CGRP with one or more other compounds to provide more effective remedy against multiple diseases is also recognized. Proposed is the use of such CGRP inhibitors in conjunction with anti-migraine agents, potentiators such as caffeine, anti-emetics, ergot alkaloids, beta-adrenergic antagonists, interleukin inhibitors, and gap junction inhibitors.[35]

An attempt developed by Chaturvedula and coworkers at finding structures that would effectively inhibit the CGRP receptor focused on many spiro compounds, including the 4,5-benzene-fused 1,9-diazaspiro[5.5]undecan-2-one **8a** (Fig. 11).[36] $IC_{50}$ and $EC_{50}$ values of 29 and 15 nM, respectively, were obtained for this compound. The closely related structure **8b**, a 4,5-benzene-fused 1,3,9-triazaspiro derivative, gave an even better result in the same study with $IC_{50}$ and $EC_{50}$ values of 5 and 3 nM, respectively.[36,36]

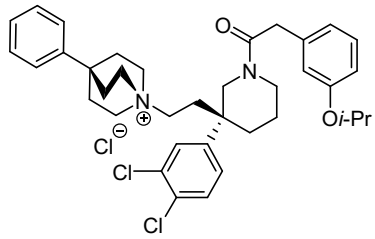



**8 a** Z = $CH_2$, **b** Z = NH

**Figure 11**. CGRP inhibitors **8a**,**b**.

### 1.3. Immune system and cell signaling disorders

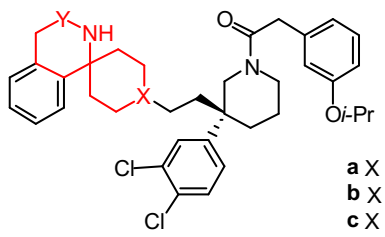
**Neurokinin receptor antagonism**. The neurokinin receptors (NK1, NK2, and NK3) that form the well-known NK receptor class are widely present in the central and peripheral nervous system. These receptors are modulated by tachykinins, a family of neurotransmitter peptides, and play an important role in functioning as a biowarning system. Destruction of such a system may result in several diseases like pain, anxiety, irritable bowel syndrome (IBS), and obstructive bronchial diseases.[37] The NK1 receptor mediates biological responses exhibited by substance P, which include pain transmission, activation of the immune system, neurogenic inflammation, and smooth muscle contraction. Since an NK1 antagonist may inhibit the binding of substance P to NK1, administration of an NK1 antagonist may prove useful in treatment of these diseases.[38] SR140333, a known inhibitor of NK1 (Fig. 12), was examined and had an $IC_{50}$ of 0.31 nM for binding NK1.[38]




SR140333

**Figure 12**. NK1 antagonist with an excellent $IC_{50}$ value.

Compound SR140333 presents a 4-phenylquinuclidinium core. Upon replacing this moiety with the 4,5-benzene-fused 1,9-diazaspiro[5.5]undecane core, compound **9a** (Fig. 13) was obtained with similar substitution at position 9 and with an $IC_{50}$ value of 31 nM for NK1 binding.[38]




**9a–d**

**a** X = N, Y = $CH_2$
**b** X = N, Y = CO
**c** X = $N^+MeI^-$, Y = $CH_2$
**d** X = $N^+MeI^-$, Y = CO

**Figure 13**. Compounds **9a**–**d** based on SR140333 tested for NK1 antagonist activity.

Additionally, having a carbonyl at position 2 of the benzene-fused diazaspiro core increased the $IC_{50}$ value to 54 nM for compound **9b**. Methylation of compounds **9a**,**b** yielded salts **9c**,**d** with $IC_{50}$ values of 2.0 and 1.9 nM, respectively. Animal testing on substance P-induced bronchoconstriction in guinea pigs showed $ID_{50}$ values of 24 and 19 μg/kg for compound **9d** and SR140333, respectively.[38] This example showed that the 1,9-diazaspiro-[5.5]undecanes with a fused benzene ring could be used as effective NK1 antagonists.

The NK2 receptor can be selectively stimulated to control smooth muscle contraction associated with asthma, pulmonary irritations, intestinal spasms, and kidney infections.[39] The administration of NK antagonists can be effective in treatment of such diseases.[37,39,40]

Development of dual NK1/NK2 antagonists was also explored.[41–45] Although the cited works were not mainly concerned with the 1,9-diazaspiro[5.5]undecane core, two of such structures (Fig. 14) were examined in their role as tachykinin antagonist (for NK1 and NK2) in bladder contraction in test animals.[45] Herein it was found that fumarate YM-44778 exhibited high binding affinities of

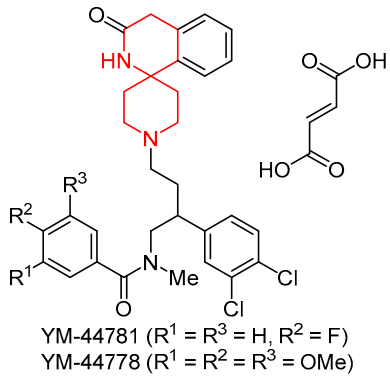



**Figure 14**. 1,9-Diazaspiro[5.5]undecanes possessing dual NK1/NK2 antagonism.

p$K_i$ 8.08 and 8.55 for binding NK1 and NK2, respectively, transfected in Chinese hamster ovary cells (CHO-K1). A related fumarate YM-44781 also exhibited high binding affinity in similar conditions, giving p$K_i$ 9.09 and 9.94 for NK1 and NK2, respectively. In drug-induced bladder contraction, antagonism of these contractions was observed after administration of YM-44778 and YM-44781 ($IC_{50}$ 100 and 27 μg/kg bodyweight, respectively). It was concluded that YM-44781 was a potent NK2 antagonist and that YM-44778 was a nonselective NK1/NK2 antagonist.

A large study aimed at finding NK1/NK2 dual antagonists for treating an inflammatory disease produced a compound library of more than 11,000 compounds.[46] Some of these compounds contained either the 4,5-benzene-fused 1,9-diazaspiro[5.5]undecan-2-one (compounds **10a**,**b**) or a 1-acetylated 4,5-benzene-fused 1,9-diazaspiro[5.5]undecane (compounds **10c**–**d**) moiety substituted at position 9 (Fig. 15). The conclusion of the study was that the investigated compounds exhibited strong activity against both NK1 and NK2 receptors.

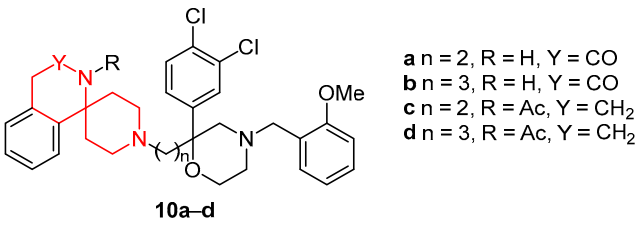



**Figure 15**. Compounds **10a**–**d** designed for dual NK1/NK2 antagonism.

**Allosteric modulators of metabotropic glutamate receptor subtype 4**. Compounds that modulate metabotropic glutamate receptor subtype 4 (mGluR4) by allosteric mechanism may also alter glutamate level or glutamatergic signaling or do so instead of allosteric modulation. Glutamate is an amino acid transmitter in the central nervous system. Glutamate is involved in many physiological functions (e.g., learning, memory, sensory perception, motor control, respiration, cardiovascular function), as well as in neurological and psychiatric diseases, caused by an imbalance in glutamatergic neurotransmission.[47–49]

In a study carried out by Brugger and coworkers, two 3,4-benzene-fused 1,9-diazaspiro[5.5]undecan-2-ones **11a**,**b** (Fig. 16) were tested for their ability to allosterically modulate mGluR4.[50] The biological assay was performed by means of a cAMP assay using HEK-293 mGluR4 cells with $EC_{20}$ L-glutamate (2.3 and 4.3 μM for mGluR4 and mGluR6, respectively). $EC_{50}$ values were determined and were found to be between 1 and 10 μM for both compounds **11a**,**b**. Several 1,5,9-triazaspiro[5.5]undecanes showed better $EC_{50}$ values at below 1 μM concentrations.

