Article 25fa pilot End User Agreement

This publication is distributed under the terms of Article 25fa of the Dutch Copyright Act (Auteurswet) with explicit consent by the author. Dutch law entitles the maker of a short scientific work funded either wholly or partially by Dutch public funds to make that work publicly available for no consideration following a reasonable period of time after the work was first published, provided that clear reference is made to the source of the first publication of the work.

This publication is distributed under The Association of Universities in the Netherlands (VSNU) ‘Article 25fa implementation’ pilot project. In this pilot research outputs of researchers employed by Dutch Universities that comply with the legal requirements of Article 25fa of the Dutch Copyright Act are distributed online and free of cost or other barriers in institutional repositories. Research outputs are distributed six months after their first online publication in the original published version and with proper attribution to the source of the original publication.

You are permitted to download and use the publication for personal purposes. All rights remain with the author(s) and/or copyrights owner(s) of this work. Any use of the publication other than authorised under this licence or copyright law is prohibited.

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please contact the Library through email: copyright@ubn.ru.nl, or send a letter to:

University Library Radboud University
Copyright Information Point PO Box 9100 6500 HA Nijmegen
You will be contacted as soon as possible.
Privileged heterocycles: bioactivity and synthesis of 1,9-diazaspiro[5.5]undecane-containing compounds

Daniel Blanco-Ania1*, Rik Heus1#, Floris P. J. T. Rutjes1

1 Radboud University, Institute for Molecules and Materials, Heyendaalseweg 135, 6526 AJ Nijmegen, the Netherlands; e-mail: d.blanco@science.ru.nl

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2017, 53(8), 827–845

Submitted March 22, 2017
Accepted after revision August 24, 2017

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 diazaspiron 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 diazaspiron compounds are used as substituents on other heterocycles they are almost always attached through position 9.

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 pathological 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\textsubscript{50}, EC\textsubscript{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. Obesity was the
The 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 show3 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
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. Additionally, ACC inhibitors may be used to treat type 2 diabetes mellitus. ACC inhibition is expected to impact both skeletal muscle and hepatic insulin sensitivity by rebalancing lipid metabolism associated with insulin resistance pathogenesis. Menhagi-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. IC50 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 containing a pyrazole ring fused to positions 3 and 4 in two different ways to achieve this ACC inhibition. Further studies were performed by using isoquinolines and quinolines as replacements for the 1,9-diazaspiro[5.5]undecane core used in the earlier SAR studies. 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 (×106 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 thermodi-
amic solubility at pH 1.2 with a factor up to 10 when
compared to compounds 1j,k. The Papp values of com-
ounds 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 com-
ounds 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. Com-
pounds 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_{\text{max}} 403 \text{ ng/ml}, AUC 2070 \text{ ng·h/l} when administered to rats
at 5 mg/kg. An intravenous dose of 1 mg/kg in rats dem-
onstrated a moderate systemic clearance of 29 \text{ ml/(min·kg)}
and volume of distribution of 1.7 l/kg. Similarly, com-
pound 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 combi-
nation with \(^{14}\text{C}\)-labeled acetate precursors of lipids. The con-
version 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 inhibi-
tors 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 \(\text{de novo}\) fatty acid
synthesis, which is greatly dependent on ACC.\(^10\) Treatment
of humans with an ACC inhibitor may reduce sebum tri-
glyceride content by 66%.\(^11\) 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).\(^11\)

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.\(^12\) Further-
more, NPY is expressed in the spinal cord and most sympa-
thetic nerve fibers, especially around blood vessels. Anta-
gonism of the NPY receptors (NPY Y 1–Y 5) has been
related to reduced food-intake in mammals,\(^13\) making NDY
agonists drug candidates for the treatment of obesity.
Various studies with mice have shown that especially the
NPY Y1 and NPY Y5 are important targets for treating
obesity.\(^14\) The treatment of obesity by NPY Y5 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 Y5
agonists inhibited the reduction of the metabolic rate.
This indicated that NPY Y5 antagonists could be used to
prevent decrease in energy expenditure due to dieting or
other anti-obesity treatments.\(^5\) It was also shown that the
combination of food restriction and administration of an
NPY Y5 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 Y5 antagonist and

Figure 5. Conversion percentage of \(^{14}\text{C}\)-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.

