




Article

Synthesis of Novel Benzo[*b*][1,6]naphthyridine Derivatives and Investigation of Their Potential as Scaffolds of MAO Inhibitors

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Abstract: In this work, 2-alkyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines were obtained and their reactivity was studied. Novel derivatives of the tricyclic scaffold, including 1-phenylethynyl (5), 1-indol-3-yl (8), and azocino[4,5-*b*]quinoline (10) derivatives, were synthesized and characterized herein for the first time. Among the newly synthesized derivatives, 5c–h proved to be MAO B inhibitors with potency in the low micromolar range. In particular, the 1-(2-(4-fluorophenyl)ethynyl) analog 5g achieved an IC₅₀ of 1.35 μM, a value close to that of the well-known MAO B inhibitor pargyline.

Keywords: benzonaphthyridine; activated alkynes; MAO inhibitors; Alzheimer's disease



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1. Introduction

Naphthyridines (pyridopyridines) are nitrogen-containing heterocyclic analogs of naphthalene. Naphthyridines are classified into six types, depending on the location of the nitrogen atoms in the benzene rings [1]. Due to the wide range of biological activities shown by its derivatives, the interest toward the 1,6-naphthyridine nucleus has increased over recent years [2–4]. Several functionalized naphthyridines and their benzo/heteroannulated analogs show biological activities, with prospective exploitation as antitumor agents [5,6], mGlu5 receptor antagonists [7], tyrosine kinase SYK inhibitors [8], and antiviral agents [9]. Moreover, benzocondensed naphthyridine is the scaffold of the alkaloid aaptamine contained in the Indonesian sponge *Aaptos suberitoides* [10,11], which is endowed with antibacterial and anticarcinogenic activities [12]. Derivatives of benzo[*b*][1,6]naphthyridine showed antiproliferative (A) and cytotoxic (B) activities against various types of cancer cells [13,14], as well as PDE5 inhibitory activity (C) (Figure 1) [15].

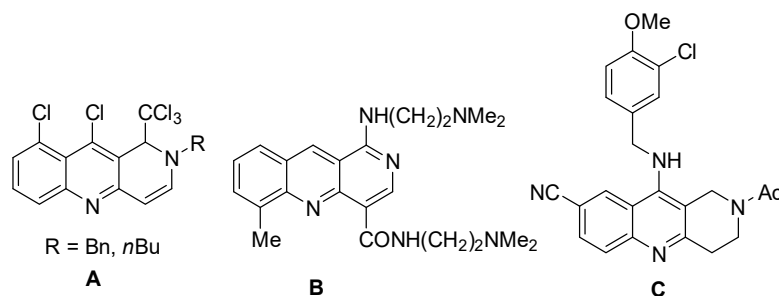


Figure 1. Biologically active derivatives of benzo[*b*][1,6]naphthyridine.

The interest in this bioactive azaheterocyclic moiety prompted us to further explore its reactivity by synthesizing new original derivatives that could possibly be targeted to the treatment of neurological disorders such as Parkinson's (PD) and Alzheimer's (AD)

diseases [16,17]. Herein, 2-alkyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines (**3**) were prepared and used as starting materials to synthesize novel derivatives, e.g., bearing X-substituted phenylethynyl or indolyl groups at C(1). A 6→8 ring expansion reaction was also applied to compounds **3** to obtain azocino[4,5-*b*]quinoline derivatives.

