DOI: 10.1002/ejoc.200900191

Synthesis of 3-Amino-8-azachromans and 3-Amino-7-azabenzofurans via Inverse Electron Demand Diels–Alder Reaction

Eduard Badarau,[a,b] Franck Suzenet,*[a] Adriana-Luminița Fînaru,[b] and Gérald Guillaumet[a]

Keywords: Heterocycles / Cycloaddition / Polycycles

The synthesis of 3-amino-8-azachromans and 3-amino-7-azabenzofurans derivatives is reported. The synthetic strategy is based on an inverse electron demand Diels–Alder approach, which employs 1,2,4-triazines that are judiciously substituted with amino alkynols. This approach permits the variation of the substituent on the aromatic core and on the amine moiety, as well as of the size of the nonaromatic ring.

Introduction

Most of the new biologically active compounds used in drug therapy are heterocycle-based derivatives because of the beneficial roles played by the incorporated heteroatoms at each step of the drug's action, from oral bioavailability to the more favorable interactions within the specific protein target. Nitrogen and oxygen are the most widely used heteroatoms in the construction of drug candidates. Even if the synthesis of such heterocycles is generally more difficult than that of their "heteroatom-free" analogues, the enhanced biological properties justify the effort.

One heterocycle that has proven its potential in the construction of therapeutic molecules is the chroman scaffold. Its favorable interactions with the serotoninergic,[1] dopaminergic,[1,2] and opioid receptors,[3] just to cite few examples, have been reported. One step further in optimizing the discovered hits, both in terms of affinity and selectivity for a specific target, could be achieved by increasing the number of heteroatoms incorporated in the main skeleton. In this paper, we report the synthesis of some analogues of the serotoninergic 5-HT$_7$R chroman-based ligands **A** (K_i = 13.4 nM)[4] and **B** (K_i = 5.29 nM for R = Me and K_i = 6.44 nM for R = Pr):[5] the 3-amino-8-azachroman and 3-amino-7-azabenzofuran derivatives **C** (Figure 1).

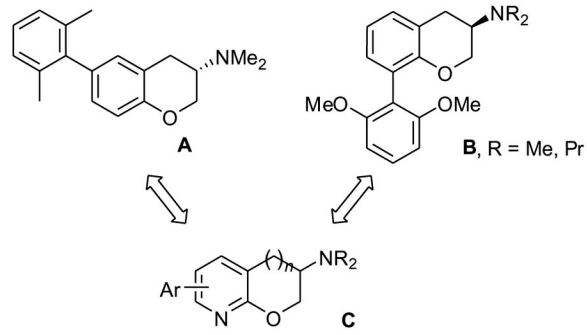


Figure 1. Isosteric relationship between chroman (**A**/**B**) and azachroman (**C**) derivatives.

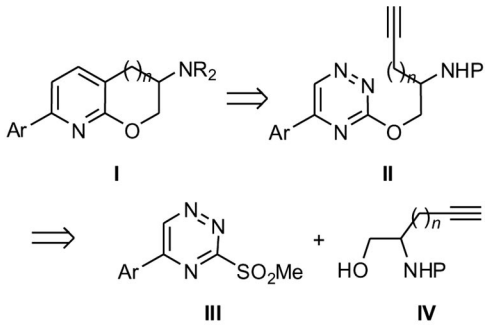
The chosen synthetic route involves the construction of the central heterocycle via a key intramolecular inverse electron demand hetero-Diels–Alder reaction between a judiciously substituted 1,2,4-triazine and an alkyne. This methodology has already been described in the literature, especially by Seitz.[6,7]

Previously, only simple, unsubstituted 2,3-dihydropyrano- or furo[2,3-*b*]pyridines could be accessed in studies by Taylor[8,9] and more recently by our team.[10] The functionalization on the nonaromatic ring was much less extensively studied compared to the functionalization of the aromatic ring. There are a few examples of halogen and hydroxy substitution from the studies of Choi et al.[11] and Shiotani et al.[12–14] A more recent article published by our group explored the synthesis of 3- or 4-hydroxy derivatives.[15] Using a more convergent strategy, we designed the synthesis of 3-aminoazachromans **C** (Figure 1) as potential 5-HT$_7$ ligands.

[a] Institut de Chimie Organique et Analytique, Université d'Orléans, UMR-CNRS 6005, UFR Sciences,
BP 6759, Rue de Chartres, 45067 Orléans Cedex 2, France
E-mail: franck.suzenet@univ-orleans.fr
[b] Centrul de Cercetare "Chimie Aplicată şi Inginerie de Proces", Universitatea din Bacău,
Calea Mărăşesti, nr. 157, 600115 Bacău, Romania
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900191.

Results and Discussion

First, we planned to validate the synthetic approach by obtaining the 7-substituted azachroman derivatives following the retrosynthetic scheme presented below. This molecular target is closely connected to the already proven stability and reactivity of 5-substituted triazines.[15] Thus, the intermediate **II** could be obtained by the substitution of a leaving group (in this case methylsulfonyl) incorporated in the triazine **III** with the alkynol **IV** (Scheme 1).



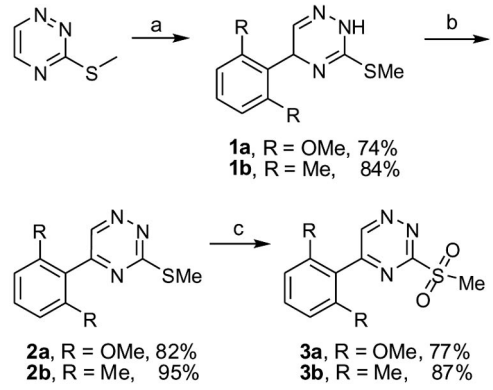
Scheme 1. Retrosynthetic analysis.

Besides the main synthetic reasons, it should be mentioned that following this approach, new chroman isosteres could be obtained with the aryl substituent at a previously unexplored position on the aromatic core, compared with the reference molecules **A** and **B**.

Synthesis of 3-Amino-8-azachromans or 7-Azabenzofurans *ortho*-Substituted to the Pyridine Nitrogen

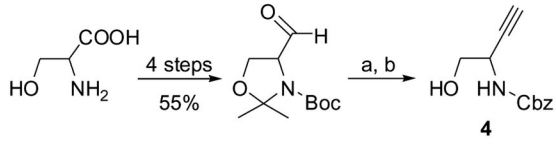
The 5-substituted triazine intermediate **III** was prepared by exploiting the relative reactivity of the different positions of the 1,2,4-triazine ring ($C^5 > C^6 > C^3$) towards organometallic reagents.[16,17] Thus, the nucleophilic addition of the aryl anion proceeded smoothly in position 5 of 3-(methylsulfanyl)-1,2,4-triazine. The aryl substituents were chosen in connection with the biological activities of the 5-HT_7 chroman-based reference ligands **A** and **B**.[4,5] The corresponding aryl anions were obtained by direct *ortho*-metalation of 1,3-dimethoxybenzene with *n*BuLi, or, in the case of the 1,3-dimethylphenyl substituent, via a halogen–metal exchange between *n*BuLi and 2-bromo-1,3-dimethylbenzene. The isolated 2,5-dihydro-1,2,4-triazines **1** were rearomatized to the corresponding triazines **2** by action of DDQ in toluene at 60 °C. The subsequent *m*CPBA oxidation step gave access to the sulfones **3** in very good overall yield (Scheme 2).

The synthesis of the required alcohol intermediates **IV** followed a different path depending on the desired final compounds. Thus, in the case of 2,3-dihydro*furo*[2,3-*b*] pyridines (**I**, $n = 0$) we chose a Garner aldehyde approach, while for the *pyrano* analogues (**I**, $n = 1$) we developed a malonate approach.



Scheme 2. (a) 1,3-Dimethoxybenzene or 2-bromo-1,3-dimethylbenzene, *n*BuLi, THF, –78 to 25 °C, 4 h; (b) DDQ, toluene, 60 °C, 3 h; (c) *m*CPBA, DCM, 0 °C to 25 °C, 3 h.

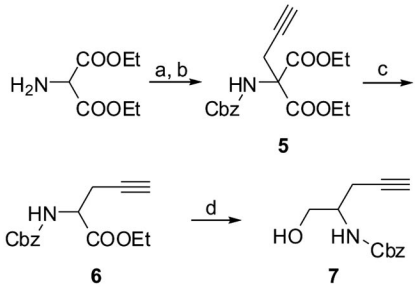
In the first case, the Garner aldehyde, a synthon widely used in various syntheses due to its pre-existing chiral centre,[18–20] was prepared on a large scale (50 mmol) following the procedure initially described by Garner.[21] Starting from commercially available D,L-serine, the aldehyde was obtained after 4 steps in 55% overall yield. The Bestmann–Ohira modification[22,23] of the Seyferth–Gilbert homologation[24,25] gave the terminal alkyne in 84% yield.[26] Finally, acidic removal of both protective groups followed by protecting the amine as a benzyl carbamate (Cbz) gave access to the desired amino alcohol intermediate **4** (Scheme 3).[26]



Scheme 3. (a) 1-Diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 25 °C, 12 h (84%); (b) i) TFA, MeOH, 25 °C, 2 h, ii) CbzCl, K_2CO_3, dioxane, satd. $NaHCO_3$, 25 °C, 12 h (87%).

