Preparation of 3,5-methanobenzo[b]azepines: a novel sp^3-rich Quinolone Isostere.

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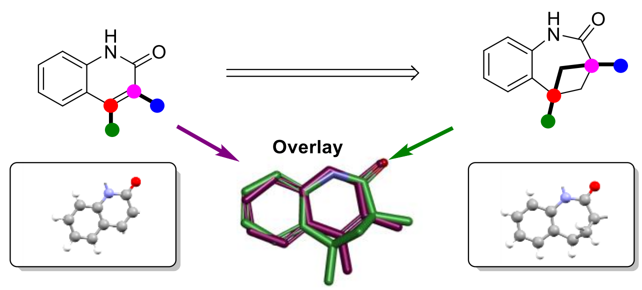
Supporting Information Placeholder

ABSTRACT:

The replacement of the aromatic ring in bioactive compounds with saturated bioisosteres has become a popular tactic to obtain novel structures with an improved physicochemical profile. In this communication, we describe an efficient synthesis of 3,5-methanobenzo[b]azepines and suggest them as isosteres of quinolones. Quinolones are aromatic, flat rings and considered as privileged scaffolds. An isosteric version of this scaffold with more 3D character would offer new options to expand their use.

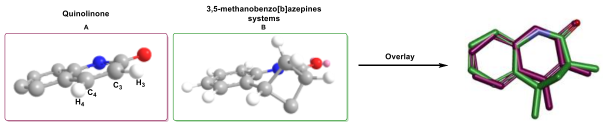


For the past decade, medicinal chemists have been asked to “escape flatland” by increasing the 3D character of their molecules, which was shown to improve overall properties of candidates.[1] This has led the synthetic community to design new motifs with increased sp^3 character. A number of novel motifs, such as bicyclo[1.1.1]pentanes and spirocycles have become mainstream and their popularity stems from their ease of use (availability of building blocks) or synthesis (poised scaffolds).[2, 3] More elaborated motifs still represent a challenge for medicinal chemists to widely adopt this concept. The role of synthetic organic chemistry in the drug discovery process becomes critical to unleash the creativity of medicinal and computational chemists, the “designers”., with a suitable balance to find between efforts required to test an hypothesis and the expected results.

With this important mission in mind, our group continues to expand the collection of isosteres available. Given the almost unimaginably vast number of at least 10^{60} small organic molecules[4] of the drug-like space, it is important to focus and explore first the isosteres of chemotypes commonly found in bioactive molecules. The emphasis shall be put on providing access to specific molecular topologies through the most diverse decoration possible to modulate the selectivity and enhance the safety pattern of the drug candidates. Moving from the classical strategies (HTS, me-too, bio-inspired molecules) to isometric replacement (scaffold-hopping) offers many advantages as a new design idea generator and is a proven tool useful for overcoming undesirable properties, such as poor exposure, toxicity, or unfavorable intellectual property (IP) position.

The quinoline and more precisely the quinolone are important rings in medicinal chemistry (Quinine, Chloroquine, Ciprofloxacin,…) and constitute the basic skeleton of several pharmacopeia-relevant and biologically-active alkaloids (Cinchonidine, Verprisine, Dictamnine).[5] The planarity of these systems sometimes can lead to solubility issues or π-stacking of the scaffold.[6] We hypothesized that, by increasing the sp^3 character, the physicochemical properties of resulting molecules would be improved compared to their aromatic congeners, with limited changes in the angle between key atoms and therefore minimal impact on the positioning of useful exit vectors (Scheme 1). Indeed, *in-silico* modeling and their superimposition showed identic dihedral angle for the 2 structures A and B. A slightly increased of the ring size in B should be noticed . This is due to a larger distance between the carbons C_3 and C_4 (2.14 Å compared 1.34 Å). Nevertheless, the exit vectors in B very closely mimic those of the quinoline A. Finally, a very good superimposition of phenyl ring and heteroatoms of the amide moiety should be noticed. Altogether, these modifications should have only a small impact on the interactions important for the activity.