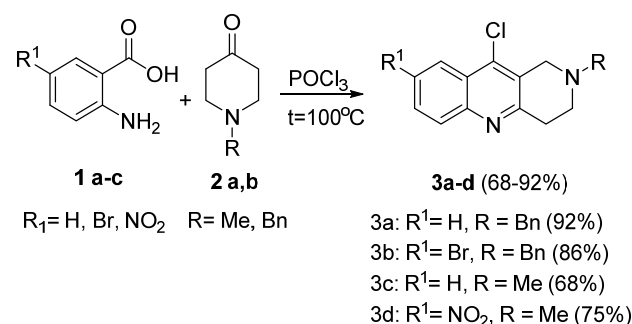
The biological study combining cheminformatics and biochemical testing focused on AD-related targets. In our ongoing search for biological activities from unconventional chemical scaffolds [18,19], we considered the newly synthesized 1,6-benzonaphthyridine derivatives as worthy of biological investigation. It must be highlighted that piperidine-fused naphthyridine derivatives were previously described by others as dual inhibitors of monoamine oxidase subtypes A and B (MAOs A and B) and of acetyl- and butyrylcholinesterase (AChE, BChE) [20]. This feature is also suggested by the shape similarity of this tricyclic scaffold with that of β -carboline, found in the alkaloid harmine and other compounds displaying inhibitory activity toward MAO subtypes [21]. In this study, relying on cheminformatic predictions, we prioritized the evaluation of inhibitory activity against MAOs A and B.

2. Results and Discussion

2.1. Chemistry

The synthesis of benzonaphthyridines is mainly based on ring-closing methods, which are used in the synthesis of quinolines. The use of Frindler [22], Pfitzinger [23] and Niementowski [24] reactions, as well as synthesis based on 2-ethynylquinolyl-3-carbaldehydes [25] and aminopyridines [26], makes it possible to obtain derivatives containing functional groups in various positions of the tricyclic system.

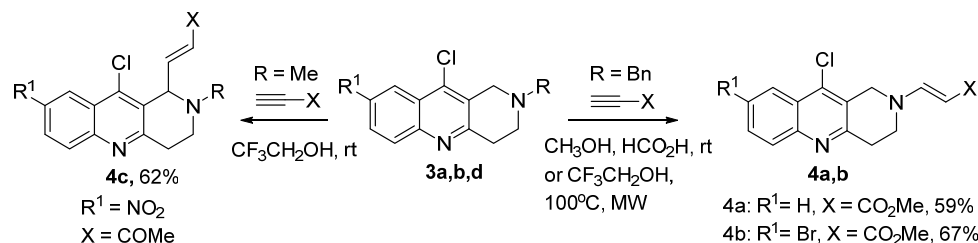
Previously, we described conversion of tetrahydrobenzo[*b*][1,6]naphthyridines, which were obtained by the Pfitzinger reaction, to various derivatives under the action of activated alkynes. The structure of the products directly depended on the nature of the substituent in position 10 and Stevens rearrangement products, ylides, 2-vinylquinolines, and benzopyridonaphthyridines can be formed [27–29]. However, the mentioned works were mainly focused on substances with acceptor substituents at position 10 because of their easy synthesis by the Pfitzinger reaction. Thus, it was of interest to perform experiments using substances with electron-donating substituents such as chlorine. N-methyl- and benzyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **3a–d** were synthesized by the Niementowski reaction based on condensation of anthranilic acids **1a–c** with the appropriate piperidones **2a,b** when heated in a phosphorus oxychloride atmosphere. After alkaline treatment of the reaction mass, compounds **3a–d** were obtained in the form of yellow crystals with yields of 68–92% (Scheme 1).



Scheme 1. Synthesis of 10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines.

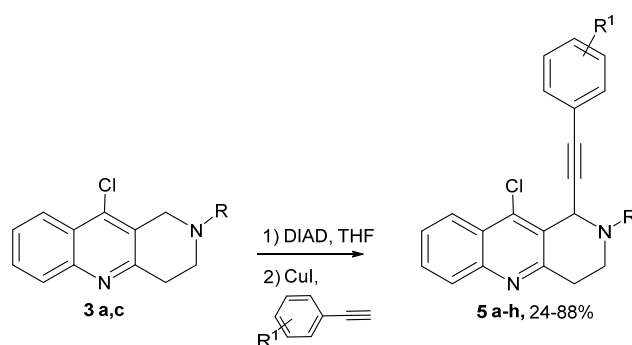
The study of the reactivity of 10-chloro-tetrahydrobenzo[*b*][1,6]naphthyridines showed that 2-methyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine **3c** was completely inactive in reactions with activated alkynes. Extended boiling and microwave activation in various solvents did not lead to the formation of products, whereas only the initial compound was released back from the reaction mass. However, the presence of an acceptor substituent at C-8 in compound **3d** made it possible to obtain product **4c**. The reaction of

2-benzyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **3a,b** with methyl propiolate proceeded at room temperature in methanol under acid catalysis conditions. The N-vinyl derivatives **4a,b** were obtained as a result of debenzoylation (Scheme 2). We previously described such transformations for N-benzyl-chromenopyridines [30].