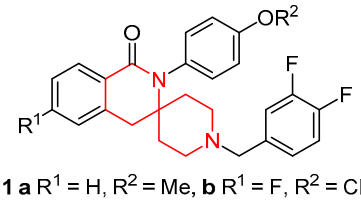



**Figure 16**. Modulators of mGluR4 **11a**,**b**.

**Inhibition of chemokine receptors CXCR3**. Chemokines are chemotactic cytokines that are involved in immune system cell signaling.[51] Chemokines are bound by chemokine receptors (e.g., CCR1–CCR9, CXCR1–CXCR5), which are G protein-coupled transmembrane receptors. In particular, the CXCR3 chemokine receptor is activated by three chemokines: IP-10, Mig, and I-TAC.[52] CXCR3 is expressed in the T cells, B cells, and NK cells among others. T cells are known to participate in autoimmune diseases (e.g., multiple sclerosis, rheumatoid arthritis, atherosclerosis, type I diabetes), allergic diseases (e.g., bronchial asthma, transplanted organ rejection) and they generate interfusions in immunologic diseases (e.g., psoriasis). Since CXCR3 is involved in migration and accumulation of T cells, inhibition of CXCR3 by an antagonist could be useful in the treatment of the aforementioned diseases. In addition, CXCR3 is expressed in the neoplasm of a malignant B cell system, making a CXCR3 antagonist effective for carcinomatous immunotherapy, metastasis control in particular. All this would make CXCR3 antagonists useful therapeutic agents in treatment, prevention or suppression of carcinoma diseases (e.g., leukemia, cancer metastasis), metabolism-related diseases (e.g., diabetes), infections or diseases with an infection (e.g., AIDS, SARS), allergic diseases, autoimmune diseases, gastrointestinal diseases (e.g., Crohn's disease, colitis ulcerosa), respiratory diseases, and neurologic diseases (e.g., infarct, thrombosis). Compounds **12a**,**b** were tested for CXCR3 inhibition[53] (Fig. 17). Compound **12b** presented better results with an $IC_{50}$ value of 1.1 μM.

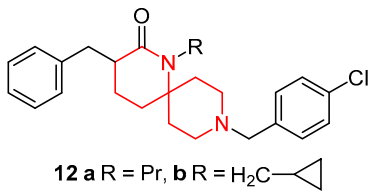
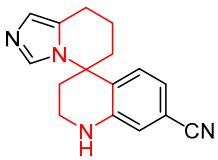



**Figure 17**. Compounds **12a**,**b** tested for CXCR3 inhibition.

### 1.4. Cardiovascular disorders

**Inhibition of aldosterone synthase**. Aldosterone synthase is expressed in the adrenal cortex and synthesizes the steroidal hormone aldosterone. Aldosterone production and secretion are regulated by the adrenocorticotropic hormone (ACTH), angiotensin II, and sodium and potassium ions.[54] Aldosterone reabsorbs sodium ions from the renal filtrate and secretes potassium ions into the renal filtrate. Treatment or delaying of states such as congestive heart failure, coronary heart disease, acute and chronic renal failure, metabolic syndrome and fibrosis among others could be done by employing cytochrome P450 aldosterone synthase (CYP11B2) inhibitors. Another function of ACTH is to regulate the production of cortisol, making inhibition of ACTH also interesting for the treatment of the cortisol-related disorders mentioned earlier, such as obesity.[55]

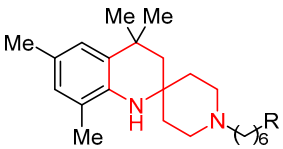
Within the large variety of arene-fused diazaspiro compounds available, a rare 1,2-imidazole-fused derivative **13** containing the 1,9-diazaspiro[5.5]undecane core, was synthesized and tested as inhibitor of aldosterone synthase (Fig. 18).[55] Compound **13** specifically inhibited CYP11B2 and could therefore be used to treat states related to aldosterone.




**13**

**Figure 18**. Compound **13** tested for inhibition of aldosterone synthase.

**Low-density lipoprotein binding in human blood plasma**. Low-density lipoproteins (LDL) are involved in causing atherosclerosis unless their oxidation is inhibited. A natural control agent is considered to be α-tocopherol, a major form of vitamin E, which acts as chain-breaking antioxidant by inhibiting LDL oxidation in plasma.[56] In an attempt to make a synthetic analog of α-tocopherol, multiple steroidal structures were made, as well as two 2,3-benzene-fused 1,9-diazaspiro[5.5]undecanes **14a**,**b** (Fig. 19).[57] Additionally, α-tocopherol mimics are interesting, since they may improve natural protection against radical species (e.g., superoxide). In order to be a successful mimic, a molecule should be able to form a stable radical cation at an ionization potential of 0.45–0.65 V. The 1,9-diazaspiro[5.5]undecanes **14a**,**b** were effective at forming such a stable radical cation with redox couples at 0.6 V. A lower amount of these diazaspiro compounds was bound (ca. 25%) to the LDL, which meant that these derivatives were not further examined in this study.



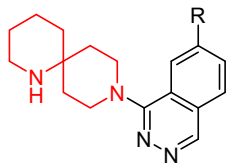

**14 a** R = Me
**b** R = $O(CH_2)_4OPh$

**Figure 19**. Compounds **14a**,**b** studied as α-tocopherol analogs.

### 1.5. Psychotic disorders

**Inhibition of phosphodiesterases**. Phosphodiesterases (PDE) are a class of intracellular enzymes involved in hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) into the corresponding nucleotide monophosphates.[58] cAMP and cGMP mainly serve as secondary messengers in regulating intracellular processes in neurons of the central nervous system.[59] The function of PDEs in the neurons is to activate cAMP- and cGMP-dependent kinases and subsequently phosphorylate proteins involved in acute regulation of synaptic transmission, neuronal differentiation and survival. A main mechanism for regulating cyclic nucleotide signaling is phosphodiesterase-catalyzed cyclic nucleotide catabolism. There are 11 families of PDEs, encoded by 21 genes.[59] Each gene can also yield splice variants, which increases the isozyme diversity. PDE families are functionally distinguished based on cyclic nucleotide substrate specificity, mechanisms of regulation, and sensitivity to inhibitors. PDEs are differentially expressed throughout the organism. Depending on the function and localization of the different PDE isozymes, they may serve distinctly in different physiological functions. These functions may mean that selective inhibition of a particular PDE family could result in selective treatment of disorders, possibly with fewer side effects.

Thus inhibitors of such an enzyme, PDE10, could be used in the treatment of psychotic disorders, such as Huntington's disease, schizophrenia, obsessive-compulsive disorder, drug-induced psychosis, and delusional disorders. According to the study developed by Humphrey, inhibition of the PDE10 family of isozymes could be achieved by some derivatives of 9-(phthalazin-1-yl)-1,9-diazaspiro[5.5]-undecanes **15a**–**d** (Fig. 20).[59]



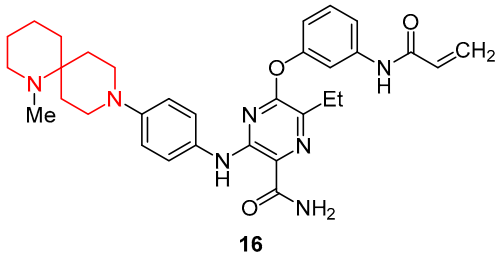

**15 a** R = H, **b** R = Cl,
**c** R = CN, **d** R = $CO_2H$

**Figure 20**. Compounds **15a**–**d** studied as inhibitors of PDE10.

### 1.6. Miscellaneous

**Inhibition of epidermal growth factor receptor T790M kinase and oxytocin antagonists**. Further use of the 1,9-diazaspiro[5.5]undecane core can be found as a substituent for other heterocyclic drugs used for treating a variety of disorders. One such disorder is the non-small cell lung cancer (NSCLC).[60] A mutation of the epidermal growth factor receptor (EGFR) at position 790 occurs in about half the patients suffering from this disorder. This T790M mutation replaces a threonine with a methionine. Irreversible inhibition of EGFR T790M kinase was shown to inhibit cell proliferation of cell lines expressing the EGFR T790M mutation and regress tumor volume in mice

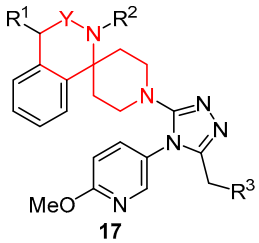
with EGFR T790M/L858R resistant mutation. To this end, a library of 254 tetrasubstituted pyrazines was developed, one of which contained the diazaspiro moiety (compound **16**, Fig. 21), but the activity was only reported for selected examples.[61]