Figure 6. Compounds 3a–n tested for NPY antagonism.
an anti-obesity drug would be effective in treating humans.\textsuperscript{2} Furthermore NPY Y\textsubscript{5} antagonism was demonstrated by compounds containing the 1,9-diazaspiro[5.5]undecane structural moiety.\textsuperscript{7} Characterization of the bioactivity was performed by employing insect cells (BRI-TN-5BI-4) infected with NPY Y\textsubscript{5}-recombinant Baculovirus. The radioligand used was iodine-125 labeled PYY ligand. Herein the IC\textsubscript{50} values of compounds 3a–n were less than 10 \textmu M, with compounds having an IC\textsubscript{50} of less than 500 nM or less than 100 nM.\textsuperscript{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 11\beta-hydroxysteroid dehydrogenase type 1.**

Inhibition of 11\beta-hydroxysteroid dehydrogenase type 1 (11\beta-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 11\beta-HSD1 inhibitory activity (IC\textsubscript{50} < 100 nM).\textsuperscript{14}

\[
\text{IC}_{50} \text{ of compound } 5b \text{ showed an AUC of 332 ng h/ml in rats.}^\text{21}
\]

\[
\text{Figure 7. 11\beta-HSD1 inhibitors 4a–d.}
\]

11\beta-Hydroxysteroid dehydrogenase pre-receptor control enzymes that modulate activation of the glucocorticoid receptor and the mineralocorticoid receptor via regulation of glucocorticoid hormones.\textsuperscript{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 11\beta-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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{23} MCH also increases the release of NPY, a contributor to feeding behavior as mentioned earlier.\textsuperscript{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.\textsuperscript{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.\textsuperscript{21}

\[
\text{Figure 8. MCH antagonists 5a–c.}
\]

**1.2. Treatment of central nervous system disorders**

**Orexin antagonism.** The family of diazaspiro[5.5]-undecanes, including the 1,9-diazaspiroindane core, 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\textsuperscript{24} (e.g., narcolepsy and insomnia) and are also considered vital in regulating feeding, metabolism, and energy homeostasis.\textsuperscript{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.\textsuperscript{26}
In the treatment of sleep disorders, antagonists for both orexin receptors (OX1R and OX2R) 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 OX1R and OX2R, as well as a selective OX2R 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](image)

**Figure 9.** 1,9-Diazaspiro[5.5]undecan-2-ones 6a–f tested for dual OX1R/OX2R antagonism and selective OX2R 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 OX1R and OX2R. 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 OX1R and OX2R, 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 OX2R inhibition was maintained in a high range, whereas OX1R values greatly varied, leading to more selective OX1R antagonists like compound 6e. For compound 6d, an excellent subnanomolar $K_i$ was obtained for OX1R ($pK_i$ 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 $\text{c}_{\text{max}}$ (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.29 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 $\mu$ 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 $\mu$ 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 $\mu$ receptors, were determined for compounds 7a–d in a study developed by Virgili-Bernardo et al.31 (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](image)

**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. Although the compounds developed with the 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. 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 antimigraine agents, potentiators such as caffeine, anti-emics, ergot alkaloids, beta-adrenergic antagonists, interleukin and gap junction inhibitors.

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 (Fig. 11). IC50 and EC50 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 IC50 and EC50 values of 5 and 3 nM, respectively.

![Figure 11. CGRP inhibitors 8a,b.](image)

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. 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.

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 IC50 value of 31 nM for binding NK1.

