Synthesis and Early ADME Evaluation of a Novel Scaffold, Tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-one

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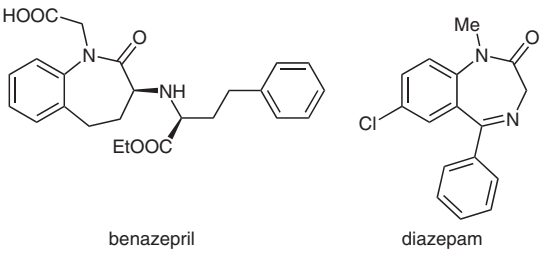
Abstract: The synthesis and preliminary ADME evaluation of novel 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones is presented. The key step is a ring expansion of 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones via a Beckmann rearrangement. The rearrangement opens up possibilities to access novel unexplored scaffolds for medicinal chemistry. The biopharmaceutical profiling revealed a strong structural dependency of the druglike properties.

Key words: bioorganic chemistry, fluorine, fused-ring systems, pyridines, ring expansion

The current development of medicinal biology requires extensive research, leading the search for new natural product-like small molecules. Since the introduction of the theory of privileged scaffolds by Evans in 1988,[1] structures which can interact with high affinity to a broad range of (unrelated) receptors,[2] many new scaffolds have been developed. These privileged structures consist, for example, of a biphenyl-, 1,4-benzodiazepin-2-one, or isoxazole structure.[3] They are typically rigid, polycyclic heteroatomic systems capable of orienting varied substituent patterns in a well-defined three-dimensional space.[4] The tendencies of derivatives of privileged structures to exhibit binding affinity toward various receptors and enzymes have made them attractive scaffolds for discovery, particularly in the case when there is only limited structural information available about the target. The utility of this approach is evident by the numerous libraries designed and constructed on such scaffolds.[2] The biological activity these scaffolds possess is widely used as a starting point for the synthesis of new biological active compounds and drugs.[5]

In this regard, the benzazepine and benzodiazepine structures are widely explored scaffolds. For example, the benzazepine structure benazepril (Figure 1) is a nonsulfhydryl angiotensin-converting enzyme inhibitor (ACE) that is used in medicine for its antihypertensive activity (Lotensin, Novartis).[6] A famous example of the most well-known benzodiazepine is diazepam (Figure 1), a $GABA_A$ receptor enhancer with hypnotic and tranquilizing activity (Valium, Hoffman-La Roche).[7] However, the N-analogues, replacing the phenyl ring by a pyridyl ring is only scarcely investigated. These aza-analogues form a challenging group of new scaffolds.



benazepril diazepam

Figure 1 Benazepril and diazepam

The introduction of a trifluoromethyl functionality in a compound has gained a lot of interest in pharmaceutical chemistry in recent years. This is due to the enhancement of metabolic stability and the high electronegativity of fluorine, which can lead to alterations in molecular conformation.[8,9] Only a few trifluoromethylated benzazepines or benzodiazepines have been synthesized.[10–15] In the class of the trifluoromethylated pyridyl analogues, only the five-membered-[16–19] or the six-membered-ring[20,21] analogues have been described. A trifluoromethylated pyridine ring condensed with a seven-membered ring has only recently been reported for the first time, by the synthesis of 3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido-[2,3-*f*]azepines and 2-(trifluoromethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepines.[22,23] However, the 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]-azepin-6-ones have never been reported.