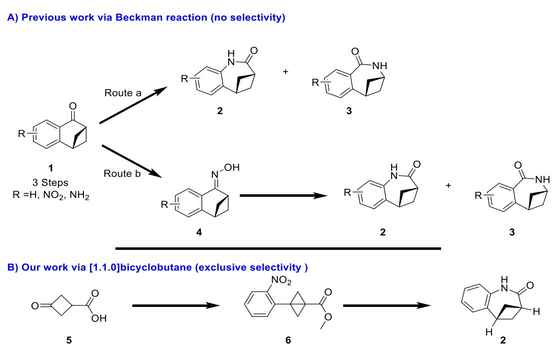
We then went on designing and implementing diverse methods for the construction of the 3,5-methanobenzo[b]azepine system to facilitate their usage in real-life medicinal chemistry projects before their adoption by the scientific community.



	A	B
Distance C_3-C_4	1.34 Å	2.14 Å
Distance H_3-H_4	2.41 Å	3.80Å
Dihedral Angle H_3-C_3-C_4-H_4	0˚	0˚
Vectors Angle	68˚	91˚
cLog P	0.81	1.46

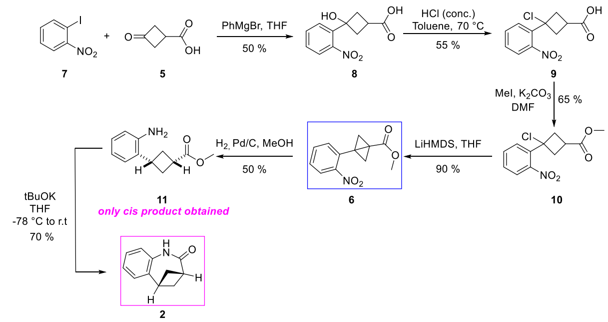
Scheme 1: Comparison of distances and dihedral angles between the reference structure and the proposed isostere

The only known prior synthetic approach towards 3,5-methanobenzo[b]azepine **2** was published by Girard *et al.*[7] The authors used either a ring expansion strategy based on either a Schmidt reaction (Scheme 2, Route a) or a Beckmann transposition (Scheme 2, Route b)[8] on tetralone derivative **1**. Unfortunately, despite the formation of the target compound **2**, in both cases the other regio-isomer 3,5-methanobenzo[c]azepine **3** was also formed.[7] Moreover, this strategy relies on harsh conditions that would not be compatible with a large variety of functional groups on the rest of the molecule.



Scheme 2: Previous work on the synthesis of 3,5-methanobenzo[c]azepine

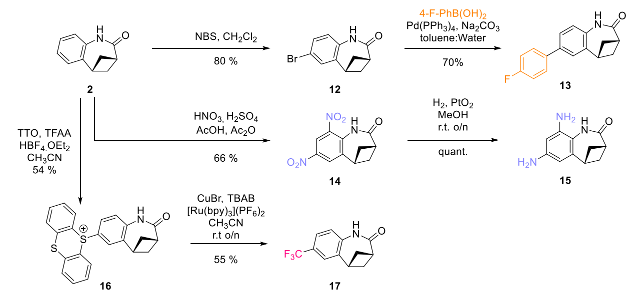
The design and application opportunities arising from these backbone would be significantly enhanced by the availability of a novel synthetic route allowing for straightforward functionalization at different positions. To this end, the synthesis of a poly-substituted *cis*-cyclobutane would be crucial to reach optimal yields and reactivity towards the desired bridged system. Our first approach focused on the use of bicyclo[1.1.0]butane **6** as a precursor of *cis*-cyclobutane (Scheme 3).



*Scheme 3: Synthesis of 1,3,4,5-tetrahydro-2H-3,5-methanobenzo[b]azepin-2-one (**2**)*