![Figure 12. NK1 antagonist with an excellent IC50 value.](image)

Additionally, having a carbonyl at position 2 of the benzene-fused diazaspiro core increased the IC50 value to 54 nM for compound 9b. Methylation of compounds 9a,b yielded salts 9c,d with IC50 values of 2.0 and 1.9 nM, respectively. Animal testing on substance P-induced bronchoconstriction in guinea pigs showed ID50 values of 24 and 19 μg/kg for compound 9d and SR140333, respectively. 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. The administration of NK2 antagonists can be effective in treatment of such diseases.

Development of dual NK1/NK2 antagonists was also explored. 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. Herein it was found that fumarate YM-44778 exhibited high binding affinities of
pKᵣ 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 pKᵣ 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-44781 and YM-44781 (IC₅₀ 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. Some gonstic for treating an inflammatory disease produced a gonist. and that YM-44778 was a nonselective NK1/NK2 anta-

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. The biological assay was performed by means of a cAMP assay using HEK-293 mGluR4 cells with EC₂₀ L-glutamate (2.3 and 4.3 μM for mGluR4 and mGluR6, respectively). EC₅₀ values were determined and found to be between 1 and 10 μM for both compounds 11a,b. Several 1,5,9-triazaspiro[5.5]undecanes showed better EC₅₀ values at below 1 μM concentrations.

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

![Figure 14](image_url)

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

![Figure 15](image_url)

**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.

Inhibition of chemokine receptors CXCR3. Chemokines are chemotactic cytokines that are involved in immune system cell signaling. Chemokines are bond 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. 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 interferences 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 (Fig. 17). Compound 12b presented better results with an IC₅₀ value of 1.1 μM.

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

![Figure 16](image_url)

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

![Figure 17](image_url)
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, and 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).\(^{56}\) Compound 13 specifically inhibited CYP11B2 and could therefore be used to treat states related to aldosterone.

![Figure 18. Compound 13 tested for inhibition of aldosterone synthase.](image)

*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.

![Figure 19. Compounds 14a,b studied as α-tocopherol analogs.](image)

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).\(^{59}\)

![Figure 20. Compounds 15a–d studied as inhibitors of PDE10.](image)

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

**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

**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 Ki 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-adrenergic agonist, leukotriene modifier, antihistamine, decongestant, antitussive, and nonsteroidal anti-inflammatory drug. The substituted quinoxalines were developed as CRTH2 inhibitors and can be used for treatment of symptoms and diseases associated with uncontrolled CRTH2 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, lipodosis, 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 IC50 value of 49.0 nM. The lowest and highest values among the 173 compounds of the study were 1.56 and 2000 nM, respectively.

**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 H1 receptor (H1-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 H1-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 (Ki) values for antagonists and inverse agonists and as EC50 values for partial agonists. All the compounds tested blocked the ability of histamine to increase Ca2+ concentrations in cells and had Ki 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

**Figure 24.** Possible histamine H1 receptor antagonist 19.
Another research looked into developing the histamine H3 receptor (H3-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).69 Because of this, it has been suggested that H3-R antagonists or inverse agonists could be used to treat disorders related to the central nervous system. In animals, antagonism of H3-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 IC50 value of 783 nM for human H3, which was around a 1000-fold higher than the best antagonist found in the study.

**Figure 25.** Compound 20 studied for H3-R antagonism.

**Cannabinoïd receptor type 2 agonists.** The cannabinoïd 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 developing cannabinoid receptor type 2 (CB2) agonists for CB2 receptor binding, some 3,4-benzene-fused 1,9-diazaspiro[5.5]undecan-5-ones were developed. Compound 23 (Fig. 27), containing 1,9-diazaspiro[5.5]undecan-2-one, was found to have the best pharmacokinetic values in this study (IC50 of 2.5 nM for PARP-1 and CC50 of 48 nM for BRCA-1).70

![Figure 27](image)

**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 (EC50 20 μM).

![Figure 28](image)

**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. CDK7 is responsible for activation of other CDKs by means of phosphorylation, making it indispensable for any type of cell cycle progression. 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). The IC\textsubscript{50} value for CDK7 inhibition of compound 25 was in the range of the lowest values of the library (≤5 nM).