Scheme 2. The reaction of compounds **3a,b,d** with activated alkynes.

We supposed that the functionalization of this system by introducing indole or phenylethynyl fragments onto the tetrahydropyridine ring would significantly expand the potential of tetrahydrobenzo[*b*][1,6]naphthyridines as biologically active compounds and reveal new ways of further achieving chemical modifications. The introduction of a substituent to the nearest position of the nitrogen atom in the tetrahydropyridine fragment was performed by imine salt formation. Such reactions are well described for tetrahydroisoquinolines [31–34], but they never have been used in case of tetrahydrobenzonaphthyridines. 1-Phenylethynylated benzonaphthyridines **5a–h** were obtained as result of the cross-combination of compounds **3** with phenylacetylene in the presence of CuI and diisopropyl diazodicarboxylate (DIAD) (Scheme 3 and Table 1).



Scheme 3. Phenylethynylation of compounds **3a,c**.

Table 1. 1- R^1 -substituted-phenylethynyl derivatives **5a–h** of compounds **3a,c** with related synthesis yields.

Cmpd 5	R	R^1	Yield, %
a	Bn	H	24
b	Bn	3-OMe	35
c	Me	H	32
d	Me	3-OMe	85
e	Me	4-OMe	88
f	Me	4-CF ₃	61
g	Me	4-F	44
h	Me	4-Cl	59

The nucleophilic addition of benzonaphthyridine tertiary nitrogen to DIAD led to the formation of a zwitterion, which then turned into an iminium salt. The target products **5** were obtained after further alkynylation of the salt with copper acetylenide. The isolation of the reaction products was hampered by the presence of substituted hydrazine in the reaction mixture. This compound was obtained from DIAD and crystallized simultaneously with the target compounds, so it was necessary to use column chromatography.

The structure of compound **5a** was determined by single crystal X-ray analysis (CCDC 2224256, Figure 2).

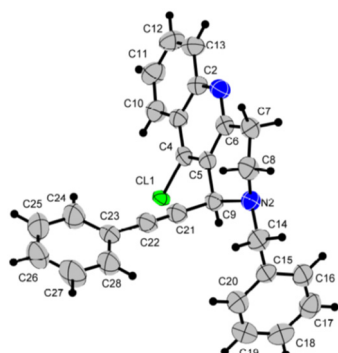
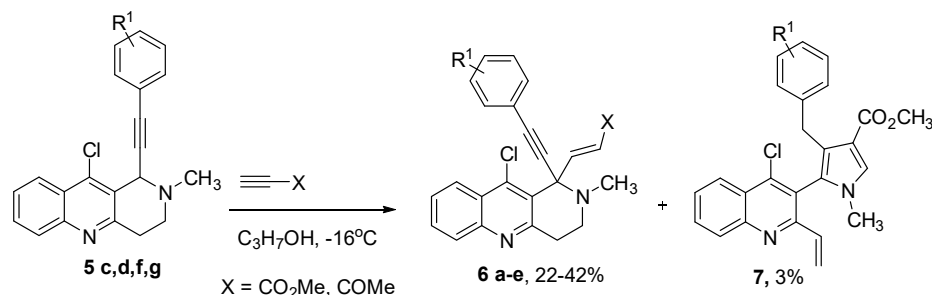


Figure 2. Single crystal X-ray analysis of compound **5a** (crystallographic data in Supplementary Materials).