**16**

**Figure 21**. Pyrazine **16** – a possible EGFR T790M kinase inhibitor.

In a different study, a library of 3,5-disubstituted 4-(pyridin-3-yl)-1,2,4-triazoles was developed with the aim of finding oxytocin antagonists. This library included three compounds **17a**–**c** (Fig. 22) with the 1,9-diazaspiro[5.5]-undecan-9-yl group as substituent.[62]




**17**

**a** Y = CO, $R^1$ = Me, $R^2$ = H, $R^3$ = H
**b** Y = $CH_2$, $R^1$ = H, $R^2$ = Me, $R^3$ = H
**c** Y = $CH_2$, $R^1$ = H, $R^2$ = Me, $R^3$ = OMe

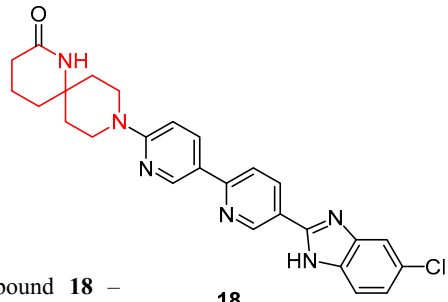
**Figure 22**. Oxytocin antagonists **17a**–**c** with a 1,2,4-triazole core.

Therapeutic use of oxytocin antagonists concentrates also on sexual dysfunctions, particularly premature ejaculation. All the compounds of this study exhibited oxytocin antagonist activity, expressed as a $K_i$ value, of less than 1 μM.[62]

Quinoxaline derivatives sometimes containing substitution at the 1,9-diazaspiro[5.5]undecane core, could be used as dopamine receptor antagonist, corticosteroid, β2-adregenic agonist, leukotriene modifier, antihistamine, decongestant, antitussive, and nonsteroidal anti-inflammatory drug. The substituted quinoxalines were developed as $CRTH_2$ inhibitors and can be used for treatment of symptoms and diseases associated with uncontrolled $CRTH_2$ stimulation, such as the aforementioned.[63]

**Inhibition of diglyceride acyltransferase**. It has been noted that the main cause of obesity is the accumulation of triacylglycerol (TG) in adipose tissue, caused by excessive caloric intake. There are two pathways that synthesize TG: a glycerol pathway in organs and a monoacylglycerol pathway involved in aliphatic acid absorption from the small intestine. The final step in TG synthesis of both these pathways is catalyzed by diglyceride acyltransferases (DGATs).[64] Of the two subtypes, DGAT1 is present in the adipose tissue, the liver, and the small intestine and is involved in lipid absorption in the small intestine, lipid accumulation in the fat cells and in the liver. DGAT1 knockout mice have been demonstrated to be resistant to fatty liver development, insulin resistance, increased fat mass, and abnormal glucose tolerance when fed a high-fat diet. In addition, energy expenditure was accelerated and transplantation of adipose tissue from DGAT1 knockout mice to wild-type mice resistant to obesity induced by a high-fat diet. On the other hand, DGAT1 overexpression in mice resulted in worsening of diabetes mellitus and obesity. These results led to the conclusion that DGAT1 inhibitors could be therapeutic drugs for treatment of obesity, type 2 diabetes mellitus, coronary artery disease, arteriosclerosis, lipidosis, fatty liver, metabolic syndrome, hypertension, and cerebrovascular disease.[65]

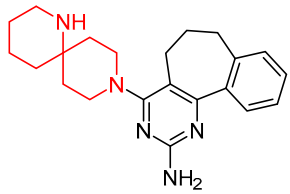
In a study developed by Liu et al. to treat obesity *via* the pathway described above, a 1,9-diazaspiro[5.5]undecan-2-one moiety was used as substituent on benzimidazole derivatives exemplified by compound **18** (Fig. 23).[65] In this study, compound **18** presented an $IC_{50}$ value of 49.0 nM. The lowest and highest values among the 173 compounds of the study were 1.56 and 2000 nM, respectively.




**18**

**Figure 23**. Compound **18** – a possible inhibitor of DGAT1.

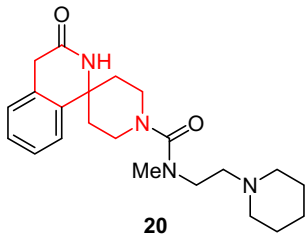
**Histamine receptor ligands**. In developing an agent that focuses on the treatment of neuropathic pain, the histamine $H_4$ receptor ($H_4$-R) has been one of the targets.[66] This receptor is also a member of the G protein-coupled receptor family, and it binds histamine to transduce signals to modulate cellular activities. Antagonists of $H_4$-R or inverse agonists may treat multiple types of pain (e.g., inflammatory pain, chemically induced pain, post-surgery pain, pain from osteoarthritis, and neuropathic pain). In this study, concentration versus response data was analyzed to obtain the compound potency as binding constant ($K_b$) values for antagonists and inverse agonists and as $EC_{50}$ values for partial agonists. All the compounds tested blocked the ability of histamine to increase $Ca^{2+}$ concentrations in cells and had $K_b$ values between 4 and 1000 nM (not reported for all compounds). One single example of a 1,9-diazaspiro[5.5]undecane derivative (compound **19**, Fig. 24) was present among them, which contained a [*d*]-fused pyrimidine ring.[67]




**19**

**Figure 24**. Possible histamine $H_4$ receptor antagonist **19**.

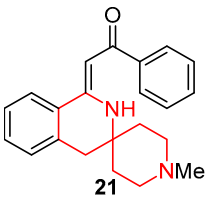
Another research looked into developing the histamine $H_3$ receptor ($H_3$-R) inverse agonists. This receptor is predominantly expressed in the central nervous system and known to control release of several neurotransmitters (e.g., norepinephrine, serotonin, GABA, dopamine, and acetylcholine).[68] Because of this, it has been suggested that $H_3$-R antagonists or inverse agonists could be used to treat disorders related to the central nervous system. In animals antagonism of $H_3$-R has been shown to enhance wakefulness, improve attentive and cognitive behaviors, and reduce feeding and body weight. In this study, a substituted urea **20** (Fig. 25), containing the 4,5-benzene-fused 1,9-diazaspiro-[5.5]undecan-2-one moiety, was examined as one of the possible antagonists.[68] However, compound **20** had an $IC_{50}$ value of 783 nM for human $H_3$, which was around a 1000-fold higher than the best antagonist found in the study.




**20**

**Figure 25**. Compound **20** studied for $H_3$-R antagonism.

**Cannabinoid receptor type 2 agonists**. The cannabinoid receptor (CB2 receptor) is a G protein-coupled receptor that may modulate inflammation and/or the immune system. It is suggested that compounds that bind the CB2 receptor may be useful for treating diseases like rheumatoid arthritis, immune dysfunction, atopic dermatitis, carcinomatous pain, etc. In a study aimed at development of a CB2 receptor-binding 3,4-dihydroisoquinoline derivatives, the 3,4-benzene-fused 1,9-diazaspiro[5.5]-undecane core was among the structural units considered. In compound **21**, an alkylidene substituent was found at position 2, along with a methylated position 9 (Fig. 26).[69]




**21**

**Figure 26**. Compound **21** developed for CB2 receptor binding.

**Poly(ADP-ribose) polymerase-1 inhibitors**. Another use of the 1,9-diazaspiro[5.5]undecane core was found in the development of poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors.[70] PARP-1 is an important member of the PARP enzyme family which is involved in the DNA damage detection and repair. Inhibitors of PARP have been demonstrated to prolong the antitumor effects of certain anticancer therapies. PARP inhibitors have also been demonstrated to work in preclinical models of reperfusion injury (stroke, myocardial infection), arthritis, inflammations, and diabetes. Furthermore, PARP inhibitors could be used in cancer patients suffering from cancers bearing a specific homologous recombination repair defect (BRCA-1 and BRCA-2 protein deficiency). In this study, pyrrolo[1,2-*a*]-pyrazin-1(2*H*)-one derivatives that could inhibit PARP-1 were developed. Compound **23** (Fig. 27), containing 1,9-diazaspiro[5.5]undecane moiety, had an $IC_{50}$ for PARP-1 and a $CC_{50}$ for BRCA-1 of 6.2 and 220 nM, respectively. The closely related 1,8-diazaspiro[4.5]decane derivative **22** was found to have the best pharmacokinetic values in this study ($IC_{50}$ of 2.5 nM for PARP-1 and $CC_{50}$ of 48 nM for BRCA-1).[70]