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. Eukaryotic initiation factor 4E 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.

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). Compounds 26a–c presented good results in this study inhibiting MNK1 and MNK2 with IC\textsubscript{50} values of <0.1 μM in all cases.

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). 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 27a exhibited a better performance than compound 27a in this study with an IC\textsubscript{50} < 100 nM (<1000 nM for compound 27a).

Leucine-rich repeat kinase inhibitors. A number of compounds with a 3-(pyridin-4-yl)-1H-indazole core were synthesized and tested for inhibition of leucine-rich repeat kinase 2 (LLRK2). 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).

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

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

**Figure 33.** ROR\text{γ} inhibitor 29 containing an arene-fused diazaspicio 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).\(^{85}\)

**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 diazaspicio 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-\text{a}, 3,4-\text{b}, 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 diazaspicio 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.

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).\(^{22}\) Phenethyl amine 31 and Boc-protected piperidin-4-one underwent the Pictet–Spengler reaction to afford spiroisouquinoline 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 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
the diazaspiron 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). The starting piperidin-4-ones 35a–c were enantio- and diastereoselectively synthesized by two consecutive Mannich reactions. 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(Oi-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.

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. This method was utilized by Poindexter and coworkers for the synthesis of NPY antagonists 3a–e (Scheme 3). 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. 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,
esters, anhydrides, aldehydes, ketones, terminal alkenes, oxiranes, and aziridines, 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 aren cycle 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 diaziaspiro core (Scheme 4). 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 NH₂ → Br. 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 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 diaziaspiro 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. 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). 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 amine as starting material (instead of a derivative of piperidin-4-one; Scheme 5). Anhydride 48 and ketimine 49 were stirred in 1,2-dichloroethane at room temperature to form diaziaspiro 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-
tatives was reported by Stanetty and coworkers in which methyl 1-methylpiperidine-4-carboxylate (51) was used as starting material (Scheme 6). 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 reaction96 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 aryl 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 hydroxyamide 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
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) resulted in imine intermediates which were then attacked by allylamines followed by addition of allyl magnesium bromide to perform a regular Grignard addition in a one-pot procedure. Then, the resulting secondary amines 62a,b were protected as their ammonium salts with p-toluene-sulfonic 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.

### 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

\[
\begin{align*}
\text{64} & \xrightarrow{HCO_{2}NH_{2}, Pd/C, MeOH, \Delta, 10 \text{ min}} \text{65} \\
\text{a-c R}_1^1 = H, \text{d-h R}_1^1 = \text{Me; a, d R}_2^2 = H, \text{b, e R}_2^2 = \text{Me; c, f R}_2^2 = \text{Ph; g R}_2^2 = \text{CH}_2\text{Cl, h R}_2^2 = 4-\text{NO}_2\text{C}_6\text{H}_4}
\end{align*}
\]

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 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 pinoal aldehydeboronate 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.\(^{109}\) Then, the resulting secondary amines 62a,b 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.
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 compound 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 strategies 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.