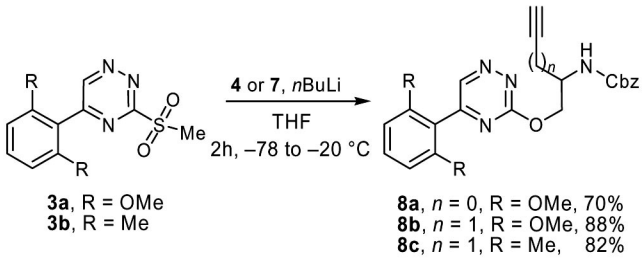
The optimized synthesis of the second alcohol intermediate started from commercially available ethyl 2-aminomalonate. After preliminary protection of the amine moiety as a Cbz group, the alkylation with propargyl bromide was carried out on the activated CH under basic conditions.[27] Subsequently, one of the two carboxylates was hydrolysed and decarboxylated using lithium bromide and water in refluxing DMF.[28] A last step required the reduction of the remaining ester moiety. Because lithium aluminium hydride accomplished the reduction to the desired product with a maximum yield of 30%, a softer hydride, lithium borohydride, was used instead, to give amino alcohol **7** in 89% yield (Scheme 4).[29]

With both key alkynol intermediates prepared, the synthesis was brought forward by substitution of the methylsulfonate of triazines **3** with the corresponding lithium alkoxides of **4** and **7** (Scheme 5). It is worth mentioning that preliminary attempts to carry out this reaction, conducted



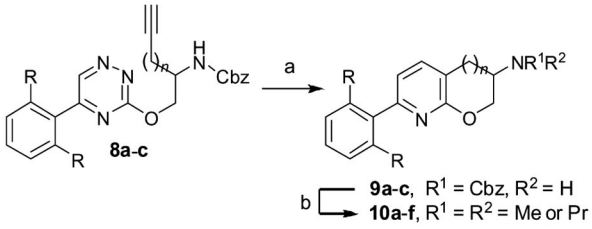
Scheme 4. (a) CbzCl, BTSA, Et_2O, 0 to 25 °C, 1 h (90%); (b) propargyl bromide, EtONa, EtOH, 80 °C, 3 h (81%); (c) LiBr, H_2O, DMF, 155 °C, 12 h (85%); (d) $LiBH_4$, THF, MeOH, –10 to 25 °C, 1 h (89%).

on the intermediates protected by the *tert*-butoxycarbonyl carbamate group, gave the formation of an oxazolidinone as a side product.



Scheme 5. Synthesis of the Diels–Alder precursors.

The inverse electron demand hetero-Diels–Alder cycloadditions of triazine substrates were conducted under microwave irradiation, using chlorobenzene as the solvent. Softer reaction conditions for the five-membered cycloaddition derivatives were in agreement with published data.[15] Subsequent carbamate hydrogenolysis[30] afforded the free amines, which were used for the next step without further purification. The final reductive amination step, conducted



Scheme 6. (a) mw, PhCl, 200–220 °C, 1.5 h, **9a**–**c**; (b) i) H_2, Pd/C, HCl, EtOH, 25 °C, 3 h; ii) HCHO or EtCHO, $NaBH_3CN$, CH_3COOH, MeOH, 25 °C, 12 h, **10a**–**f**.

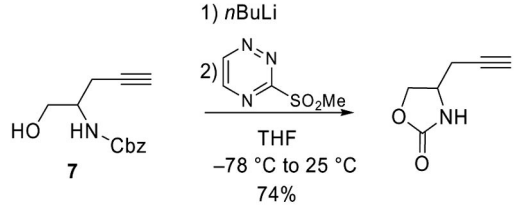
Table 1. Yields for steps a and b (Scheme 6).

n	R	Yields Step a	Step b $R^1 = R^2 = Me$	$R^1 = R^2 = Pr$
0	OMe	**9a**, 95%	**10a**, 71%	**10b**, 40%
1	OMe	**9b**, 83%	**10c**, 70%	**10d**, 67%
1	Me	**9c**, 73%	**10e**, 86%	**10f**, 80%

in correlation with the reference active molecules **A** and **B**, allowed us to obtain the corresponding dialkylated compounds **10a**–**f** (Scheme 6, Table 1).[31]

Synthesis of 3-Amino-8-azachromans or 7-Azabenzofurans *meta*-Substituted to the Pyridine Nitrogen

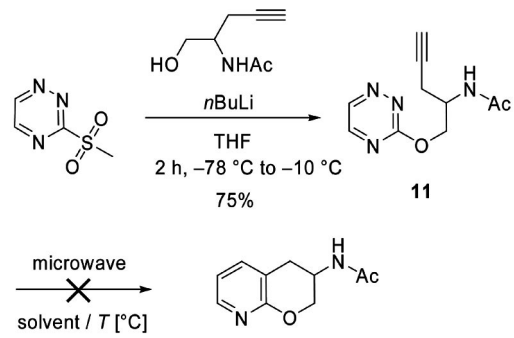
Because the proposed synthetic route was successfully applied to the *ortho*-substituted derivatives, we further planned to obtain the direct analogues of ligand **A** in the pyridine series. Thus, for the synthesis of *meta*-substituted derivatives, the same synthetic approach described above was envisaged. After the synthesis of the particularly unstable 3-(methylsulfonyl)-1,2,4-triazine following the protocols described in the literature,[9,15] the next substitution step was performed under the same conditions as for the 5-substituted triazine (see Scheme 5). This reaction did not provide the desired compound, but only the oxazolidinone side product. The replacement of *n*BuLi with sodium hydride to generate the alkoxide did not lead to any improvement (Scheme 7).



Scheme 7. Preliminary assay for non-substituted 1,2,4-triazine.

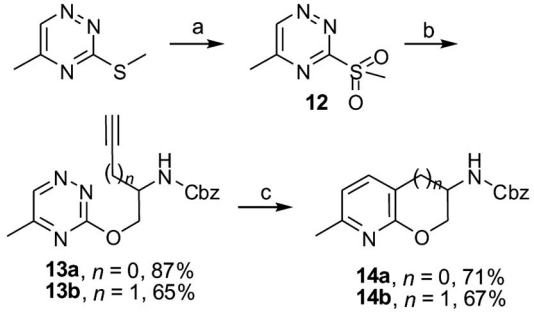
At this stage, it seemed important to try different protecting groups of the amine moiety that did not incorporate potential leaving groups in their structures.

Thus, after the *N*-acetyl protection of ethyl 2-aminomalonate, the synthesis of the corresponding alkynol followed the same route as for compound **7** (see Scheme 4). With this new protective group, the difficulties around the aromatic nucleophilic substitution were avoided, and alkyne **11** was isolated in 75% yield. Unfortunately, the subsequent Diels–Alder cycloaddition gave only degradation products of the starting material under all the different experimental conditions we used: 180–220 °C as the temperature range, PhCl, 1,2-dichlorobenzene and DMF as solvents, 15 min to 1 h as time interval (Scheme 8).



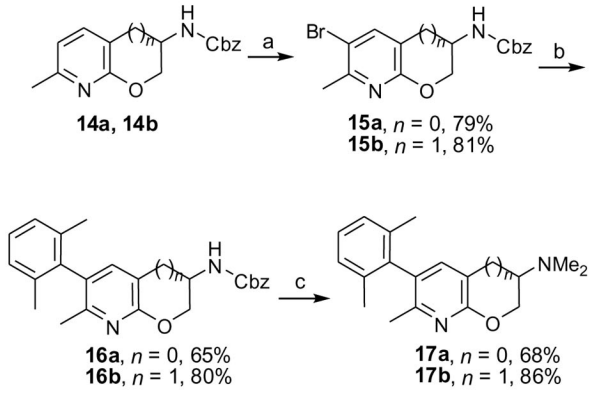
Scheme 8. Preliminary cycloaddition assays.

Similar negative results were obtained in the case of benzophenone imine as the protecting group. To overcome this synthetic issue, a new modification was considered. Our attention was concentrated this time to the diene partner of the Diels–Alder cycloaddition, the 1,2,4-triazine. Starting from the more stable 5-methyl-1,2,4-triazine[9] and *N*-Cbz alkynol **7**, the S_NAr and cycloaddition reactions were in this case successful, and led to the desired furo- or pyranopyridines **14** (Scheme 9).



Scheme 9. (a) *m*CPBA, DCM, 0 °C to 25 °C, 1 h (67%); (b) **7**, *n*BuLi, THF, –78 °C to 25 °C, 2 h; (c) i) for $n = 0$: PhCl, 180 °C, 1 h, ii) for $n = 1$: PhCl, 220 °C, 1.5 h.

The resulting cycloadducts **14** were halogenated with bromine in refluxing methanol.[9] The bromo derivatives were subsequently engaged in a Suzuki coupling reaction with 1,3-dimethylphenylboronic acid to afford compounds **16**. A further hydrogenation step followed by a reductive amination step led to the final compounds **17** (Scheme 10).



Scheme 10. (a) Br_2, $NaHCO_3$, MeOH, 65 °C, 1–3 h; (b) $Pd(PPh_3)_4$, 1,3-dimethylphenylboronic acid, toluene, EtOH, 110 °C, 24 h; (c) i) H_2, Pd/C, HCl 1 M, EtOH, 25 °C, 12 h; ii) HCHO, $NaBH_3CN$, CH_3COOH, MeOH, 25 °C, 24 h.