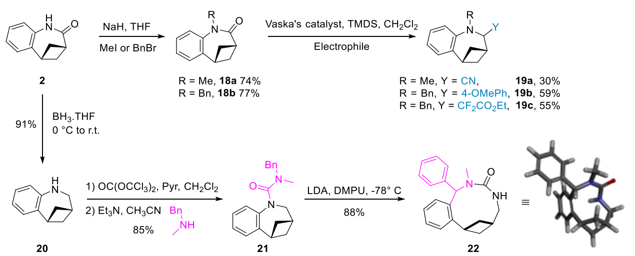
The synthesis of 1,3,4,5-tetrahydro-2H-3,5-methanobenzo[b]azepin-2-one (**2**) started with 1-iodo-2-nitrobenzene (**7**) and 3-oxocyclobutane-1-carboxylic acid (**5**). The synthesis of the bicyclo[1.1.0]butane **6** was performed in 4 steps with a global yield of 16%. The synthesis commenced with an organometallic addition into the commercially available ketone **5** to furnish **8** in medium yield. Alcohol **8** was converted to the chloride **9**, and subsequent esterification and cyclization gave intermediate **6** with all steps proceeding in decent to excellent yield.[9] With the bicyclo[1.1.0]butane **6** in hand, Pd/C-mediated hydrogenation at 1 atm of H_2 exclusively formed the *cis*-cyclobutane isomer (as observed by Xiao *et al.* in works submitted during the time of our studies)[10] while reducing the nitro group to the corresponding aniline **11** in 1 step. Subsequent treatment of **11** with potassium tert-butoxide delivered the desired cyclized product **2** in good yield.[11]

With a robust synthetic strategy in hand towards key intermediate **2**, we explored its derivatization at various positions of the aromatic ring using a late-stage functionalization approach to avoid lengthy syntheses starting from multi-substituted iodo-nitrobenzenes analogs of **7**. (Scheme 4). Electrophilic aromatic bromination delivered one regioisomer **12** in 80% yield, where the bromine at position 7 could serve as a handle to introduce other groups, as demonstrates by the Suzuki coupling to give compound **13**. Mono-nitration was not observed and only bis-nitrated was obtained in 66% yield, which could then be reduced to obtain bis-aniline **15**. Finally, the incorporation of a trifluoromethyl group was introduced using the late-stage functionalization strategy developed by the Ritter group.[12] The two steps procedure (thianthrenation followed by chemoselective photoredox-mediated trifluoromethylation of the arylthianthrenium salt) was successfully completed to reach scaffold **17**. The successful reactivity of arylthianthrenium salt **16** demonstrates that the chemistry developed by Ritter and coworkers could be applied and groups such as NH_2, F, aryl, ester, amide could be introduced.[13] This showcased the reactivity and stability of the scaffold under classical and more modern medicinal chemistry transformations and therefore validates it as useful chemotype to serve as a platform for library design (fragments, DEL, etc.).



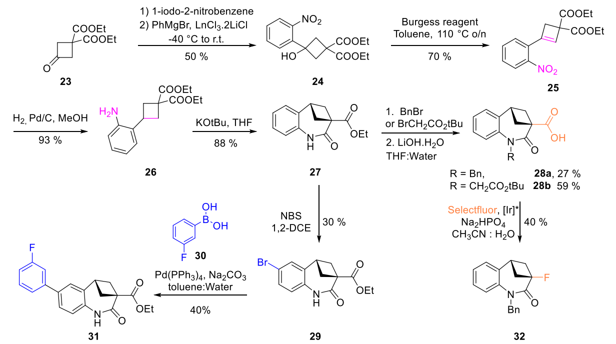
Scheme 4: Functionalization of the aromatic ring of 2.

A methodic scan of all vectors was then performed to further characterize the reactivity of each and assess the compatibility with late-stage functionalization methodologies. First, the nitrogen of **2** could be alkylated using sodium hydride as a base and methyl iodide or benzyl bromide as electrophilic partners (Scheme 5). With tertiary amides available, functionalization of the C-position of the lactam amide using reductive coupling strategies developed by Dixon[14] formed compounds **19a**, **19b** and **19c** (30%, 59 and 55%), which opens additional options for derivatization. Amide **2** could also be reduced to the aniline **20** in 91% yield. Following urea formation to give intermediate **21** as a platform for ring expansion, a Smile's rearrangement yielded an interesting ring-expanded 10-membered cyclic urea **22** in very good yield (88%).[15]

