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Investigation into selective debenzylation and ring cleavage of quinazoline based heterocycles

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ABSTRACT

The selective cleavage of different benzyl bonds within tetrahydroquinazoline and dihydroquinazolinone derived structures can be achieved by the usage of different reduction and debenzylation conditions thereby providing selective removal of *O*-benzyl protection groups as well as the cleavage of the ring structure within the quinazoline and quinazolinone systems.

Over the last decades compounds bearing a quinazoline based structure have been in the focus of different research areas first due to their occurrence as a common core structure in several natural products[1,2] like the alkaloids rutaecarpine **1**, evodiamine **2**, dehydroevodiamine **3**, mackinazolinone **4** and vasicinone **5** (Fig. 1A). And as a result of its promising pharmacological effects in different medicinal applications, the quinazoline core has become to a privileged structure in medicinal chemistry.[3–12]

Therefore, many groups used this nitrogen bridgehead core structure as a key element in the development of numerous experimental therapeutics and prospective drug candidates, also including chemical modifications of the above described natural compounds. Such synthetic compounds are developed for diverse therapeutic applications, such as anticonvulsant agents,[13] in the treatment of cancer,[14,15] as cholinesterase inhibitors for Alzheimer's disease treatment,[16–19] vasodilators,[20] anti-inflammatory agents,[21] as a retrograde transport inhibitor for Shiga toxin treatment[22] or with regard to their effects on different receptors like the serotonin receptor 7 (5-HT_7 receptor),[23] the thyroid stimulating hormone (TSH) receptor[24] or the histamine H_3 receptor.[25,26] A few examples of recently published compounds bearing quinazoline derived moieties are presented in Figure 1B.

Herein different ways for selective heteroatom (*N* and *O*)-carbon-bond cleavage of the different benzyl positions within the tetrahydroquinazoline structure **9** and its precursor dihydroquinazolinone **10** will be described. Both compounds bear a quinazoline derived core structure like the above mentioned natural products and experimental therapeutics. These compounds were used as intermediates for the synthesis of selective butyrylcholinesterase inhibitors[16] and dual-acting AChE inhibitors/hH_3 antagonists.[26] In these structures

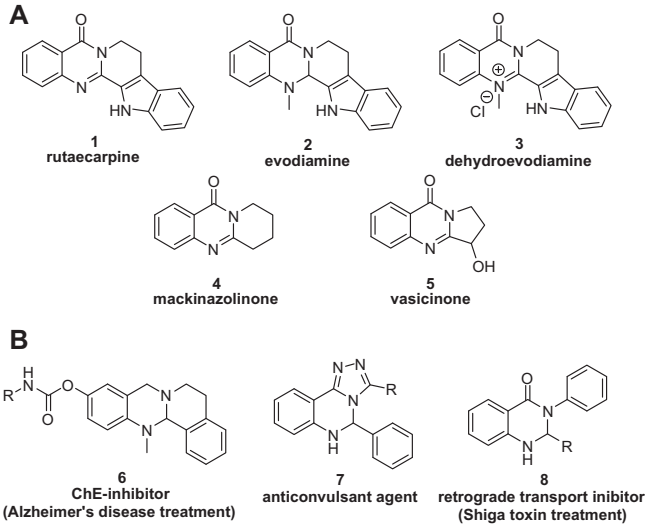

Figure 1. (A) Molecules bearing a quinazoline derived core: (A) The alkaloids rutaecarpine **1**, evodiamine **2**, dehydroevodiamine **3**, mackinazolinone **4** and vasicinone **5**. (B) Examples of some synthetic experimental therapeutics with related chemical structures.[13,16,22]

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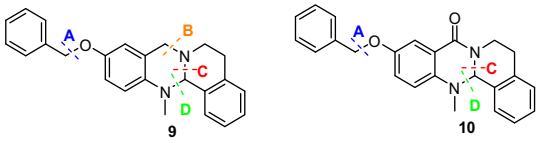


Figure 2. Illustration of benzyl bonds of tetrahydroquinazoline **9** and dihydroquinazolinone **10** that might be cleaved under debenzylation conditions.