Conclusions

In conclusion, in the present article we designed the synthesis of 3-amino-2,3-dihydrofuro- and 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines by applying the inverse electron demand Diels–Alder cycloaddition methodology. For this key step, we also emphasized the differences of reactivity of a few triazine substrates in correlation with the protecting group of the amine moiety. The synthetic route exposed herein opens the way to the synthesis of many hetero-analogues of compounds with already-proven biological activities. Our particular azachroman analogues **10a**–**f** and **17a**–**b** were tested for their binding affinities with 5-HT_7 receptors according to the protocols described in the literature,[32] and they were found inactive. Using an analogous methodology, further studies are currently underway in order to obtain the enantiopure derivatives. These results will be published in the near future.

Experimental Section

General: Microwave-assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument equipped with a safety pressure shutoff. ^1H NMR and ^{13}C NMR were recorded with Bruker Avance DPX250 (250.131 MHz) and Bruker Avance II (400 MHz) spectrometers in $CDCl_3$, using tetramethylsilane as an internal standard. Multiplicities were determined by the DEPT 135 sequence; chemical shifts are reported in parts per million (ppm). Coupling constants are reported in units of Hertz [Hz]. Infrared (IR) spectra were recorded with a Perkin–Elmer Paragon 1000 PC FTIR using NaCl films or KBr pellets. Low-resolution mass spectra (MS) were recorded with a Perkin–Elmer SCIEX AOI 300 spectrometer. High-resolution mass spectra were recorded with a Q-Tof micro Waters spectrometer. Melting points were determined in open capillary tubes and are uncorrected. Flash chromatography was performed on Merck 40–70 nM (230–400 mesh) silica gel under nitrogen pressure. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} precoated plates. Visualization was made with ultraviolet light ($\lambda = 254$ nm) and, if necessary, an ethanolic solution of potassium permanganate. Reactions requiring anhydrous conditions were performed under nitrogen. Toluene and tetrahydrofuran were freshly distilled from sodium/benzophenone under argon prior to use. Dichloromethane was distilled from calcium hydride under argon prior to use.

Synthesis of 5-Aryl-3-(methylsulfonyl)-1,2,4-triazines 3

5-(2,6-Dimethoxyphenyl)-3-(methylsulfanyl)-2,5-dihydro-1,2,4-triazine (1a): At –78 °C and under nitrogen, *n*-butyllithium (1.6 M in THF, 75.6 mL, 121 mmol) was added to a solution of 1,3-dimethoxybenzene (14.40 mL, 110 mmol) in anhydrous THF (140 mL). The mixture was vigorously stirred for 1 h at 0 °C and two additional hours at room temp. before adding slowly a solution of 3-(methylsulfanyl)-1,2,4-triazine (20 g, 157.3 mmol) in anhydrous THF (20 mL). After the complete consumption of the starting material, the reaction was quenched with satd. NaCl (100 mL), and then extracted with ethyl acetate (3×100 mL). The organic layer was dried with $MgSO_4$, evaporated, and purified by silica gel column chromatography (petroleum ether/ethyl acetate, 8:2) to give the desired compound **1a**; yield 21.94 g (75%); white solid; m.p. 141–143 °C. IR (KBr): $\tilde{\nu} = 3284, 2928, 1599, 1250$ cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.29$ (br. s, 1 H), 7.26 (t, $J = 8.4$ Hz, 1 H), 6.72 (d, $J = 1.4$ Hz, 1 H), 6.60 (d, $J = 8.4$ Hz, 2 H), 5.10 (d, $J = 1.4$ Hz, 1 H), 3.80 (s, 6 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 159.1$ (C), 152.9 (C), 143.0 (CH), 129.5 (CH), 116.6 (C), 104.7 (2 CH), 56.1 (2 CH_3), 50.2 (CH), 14.1 (CH_3) ppm. MS: $m/z = 266$ [M + H]$^+$. HRMS: calcd. for $C_{12}H_{15}N_3O_2S$ 266.0963, found 266.0951.

5-(2,6-Dimethylphenyl)-3-(methylsulfanyl)-2,5-dihydro-1,2,4-triazine (1b): To a stirred solution of 2-bromo-1,3-dimethylbenzene (10.1 mL, 75.49 mmol) in anhydrous THF (150 mL) under nitrogen, *n*-butyllithium (1.5 M in THF, 54.5 mL, 81.78 mmol) was

added at –78 °C. After 45 min at –78 °C, a solution of 3-(methylsulfanyl)-1,2,4-triazine (8.0 g, 62.91 mmol) in anhydrous THF (10 mL) was added via cannula over 15 min. The reaction mixture was stirred for 45 min at –78 °C, warmed slowly to room temperature over 1.5 h, and subsequently quenched with 10% $NaHCO_3$ (100 mL). The layers were separated, the water layer was extracted with ethyl acetate (3 × 100 mL), the combined organic layers dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 8:2) to afford compound **1b**; yield 12.66 g (86%); yellow solid; m.p. 119–121 °C. IR (KBr): $\tilde{\nu}$ = 3392, 3014, 1610, 1420, 1142, 756 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 8.15 (s, 1 H), 7.06–7.19 (m, 3 H), 6.75 (d, J = 1.0 Hz, 1 H), 4.88 (d, J = 1.0 Hz 1 H), 2.45 (s, 3 H), 2.34 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 152.8 (C), 142.6 (CH), 137.4 (C), 135.8 (C), 129.3 (2 CH), 127.8 (CH), 55.5 (C), 21.1 (2 CH_3), 13.9 (CH_3) ppm. MS: m/z = 234.5 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{15}N_3S$ 234.1065, found 234.1077.

General Procedure for the Preparation of Triazines 2a and 2b: DDQ (45.23 mmol) was added to a suspension of the corresponding 2,5-dihydro-1,2,4-triazine **1a** or **1b** (36 mmol) in toluene (300 mL). The reaction mixture was heated at 60 °C for 2 h, cooled to room temperature, and poured into satd. K_2CO_3 (200 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 200 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 7:3) to afford the corresponding triazines **2a** and **2b**.

5-(2,6-Dimethoxyphenyl)-3-(methylsulfanyl)-1,2,4-triazine (2a): Yield 8.08 g (85%); yellow solid; m.p. 102–104 °C. IR (KBr): $\tilde{\nu}$ = 2931, 1600, 1258, 1128 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 8.89 (s, 1 H), 7.38 (t, J = 8.5 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 2 H), 3.75 (s, 6 H), 2.68 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 173.3 (C), 158.4 (C), 155.1 (C), 147.9 (CH), 132.3 (CH), 112.8 (C), 104.3 (2 CH), 56.1 (CH_3), 14.1 (CH_3) ppm. MS: m/z = 264.0 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{13}N_3O_2S$ 264.0807, found 264.0803.

5-(2,6-Dimethylphenyl)-3-(methylsulfanyl)-1,2,4-triazine (2b): Yield 7.91 g (95%); yellow solid; m.p. 82–84 °C. IR (KBr): $\tilde{\nu}$ = 3010, 1530, 1239, 784, 756 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 8.85 (s, 1 H), 7.25 (dd, J = 6.7, 8.4 Hz, 1 H), 7.11 (apparent d, J = 7.3 Hz, 2 H), 2.65 (s, 3 H), 2.10 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 173.9 (C), 159.1 (C), 146.3 (CH), 135.7 (C), 133.8 (C), 129.7 (CH), 128.1 (2 CH), 20.2 (2 CH_3), 13.8 (CH_3) ppm. MS: m/z = 232.5 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{13}N_3S$ 232.0908, found 232.0919.

General Procedure for the Preparation of Methyl Sulfones 3a and 3b: To a solution of the corresponding 3-(methylsulfanyl)-1,2,4-triazine **2a** or **2b** (22.5 mmol) in anhydrous DCM (100 mL), *m*CPBA (45 mmol) was added in portions at 0 °C over 10 min. The reaction mixture was stirred for 1 h at room temp., and the resulting suspension was filtered. The filtrate was washed with saturated solutions of sodium hydrogen carbonate (2 × 70 mL) and sodium thiosulfate (2 × 100 mL). The organic layer was dried with $MgSO_4$, the solvent was removed in vacuo, and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 5:5) to give the corresponding sulfone **3a** and **3b**.

5-(2,6-Dimethoxyphenyl)-3-(methylsulfonyl)-1,2,4-triazine (3a): Yield 5.13 g (77%); yellow solid; m.p. 126–128 °C. IR (KBr): $\tilde{\nu}$ = 2938, 1598, 1537, 1376, 1263, 1134, 760 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 9.42 (s, 1 H), 7.44 (t, J = 8.5 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 2 H), 3.78 (s, 6 H), 3.46 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 166.6 (C), 158.6 (C), 158.0 (C), 153.9 (CH), 133.8 (CH), 111.4 (C), 104.4 (2 CH), 56.2 (2 CH_3), 39.8 (CH_3) ppm. MS: m/z = 296.5 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{13}N_3O_4S$ 296.0705, found 296.0714.

5-(2,6-Dimethylphenyl)-3-(methylsulfonyl)-1,2,4-triazine (3b): Yield 5.17 g (87%); yellow solid; m.p. 146–148 °C. IR (KBr): $\tilde{\nu}$ = 3000, 1543, 1327, 1138, 764 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 9.40 (s, 1 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.19 (d, J = 7.6 Hz, 2 H), 3.53 (s, 3 H), 2.17 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 166.9 (C), 162.4 (C), 152.9 (CH), 136.4 (C), 132.4 (C), 131.0 (CH), 128.8 (2 CH), 39.8 (CH_3), 20.5 (2 CH_3) ppm. MS: m/z = 264.0 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{13}N_3O_2S$ 264.0807, found 264.0820.