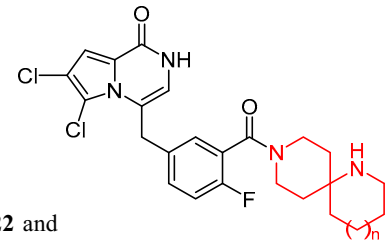
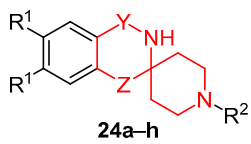



**Figure 27**. Compounds **22** and **23** as PARP-1 inhibitors.

**22** (n = 0), **23** (n = 1)

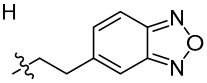
**Class III antiarrhythmic agent**. Arrhythmia can occur as complication to cardiac diseases (e.g., myocardial infarction and heart failure) and includes irregular, too fast or too slow heartbeats and may cause a ventricular fibrillation, which could lead to sudden death.[71] Of all the possible antiarrhythmic agents (classes I–V), the class III agents effect potassium levels and selectively prolong the duration of the action potential without a depression of the maximum velocity of the upstroke of the action potential.[72] As such, class III agents are not considered able to cause a myocardial depression or induce arrhythmia like class I agents would be. In search for class III antiarrhythmic agents, some 3,4-benzene-fused 1,9-diazaspiro[5.5]undecan-5-ones were synthesized (compounds **24a**–**h**; Fig. 28).[73] The study concluded that most of the compounds tested performed better than sotalol in the same protocol ($EC_{25}$ 20 μM).



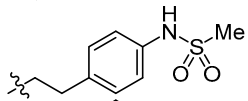

**24a–h**

**a** Y = $CH_2$, Z = CO, $R^1$ = OMe, $R^2$ = H

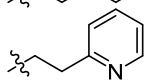
**b** Y = $CH_2$, Z = CO, $R^1$ = OMe, $R^2$ =



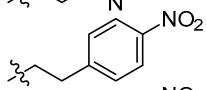

**c** Y = $CH_2$, Z = CO, $R^1$ = OMe, $R^2$ =



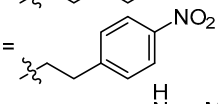

**d** Y = $CH_2$, Z = CO, $R^1$ = OMe, $R^2$ =



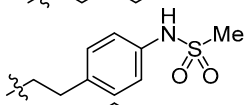

**e** Y = $CH_2$, Z = CO, $R^1$ = OMe, $R^2$ =




**f** Y = $CH_2$, Z = $CH_2$, $R^1$ = OMe, $R^2$ =




**g** Y = CO, Z = $CH_2$, $R^1$ = H, $R^2$ =




**h** Y = CO, Z = $CH_2$, $R^1$ = H, $R^2$ =

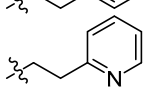
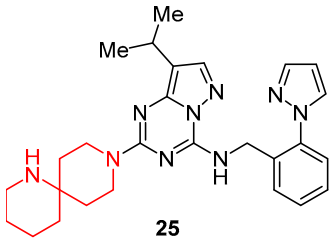



**Figure 28**. Class III antiarrhythmic agents **24a**–**h** featuring an arene-fused spiro core.

**Cyclin-dependent kinase inhibitors**. Cyclin-dependent kinases (CDKs) are involved in cell cycle progression.[74] CDK7 is responsible for activation of other CDKs by means of phosphorylation, making it indispensable for any type of cell cycle progression.[75] In particular, CDK7 is a transcription regulator, since it participates in phosphorylation of the largest subunit of RNA polymerase II at its carboxy terminal domain. As such, inhibition of CDK7 may be used for treatment of cancer, cardiac hypertrophy, and inhibition of virus replication (e.g., HIV, EBV, HCV). A study to find anticancer agents developed multiple pyrazolo[1,5-*a*][1,3,5]triazine derivatives, including one compound containing the 1,9-diazaspiro[5.5]undecane moiety (compound **25**) as a substituent (Fig. 29).[76] The $IC_{50}$ value for CDK7 inhibition of compound **25** was in the range of the lowest values of the library (≤5 nM).

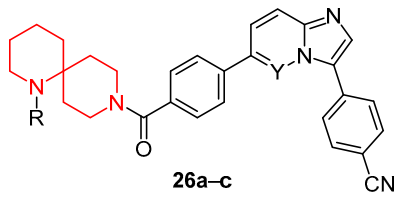



**25**

**Figure 29**. Possible CDK7 inhibitor **25** with the 1,9-diazaspiro-[5.5]undecane as a substituent.

**MNK inhibitors**. Another specific anticancer approach is the inhibition of MAP kinase signal-integrating kinases (MNKs). One of the functions of MNKs (MNK1 and MNK2) is the phosphorylation of eukaryotic initiation factor 4E (eIF4E) at serine 209.[77] Eukaryotic initiation factor 4E is dysregulated in cancers (e.g., leukemia, breast and prostate cancer), and its overexpression can cause neoplastic transformation in cells. It is believed that phosphorylation of eIF4E is necessary for its oncogenic activity. Because this phosphorylation is done by MNKs, developing an antagonist for MNKs may prove useful in the treatment of eIF4E dependent cancers.[78]

Herein the 1,9-diazaspiro[5.5]undecane moiety was used as a substituent attached to a polycyclic aromatic core *via* position 9 (compounds **26a**–**c**; Fig. 30).[78] Compounds **26a**–**c** presented good results in this study inhibiting MNK1 and MNK2 with $IC_{50}$ values of <0.1 μM in all cases.



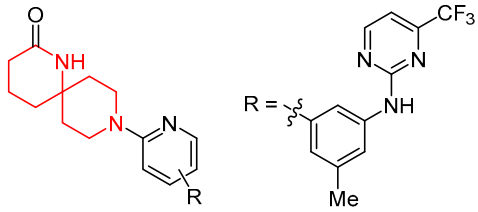

**26a–c**

**a** R = H, Y = N; **b** R = H, Y = CH; **c** R = Ac, Y = CH

**Figure 30**. MNK inhibitors **26a**–**c**.

**Spleen tyrosine kinase inhibitors**. Spleen tyrosine kinase (Syk) is a protein tyrosine kinase, which is an important mediator for immunoreceptor signaling in diverse inflammatory cells (e.g., mast cells, B cells, macrophages, and neutrophils).[79] The immunoreceptors are important for mediating allergic diseases and antibody-mediated autoimmune diseases. For example, Syk has already been shown to be important in B cell differentiation and activation, since Syk deficiency in mice leads to blocking of B cell development, which may result in reduced rheumatoid factor production in patients with rheumatoid arthritis. Furthermore, inhibition of Syk may be useful for treatment or prevention of several inflammatory, allergic, and autoimmune diseases (e.g., cancer, asthma, COPD, ARDS, Crohn's disease, AIDS, psoriasis, multiple sclerosis, bronchitis, dermatitis, ITP, and urticaria).

In a study in which a large number of substituted *N*-phenylpyrimidin-2-amines were tested for Syk inhibition, among the substituents on the core structure was also the 1,9-diazaspiro[5.5]undecan-2-one moiety, attached to the core at position 9 (compounds **27a**,**b**; Fig. 31). Compound **27b** exhibited a better performance than compound **27a** in this study with an $IC_{50}$ < 100 nM (<1000 nM for compound **27a**).[80]

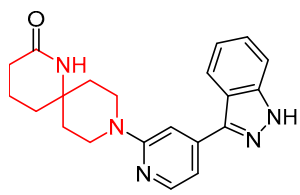



**27 a** (4-R), **b** (5-R)

**Figure 31**. Compounds **27a**,**b** tested as Syk inhibitors.

**Leucine-rich repeat kinase inhibitors**. A number of compounds with a 3-(pyridin-4-yl)-1*H*-indazole core were synthesized and tested for inhibition of leucine-rich repeat kinase 2 (LLRK2).[81] Biochemical *in vitro* studies have shown that mutant LLRK2 harboring proteins associated with Parkinson's disease have increased kinase activity and decreased GTP hydrolysis. This suggests that LLRK2 inhibitors may block aberrant LLRK2-dependent signaling in Parkinson's disease and other neurodegenerative diseases (e.g., Lewy body dementia).[82]

In this study, the $IC_{50}$ values for inhibition of LLRK2 were initially tested. A reasonable $IC_{50}$ value of 14 nM was found for the 1,9-diazaspiro[5.5]undecan-2-one derivative **28** (Fig. 32).[81] The best $IC_{50}$ values were below 0.6 nM.