The phenylethynyl derivatives of benzo[*b*][1,6]naphthyridines **5** turned out to be much more reactive towards activated alkynes. The reaction with methyl propiolate in trifluoroethanol and acetonitrile took place at room temperature after 10 min with the formation of complex separable mixtures. After selecting the reaction conditions, we obtained satisfactory results using subzero temperatures and isopropanol as a solvent. As a result of the interaction of compounds **5d,g** with methyl propiolate under these conditions, two products were formed: the Stevens rearrangement products **6a,b** and 2-vinylquinoline **7**. The reaction of compounds **5g** and **5d** also yielded quinoline **7**. Under the same conditions, the interaction of compounds **5c,d,f,g** with acetylacetylene led to the formation of products **6c–f**, the only products with good yields (Scheme 4 and Table 2).



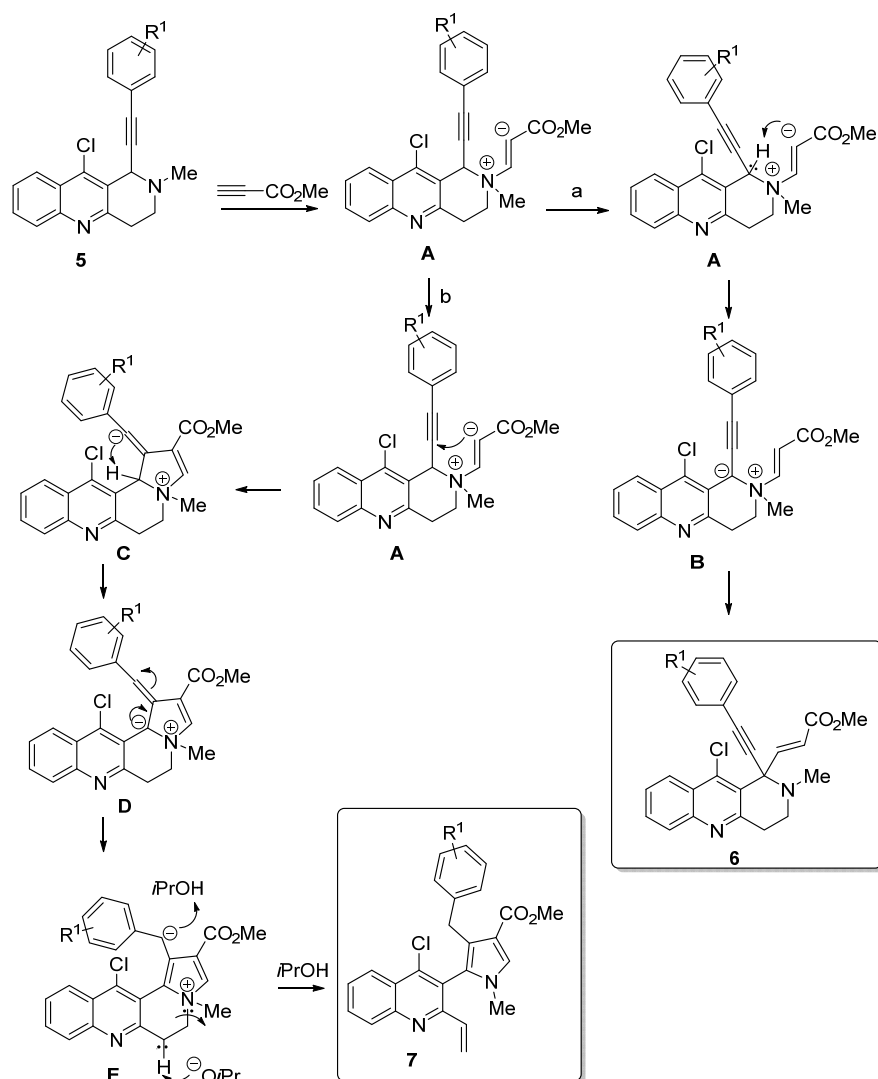
Scheme 4. The reaction of compound **5c,d,f,g** with activated alkynes.

Table 2. Compounds **6a–e** with related reaction yields.