Benzyl (1-Hydroxybut-3-yn-2-yl)carbamate (4): A solution of *tert*-butyl 4-ethynyl-2,2-dimethyl-oxazolidine-3-carboxylate (2 g, 8.88 mmol; for its preparation see Meffre et al.[26]) in methanol (8 mL) was slowly poured into TFA (40 mL) at 25 °C. After 2 h of vigorous stirring, the reaction mixture was coevaporated with Et_2O (3 × 50 mL; never to dryness). Dioxane (40 mL) and satd. $NaHCO_3$ (40 mL) were added, and the pH was adjusted to 8 by addition of solid $NaHCO_3$. Subsequently, potassium carbonate (1.6 g, 11.54 mmol) and benzyl chloroformate (1.52 mL, 10.66 mmol) were added, and the mixture was stirred overnight. The reaction was quenched by addition of water (50 mL), the aqueous layer was extracted with AcOEt (3 × 100 mL), the combined organic extracts were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude amino alcohol was purified by flash column chromatography (petroleum ether/ethyl acetate, 5:5); yield 1.87 g (87%); white solid; m.p. 60–62 °C. IR (KBr): $\tilde{\nu}$ = 3287, 2954, 2108, 1700, 1538, 1252, 1035, 752, 696 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.38 (m, 5 H), 5.37–5.38 (m, 1 H), 5.12 (s, 2 H), 4.58–4.62 (m, 1 H), 3.74 (t, J = 6.1 Hz, 2 H), 2.44 (t, J = 6.1 Hz, 1 H), 2.35 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 156.0 (C), 136.1 (C), 128.7 (CH), 128.4 (2 CH), 128.3 (2 CH), 80.6 (C), 72.9 (CH), 67.4 (CH_2), 65.3 (CH_2), 45.7 (CH) ppm. MS: m/z = 220.5 $[M + H]^+$, 242.0 $[M + Na]^+$. HRMS: calcd. for $C_{12}H_{13}NO_3$ 242.0793, found 242.0799.

Synthesis of the Amino Alcohol Intermediate 7

Diethyl 2-[(Benzyloxycarbonyl)amino]-2-(prop-2-ynyl)malonate (5): Diethyl 2-[(benzyloxycarbonyl)amino]malonate[27] (12 g, 38.79 mmol) was added to a solution of sodium ethanolate (1 M, 40.7 mL, 40.73 mmol) at room temperature. After 30 min of vigorous stirring at room temperature, propargyl bromide (80% in toluene, 4.6 mL, 42.67 mmol) was added, and the reaction mixture was refluxed for 3 h. The solvent was evaporated, and the residue was hydrolyzed with satd. NaCl (30 mL). The aqueous phase was extracted with AcOEt (3 × 100 mL), the combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. Subsequent purification of the crude alkylation derivative by flash column chromatography (petroleum ether/ethyl acetate, 9:1) yielded the desired alkyne **5**; yield 11.49 g (80%); colorless oil. IR (NaCl): $\tilde{\nu}$ = 3424, 3288, 2983, 2115, 1745, 1496, 1306, 1042, 700 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.36 (m, 5 H), 6.37 (br. s, 1 H), 5.11 (s, 2 H), 4.25 (q, J = 7.1 Hz, 4 H), 3.28 (d, J = 2.3 Hz, 2 H), 1.99 (t, J = 2.5 Hz, 1 H), 1.23 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 166.6 (C), 154.5 (C), 136.2 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 78.2 (C), 71.7 (CH), 67.2 (CH_2), 65.8 (C), 63.1 (2 CH_2), 24.4 (CH_2), 14.0 (2 CH_3) ppm. MS: m/z = 370.0 $[M + Na]^+$. HRMS: calcd. for $C_{18}H_{21}NO_6$ 370.1267, found 370.1249.

Ethyl 2-[(Benzyloxycarbonyl)amino]pent-4-ynoate (6): Lithium bromide (6.41 g, 61.12 mmol) and water (2.2 mL, 122.23 mmol) were added to a solution of diester **5** (19.3 g, 55.56 mmol) in DMF (120 mL). The reaction mixture was refluxed overnight, and after the complete conversion of the starting material, the solvent was evaporated. The residue was hydrolyzed with 100 mL of satd. NaCl, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography over silica gel (petroleum ether/ethyl acetate, 9:1) afforded the corresponding monoester **6**; yield 13.21 g (85%); white solid; m.p. 45–47 °C. IR (KBr): ṽ = 3366, 3234, 2983, 2123, 1728, 1524, 1214, 1061, 747 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.36 (m, 5 H) 5.65 (d, J = 7.3 Hz, 1 H), 5.13 (s, 2 H), 4.52 (dt, J = 4.7, 8.9 Hz, 1 H), 4.19–4.28 (m, 2 H), 2.77 (dd, J = 2.5, 4.1 Hz, 2 H), 2.03 (t, J = 2.6 Hz, 1 H), 1.29 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 170.3 (C), 155.7 (C), 136.2 (C), 128.6 (CH), 128.3 (CH), 128.2 (CH), 78.4 (C), 71.9 (C), 67.2 (CH_2), 62.0 (CH_2), 52.4 (CH), 22.9 (CH_2), 14.3 (CH_3) ppm. MS: m/z = 298.0 $[M + Na]^+$. HRMS: calcd. for $C_{15}H_{17}NO_4$ 298.1055, found 298.1057.

Benzyl (1-Hydroxypent-4-yn-2-yl)carbamate (7): Lithium borohydride (1.52 g, 69.74 mmol) was added by portions to a solution of ester **6** (6.4 g, 23.25 mmol) in anhydrous THF (90 mL) at –10 °C, followed by the addition of anhydrous methanol (20 mL). The reaction mixture was allowed to return to room temperature over 30 min, and the solvent was evaporated. Water (80 mL) was added to the resulting residue, and after the complete hydrolysis of the hydride, the aqueous layer was extracted with AcOEt (3 × 100 mL). The organic layer was dried with $MgSO_4$, the solvent was removed in vacuo, and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 5:5) to give the desired alcohol **7**; yield 4.89 g (89%); white solid; m.p. 66–68 °C. IR (KBr): ṽ = 3409, 3300, 2950, 2128, 1714, 1536, 1232, 1061, 741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.34 (s, 5 H), 5.43 (d, J = 8.3 Hz, 1 H), 5.09 (s, 2 H), 3.82–3.90 (m, 1 H), 3.63–3.78 (m, 2 H), 3.03 (br. s, 1 H), 2.48 (d, J = 3.8 Hz, 2 H), 2.02 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 156.4 (C), 136.2 (C), 128.6 (CH), 128.3 (CH), 128.2 (CH), 80.1 (C), 71.1 (CH), 67.0 (CH_2), 63.4 (CH_2), 51.2 (CH), 21.1 (CH_2) ppm. MS: m/z = 256.5 $[M + Na]^+$. HRMS: calcd. for $C_{13}H_{15}NO_3$ 256.0950, found 256.0941.

Synthesis of the *ortho*-Substituted Derivatives

General Procedure for the Preparation of Triazines 8a–c: Under nitrogen atmosphere, *n*-butyllithium (1.5 M in THF, 5.78 mmol) was slowly added at –78 °C to a solution of the corresponding alcohol (5.5 mmol) in anhydrous THF (60 mL). After 40 min at –78 °C, a solution of the corresponding triazine (6.70 mmol) in anhydrous THF (25 mL) was added. The mixture was stirred for 45 min at –78 °C and 1 h at –30 °C, before it was quenched at low temperature with 5% $NaHCO_3$. The aqueous layer was separated and extracted with AcOEt (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, the solvent was evaporated, and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:5) to give the derivatives **8a**–**c**.

Benzyl {1-[5-(2,6-Dimethoxyphenyl)-1,2,4-triazin-3-yloxy]but-3-yn-2-yl}carbamate (8a): Yield 1.65 g (69%); white solid; m.p. 54–56 °C. IR (KBr): ṽ = 3304, 2946, 2121, 1717, 1600, 1520, 1226, 1108, 1025, 768 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 8.97 (s, 1 H), 7.39 (t, J = 8.4 Hz, 1 H), 7.31–7.32 (m, 5 H), 6.63 (d, J = 8.4 Hz, 2 H), 5.63 (d, J = 7.0 Hz, 1 H), 5.09 (s, 2 H), 4.99–5.04 (m, 1 H), 4.63–4.76 (m, 2 H), 3.74 (s, 6 H), 2.33 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 165.0 (C), 158.4 (C), 158.3 (C), 155.5 (C), 147.9 (CH), 136.1 (C), 132.5 (CH), 128.5 (2 CH), 128.2 (CH), 128.1 (2 CH), 112.3 (C), 104.2 (2 CH), 79.9 (C), 72.8 (CH), 69.1 (CH_2), 67.2 (CH_2), 56.0 (CH_3), 42.8 (CH) ppm. MS: m/z = 435.5 $[M + H]^+$, 457.5 $[M + Na]^+$. HRMS: calcd. for $C_{23}H_{22}N_4O_5$ 435.1668, found 435.1659.