References

1. World Health Organization. http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed July 10, 2017).
2. Macneil, D. J.; McIntyre, J. H.; Van der Ploeg, L. H. T.; Ishihara, A.; World Health Organization. http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed July 10, 2017).
3. World Health Statistics 2015; Part II: Global Health Indicators. World Health Organization, p. 101. http://www.who.int/gho/publications/world_health_statistics/EN_WHS2015_Part2.pdf?ua=1 (accessed July 10, 2017).
4. Griffith, D. A.; Dow, R. L.; Bagley, S. W.; Smith, A. US Patent 20120108619.
5. Huard, K.; Bagley, S. W.; Menhaji-Klotz, E.; Prévost, C.; Southers, J. A.; Smith, A. C.; Edwards, D. J.; Huard, K.; Allanson, N. M.; Blaney, E. L.; Garcia-Irizarry, C. N.; Kohrt, J. T.; Griffith, D. A.; Dow, R. L. J. Org. Chem. 2012, 77, 10050.
6. Griffith, D. A.; Dow, R. L.; Huard, K.; Edmonds, D. J.; Bagley, S. W.; Polivkova, J.; Geng, D.; Garcia-Irizarry, C. N.; Southers, J. A.; Esler, W.; Arom, P.; Loomis, K.; McPherson, K.; Bahnick, K. B.; Prévost, C.; Banks, T.; Moore, D. E.; Mathiowetz, A. M.; Menhaji-Klotz, E.; Smith, A. C.; Doran, S. D.; Beebe, D. A.; Dunn, M. F. J. Med. Chem. 2013, 56, 7110.
7. Esler, W. P.; Sonnenberg, G. E. W. O Patent 2015 036892.
8. Well, D. Nurse Pract. 2013, 38 (10), 22.
9. Janicek-Dolphin, N.; Cook, J.; Thiboutot, D.; Harness, J.; Lucas, A. Br. J. Dermatol. 2010, 163, 683.
10. Downie, M. M.; Kealey, T. J. Invest. Dermatol. 1998, 111, 199.
11. Poindexter, G. S.; Antal, I.; Giupponi, L.; Stoffel, R. H.; Bruce, M. A. US Patent 6348472.
12. Yulyaningsih, E.; Zhang, L.; Herzog, H.; Sainsbury, A. Bioorg. Med. Chem. Lett. 2011, 163, 1170.
13. Takahashi, T.; Haga, Y.; Sakamoto, T.; Moriya, M.; Okamoto, O.; Nonoshita, K.; Shibata, T.; Suga, T.; Takahashi, H.; Hirohashi, T.; Sakuraba, A.; Ishii, Y.; Ishihara, A.; Ichikawa, A.; Iwasa, H.; Ohe, T.; Ishihara, A.; Ishii, Y.; Kanatani, A.; Hakami, T. Bioorg. Med. Chem. Lett. 2009, 19, 3511.
14. Claremon, D. A.; Tice, C. M.; Ye, Y.; Singh, S. B.; He, W.; Zhao, W.; Simpson, R. D. W. O Patent 2009 108332.
15. Wake, D. J.; Walker, B. R. Mol. Cell. Endocrinol. 2004, 215, 45.
16. Morton, N. M.; Seckl, J. R. In Obesity and Metabolism; Corbonitis, M., Ed.; Karger: Basel, 2008, p. 146.
17. Gathercole, L. R.; Lavery, G. G.; Morgan, S. A.; Cooper, M. S.; Sinclair, A. J.; Tomlinson, J. W.; Stewart, P. M. Endocr. Rev. 2013, 34, 525.
18. Burnett, D. A.; Wu, W.-L.; Rasika, T. K.; Domalski, M. S. US Patent 2004024002.
19. Rivera, G.; Bocanegra-Garcia, V.; Galiano, S.; Cirauqui, N.; Ceras, J.; Perez, S.; Aldana, I.; Monge, A. Curr. Med. Chem. 2008, 15, 1025.