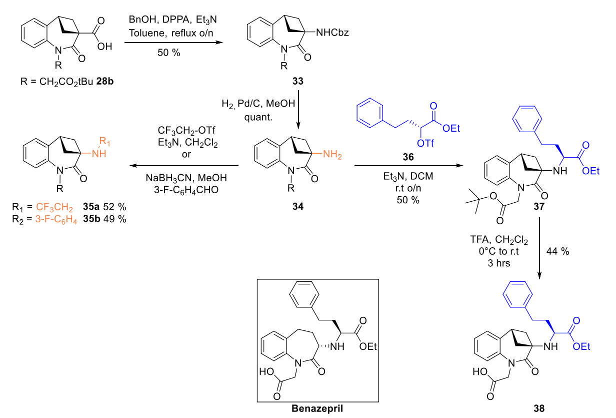


*Scheme 5: Reductive couplings and ring expansion of **2***

A new versatile system was achieved by diversification at the position 3 of the scaffold. The strategy was reevaluated and 1,1-diethyl 3-oxocyclobutane-1,1-dicarboxylate (**23**) was selected as starting material to provide an additional functional handle (Scheme 6). By following the preceding protocol, the tertiary alcohol **24** was firstly obtained in low yield (<10%). Addition of $LnCl_3$.2 LiCl,[16] enhanced the yield of **24** to 50%. Dehydration using Burgess reagent, followed by a Pd/C-mediated hydrogenation at 1 atm of H_2 led to aniline **26**. The final cyclization was performed using the optimized conditions leading to 3-substituted 3,5-methanobenzo[b]azepine **27** (88%). Alkylation of the amide using benzyl bromide or with *tert*-butyl bromoacetate offered an additional growth opportunity out of this exit vector. After saponification of the ethyl esters, the carboxylic acids **28a**, **28b** were obtained in good yields (2 steps). Electrophilic bromination (NBS, 1,2-DCE) of **27** gave **29** in moderate yield (30%). As previously described for intermediate **12**, the bromine at position 7 could serve as a handle to introduce other groups. This was demonstrated by a Suzuki coupling to give highly substituted 3,5-methanobenzo[b]azepines **31** in 40% yield. The carboxylic acid function at C3 in **28a** could also serve as a useful handle through a radical fluoro-decarboxylation under photoredox condition.[17] Fluorinated analogue **32** was obtained in 30% yield and the only by-product isolated was the hydro-decarboxylated compound **18b**. Remarkably, a radical at position 3 is tolerated and no opening or rearrangement of the cyclobutyl ring was observed. From **28b**, a Curtius reaction installed a nitrogen atom on the position 3 in 50% yield (Scheme 7). Reductive deprotection of amine **33** was quantitative and the resulting primary amine was selectively alkylated to deliver highly functionalized derivatives **35a** and **35b** by SN_2 reaction (CH_2Cl_2, Et_3N, R-OTf) or reductive amination in good yield, highlighting the versatility of this new scaffold and its potential uses in medicinal chemistry. As an example, a bridged analogue of benazepril, compound **38**, could be synthesized in 2 steps from **34** and activated-alcohol[18] **36** in 22% overall yield. (Scheme 7).



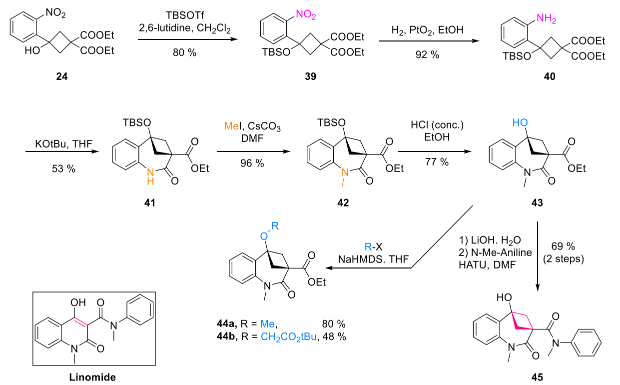
Scheme 6: Position 3 functionalization, [Ir] = (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$.



Scheme 7: Incorporation of the scaffold in a medicinal chemistry relevant structure