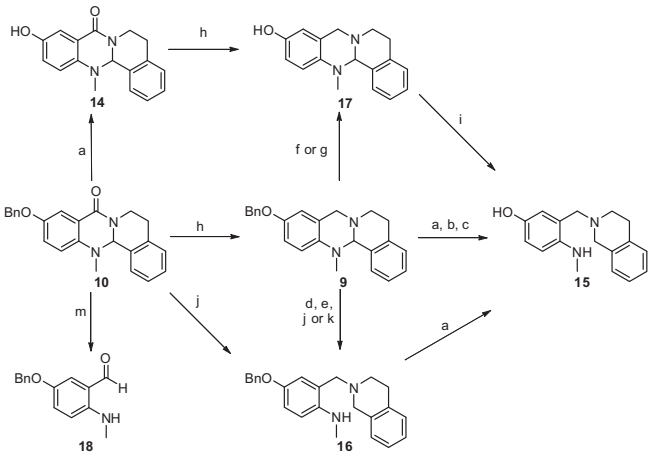
four different benzyl-bonds can be distinguished; **A**: the *O*-benzyl-protection group, **B**: the benzylamine *N*–*C* bond (only in **9**), **C**: the central *N*–*C* bond and **D**: the anilinic *N*–*C* bond (Fig. 2).

This letter shall provide a systematic overview on conditions suitable to selectively cleave and reduce the respective bonds where possible, for example, to induce more flexibility into similar biologically active compounds, and to prevent undesired cleavage reactions during debenzylation and reduction chemistry.

The starting point for this investigation was the synthesis of tetrahydroquinazoline **9** in four steps as described in Scheme 1. Hydroxyl anthranilic acid **11** was treated with triphosgene to yield hydroxy isatoic anhydride **12** quantitatively in high purity, followed by the selective *N*-methylation to yield compound **13**.[16] Compound **13** was then first *O*-benzyl protected and subsequently fused to the tetracyclic dihydroquinazolinone **14** in a two-step one-pot-synthesis with a yield of 53%. Benzylation and ring-fusion can also be performed in two separate steps, but this led to much lower yields. Ring fusion is also possible without protection of the phenol group, but only with a yield of 23%.[16] Tetrahydroquinazoline **9** was synthesized by the reduction of **10** with $LiAlH_4$ in 80% yield.

The described synthetic procedure can of course also be used for other substitution patterns in the aromatic systems of the anthranilic acid derivative as well as for the dihydroisoquinoline compound providing the synthetic basis for performing structure–activity relationship (SAR) investigations in medicinal chemistry approaches.[16,17]

The standard strategy for *O*-debenzylation (cleavage of bond **A**) of dihydroquinazolinone **10** and tetrahydroquinazoline **9** applies the usage of Pd/C and hydrogen in methanol. For compound **10** this procedure led to the desired cleavage of bond **A** to yield the phenolic compound **14** quantitatively (Scheme 2 and Table 1, path *a*). Interestingly, in the case of tetrahydroquinazoline **9**, under these conditions bond **A** was cleaved but additionally also aniline bond **D** was reduced yielding compound **15** in moderate yield (44%). As these conditions were not applicable for the selective *O*-debenzylation of compound **9**, hydrogenation with Pd/C as the catalyst was performed applying different solvent systems. Using EtOH and