Benzyl {1-[5-(2,6-Dimethoxyphenyl)-1,2,4-triazin-3-yloxy]pent-4-yn-2-yl}carbamate (8b): Yield 2.25 g (87%); yellow oil. IR (NaCl): ṽ = 3298, 2946, 2118, 1718, 1599, 1515, 1255, 1110 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 8.96 (s, 1 H), 7.39 (t, J = 8.5 Hz, 1 H), 7.30–7.34 (m, 5 H), 6.63 (d, J = 8.5 Hz, 2 H), 5.44 (d, J = 8.7 Hz, 1 H), 5.09 (s, 2 H), 4.76–4.82 (m, 1 H), 4.57–4.64 (m, 1 H), 4.28–4.37 (m, 1 H), 3.75 (s, 6 H), 2.67–2.70 (m, 2 H), 2.01 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 165.0 (C), 158.4 (C), 155.8 (C), 147.9 (CH), 136.3 (C), 132.5 (CH), 128.6 (2 CH), 128.2 (CH), 128.1 (2 CH), 112.3 (C), 104.2 (2 CH), 79.7 (C), 71.3 (CH), 68.0 (CH_2), 67.0 (CH_2), 56.0 (2 CH_3), 48.9 (CH), 21.6 (CH_2) ppm. MS: m/z = 449.5 $[M + H]^+$, 471.5 $[M + Na]^+$. HRMS: calcd. for $C_{24}H_{24}N_4O_5$ 471.1644, found 471.1643.

Benzyl {1-[5-(2,6-Dimethylphenyl)-1,2,4-triazin-3-yloxy]pent-4-yn-2-yl}carbamate (8c): Yield 1.98 g (82%); Yellow oil. IR (NaCl): ṽ = 3410, 2954, 2248, 1724, 1536, 1066, 734 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 8.94 (s, 1 H), 7.29–7.35 (m, 6 H), 7.15 (d, J = 7.6 Hz, 2 H), 5.50 (d, J = 5.4 Hz, 1 H), 5.11 (s, 2 H), 4.78 (dd, J = 5.4, 10.8 Hz, 1 H), 4.64 (dd, J = 5.4, 10.8 Hz, 1 H), 4.30–4.42 (m, 1 H), 2.68–2.71 (m, 2 H), 2.12 (s, 6 H), 2.05 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 165.1 (C), 162.5 (C), 155.7 (C), 146.2 (CH), 136.2 (C), 135.7 (C), 133.6 (C), 129.8 (2 CH), 128.5 (2 CH), 128.1 (2 CH), 79.4 (C), 71.5 (CH), 68.2 (CH_2), 66.9 (CH_2), 48.6 (CH), 21.5 (CH_2), 20.2 (2 CH_3) ppm. MS: m/z = 417 $[M + H]^+$, 439.5 $[M + Na]^+$. HRMS: calcd. for $C_{24}H_{24}N_4O_3$ 439.1746, found 439.1730.

General Procedure for the Preparation of Cycloadducts 9a–c: The corresponding compound **8a**–**c** (1.11 mmol) was dissolved in chlorobenzene (5 mL) and heated at 200–220 °C under microwave irradiation for 1.5 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 4:6) to afford the corresponding cycloaddition derivatives **9a**–**c**.

Benzyl {6-(2,6-Dimethoxyphenyl)-2,3-dihydrofuro[2,3-*b*]pyridin-3-yl}carbamate (9a): Yield 0.43 g (95%); white solid; m.p. 68–70 °C. IR (KBr): ṽ = 3320, 2964, 1712, 1602, 1472, 1250, 1110, 753 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.68 (d, J = 7.4 Hz, 1 H), 7.35 (m, 5 H), 7.28 (t, J = 8.4 Hz, 1 H), 6.89 (d, J = 7.4 Hz, 1 H), 6.60 (d, J = 8.4 Hz, 2 H), 5.45–5.50 (m, 1 H), 5.28–5.33 (m, 1 H), 5.13 (s, 2 H), 4.72–4.80 (m, 1 H), 4.33–4.39 (m, 1 H), 3.70 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 167.9 (C), 158.1 (C), 155.8 (C), 154.8 (C), 136.2 (C), 134.6 (CH), 129.9 (CH), 128.7 (2 CH), 128.4 (CH), 128.2 (2 CH), 119.7 (CH), 118.5 (C), 116.6 (C), 104.2 (2 CH), 75.9 (CH_2), 67.2 (CH_2), 56.1 (2 CH_3), 51.8 (CH) ppm. MS: m/z = 407.0 $[M + Na]^+$.

Benzyl {7-(2,6-Dimethoxyphenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-3-yl}carbamate (9b): Yield 0.41 g (88%); white solid; m.p. 167–169 °C. IR (KBr): ṽ = 3338, 2942, 1715, 1602, 1472, 1248, 1111, 755 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.41 (d, J = 7.5 Hz, 1 H), 7.33 (br. s, 5 H), 7.27 (t, J = 8.4 Hz, 1 H), 6.91 (d, J = 7.5 Hz, 1 H), 6.59 (d, J = 8.4 Hz, 2 H), 5.39 (d, J = 6.4 Hz, 1 H), 5.10 (s, 2 H), 4.27 (br. s, 3 H), 3.70 (s, 6 H), 3.11 (d, J = 16.6 Hz, 1 H), 2.84 (d, J = 16.6 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 159.7 (C), 158.1 (C), 155.8 (C), 152.0 (C), 139.6 (CH), 136.3 (C), 129.6 (CH), 128.6 (2 CH), 128.2 (3CH), 120.5 (CH), 118.4 (C), 112.2 (C), 104.0 (2 CH), 68.8 (CH_2), 66.9 (CH_2),

56.0 (2 CH_3), 43.7 (CH), 31.0 (CH_2) ppm. MS: *m*/*z* = 421.5 [M + H]$^+$. HRMS: calcd. for $C_{24}H_{24}N_2O_5$ 421.1763, found 421.1778.

Benzyl {7-(2,6-Dimethylphenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-3-yl}carbamate (9c): Yield 0.31 g (71%); white solid; m.p. 65–67 °C. IR (KBr): $\tilde{\nu}$ = 3332, 3018, 1710, 1572, 1536, 1244, 755 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, *J* = 7.5 Hz, 1 H), 7.35 (m, 5 H), 7.16 (dd, *J* = 6.3, 8.6 Hz, 1 H), 7.06 (d, *J* = 7.4 Hz, 2 H), 6.84 (d, *J* = 7.5 Hz, 1 H), 5.27 (d, *J* = 5.3 Hz, 1 H), 5.12 (s, 2 H), 4.29–4.38 (m, 3 H), 3.17 (dd, *J* = 3.8, 16.7 Hz, 1 H), 2.88 (dd, *J* = 3.8, 16.7 Hz, 1 H), 2.07 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 160.0 (C), 157.6 (C), 155.8 (C), 140.1 (CH), 139.9 (C), 136.2 (C), 135.9 (C), 128.7 (2 CH), 128.4 (CH), 128.3 (2 CH), 127.8 (CH), 127.5 (2 CH), 119.0 (CH), 112.1 (C), 69.1 (CH_2), 67.2 (CH_2), 43.8 (CH), 31.1 (CH_2), 20.4 (2 CH_3) ppm. MS: *m*/*z* = 389.5 [M + H]$^+$. HRMS: calcd. for $C_{24}H_{24}N_2O_3$ 389.1865, found 389.1856.

General Procedure for the Preparation of Triazines 10a–f: To a solution of the protected amines **9a**–**c** (0.5 mmol) in ethanol (10 mL) was added 10% Pd/C (0.02 g), and hydrogen was bubbled through the suspension for 15 min at room temperature. 1*N* HCl (0.5 mmol) was added, and the reaction mixture was stirred under hydrogen atmosphere until the complete consumption of the starting material (10 h). The mixture was filtered through Celite, diluted with satd. K_2CO_3 (25 mL), and extracted with DCM (3 × 50 mL). The separated organic layers were dried with $MgSO_4$, and the solvent was evaporated to give the free amines, which were used without further purification.

To a solution of the corresponding previously obtained primary amines (0.30 mmol) in methanol (5 mL) was added the corresponding aldehyde (2.40 mmol) and sodium borohydride (2.40 mmol). The pH of the reaction was adjusted to 6 by addition of acetic acid, and the mixture was stirred for 24 h at room temp. before being poured into 1 M NaOH (10 mL). The aqueous phase was extracted with DCM (3 × 30 mL), the organic layer was dried with $MgSO_4$, and the solvents were evaporated in vacuo. The final dialkylated compounds **10a**–**f** were isolated by flash chromatography (DCM/MeOH, 95:5).

6-(2,6-Dimethoxyphenyl)-3-(dimethylamino)-2,3-dihydrofuro[2,3-*b*]-pyridine (10a): Yield 0.06 g (71%); white solid; m.p. 151–153 °C. IR (KBr): $\tilde{\nu}$ = 2938, 1598, 1250, 1110, 753 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.67 (d, *J* = 7.4 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 7.4 Hz, 1 H), 6.61 (d, *J* = 8.4 Hz, 2 H), 4.57–4.62 (m, 1 H), 4.46–4.51 (m, 2 H), 3.71 (s, 6 H), 2.29 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 168.5 (C), 158.2 (C), 154.0 (C), 135.2 (CH), 129.7 (CH), 118.9 (CH), 115.9 (C), 104.2 (2 CH), 70.4 (CH_2), 64.7 (CH), 56.1 (2 CH_3), 40.8 (2 CH_3) ppm. MS: *m*/*z* = 301.5 [M + H]$^+$. HRMS: calcd. for $C_{17}H_{20}N_2O_3$ 301.1552, found 301.1551.