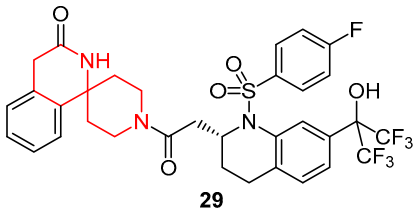



**28**

**Figure 32**. LLRK2 inhibitor **28**.

**RORγ inhibitors**. A large number of multisubstituted arene-fused piperidines were tested for inhibition of retinoid-related orphan receptor gamma 2 (RORγ2).[83,84]

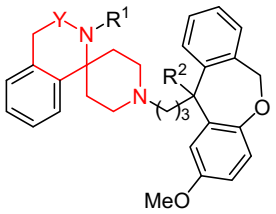
One of the compounds used in this study had a 4,5-benzene-fused 1,9-diazaspiro[5.5]undecan-2-one moiety (compound **29**; Fig. 33). The $IC_{50}$ value for compound **29** was good at 31 nM, whereas the best performing compounds had $IC_{50}$ values of 10 nM.[83]




**29**

**Figure 33**. RORγ inhibitor **29** containing an arene-fused diaza-spiro substituent.

**CC chemokine receptor type 1 inhibitors**. Finally, on the search of CC chemokine receptor type 1 (CCR1) inhibitors, a library of 264 oxepine derivatives was synthesized. Three 4,5-benzene-fused 1,9-diazaspiro[5.5]-undecanes were attached at position 9 *via* a propylene linker to two of the oxepine core structures (compounds **30a**–**f**; Fig. 34).[85]




**30a–f**

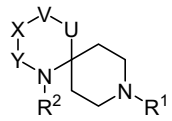
**a** Y = $CH_2$, $R^1$ = H, $R^2$ = H
**b** Y = CO, $R^1$ = H, $R^2$ = H
**c** Y = CO, $R^1$ = Me, $R^2$ = H
**d** Y = $CH_2$, $R^1$ = H, $R^2$ = CN
**e** Y = CO, $R^1$ = H, $R^2$ = CN
**f** Y = CO, $R^1$ = Me, $R^2$ = CN

**Figure 34**. Oxepine core compounds **30a**–**f** with 4,5-benzene-fused 1,9-diazaspiro[5.5]undecane substituents.

This library was developed for treating diseases associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function (e.g., rheumatoid arthritis, atherosclerosis, arteriosclerosis, type 1 diabetes mellitus, Crohn's disease, psoriasis, multiple sclerosis). Inhibition of CCR1 was only determined for selected compounds from the library, excluding those with the diazaspiro substituents.[85]

## 2. SYNTHESIS

The choice of the method of synthesis of the desired 1,9-diazaspiro[5.5]undecanes depends on the position of the arene ring fusion to the spirocyclic core. All encountered examples are summarized in Figure 35: they include 2,3-, 3,4-, and 4,5-arene-fused 1,9-diazaspiro[5.5]undecanes, as well as a few examples of completely saturated core structures. The arene fusion location determines which bond is made last to perform the cyclization to the diazaspiro compound. In all the syntheses of these spiro dipiperidines, a 4-substituted piperidine derivative (most often a piperidin-4-one) was used as a template and the other piperidine ring was constructed at this position 4.




$R^1$ = alkyl, aryl, carbonyl
$R^2$ = H, alkyl, aryl, carbonyl
Y = $CH_2$, CO
U, V, X = $CH_2$
X, Y = arene-fused; U, V = $CH_2$
V, X = arene-fused; U = $CH_2$, $CHCO_2H$
U, V = arene-fused; X = $CH_2$

**Figure 35**. General structure of the synthesized 1,9-diazaspiro-[5.5]undecanes.

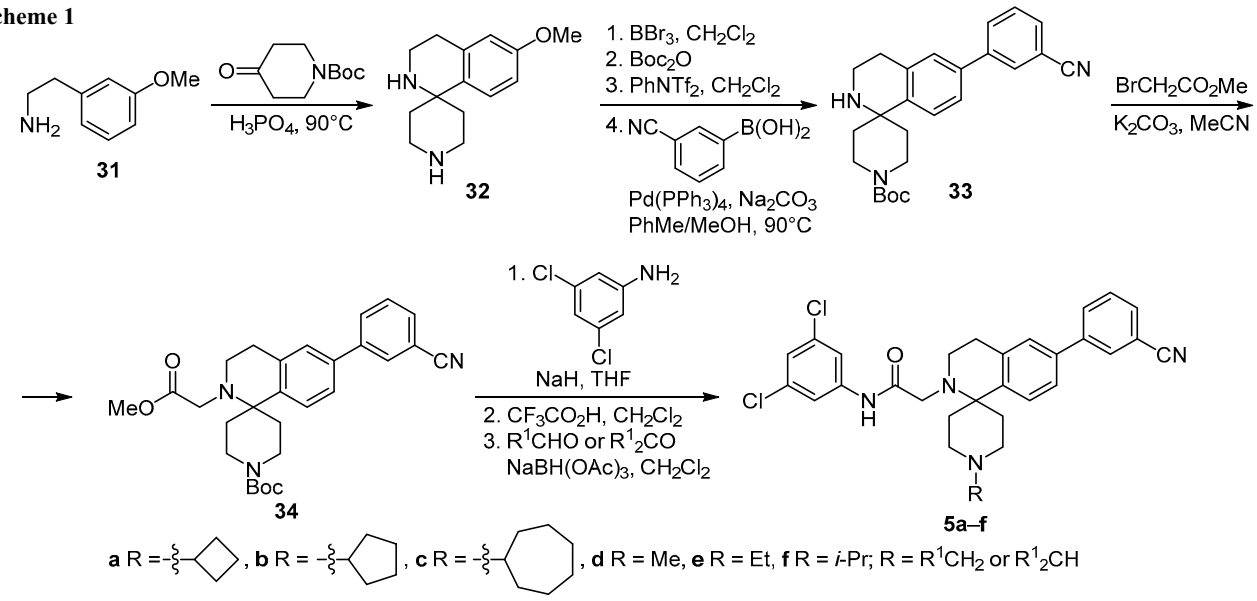
Depending on what arene-fusion pattern was to be realized a different bond between two of the atoms 1–5 could be formed in the final step of the ring closure, with the exception of the bond between carbons 4 and 5. Substitution at position 9 was sometimes included before ring-closure steps, but in most cases a protected piperidin-4-one was used, allowing derivatization after cyclization. Substitution at position 1 was often included before the final ring-closing step. Besides arene fusion, the most important feature is the presence of a carbonyl at position 2, often found in combination with arene fusion. Substitution on carbons 7, 8, 10, or 11 was rarely found, likely also due to the use of piperidine starting materials that did not contain any such substitution beforehand.

### 2.1. 4,5-Arene-fused scaffolds

Arene fusion at positions 4 and 5 of the 1,9-diazaspiro-[5.5]undecane spirocyclic system has been the most common feature in search of compounds with biological activity against several targets. These structures often present a 4,5-benzene fusion and may also contain a carbonyl at position 2. The key transformation for the synthesis of this type of compounds is the one hundred year-old Pictet–Spengler reaction.[86,87] In this reaction, a readily available phenethyl amine derivative (or tryptamine derivative) undergoes intramolecular electrophilic aromatic substitution after condensation with a piperidin-4-one derivative (or synthetic equivalent).