In our research towards innovative bioactive heterocyclic scaffolds, we have reported small natural-like molecules as anticancer chalcone derivatives,[24] insect repellant/antifeedant methanoproline analogues,[25,26] or epibatidine-like nicotinic acetylcholine receptor inhibitors.[27,28]

In this paper, we present the synthesis of new 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones, synthesized by a Beckmann rearrangement as the

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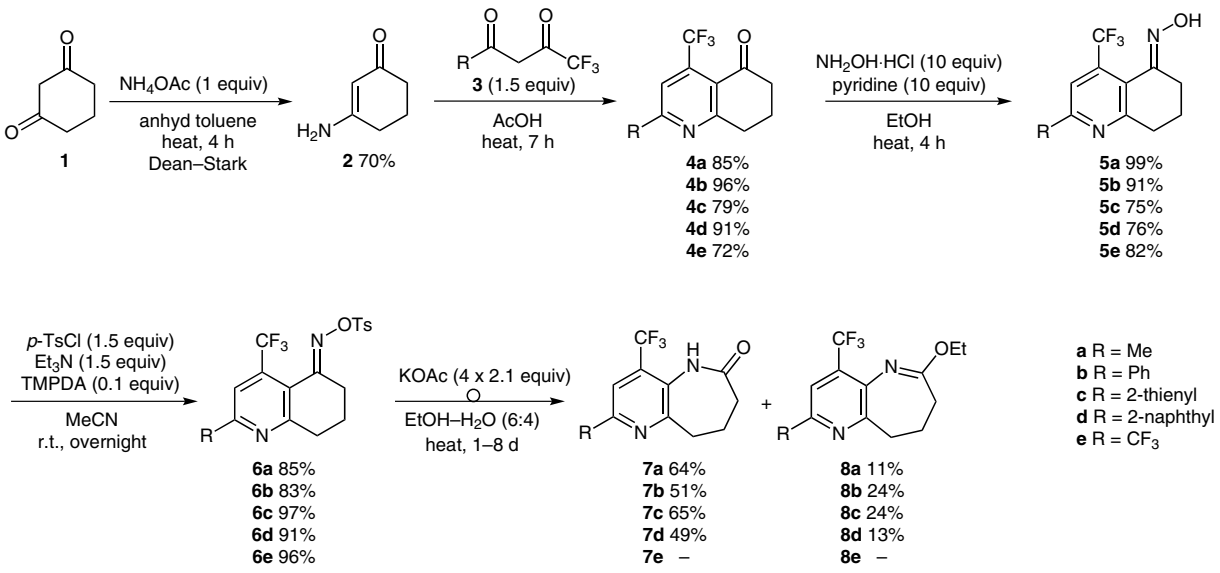


Scheme 1 Synthesis of tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones

key step in the synthesis, and the 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones.

The synthesis started with the formation of 3-aminocyclohex-2-en-1-one **2** by the condensation of cyclohexane-1,3-dione **1** with one equivalent of ammonium acetate under Dean–Stark conditions (Scheme 1). The pure compound was obtained in 70% yield after recrystallization from ethyl acetate.[29,30]

The enaminone **2** was reacted with 1.5 equivalents of different 1-substituted-4,4,4-trifluoro-1,3-diones **3** in refluxing acetic acid for seven hours leading to the corresponding 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones **4**.[31,32] The reaction started by nucleophilic addition of 3-aminocyclohex-2-en-1-one **2** to the 2-position to the most electropositive keto functionality of **3**, followed by ring closure via intramolecular imine formation towards the pyridine moiety. Because of the electron-withdrawing and thus regiodirecting potency of the trifluoromethyl group, this resulted in only one regioisomer, the 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones **4**, with no formation of the 2-trifluoromethyl-substituted regioisomer. Purification was performed by recrystallization in isopropanol (**4b** and **4c**), column chromatography (**4d** and **4e**), or column chromatography followed by recrystallization in isopropanol (**4a**), resulting in good to excellent yields (72–96%).

For the synthesis of 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones, a ring expansion had to be performed on the 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones **4**, introducing a nitrogen atom. This can be performed in a one-step sequence via the Schmidt rearrangement or a two-step approach via the Beckmann rearrangement. The Schmidt rearrangement has been extensively evaluated for the nontrifluoromethylated 7,8-dihydroquinolin-5(6*H*)-one, but was not successful. Therefore, the Beckmann rearrangement was chosen as the approach for the ring expansion towards the seven-membered ring.