Compound 6	X	R ¹	Yield, %
a	CO ₂ Me	4-F	27
b	CO ₂ Me	3-OMe	22
c	COMe	H	37
d	COMe	3-OMe	34
e	COMe	4-CF ₃	42

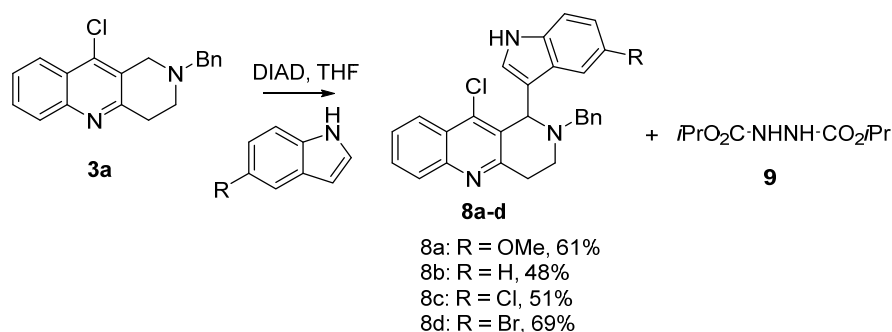
Similarly, the Stevens rearrangement occurred in the case of 1-phenylethynyl-substituted- β -carbolines reacted with activated alkynes [35].

The formation of products **6** and **7** started with the Michael addition of nitrogen of the tetrahydropyridine fragment to the activated alkyne leading to the formation of the zwitterion **A**. Then, either a Stevens rearrangement (route **a**) took place with the formation of compound **6**, or further attack on the triple bond of the phenylethynyl fragment yielded adduct **C** (route **b**) and then proton migration and Hoffmann elimination completed this cascade of transformations to give minor product **7** (Scheme 5).



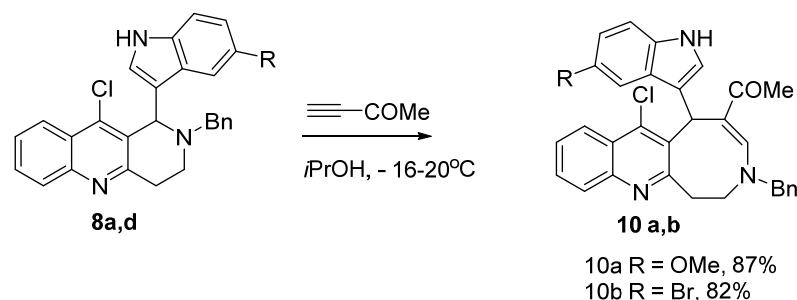
Scheme 5. Mechanism of interaction of **5c,d,f,g** with activated alkynes.

Besides phenylethynylation, we introduced an indole fragment at position C1 of benzonaphthyridines **3**. At the first stage, iminium salts were obtained by interaction of benzonaphthyridines **3** with DIAD, and these salts reacted with substituted indoles at the second stage. The reaction was carried out in absolute THF and benzonaphthyridines **8** were isolated by column chromatography. The isolation of the products was hampered by the presence of substituted hydrazine as in the case of phenethynylation. Thus, only compound **8a** was isolated in its individual form, whereas compounds **8b-d** were isolated in mixture with hydrazine **9** (Scheme 6).



Scheme 6. Synthesis of 1-indol-3-yl derivatives of benzo[*b*][1,6]naphthyridines **8**.

The interaction of 1-indol-3-yl derivatives of benzo[*b*][1,6]naphthyridines **8** with acetylacetylene in isopropanol led to the expansion of the tetrahydropyridine fragment, with the formation of azocine **10** (Scheme 7).



Scheme 7. Interaction of compound **8** with activated alkynes.

Here, we describe the first example of the formation of tetrahydroazocino[4,5-*b*]quinolines; however, such transformations have been studied for other heterocyclic systems annulated with the tetrahydropyridine fragment and the mechanism of azocine fragment formation has been presented [36–41].