6-(2,6-Dimethoxyphenyl)-3-(dipropylamino)-2,3-dihydrofuro[2,3-*b*]-pyridine (10b): Yield 0.04 g (40%); colorless oil. IR (NaCl): $\tilde{\nu}$ = 2923, 2360, 1703, 1587, 1471, 1250, 1106, 973 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.63 (d, *J* = 7.3 Hz, 1 H), 7.28 (t, *J* = 8.4 Hz, 1 H), 6.84 (d, *J* = 7.3 Hz, 1 H), 6.61 (d, *J* = 8.4 Hz, 2 H), 4.73–4.77 (m, 1 H), 4.48–4.56 (m, 2 H), 3.72 (s, 6 H), 2.38–2.51 (m, 4 H), 1.42–1.51 (m, 4 H), 0.87 (t, *J* = 7.3 Hz, 6 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 168.6 (C), 158.3 (C), 153.5 (C), 134.9 (CH), 129.6 (CH), 119.1 (C), 118.9 (CH), 117.7 (C), 104.2 (2 CH), 71.5 (CH_2), 61.5 (CH), 56.2 (2 CH_3), 52.8 (2 CH_2), 21.8 (2 CH_2), 11.9 (2 CH_3) ppm. MS: *m*/*z* = 357.0 [M + H]$^+$. HRMS: calcd. for $C_{21}H_{28}N_2O_3$ 357.2178, found 357.2183.

7-(2,6-Dimethoxyphenyl)-3-(dimethylamino)-3,4-dihydro-2*H*-pyrano-[2,3-*b*]pyridine (10c): Yield 0.07 (70%); yellowish oil. IR (NaCl): $\tilde{\nu}$ = 2938, 1606, 1471, 1248, 1110, 749 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C: δ = 7.45 (d, *J* = 7.5 Hz, 1 H), 7.27 (t, *J* = 8.4, 1 H), 6.89 (d, *J* = 7.5 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 2 H), 4.48–4.54 (m, 1 H), 3.99–4.09 (m, 1 H), 3.71 (s, 6 H), 2.77–3.02 (m, 3 H), 2.41 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 160.4 (C), 158.2 (C), 151.5 (C), 139.1 (CH), 129.5 (CH), 119.8 (CH), 118.8 (C), 113.4 (C), 104.1 (2 CH), 68.2 (CH_2), 57.1 (CH), 56.0 (2 CH_3), 42.8 (2 CH_3), 29.2 (CH_2) ppm. MS: *m*/*z* = 315.5 [M + H]$^+$. HRMS: calcd. for $C_{18}H_{22}N_2O_3$ 315.1471, found 315.1460.

7-(2,6-Dimethoxyphenyl)-3-(dipropylamino)-3,4-dihydro-2*H*-pyrano-[2,3-*b*]pyridine (10d): Yield 0.07 g (67%); yellowish oil. IR (NaCl): $\tilde{\nu}$ = 2962, 1602, 1472, 1248, 1111, 752 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.45 (d, *J* = 7.5 Hz, 1 H), 7.26 (t, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 7.5 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 4.43 (dd, *J* = 2.9, 10.5 Hz, 1 H), 4.01 (dd, *J* = 2.9, 10.5 Hz, 1 H), 3.71 (s, 6 H), 3.26 (ddd, *J* = 3.6, 9.9, 19.3 Hz, 1 H), 2.88 (d, *J* = 8.4 Hz, 1 H), 2.53 (t, *J* = 7.4 Hz, 4 H), 1.47 (sext., *J* = 7.4 Hz, 4 H), 0.89 (t, *J* = 7.4 Hz, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 160.6 (C), 158.3 (C), 151.4 (C), 139.2 (CH), 129.5 (CH), 119.5 (CH), 118.9 (C), 114.4 (C), 104.1 (2 CH), 68.4 (CH_2), 56.1 (2 CH_3), 52.9 (CH), 52.8 (2 CH_2), 28.0 (CH_2), 21.9 (2 CH_2), 11.8 (2 CH_3) ppm. MS: *m*/*z* = 371.5 [M + H]$^+$. HRMS: calcd. for $C_{22}H_{30}N_2O_3$ 371.2335, found 371.2330.

3-(Dimethylamino)-7-(2,6-dimethylphenyl)-3,4-dihydro-2*H*-pyrano-[2,3-*b*]pyridine (10e): Yield 0.07 g (86%); white solid; m.p. 76–78 °C. IR (KBr): $\tilde{\nu}$ = 2958, 1604, 1572, 1466, 1254, 752 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.47 (d, *J* = 7.4 Hz, 1 H), 7.14 (dd, *J* = 6.2, 8.2 Hz, 1 H), 7.04 (d, *J* = 8.2 Hz, 2 H), 6.79 (d, *J* = 7.4 Hz, 1 H), 4.51–4.58 (m, 1 H), 4.03–4.11 (m, 1 H), 2.76–3.03 (m, 3 H), 2.42 (s, 6 H), 2.06 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 160.6 (C), 157.0 (C), 140.2 (C), 139.6 (CH), 136.0 (C), 127.7 (CH), 127.4 (2 CH), 118.2 (CH), 113.5 (C), 68.5 (CH_2), 57.0 (CH), 42.8 (2 CH_3), 29.1 (CH_2), 20.4 (2 CH_3) ppm. MS: *m*/*z* = 283.5 [M + H]$^+$. HRMS: calcd. for $C_{18}H_{22}N_2O$ 283.1810, found 283.1820.

7-(2,6-Dimethylphenyl)-3-(dipropylamino)-3,4-dihydro-2*H*-pyrano-[2,3-*b*]pyridine (10f): Yield 0.08 g (80%); yellow oil. IR (NaCl): $\tilde{\nu}$ = 2962, 1600, 1567, 1462, 1244, 1027, 754 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, *J* = 7.4 Hz, 1 H), 7.14 (dd, *J* = 6.2, 8.6 Hz, 1 H), 7.05 (d, *J* = 7.4 Hz, 2 H), 6.77 (d, *J* = 7.4 Hz, 1 H), 4.46 (dd, *J* = 3.0, 10.4 Hz, 1 H), 4.05 (t, *J* = 10.4 Hz, 1 H), 3.20–3.32 (m, 1 H), 2.90 (d, *J* = 8.6 Hz, 2 H), 2.51–2.57 (m, 4 H), 2.06 (s, 6 H), 1.48 (sext., *J* = 7.3 Hz, 4 H), 0.89 (t, *J* = 7.3 Hz, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 160.8 (C), 156.7 (C), 140.2 (C), 139.7 (CH), 136.0 (C), 127.7 (CH), 127.4 (2 CH), 117.9 (CH), 114.4 (C), 68.6 (CH_2), 52.8 (CH, 2 CH_2), 28.0 (CH_2), 21.9 (2 CH_2), 20.3 (2 CH_3), 11.8 (2 CH_3) ppm. MS: *m*/*z* = 339.5 [M + H]$^+$. HRMS: calcd. for $C_{22}H_{30}N_2O$ 339.2436, found 339.2424.

Synthesis of the *meta*-Substituted Derivatives

5-Methyl-3-methylsulfonyl-1,2,4-triazine (12): Under inert atmosphere, 5-methyl-3-(methylsulfanyl)-1,2,4-triazine (1.5 g, 10.62 mmol; for its preparation see Taylor et al.[9]) was dissolved in anhydrous DCM (70 mL). The reaction mixture was cooled to 0 °C and treated with *m*CPBA (70%, 5.76 g, 23.37 mmol). The mixture was allowed to return to room temperature over 15 min and then stirred for an additional hour. The suspension was rapidly filtered through a sintered glass funnel, and the filtrate was evaporated under reduced pressure (never to dryness!). Diethyl ether was added to the resulting wet solid and, after 2–3 min of slowly stirring under inert atmosphere, the precipitated sulfone was filtered through a sintered glass funnel (if necessary, another precipitation step could be conducted after the evaporation of the recovered filtrate); yield

1.39 g (67%); orange solid; m.p. 66–68 °C. IR (KBr): $\tilde{\nu}$ = 3034, 1548, 1310, 1135, 957, 759, 557, 535 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 9.33 (s, 1 H), 3.48 (s, 3 H), 2.76 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 166.4 (C), 163.1 (C), 152.3 (CH), 39.7 (CH_3), 22.3 (CH_3) ppm. MS: *m*/*z* = 174.0 $[M + H]^+$. HRMS: calcd. for $C_5H_7N_3O_2S$ 196.0157, found 196.0152 $[M + Na]^+$.

General Procedure for the Preparation of Triazines 13a and 13b: Compounds **13a** and **13b** were obtained following the same experimental protocol employed for the synthesis of **8a**–**c** using the appropriate amino alcohol **4/7** and the triazine **12**.

Benzyl [1-(5-Methyl-1,2,4-triazin-3-yloxy)but-3-yn-2-yl]carbamate (13a): Yield 1.60 g (87%); colorless oil. IR (NaCl): $\tilde{\nu}$ = 3315, 3226, 2119, 1688, 1531, 1339, 1265, 1243, 1084, 1046 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.85 (s, 1 H), 7.28–7.35 (m, 5 H), 5.12 (d, *J* = 6.0 Hz, 1 H), 5.11 (s, 2 H), 4.99–5.04 (m, 1 H), 4.68 (d, *J* = 4.7 Hz, 2 H), 2.51 (s, 2 H), 2.36 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C): δ = 164.6 (C), 162.7 (C), 155.5 (C), 145.9 (CH), 136.1 (C), 128.6 (2 CH), 128.2 (CH), 128.1 (2 CH), 79.7 (C), 73.0 (CH), 69.3 (CH_2), 67.2 (CH_2), 42.8 (CH), 21.6 (CH_3) ppm. MS: *m*/*z* = 335.5 $[M + H]^+$. HRMS: calcd. for $C_{16}H_{16}N_4O_3$ 335.1120, found 335.1137.