As starting material for the Beckmann rearrangement, the oximes **6** were synthesized using hydroxylamine hydrochloride. Therefore, compounds **4** were reacted with a large excess of hydroxylamine hydrochloride in the presence of pyridine in refluxing ethanol.[33,34] After four hours of reflux, the oximes **5** were obtained in good to excellent yields (75–99%) by addition of water to the reaction mixture and filtration of the oximes. An azeotropic distillation with toluene removed any residual water. No purification was needed to obtain the pure 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-one oximes **5**. Only in the case of **5e**, the oxime had to be washed with 5% NaCl and $NaHCO_3$ to remove residual pyridine hydrochloride.

In analogous research towards the nontrifluoromethylated 5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones, several reaction conditions for the Beckmann rearrangement of 7,8-dihydroquinolin-5(6*H*)-one oxime were evaluated, and no direct procedure starting from the oxime proved to be successful. Only the tosylation of the oxime, thus introducing a better leaving group, and subsequently rearrangement towards the lactam effectuated the desired Beckmann rearrangement. Therefore, the tosylation of the oximes **5** was performed by the use of 1.5 equivalents *p*-TsCl, 1.5 equivalents Et_3N, and a catalytic amount of TMPDA (*N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine) in acetonitrile at room temperature.[35,36] After reaction, the crude mixture was filtered and the filtrate was evaporated. The residue was dissolved in THF, filtered, and the filtrate was evaporated again. Pure compounds **6** were obtained after column chromatography in good to excellent yields (83–97%).

The Beckmann rearrangement starting from the *O*-tosyl oximes **6** is depicted in the next step.[37,38] In the presence of potassium acetate, the tosylate leaving group was ex-

pelled, and after rearrangement the desired 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones **7** were formed after refluxing in an ethanol–water mixture (6:4) for several days. When necessary, an extra 2.1 equivalents of potassium acetate were added. Also the imidates **8** were formed, due to the attack of the cosolvent ethanol to the intermediate nitrilium ion. After reaction, the reaction mixture was basified with 5 M NaOH and extracted with chloroform. The organic fraction was dried with magnesium sulfate and evaporated. The pure compounds **7** were obtained by column chromatography in moderate yields (51–65%). Next to the desired trifluorated compounds, also the 2-substituted 6-ethoxy-4-(trifluoromethyl)-8,9-dihydro-7*H*-pyrido[3,2-*b*]azepines **8** could be isolated from the reaction mixture by column chromatography. For **6e**, the 2-trifluoromethyl analogue, the Beckmann rearrangement did not result in either **7e** or **8e**. Only the corresponding **4e** was recovered after reaction. The Beckmann rearrangement probably did not proceed because of the strong electron-withdrawing group in the 2-position, hence inhibiting the aryl migration during the rearrangement, even after refluxing for a long time. Increasing the ratio **7**/**8** towards the desired 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones **7** was not possible, even in other reaction conditions.

The Beckmann rearrangement proceeds regioselectively towards the 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones **7**. The regioisomeric compounds, 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*c*]azepin-6-ones, were not formed. This is because the aryl migration proceeds better due to the stabilizing pyridonium intermediate **9** (Scheme 2).[39] The ^{13}C NMR shift of the CH_2C_qN is situated around 155 ppm instead of around 165 ppm as in the case of 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*c*]azepin-6-ones.

In order to ascertain the regioselectivity of the Beckmann rearrangement of the pyridoazepinones, the X-ray structure of compound **7c** (Figure 2) has been established and proofs the regioselectivity directed by the pyridonium intermediate.

Because of the potential of the 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones for medicinal chemistry, the biopharmaceutical properties were evaluated of selected examples of the synthesized library (i.e., **4a**–**e**, **7a**–**d**, **8b**).