For example, Sasikumar et al. utilized this reaction to synthesize 4,5-benzene-fused 1,9-diazaspiro[5.5]undecanes **5a**–**f** in search of bioactive compounds prepared for MCH-R1 antagonism (Scheme 1).[23] Phenethyl amine **31** and Boc-protected piperidin-4-one underwent the Pictet–Spengler reaction to afford spiroisoquinoline **32**. Compound **32** was then demethylated by the reaction of boron tribromide. Reintroduction of the Boc group (it was undesirably eliminated in the first step), followed by triflation of the phenolic hydroxyl group using $PhNTf_2$ and subsequent Suzuki coupling[88] with 3-cyanophenylboronic acid yielded the biaryl compound **33**. Alkylation of compound **33** at position 1 using methyl 2-bromoacetate afforded acetate **34**. Then, acylation of 3,5-dichloroaniline with ester **34** in the presence of NaH in THF gave the corresponding amide. Elimination of the Boc group was achieved by trifluoroacetic acid to afford the free amine at position 9 of

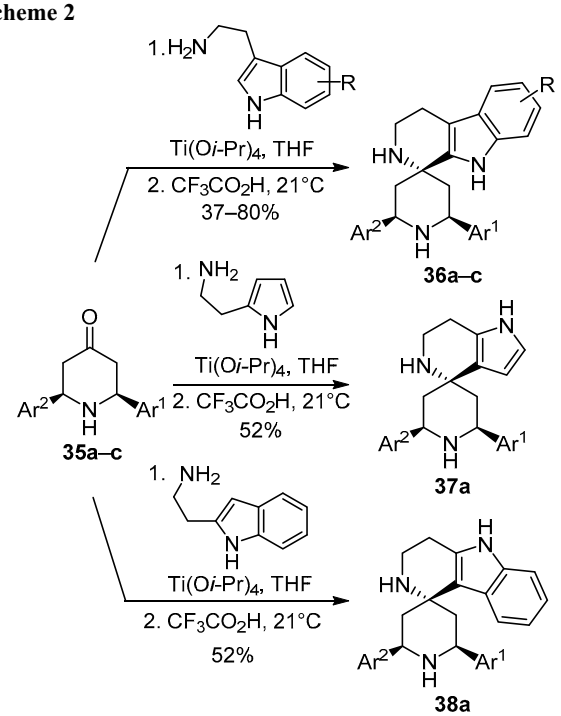
**Scheme 1**




the diazaspiro core, which was used for reductive amination of aldehydes and ketones under standard reaction conditions ($NaBH(OAc)_3$ as reductant) furnished the final compounds **5a**–**f**. This route allowed the synthesis of 4,5-benzene-fused 1,9-diazaspiro[5.5]undecane core with three variation points: in the condensed aryl group and at positions 1 and 9. A library of compounds was synthesized using this methodology to optimize the binding affinity of these antagonists of MCH-R1.

A similar strategy was also employed by Rutjes and coworkers to synthesize a 13-compound library of 4,5-indole-fused 1,9-diazaspiro[5.5]undecanes and an isolated example of 4,5-pyrrole-fused 1,9-diazaspiro[5.5]-undecane (Scheme 2).[89] The starting piperidin-4-ones **35a**–**c** were enantio- and diastereoselectively synthesized by two consecutive Mannich reactions.[90,91] Then, the corresponding imines were preformed with substituted tryptamines (R = H, 5-F, 5-OH, and 6-OMe), 2-(2-indolyl)ethanamine, or 2-(2-pyrrolyl)ethanamine using Ti(O*i*-Pr)$_4$ in THF at 21°C. Finally, the Pictet–Spengler reactions were carried out by addition of trifluoroacetic acid to diastereoselectively afford a 13-compound library of 4,5-indole-fused 1,9-diazaspiro[5.5]undecanes **36a**–**c** and **38a** (the indole fusion presents a different orientation in the latter case) and a 4,5-pyrrole-fused 1,9-diazaspiro[5.5]undecane (**37a**) in yields from 37 to 80% after two steps.

**Scheme 2**

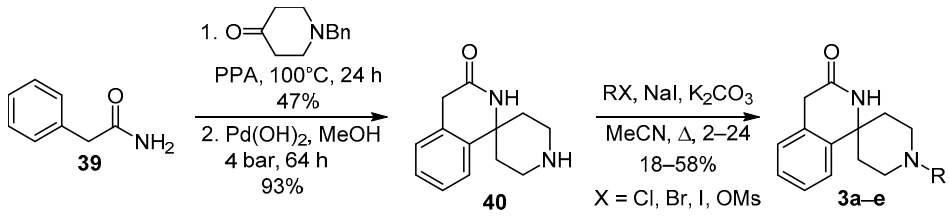



$Ar^1$ = 3,4-$(MeO)_2C_6H_3$;
**a** $Ar^2$ = 4-$FC_6H_4$, **b** $Ar^2$ = 4-$(CF_3)C_6H_4$, **c** $Ar^2$ = 4-$(SF_5)C_6H_4$,
R = H, 5-F, 5-OH, 6-OMe

The Pictet–Spengler reaction can also be employed to synthesize 1,9-diazaspiro[5.5]undecan-2-ones by using the corresponding amide derivative of a phenethyl amine. If an amide instead of an amine was used, elevated temperatures (80–120°C) in combination with polyphosphoric acid were employed.[11,30] This method was utilized by Poindexter and coworkers for the synthesis of NPY antagonists **3a**–**e** (Scheme 3).[11] Thus, phenylacetamide **39** was reacted with 1-benzylpiperidin-4-one and polyphosphoric acid at 100°C for 24 h to obtain the corresponding benzylated 4,5-benzene-fused 1,9-diazaspiro[5.5]undecane in 47% yield, which afforded the target scaffold **40** upon debenzylation under standard conditions in 93% yield. Compound **40** was alkylated with several alkylating agents to yield the final compounds **3a**–**e** in variable yields (18–58%).

Instead of a piperidin-4-one derivative for the Pictet–Spengler reaction, an acetal-protected piperidin-4-one in a form of dioxane or dioxolane may also be used as reactant.[14] Further substitution at position 9 of 4,5-benzene-fused 1,9-diazaspiro[5.5]undecanes is usually introduced by reactions with many different reagents (e.g., alkyl chlorides or triflates, carboxylic acids, acyl chlorides,

**Scheme 3**




**a** R = $C_9H_{19}$, **b** R = $C_{10}H_{21}$, **c** R = $CH_2CH{=}CH_2$, **d** R = $CH_2CH(OMe)_2$, **e** R = $(CH_2)_4N(CH_2Ph)_2$

esters, anhydrides, aldehydes, ketones, terminal alkenes, oxiranes, and aziridines),[23,30,44] as exemplified in Schemes 1, 3, 4, and 8.

### 2.2. 3,4-Arene-fused scaffolds

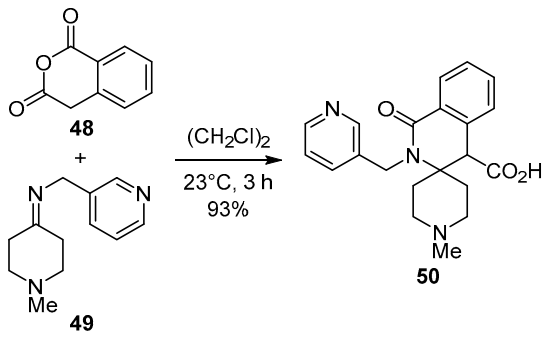
The use of 3,4-arene-fused 1,9-diazaspiro[5.5]undecanes has been less frequent than that of its 4,5-arene-fused counterparts. New synthetic pathways have been developed to make the 1,9-diazaspiro derivatives with this type of arene fusion.

In a procedure developed by Menhaji-Klotz et al. to access ACC inhibitors with a 3,4-pyrazole-fused spirocyclic moiety a pyrazole derivative was coupled to ethyl piperidine-4-carboxylate, after which a ring closing yielded the desired 3,4-pyrazole-fused diazaspiro core (Scheme 4).[4,5] The necessary iodomethyl pyrazole **43** was obtained in five steps from pyrazole **41** through compound **42**, using the Sandmeyer reaction as the key step for the transformation $NH_2 \rightarrow Br$.[92] Deprotonation of piperidine **44** using LiHMDS and subsequent alkylation with iodide **43** afforded carboxylic acid **45**, after hydrolysis of the corresponding ester under standard conditions (63% yield after four steps). Carboxylic acid **45** was then converted into an acyl azide by using diphenylphosphoryl azide, which underwent a Curtius rearrangement[93] to give isocyanate **46** after 2 h at 85°C in toluene in 91% yield. Because of safety concerns with the Curtius reaction on large scale, transformation of compound **45** into compound **46** was optimized in flow. The ring closing reaction to give diazaspiro compound **47** was performed at –42°C using *s*-BuLi or *t*-BuLi in quantitative yield. Further derivatization to synthesize the final ACC inhibitors **1** was performed by Boc deprotection using HCl/dioxane and subsequent amide formation with the corresponding carboxylic acids, propylphosphonic anhydride (T3P), and trimethylamine at room temperature. A similar approach was used to make compound **2** which also showed good ACC inhibition.[5] Another procedure featured a similar synthesis for more ACC inhibitors including different *N*-pyrazole substitutions, as well as bridging structures (e.g., 8,10-ethano bridge).[4]