Benzyl [1-(5-Methyl-1,2,4-triazin-3-yloxy)pent-4-yn-2-yl]carbamate (13b): Yield 1.25 g (65%); white solid; m.p. 136–138 °C. IR (KBr): $\tilde{\nu}$ = 3305, 3010, 2129, 1708, 1556, 1551, 1220, 1086, 764 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 8.85 (s, 1 H), 7.29–7.35 (m, 5 H), 5.43 (d, *J* = 8.4 Hz, 1 H), 5.10 (s, 2 H), 4.73 (dd, *J* = 5.0, 10.8 Hz, 1 H), 4.6 (dd, *J* = 5.0, 10.8 Hz, 1 H), 4.27–4.35 (m, 1 H), 2.65–2.69 (m, 2 H), 2.51 (s, 3 H), 2.04 (t, *J* = 2.6 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 164.7 (C), 162.5 (C), 155.7 (C), 145.8 (CH), 136.3 (C), 128.6 (2 CH), 128.2 (CH), 128.1 (2 CH), 79.4 (C), 71.5 (CH), 68.0 (CH_2), 67.0 (CH_2), 48.7 (CH), 21.6 (CH_3), 21.5 (CH_2) ppm. MS: *m*/*z* = 349.0 $[M + Na]^+$. HRMS: calcd. for $C_{17}H_{18}N_4O_3$ 349.1277, found 349.1274.

Benzyl {6-Methyl-2,3-dihydrofuro[2,3-*b*]pyridin-3-yl}carbamate (14a): A solution of compound **13a** (0.5 g, 1.60 mmol) in chlorobenzene (5 mL) was heated at 180 °C under microwave irradiation for 1 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (DCM/MeOH, 95:5) to afford the corresponding cycloaddition compound **14a**; yield 0.32 g (71%); white solid; m.p. 132–134 °C. IR (KBr): $\tilde{\nu}$ = 3294, 2949, 1679, 1596, 1531, 1258, 1069, 753 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.48 (d, *J* = 7.4 Hz, 1 H), 7.29–7.33 (m, 5 H), 6.65 (d, *J* = 7.4 Hz, 1 H), 5.69 (d, *J* = 7.6 Hz, 1 H), 5.33–5.41 (m, 1 H), 5.09 (s, 2 H), 4.65 (t, *J* = 10.2 Hz, 1 H), 4.31 (dd, *J* = 4.2, 10.2 Hz, 1 H), 2.83 (s, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C): δ = 167.8 (C), 159.1 (C), 155.9 (C), 136.2 (C), 134.9 (CH), 128.7 (2 CH), 128.4 (CH), 128.2 (2 CH), 116.4 (CH), 115.6 (C), 76.0 (CH_2), 67.2 (CH_2), 51.6 (CH), 24.2 (CH_3) ppm. MS: *m*/*z* = 285.5 $[M + Na]^+$. HRMS: calcd. for $C_{16}H_{16}N_2O_3$ 285.1239, found 285.1258.

Benzyl {7-Methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-3-yl}carbamate (14b): A solution of compound **13b** (0.5 g, 1.54 mmol) in chlorobenzene (5 mL) was heated at 240 °C under microwave irradiation for 1 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (DCM/MeOH, 95:5) to afford the corresponding cycloaddition compound **14b**; yield 0.31 g (67%); beige solid; m.p. 133–135 °C. IR (KBr): $\tilde{\nu}$ = 3025, 1708, 1558, 1551, 1258, 1106, 1067, 694 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.35 (m, 5 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 5.13–5.15 (m, 1 H), 5.09 (s, 2 H), 4.25–4.29 (m, 3 H), 3.07 (dd, *J* = 4.4, 16.6 Hz, 1 H), 2.75–2.81 (m, 1 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 159.5 (C), 156.4 (C), 155.8 (C), 140.1 (CH), 136.2 (C), 128.7 (2 CH), 128.4 (CH), 128.2 (2 CH), 117.7 (CH), 110.7 (C), 69.0 (CH_2), 67.1 (CH_2), 43.8 (CH), 30.8 (CH_2), 24.0 (CH_3) ppm. MS: *m*/*z* = 298.5 $[M + H]^+$. HRMS: calcd. for $C_{17}H_{18}N_2O_3$ 299.1396, found 299.1400.

General Procedure for the Preparation of Triazines 15a and 15b: To a solution of the corresponding cycloadduct **14a** or **14b** (0.35 mmol) in methanol (2 mL) was added sodium hydrogen carbonate (1.06 mmol) and a solution of bromine in methanol (2 M, 0.77 mmol). The reaction mixture was refluxed for 2 h and quenched by the addition of satd. $NaHCO_3$ (15 mL). The aqueous phase was extracted with DCM (3 × 30 mL), then the organic layer dried with $MgSO_4$ and evaporated in vacuo. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:5) to give the desired halogenated compounds **15a** and **15b**.

Benzyl {5-Bromo-6-methyl-2,3-dihydrofuro[2,3-*b*]pyridin-3-yl}carbamate (15a): Yield 0.10 g (79%); white solid; m.p. 117–119 °C. IR (KBr): $\tilde{\nu}$ = 3279, 1677, 1533, 1417, 1260, 1229, 1053, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.69 (s, 1 H), 7.30–7.37 (m, 5 H), 5.62 (d, *J* = 7.6 Hz, 1 H), 5.40–5.44 (m, 1 H), 5.11 (s, 2 H), 4.72 (t, *J* = 9.8 Hz, 1 H), 4.35 (dd, *J* = 4.3, 9.8 Hz, 1 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C): δ = 166.5 (C), 157.2 (C), 155.8 (C), 138.3 (CH), 136.0 (C), 128.7 (2 CH), 128.5 (CH), 128.3 (2 CH), 118.5 (C), 112.3 (C), 76.5 (CH_2), 67.4 (CH_2), 51.3 (CH), 24.9 (CH_3) ppm. MS: *m*/*z* = 363.0 $[M + H]^+$ for ^{79}Br, 365.0 $[M + H]^+$ for ^{81}Br. HRMS: calcd. for $C_{16}H_{15}BrN_2O_3$ 363.0344, found 363.0344 for ^{79}Br.

Benzyl {6-Bromo-7-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-3-yl}carbamate (15b): Yield 0.11 g (81%); white solid; m.p. 144–146 °C. IR (KBr): $\tilde{\nu}$ = 3216, 3027, 1710, 1530, 1448, 1431, 1242, 1168, 1060 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.48 (s, 1 H), 7.30–7.35 (m, 5 H), 5.24 (d, *J* = 7.3 Hz, 1 H), 5.07 (s, 2 H), 4.22–4.29 (m, 3 H), 3.05 (dd, *J* = 4.6, 16.7 Hz, 1 H), 2.76–2.82 (m, 1 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 158.4 (C), 155.8 (C), 154.7 (C), 142.9 (CH), 136.1 (C), 128.7 (2 CH), 128.4 (CH), 128.2 (2 CH), 113.4 (C), 113.1 (C), 69.1 (CH_2), 67.1 (CH_2), 43.3 (CH), 30.5 (CH_2), 24.3 (CH_3) ppm. MS: *m*/*z* = 377.0 $[M + H]^+$ for ^{79}Br, 379 $[M + H]^+$ for ^{81}Br $[M + H]^+$. HRMS: calcd. for $C_{17}H_{17}BrN_2O_3$ 377.0501, found 377.0489 for ^{79}Br.

General Procedure for the Suzuki Palladium Coupling Reaction: To a solution of the corresponding bromide (0.53 mmol) in toluene (12 mL) were added successively 1,3-dimethylphenylboronic acid (0.1 g, 0.64 mmol), ethanol (6 mL) and satd. $NaHCO_3$ (4 mL). The mixture was degassed and flushed with nitrogen several times before adding tetrakis(triphenylphosphane)palladium (0.061 g, 0.05 mmol) in one portion. The mixture was degassed one more time and then refluxed under nitrogen for 20 h. The organic solvent was removed, the residue was hydrolyzed with water (15 mL), and the aqueous phase was extracted with DCM (3 × 25 mL). The combined organic layers were dried with $MgSO_4$, the solvent was evaporated, and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give the desired coupling derivatives **16a** and **16b**.

Benzyl {5-(2,6-Dimethylphenyl)-6-methyl-2,3-dihydrofuro[2,3-*b*]pyridin-3-yl}carbamate (16a): Yield 0.13 g (65%); yellowish oil. IR (NaCl): $\tilde{\nu}$ = 3304, 2956, 1695, 1524, 1416, 1227, 1087, 1008, 909, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.36 (m, 6 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 5.50–5.51 (m, 1 H), 5.20 (m, 1 H), 5.12 (s, 2 H), 4.81 (t, *J* = 9.7 Hz, 1 H), 4.39 (dd, *J* = 4.4, 9.7 Hz, 1 H), 2.11 (s, 3 H), 1.95 (s, 3 H), 1.53 (s,

3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C): δ = 166.9 (C), 156.7 (C), 155.8 (C), 138.5 (C), 136.5 (C), 136.3 (C), 136.1 (C), 135.8 (CH), 129.0 (C), 128.7 (2 CH), 128.5 (CH), 128.3 (2 CH), 127.7 (2 CH), 127.7 (CH), 116.4 (C), 76.1 (CH_2), 67.4 (CH_2), 51.8 (CH), 22.2 (CH_3), 20.6 (2 CH_3) ppm. MS: *m*/*z* = 389.5 $[M + H]^+$. HRMS: calcd. for $C_{24}H_{24}N_2O_3$ 389.1865, found 389.1881.