To estimate the intestinal solubility of the compounds, FaSSIF was used as biorelevant medium, accurately mimicking the in vivo intraluminal environment.[40–42] A broad range of solubility values was obtained for this series,

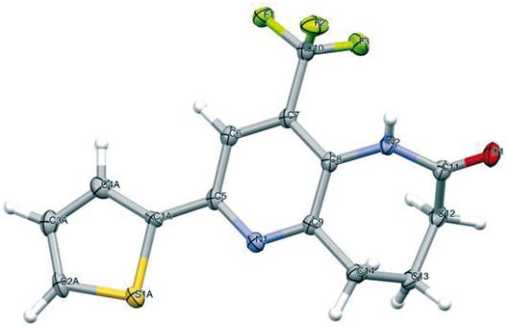
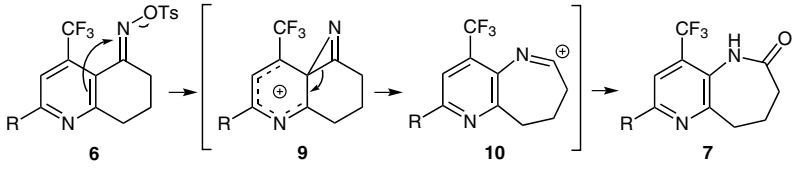


Figure 2 Asymmetric unit of the crystal structure of **7c**, showing thermal displacement ellipsoids at the 50% probability level and atom labeling scheme of the non-hydrogen atoms. The disorder of the thiophene ring is omitted for clarity (CCDC 1000039).

ranging from 3.0 μM for compound **4d** to 13.2 mM for compound **4a** (see Supporting Information).

Similar as for the intestinal solubility, the compounds' structure highly influenced the intestinal permeability, illustrated by the broad range in P_{app} values (see Supporting Information).[43] With exception of compound **8b**, the P_{app} values of the series of selected examples were significantly higher than that of a paracellular marker atenolol ($5.3 \cdot 10^{-6}$ cm/s) and lower than that of a transcellular marker indomethacin ($93.3 \cdot 10^{-6}$ cm/s). The compounds were also incubated in the presence of the P-glycoprotein (P-gp) inhibitor GF120918 (4 μM) to measure the effect on the absorptive permeability of Caco-2 for the selected examples.[44] None of the compounds showed a significant increase in P_{app} when GF120918 was included in the medium. Conversely, a 3.2-fold increase in P_{app} value was observed for a known P-gp substrate indinavir.[45] Thus, the intestinal absorption of these compounds is not expected to be modulated by P-gp-mediated efflux transport in the intestine.

Furthermore, hepatic metabolism was evaluated in a pool of human liver microsomes (HLM). Intrinsic clearance (Clint) values were obtained using the 'in vitro $t_{1/2}$ method' (see Supporting Information).[46] A broad range of Clint values were observed with 230 ± 39 and 0 ± 0 mL/min/kg body weight for **7b** and **7a**, respectively. Compound **7a** was not metabolized under the experimental conditions; cytochrome P450 (CYP) enzymes are unlikely to be involved in its metabolism. Verapamil, used as a positive control, is known to be extensively metabolized. Compounds **7b**, **7c**, **4c**, and **4b** were more extensively metabolized. However, **4e**, **4d**, **8b**, **7d**, **4a**, and **7a** showed higher metabolic stability.



Scheme 2 Regioselectivity of the Beckmann rearrangement

In conclusion, a very convenient approach towards 2-substituted 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido-[3,2-*b*]azepin-6-ones has been presented by the use of a Beckmann rearrangement of 2-substituted 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones. This is the first report on this new scaffold, not only comprising the largely unexplored 5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-one moiety, but also a trifluoromethyl group, both being a biological interesting moiety. Moreover, the biopharmaceutical profile of a series of selected examples of 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones and 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]-azepin-6-ones indicated a remarkable structural dependency of intestinal solubility, permeability, and hepatic metabolism, likely influencing the candidate selection process.