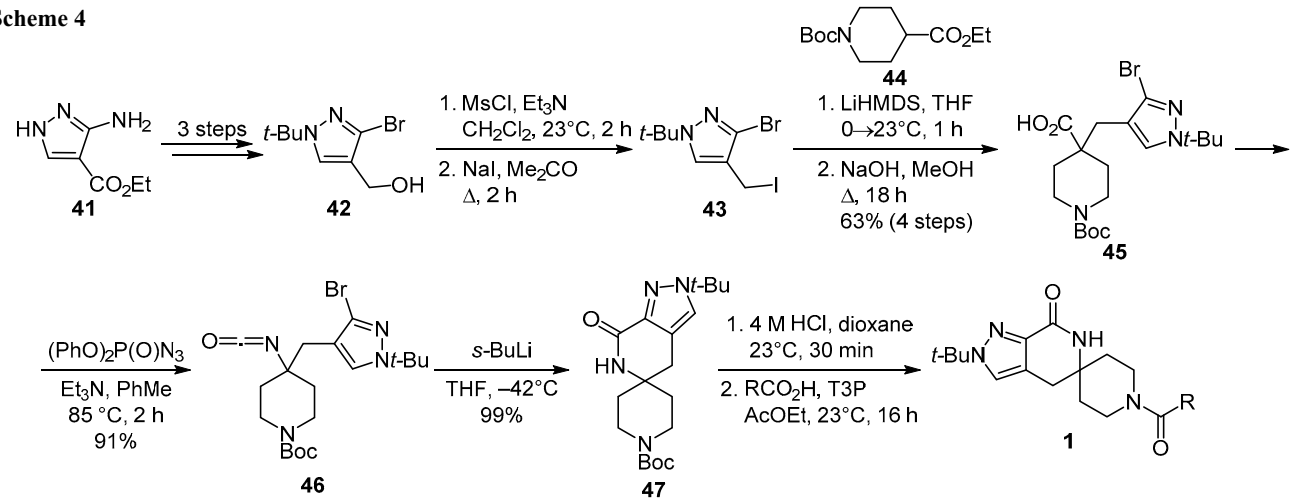
A different method for the preparation of 3,4-benzene-fused 1,9-diazaspiro[5.5]undecanes was developed by Stoyanova et al. This method was used as a one-step procedure with an imine as starting material (instead of a derivative of piperidin-4-one; Scheme 5).[94] Anhydride **48** and ketimine **49** were stirred in 1,2-dichloroethane at room temperature to form diazaspiro compound **50** in excellent yield after filtration and washing with dichloromethane. Acid **50** was further transformed into five different amides, but no application for these compounds was pursued.

Another short synthesis of these 3,4-benzene- and, as the only example in the literature, 3,4-thiophene-fused deriva-

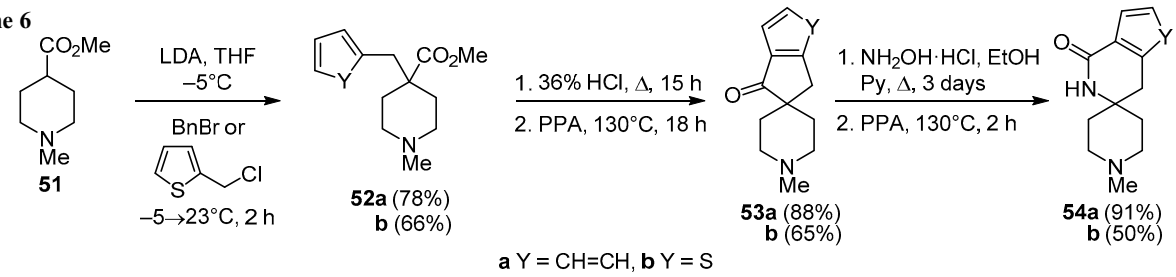
**Scheme 5**



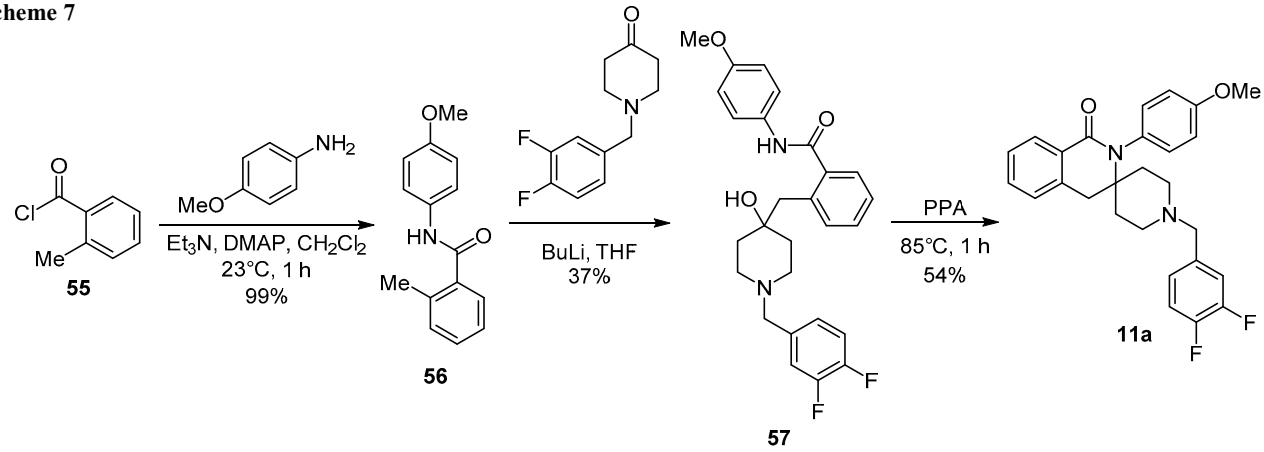

**Scheme 4**



**Scheme 6**




**Scheme 7**



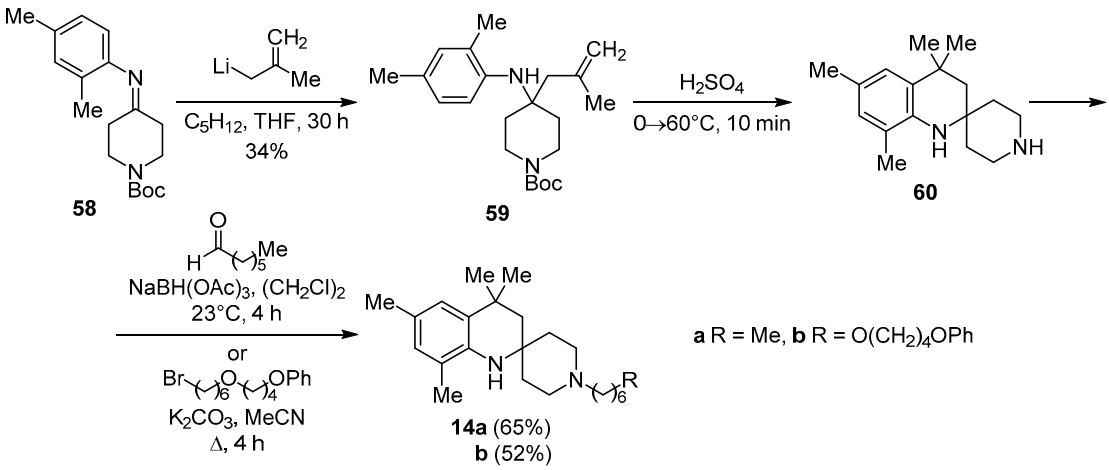

tives was reported by Stanetty and coworkers in which methyl 1-methylpiperidine-4-carboxylate (**51**) was used as starting material (Scheme 6).[95] Piperidine **51** was alkylated with benzyl bromide and (2-thienyl)methyl chloride after deprotonation with lithium diisopropylamide (LDA) to obtain compounds **52a** and **52b**, respectively, in good yields. Hydrolysis of esters **52a**,**b** to the corresponding carboxylic acids was performed by refluxing with concentrated hydrochloric acid. Then, a Friedel–Crafts reaction[96] using polyphosphoric acid yielded the corresponding cyclic ketones **53a**,**b**. These ketones were transformed into oximes by treatment with hydroxyl amine hydrochloride and pyridine in ethanol. The oximes underwent a Beckmann rearrangement[97] upon treatment with polyphosphoric acid to afford the final products **54a** and **54b** in 91 and 50% yield, respectively.