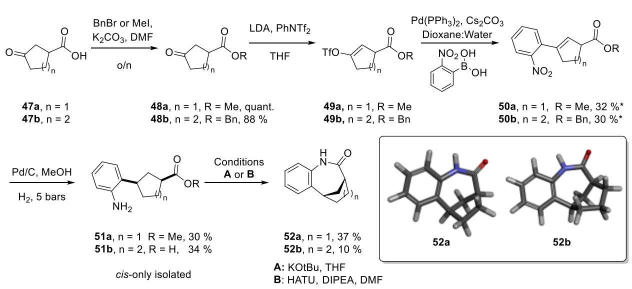
We then turned our attention to the vectorization of the benzylic position 5 (Scheme 8). From **24**, the tertiary alcohol was protected with a TBDMS group and subjected to hydrogenolysis (H_2, PtO_2) to obtain aniline **40** quantitatively. Five-substituted 3,5-methanobenzo[b]azepines **41** was obtained using the optimized conditions described herein. *N*-methylation followed by TBDMS deprotection led to 5-hydroxy-5-methanobenzo[b]azepine **43**. The reactivity of the tertiary alcohol was then studied. Compound **43** was successfully O-methylated using MeI as alkylating agent and NaH. Alkylation of the tertiary alcohol with tert-butyl-bromoacetate gave **44b** in 48% yield and created a handle for further decoration of the scaffold out of this exit vector.

Taking advantage of the methods and strategies described above, we aimed for the synthesis of a bridged analogue of anti-cancer drug Linomide.[19] Ester **43** was saponified and the acid coupled to *N*-methyl-aniline to give analogue **45** in 69 % yield (two steps).



Scheme 8: Syntheses of 5-substituted 3,5-methanobenzo[b]azepines and quinolone-analogue

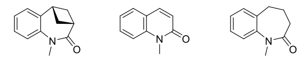
To further expand the chemical space of this scaffold, the size of the ring was enlarged by replacing the cyclobutane by a cyclopentane and a cyclohexane. The synthetic strategy had to be redesigned and involved a Suzuki coupling using vinyl triflates as partners (Scheme 9). From commercially available cyclopentane and cyclohexane derivatives **47a** and **47b**, the carboxylic acid moiety was esterified under basic conditions leading to methyl and benzyl esters **48a** and **48b**, respectively. Vinyl triflates **49a** and **49b** were formed, in quantitative yield, using LDA as base in presence of phenyl triflimide. The Suzuki reaction under classical conditions led to key intermediates **50a** and **50b**. As envisioned, the reductions of cyclopentene and cyclohexene **50a** and **50b** allowed the simultaneous reduction of the nitro groups and the double bond as *cis* isomers. During the reduction of **50b**, the benzyl ester was hydrolyzed yielding carboxylic acid **51b**. Finally, cyclization of **51a** occurred under the conditions in Scheme 9 (conditions A) leading to **52a** in 37 % yield, while conditions B were used on **51b** to give **52b** in an unoptimized yield of 10%.



*Scheme 9. Synthesis of larger bridge azepines 52a and 52b, *isolated yield after two steps.*

To evaluate the usefulness of these new scaffolds in the context of medicinal chemistry efforts and isoteric replacement strategies, we collected information on their physicochemical properties and compared them with more classical 2D/flat analogues. For example, water solubility experiment were performed (at pH = 7) on **18a** and compared with *N*-methyl-quinolone (**54**) and *N*-Methyl-benzazepine (**55**) (see supporting information). As expected, the presence of sp^3 character improves the water solubility of **18a** (0.145M) compared to quinone **54** (0.071M) and azepine **55** (0.073).

Table 1: Solubility studies between N-methylquinone ring (54), N-Methyl-benzazepine (55) and N-methyl 3,5-methanobenzo[b]azepines (18a)



Compound	18a	54	55
Solubilty (M)	0.145	0.071	0.073

In conclusion, we have developed an efficient synthesis of 3,5-methanobenzo[b]azepines and their decoration to populate the medchem-relevant chemical space around these scaffolds. Our approach allows the functionalization of several positions and is offering a wide array of diversity in order to implement this innovative scaffold in medicinal chemistry relevant structures. This new method uses bicyclo[1.1.0]butane **10** or cyclobutene **25** as key intermediates to produce exclusively *cis* isomers. We also demonstrated that the synthesis via Suzuki's reaction could be applied to others cyclic γ-keto-acids to obtain new larger bridged azepines. Finally, the introduction of sp^3-character is beneficial for aqueous solubility, which is a key characteristic for drug-like compounds.[3] Further studies on this scaffold are ongoing and could lead to new bio-active molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available: detailed experimental procedures and characterization of products.

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COMPETING INTERESTS

The authors are employees and CEO (T. C. F.) of SpiroChem AG, a Innovative Contract Research Organization (iCRO) commercializing synthesis services building blocks, fragments and virtual libraries.

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