20. Chen, X.; Dai, K.; Fan, P.; Fu, Y.; Li, L.; Mihalic, J. T. W. O Patent 20040258459.
21. Luthin, D. R. Life Sci. 2007, 81, 423.
22. MacNeil, D. J.; Bednarek, M. A. Peptides 2009, 30, 2008.
23. Rasika, T. K.; Qian, L.; Wu, W.-L.; Burnett, D. A.; Greenlee, W. J.; Onneil, K.; Haines, B. E.; van Heek, M.; Graziano, M. Bioorg. Med. Chem. Lett. 2006, 16, 4917.
24. Roecker, A. J.; Cox, C. D.; Coleman, P. J. Med. Chem. 2016, 59, 504.
25. Stein, M. A., Sciarretta, C.; Pasquali, A.; Jenck, F. Front. Pharmacol. 2013, 4, 165.
26. Badger, S.; Benkhe, D.; Betschart, C.; Chaudhari, V.; Cote, A.; Himrichs, J. H.-H.; Ofner, S.; Pandit, C. W. O Patent 2011067747.
27. Betschart, C.; Hintermann, S.; Behneke, D.; Cotes, A.; Fendt, M.; Gee, C. E.; Jacobson, L. H.; Laue, G.; Ofner, S.; Chaudhari, V.; Badger, S.; Pandit, C.; Wagner, J.; Hoyer, D. J. Med. Chem. 2013, 56, 7590.
28. Goldberg, D. S.; McGee, S. J. BMC Public Health 2011, 11, 770.
29. Opioids and Pain Relief: A Historical Perspective. Progress in Pain Research and Management; Meldrum, M. L., Ed.; IASP Press: Seattle, 2003.
30. Almansa-Rosales, C.; Garcia-Lopez, M.; Caamaño-Moure, A.-M. W. O Patent 2016078770.
31. Paddock, R.; Beer, E. G.; Bellville, J. W.; Ciliberti, B. J.; Forrest, W. H., Jr.; Miller, E. V. Clin. Pharmacol. Ther. 1969, 10, 355.
32. Akiyama, Y.; Kudoi, T.; Mori, T.; Asai, K.; Miike, N.; Yanagisawa, Y.; Watanabe, T.; Tsushima, M.; Hiranuma, T. EP Patent 1142587.
33. Virgil-Bernado, M.; Alegret-Molina, C.; Almansa-Rosales, C. W. O Patent 2016078771.
34. Durham, P. L.; Vause, C. V. CNS Drugs 2010, 24, 539.
35. Bell, I. M.; Zhao, L.; Fraley, M.; Zhu, C.; Bifu, T.; Brardic, E. J.; Wang, C.; Zartman, C. B.; Gallicchio, S.; Nguyen, D.; Crowley, B.; Potterger, C. W. O Patent 2016022644.
36. Chaturvedula, P. V.; Pin, S.; Tholady, G.; Conway, C. M.; Mazar, J. E.; Dubowehik, G. M. Bioorg. Med. Chem. Lett. 2011, 22, 4719.
37. Nagasawa, M.; Kawai, N.; Tanaka, N.; Nakamura, H.; Tsuzuki, N.; Murata, M. W. A. E Patent 1650198.
38. Kubota, H.; Okamoto, Y.; Fujii, M.; Ikeda, K.; Takeuchi, M.; Shibanuma, T.; Isomura, Y. Bioorg. Med. Chem. Lett. 2008, 18, 1541.
39. Aleotti, A.; Altamura, M.; Maggi, C. A. W. O Patent 2006045820.
40. Lecci, A.; Capriati, A.; Maggi, C. A. Br. J. Pharmacol. 2004, 114, 1249.
41. Ting, P. C.; Le, J. F.; Anthes, J. C.; Shih, N.-Y.; Piwinski, J. Bioorg. Med. Chem. Lett. 2000, 10, 2333.
42. Ting, P. C.; Le, J. F.; Anthes, J. C.; Shih, N.-Y.; Piwinski, J. I. Bioorg. Med. Chem. Lett. 2001, 11, 491.
43. Ting, P. C.; Lee, J. F.; Shihi, N.-Y.; Piwinski, J. J.; Anthes, J. C.; Chapman, R. W.; Rizzo, C. A.; Hey, J. A.; Ng, K.; Nomeir, A. A. Bioorg. Med. Chem. Lett. 2002, 12, 2125.