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Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (2H, tt, *J* = 6.1 Hz, *J* = 6.1Hz, $CH_2CH_2CH_2$), 2.30 (2 H, t, *J* = 6.1 Hz, $CH_2C_qNH_2$), 2.35 (2 H, t, *J* = 6.1Hz, CH_2CO), 4.59 (2 H, br. s, NH_2), 5.26 (1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 28.8, 35.9, 99.9, 167.2, 198.0.
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(32) 3-Aminocyclohex-2-en-1-one (5 g, 1 equiv) was dissolved in AcOH (200 mL) and an appropriate 1-substituted 4,4,4-trifluoro-1,3-dione (1.5 equiv) was added and refluxed for 7 h.
Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20 (2 H, tt, *J* = 6.1, 6.1 Hz, $CH_2CH_2CH_2$), 2.67 (3 H, s, CH_3), 2.75 (2 H, t, *J* = 6.1Hz, CH_2CO), 3.20 (2 H, t, *J* = 6.1Hz, CH_2C_qN), 7.45 (1 H, s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 25.1, 33.6, 39.8, 120.0, 122.5, 123.2, 137.3, 163.7, 165.4, 195.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –61.7.
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Compound **5a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (2 H, tt, *J* = 6.5Hz, 6.5Hz, $CH_2CH_2CH_2$), 2.62 (3 H, s, CH_3), 2.88 (2 H, t, *J* = 6.5Hz, CH_2C_qNO), 2.93 (2 H, t, *J* = 6.5Hz, CH_2C_qN), 7.36 (1 H, s, CH), 8.45 (1H, br. s, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2, 23.8, 24.3, 33.3, 119.6, 122.9, 122.9, 135.8, 152.4, 158.2, 162.2. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –60.05.

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(36) The appropriate 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-one oxime (1 equiv) was dissolved in MeCN. To this solution, *p*-toluenesulfonyl chloride (1.5 equiv), Et_3N (1.5 equiv) and *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (0.1 equiv) were added and stirred overnight at r.t.Compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (2H, tt, *J* = 6.5Hz, *J* = 6.5Hz, $CH_2CH_2CH_2$), 2.44 (3H, s, CH_3C_qCHCH), 2.61 (3 H, s, CH_3C_qN), 2.92 (2 H, t, *J* = 6.5Hz, CH_2CNO), 2.96 (2 H, t, *J* = 6.5Hz, $CH_2CH_2CH_2C_qN$), 7.33 (2 H, d, *J* = 7.7Hz, 2 × CH_3C_qCH); 7.34 (1 H, s, CF_3C_qCH), 7.88 (2 H, d, *J* = 7.7Hz, 2 × CH_3C_qCHCH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 21.8, 24.6, 26.0, 33.5, 119.1, 119.5, 122.3, 129.2, 129.7, 132.3, 136.3, 145.2, 160.4, 160.9, 162.9. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –60.2.

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Compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32–2.42 (4 H, m, $COCH_2CH_2$), 2.62 (3 H, s, CH_3), 3.08–3.14 (2 H, m, CH_2C_qN), 7.32 (1 H, s, CH), 7.99 (1 H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 27.2, 32.3, 33.0, 117.8, 122.4, 128.2, 129.7, 156.1, 157.0, 174.0. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –63.2.
Compound **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (3 H, t, *J* = 7.1 Hz, CH_3CH_2), 2.24–2.41 (4 H, m, $COCH_2CH_2$), 2.55 (3 H, s, CH_3), 2.84 (2 H, t, *J* = 7.1 Hz, CH_2C_qN), 4.35 (2 H, q, *J* = 7.1 Hz, CH_3CH_2), 7.25 (1 H, s, CH). ^{13}C NMR (100MHz, $CDCl_3$): δ = 14.0, 22.8, 29.0, 30.5, 33.1, 62.4, 117.9, 122.9, 129.8, 138.3, 152.2, 153.8, 168.1. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –63.2.

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