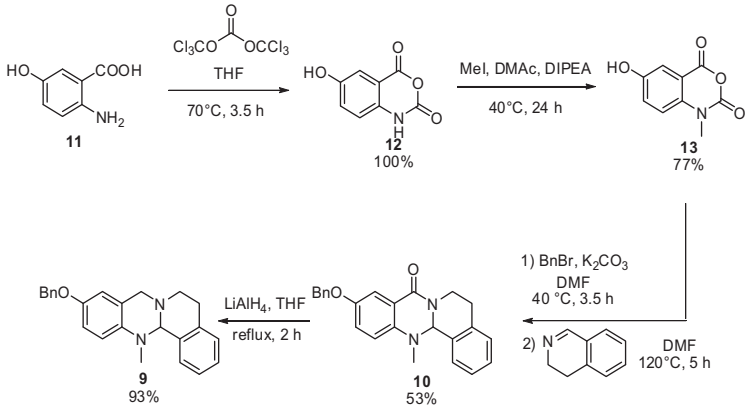


Scheme 2. Reaction pathways during debenzylation and reduction reactions of tetrahydroquinazoline **9** and dihydroquinazolinone **10** towards different products.

Table 1
Reaction conditions for debenzylation strategies via Scheme 2

Path	Starting-material	Product	Conditions	Yield (%)
a	**10**	**14**	H_2, Pd/C, methanol, 50 °C	100
a	**16**	**15**	H_2, Pd/C, methanol, 50 °C	49
a	**9**	**15**	H_2, Pd/C, methanol, 50 °C	44
b	**9**	**15**	H_2, Pd/C, ethanol, 50 °C	37
c	**9**	**15**	H_2, Pd/C, acetic acid, 50 °C	14
d	**9**	**16**	H_2, Pd/C, THF, rt	93
e	**9**	**16**	H_2, PtO_2, methanol, 50 °C	80
f	**9**	**17**	$AlCl_3$, $PhNMe_2$ CH_2Cl_2, rt	65
g	**9**	**17**	concd HCl, reflux	80
h	**14**	**17**	$LiAlH_4$, THF, reflux	98
h	**10**	**9**	$LiAlH_4$, THF, reflux	93
i	**17**	**15**	H_2, Pd/C, methanol, rt	28
j	**9**	**16**	BH_3·THF, THF, reflux	42
j	**10**	**16**	BH_3·THF, THF, reflux	47
k	**10**	—	$NaBH_4$, ethanol, reflux	—
k	**9**	**16**	$NaBH_4$, ethanol, reflux	60
l	**10**	—	$NaCNBH_3$, acetic acid, 50 °C	—
m	**10**	**18**	$LiAlH_4$, THF, rt	19

AcOH resulted into the same reaction product as with MeOH (path *b* and *c*). Only the usage of dry THF as the solvent surprisingly led to the selective hydrogenation of the anilinic *N*–*C*-bond **D** to aniline **16** (path *d*) in excellent yield without affecting the *O*-benzyl bond **A**. A different catalyst for hydrogenation with H_2 can also result in different products, but even the usage of PtO_2 in MeOH just led to



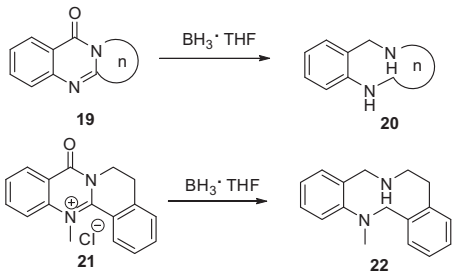
Scheme 1. Synthesis of dihydroquinazolinone **9** and tetrahydroquinazoline **10**.

cleavage of **D** yielding aniline **16** (80%) (path *e*). Cleavage of **A** in the *O*-benzyl protected tetrahydroquinazoline **9** towards the unprotected tetrahydroquinazoline **17** was finally achieved by two different reactions. The conditions of the first one have been reported by Akiyama et al.[27] and used a combined system of the Lewis acid $AlCl_3$ and the Lewis base *N*,*N*-dimethylaniline in methylene chloride at room temperature and yielded 65% of product **17** (path *f*). The second reaction applied harsher reaction conditions, whereby usage of concentrated HCl under reflux conditions for 16 h gave **17** in a yield of 80% (path *g*). Although both reactions led to the desired product, both have the disadvantage that column chromatography was necessary for purification. Therefore, the synthesis of tetrahydroquinazoline **17** was more easily achieved via reduction of **14** by $LiAlH_4$ (path *h*) in an excellent yield of 98% and without the necessity of column chromatography purification. Altering the sequence of $LiAlH_4$ reduction and debenzylation with hydrogen of **10** (changing pathway *a* followed by *h* into pathway *h* followed by *a*) yields two different products (**15** and **17**). It was further demonstrated that the usage of Pd/C and H_2 in MeOH selectively cleaved bond **D** in the case of tetrahydroquinazoline **17** (path *i*) and cleaved bond **A** in the case of aniline **16**, both ultimately leading to compound **15** in low yields. The low yields can be explained by the low stability of **15**, as its *p*-amino phenol structure rapidly undergoes decomposition under oxygen exposure and during heating. GC–MS studies show that bond **D** is also cleaved thereby leading to complete decomposition of the ring system and yielding isoquinoline and dehydroisoquinoline as well as *p*-aminomethyl phenols bearing a methyl group adjacent to the *N*-methyl amino one.