Benzyl {6-(2,6-Dimethylphenyl)-7-methyl-3,4-dihydro-2*H*-pyrano-[2,3-*b*]pyridin-3-yl}carbamate (16b): Yield 0.17 g (80%); colorless oil. IR (NaCl): $\tilde{\nu}$ = 1709, 1534, 1448, 1425, 1236, 1147, 1099, 909 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.36 (m, 5 H), 7.07–7.20 (m, 4 H), 5.26 (d, *J* = 7.2 Hz, 1 H), 5.11 (s, 2 H), 4.28–4.33 (m, 3 H), 3.12 (dd, *J* = 4.4, 16.6 Hz, 1 H), 2.77–2.83 (m, 1 H), 2.09 (s, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 158.6 (C), 155.8 (C), 153.9 (C), 140.6 (CH), 138.2 (C), 136.4 (C), 136.3 (C), 136.2 (C_q), 130.0 (C), 128.7 (2 CH), 128.4 (CH), 128.2 (2 CH), 127.6 (CH), 127.6 (2 CH), 111.3 (C), 69.0 (CH_2), 67.1 (CH_2), 43.8 (CH), 30.7 (CH_2), 21.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3) ppm. MS: *m*/*z* = 403.5 $[M + H]^+$. HRMS: calcd. for $C_{25}H_{26}N_2O_3$ 403.2022, found 403.2023.

General Procedure for the Preparation of the Final Derivatives 17a and 17b: The compounds **17a** and **17b** were obtained following the same experimental procedure used for the synthesis of compounds **10a**–**f** starting from the corresponding Cbz-protected amines **16a** and **16b** (0.4 mmol).

3-(Dimethylamino)-5-(2,6-dimethylphenyl)-6-methyl-2,3-dihydro-furo[2,3-*b*]pyridine (17a): Yield 0.08 g (68%); colorless oil. IR (NaCl): $\tilde{\nu}$ = 2924, 2360, 1584, 1143, 1414, 1229, 771 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.18 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.12 (d, *J* = 7.4 Hz, 2 H), 4.55–4.61 (m, 2 H), 4.46–4.52 (m, 1 H), 2.24 (s, 6 H), 2.12 (s, 3 H), 1.99 (s; 3 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C): δ = 167.6 (C), 155.8 (C), 139.0 (C), 136.6 (CH), 136.5 (C), 136.5 (C), 128.0 (C), 127.7 (2 CH), 127.6 (CH), 115.0 (C), 71.6 (CH_2), 64.6 (CH), 40.7 (2 CH_3), 22.2 (CH_3), 20.7 (CH_3), 20.6 (CH_3) ppm. MS: *m*/*z* = 283.5 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{22}N_2O$ 283.1810, found 283.1822.

3-(Dimethylamino)-6-(2,6-dimethylphenyl)-7-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (17b): Yield 0.10 g (86%); white solid; m.p. 112–114 °C. IR (KBr): for the fumaric salt $\tilde{\nu}$ = 3401, 2921, 2452, 1706, 1568, 1450, 1292, 1248, 1153, 980, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.16 (dd, *J* = 6.3, 8.5 Hz, 1 H), 7.07–7.11 (m, 3 H), 4.94–4.53 (m, 1 H), 4.07–4.12 (m, 1 H), 2.77–2.94 (m, 3 H), 2.40 (s, 6 H), 2.08 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C): δ = 159.3 (C), 153.2 (C), 140.2 (CH), 138.6 (C), 136.6 (C), 136.5 (C), 129.2 (C), 127.5 (3CH), 112.8 (C), 68.5 (CH_2), 57.2 (CH), 42.8 (2 CH_3), 28.6 (CH_2), 21.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3) ppm. MS: *m*/*z* = 297.0 $[M + H]^+$. HRMS: calcd. for $C_{19}H_{24}N_2O$ 297.1980, found 297.1967.

Supporting Information (see also the footnote on the first page of this article): ^{13}C NMR spectra of compounds **1**–**17**.

Acknowledgments

Authors acknowledge Prof. Andrzej Bojarski (Polish Academy of Sciences, Cracow, Poland) for fruitful discussions and for the biological evaluation of the final compounds.

[1] T. Podona, B. Guardiola-Lemaitre, D.-H. Caignard, G. Adam, B. Pfeiffer, P. Renard, G. Guillaumet, *J. Med. Chem.* **1994**, *37*, 1779–1793.
[2] P. Caldirola, R. Chowdhury, L. Unelius, N. Mohell, U. Hacksell, A. M. Johansson, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1583–1586.
[3] G.-H. Chu, M. Gu, J. A. Cassel, S. Belanger, T. M. Graczyk, R. N. DeHaven, N. Conway-James, M. Koblish, P. J. Little, D. L. DeHaven-Hudkins, R. E. Dolle, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5114–5119.
[4] P. Holmberg, L. Tedenborg, S. Rosqvist, A. M. Johansson, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 747–750.
[5] P. Holmberg, D. Sohn, R. Leideborg, P. Caldirola, P. Zlatoidsky, S. Hanson, N. Mohell, S. Rosqvist, G. Nordvall, A. M. Johansson, R. Johansson, *J. Med. Chem.* **2004**, *47*, 3927–3930.
[6] G. Seitz, L. Görge, S. Dietrich, *Tetrahedron Lett.* **1985**, *26*, 4355–4358.
[7] G. Seitz, *Arch. Pharm. (Weinheim)* **1985**, *318*, 1051–1058.
[8] E. C. Taylor, J. E. Macor, *Tetrahedron Lett.* **1986**, *27*, 431–432.
[9] E. C. Taylor, J. E. Macor, J. L. Pont, *Tetrahedron* **1987**, *43*, 5145–5158.
[10] Y. Hajbi, F. Suzenet, M. Khouili, S. Lazar, G. Guillaumet, *Synlett* **2009**, 92–96.
[11] W.-B. Choi, I. N. Houpis, H. R. O. Churchill, A. Molina, J. E. Lynch, R. P. Volante, P. J. Reider, A. O. King, *Tetrahedron Lett.* **1995**, *36*, 4571–4574.
[12] S. Shiotani, H. Morita, M. Inoue, T. Ishida, Y. Iitaka, A. Itai, *J. Heterocycl. Chem.* **1984**, *21*, 725–736.
[13] H. Morita, S. Shiotani, *J. Heterocycl. Chem.* **1986**, *23*, 1465–1469.
[14] S. Shiotani, H. Morita, *J. Heterocycl. Chem.* **1992**, *29*, 413–422.
[15] Y. Hajbi, F. Suzenet, M. Khouili, S. Lazar, G. Guillaumet, *Tetrahedron* **2007**, *63*, 8286–8297.
[16] S. Konno, M. Sagi, N. Yoshida, H. Yamanaka, *Heterocycles* **1987**, *26*, 3111–3114.
[17] F.-A. Alphonse, F. Suzenet, A. Keromnes, B. Lebret, G. Guillaumet, *Synthesis* **2004**, 2893–2899.
[18] S. Hanessian, G. Yang, J.-M. Rondeau, U. Neumann, C. Betschart, M. Tintelnot-Blomley, *J. Med. Chem.* **2006**, *49*, 4544–4567.
[19] J. Chen, X. Chen, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 87–89.
[20] A. Avenoza, J. H. Busto, C. Cativiela, F. Corzana, J. M. Peregrina, M. M. Zurbano, *J. Org. Chem.* **2002**, *67*, 598–601.
[21] P. Garner, J. M. Park, *J. Org. Chem.* **1987**, *52*, 2361–2364.
[22] S. Müller, B. Liepold, G. Roth, H. J. Bestmann, *Synlett* **1996**, 521–522.
[23] S. Ohira, *Synth. Commun.* **1989**, *19*, 561–564.
[24] D. Seyferth, R. S. Marmor, P. Hilbert, *J. Org. Chem.* **1971**, *36*, 1379–1386.
[25] J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837–1845.
[26] P. Meffre, L. Gauzy, E. Branquet, P. Durand, F. Le Goffic, *Tetrahedron* **1996**, *52*, 11215–11238.
[27] L. Jacob, B.-L. Chen, D. Stec, *Synthesis* **1993**, 611–614.
[28] R. Chen, V. Lee, R. Adlington, J. Baldwin, *Synthesis* **2007**, 113–117.
[29] M. P. Bosch, F. Campos, I. Niubo, G. Rosell, J. L. Diaz, J. Brea, M. I. Loza, A. Guerrero, *J. Med. Chem.* **2004**, *47*, 4041–4053.
[30] S. Albrecht, A. Defoin, E. Salomon, C. Tarnus, A. Wetterholm, J. Z. Haeggström, *Bioorg. Med. Chem.* **2006**, *14*, 7241–7257.
[31] L. Bjoerk, B. B. Hoeoek, D. L. Nelson, N. E. Anden, U. Hacksell, *J. Med. Chem.* **1989**, *32*, 779–783.
[32] M. H. Paluchowska, R. Bugno, B. Duszynska, E. Tatarczynska, A. Nikiforuk, T. Lenda, E. Chojnacka-Wojcik, *Bioorg. Med. Chem.* **2007**, *15*, 7116–7125.

Received: February 24, 2009
Published Online: June 5, 2009