Another synthesis of 3,4-benzene-fused 1,9-diazaspiro-[5.5]undecanes was developed by Brugger et al. and used the strategy of transforming the piperidin-4-one carbonyl carbon into spiro carbon atom (Scheme 7).[50] The synthesis of the mGluR4 modulator **11a** commenced with the synthesis of amide **56** by the reaction of *p*-anisidine and aroyl chloride **55** in quantitative yield. The treatment of amide **56** with 2 equiv of BuLi generated a dianion that was selectively hydroxyalkylated at the methyl group with 1-(3,4-difluorobenzyl)piperidin-4-one to afford hydroxy amide **57** in poor yield (37%). Finally, this amide underwent cyclization *via* an $S_N1$ mechanism to diazaspiro **11a** by reaction with polyphosphoric acid in a fair yield.

### 2.3. 2,3-Arene-fused scaffolds

The most rare fusion pattern among the arene-fused diazaspiro compounds is the arene-fusion at positions 2 and 3. A method to synthesize such arene-fused 1,9-diazaspiro-[5.5]undecanes was presented by Brown and coworkers (Scheme 8).[57]

**Scheme 8**

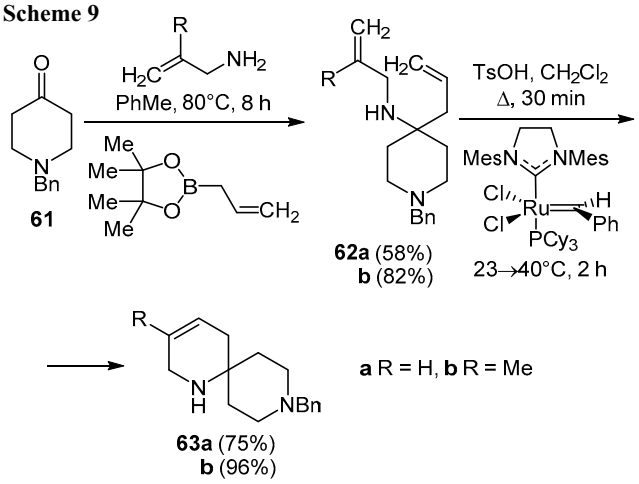


One of the examples presented in this study was the synthesis of imine **58** by condensation of Boc-protected piperidin-4-one with 2,4-dimethylaniline. Imine **58** was used in the next step without further purification. Nucleophilic addition of isobutenyllithium (Grignard reagents have also been used for this reaction)[98] to imine **58** yielded piperidine **59** in poor yield, which upon treatment with sulfuric acid underwent cyclization by a Friedel–Crafts alkylation to give the 2,3-benzene-fused 1,9-diazaspiro[5.5]-undecane **60**. Additionally, sulfuric acid removed the Boc group, leaving position 9 available for further derivatization. For example, compound **60** was further transformed into compounds **14a**,**b** on the quest for α-tocopherol analogs under standard reductive amination and alkylation conditions.[57]

### 2.4. Aliphatic scaffolds

The number of biologically active 1,9-diazaspiro[5.5]-undecanes without arene fusion throughout the literature is significantly lower than their arene-fused counterparts. Although the absence of arene fusion is less common when the 1,9-diazaspiro[5.5]undecanes were used as core structures of the respective studies, they were encountered more often when they were used as substituents of other main structures. Gracias et al. developed a method to make a 1,8-diazaspiro[5.5]undecane with a Petasis reaction. An adaptation of this method was used to synthesize 1,9-diazaspiro[5.5]undecanes (Scheme 9).[99]

**Scheme 9**

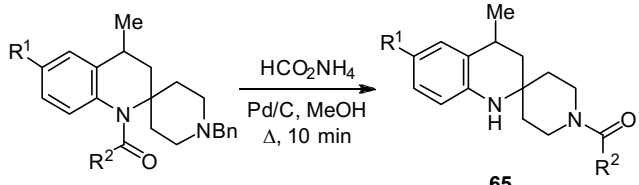



The Petasis reaction is a multicomponent reaction in which a carbonyl, an amine, and a boronic acid (or boronate) react to form substituted amines.[100] In this particular case, the condensation of allyl amines with piperidinone **61** resulted in imine intermediates which were then attacked by the allyl group of pinacol allylboronate to form secondary amines **62a**,**b** in good to very good yields. A different method to synthesize the same kind of amines consisted of a similar reaction of a piperidone derivative with allylamine followed by addition of allyl magnesium bromide to perform a regular Grignard addition in a one-pot procedure.[101] Then, the resulting secondary amines **62a**,**b** were protected as their ammonium salts with *p*-toluenesulfonic acid and converted to spiro dipiperidines **63a**,**b** by ring closing metathesis catalyzed by Grubbs catalyst (5 mol %; second generation) in high yields. In the absence of the pretreatment with acid the reaction failed to undergo ring closure.[99]

### 2.5. 1→9 Acyl group shift

The study presented in this section does not describe a formation of the 1,9-diazaspiro[5.5]undecane core, but shows a rearrangement that 2,3-benzene-fused 1,9-diazaspiro[5.5]undecanes can undergo. A study performed by Vargas et al. described an acyl shift from nitrogen 1 to nitrogen 9 in some 2,3-benzene-fused 1,9-diazaspiro[5.5]-undecanes **64** (Scheme 10).[102] This acyl group rearrangement may reduce the protection–deprotection steps needed to achieve the final acyl derivatives.

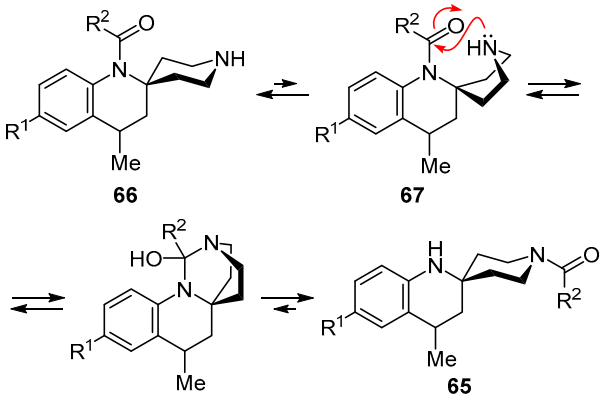
**Scheme 10**




**a**–**c** $R^1$ = H, **d**–**h** $R^1$ = Me; **a**,**d** $R^2$ = H, **b**,**e** $R^2$ = Me, **c**,**f** $R^2$ = Ph, **g** $R^2$ = $CH_2Cl$, **h** $R^2$ = 4-$NO_2C_6H_4$

Compounds **65a**–**h** were synthesized with very short reaction times in yields averaging >84%. A clear advantage of this approach is that deprotection at position 9 and subsequent acylation could be combined. The cited study presented a rationale for the 1→9 acyl shift (Scheme 11).[102] Once position 9 of compounds **64** was debenzylated by hydrogenolysis, the resulting free secondary amine **66** could react with the amide at position 1 through a boat conformation **67**. The equilibrium between the two amides was shifted to compound **65** because the leaving group was an aniline instead of an amine. Proof of the intramolecular nature of this reaction was provided by performing the reaction in the presence of piperidine or morpholine, with no observation of acylated products of these external amines.

**Scheme 11**



The present review has provided a comprehensive overview of the biological activity and synthesis of the 1,9-diazaspiro[5.5]undecanes. The different forms of the 1,9-diazaspiro[5.5]undecane core (1,2-, 2,3-, 3,4-, and 4,5-(hetero)arene-fused and the saturated core structures) have been investigated in a broad range of medicinal applications. As a result, an impressive number of research publications and patents have been published in this field. The vast array of biological properties displayed by this family of compounds opens a door for the development of new therapeutics for a variety of diseases. The synthetic strategies toward these scaffolds are determined by their substitution pattern. It is worth mentioning that most of the synthetic methods start with a 4-substituted piperidine moiety and construct the second piperidine ring from this substitution at position 4. Variable cyclization methods are used for the generation of this spiro linkage, the Pictet–Spengler reaction being the method of choice for the 4,5-arene-fused scaffolds, the most common among these compounds.

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