Earlier investigations had already shown how to selectively open the central *N*–*C* bond **C** of quinazolinones **19** and the related structure **21** using BH_3·THF to yield medium sized heterocyclic ring systems **20** and **22**[28–30] (Scheme 3).

Therefore, borane reduction was applied for the reductive removal of the amide oxygen and cleavage of the central *N*–*C* bond **C** in dihydroquinazolinone **10** in one step. Interestingly, the usage of BH_3·THF did not lead to the expected cleavage of the central *C*–*N* bond **C**, but rather reduced the amide bond and cleaved the anilinic bond **D** to give the ring opened compound **16** in 47% yield (path *j*). As it was expected that milder reducing agents were necessary to break the anilinic bond **D**, quinazolinone **10** was treated with $NaBH_4$ (path *k*) and $NaCNBH_3$ (path *l*), respectively, but in both cases no reaction took place. Besides, for tetrahyroquinazoline **9** cleavage of the anilinic bond **D** to compound **16** was achieved by treatment with BH_3·THF in 42% yield (path *j*). Alternatively compound **16** was obtained from **9** using $NaBH_4$ in 60% yield (path *k*). From these results it can be expected that cleavage of the central *C*–*N* bond **C** with BH_3·THF is only possible in quinazolinones (Scheme 3) as described in the literature and not in dihydroquinazolinones like compound **10**.

Besides this, the cleavage of the central *C*–*N* bond **C** with $LiAlH_4$ was also applied on tetrahydroquinazoline **10**. Since compound **10** was smoothly reduced to compound **9** by excess of $LiAlH_4$ at high temperature as described above (path *h*), the product formation at lower temperature was subsequently investigated. Interestingly, reduction towards tetrahydroquinazoline **9** starting from **10** was completely suppressed when only 1 equiv of $LiAlH_4$ was used at room temperature. In this case, besides starting material **10** (63%), only aldehyde **18** (19%) was isolated (path *m*).



Scheme 3. Selective cleavage of bond **C**.[28–30]

In conclusion, first the syntheses of the quinazolin derived structures tetrahydroquinazoline **9** and dihydroquinazolinone **10** were achieved. Both compounds bear different *N*- and *O*-benzyl bonds which were selectively cleaved under different debenzylation and reduction conditions. Thereby the best conditions for the selective cleavage of the *O*-benzyl bond **A** in dihydroquinazolinone **10** was the usage of Pd/C with hydrogen in methanol (path *a*, 100% yield) and for tetrahydroquinazoline **9** the usage of concentrated HCl-solution (path *g*, 80% yield). The cleavage of the anilinic bond **D** was in the case of **10** achieved via reduction with BH_3·THF (path *j*, 47%) and in the case of **9** using Pd/C and hydrogen in dry THF (path *d*, 93% yield). Furthermore, it is remarkable, that applying 1 equiv of $LiAlH_4$ on dihydro-quinazolinone **10** led to the cleavage of the amide bond and the benzylamine *N*–*C* bond **C** in one step (path *m*, 19% yield) therefore leading to aldehyde **18**.

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Supplementary data

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.109.

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