2.2. Evaluation of Monoamine Oxidase (MAO) Inhibition

Taking advantage of PLATO, a free online platform for structure-based target prediction [42] that relies on a multi-fingerprint similarity search algorithm [43,44], we submitted derivatives **3a–d**, **5a–h**, **8a–b**, and **10a–c** for bioactivity prediction. Interestingly, MAOs were found among the targets predicted with higher probability along with binding affinities for dopamine and opioid receptor subtypes only for the N(2)-methyl analogues **5c–h** bearing phenylethynyl groups at C1. In contrast, N(2)-benzyl analogs **5a–b** and compounds **3**, **8**, and **10** were unpredicted as MAO ligands.

Compounds **5c–h** were then tested on human (h) recombinant MAO A and B using previously reported assays [16,17]. The MAO-B-selective inhibitor, pargyline, was used as the positive control. Each compound was first tested at a concentration of 10 μM and then lower scalar concentrations were tested when >60% inhibition was achieved at 10 μM . The IC_{50} values were calculated from the best-fitting inhibition–concentration curves. The MAO A and B inhibition data are summarized in Table 3.

Table 3. Inhibitory activities of compounds **5c–h**.

Cmpds 5	MAO A % Inhibition ^a	MAO B	
		% Inhibition ^a	IC_{50} (μM) ^b
c	24 \pm 8	28 \pm 1	
d	49 \pm 2		7.09 \pm 0.07
e	24 \pm 9	42 \pm 6	
f	20 \pm 1		14.3 \pm 0.9
g	39 \pm 3		1.35 \pm 0.07
h	38 \pm 4		8.65 \pm 1.01
Pargyline	10.9 \pm 0.6		2.69 \pm 0.48

^a Inhibition (%) at 10 μM concentration. ^b Half-maximal inhibitory concentration (IC_{50} , μM). Each value represents mean \pm SD (n = 3).

All of the tested compounds showed a certain selectivity toward MAO B, with most of them achieving IC_{50} values in the low micromolar range. The 4-F derivative **5g** showed a noteworthy IC_{50} (1.35 μM), a value that is even lower than that of the reference pargyline. The absence of chemical groups able to create covalent bonds, such as the propargylamine fragment in pargyline, suggested a tight, yet reversible, interaction at the binding site of the enzyme for **5g**. Compounds **5c–h** were also assayed as inhibitors of human

cholinesterases [45], but they proved to be inactive as AChE inhibitors and scarcely active toward BChE at 10 μM . Meanwhile, the 4-Cl derivative **5h** displayed less than 44% antiaggregating activity against amyloidogenic A β (1-40) peptide at 100 μM .

3. Materials and Methods

3.1. Chemistry

Materials and general procedures. All reagents and solvents were purchased from Merck (Darmstadt, Germany), J.T. Baker (Phillipsburg, NJ, USA), or Sigma-Aldrich Chemical Co. (St. Louis, MO, USA) and, unless specified, used without further purification. The melting points (m.p.) of all of the compounds were determined using a SMELTING POINT 10 apparatus in open capillaries (Bibby Sterilin Ltd., Stone, UK). IR spectra were recorded using an Infracum FT-801 FTIR spectrometer (ISP SB RAS, Novosibirsk, Russia). The samples were analyzed as KBr disk solids and the more important frequencies are shown in cm^{-1} . ^1H and ^{13}C NMR spectra were recorded in chloroform- d_3 (CDCl_3) or dimethylsulfoxide- d_6 ($\text{DMSO}-d_6$) solutions at 25 $^\circ\text{C}$ with a 600-MHz NMR spectrometer (JEOL Ltd., Tokyo, Japan). Peak positions were given in parts per million (ppm), referenced to the appropriate solvent residual peak, and signal multiplicities were collected by: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet), br.s (broad singlet), and m (multiplet). MALDI mass spectra were recorded using a Bruker autoflex speed instrument operating in positive-ion reflectron mode (Bremen, Germany). The data of compound **5a** were collected at room temperature using an STOE diffractometer Pilatus100K detector, focusing on mirror collimation Cu $K\alpha$ (1.54086 \AA) radiation, in rotation method mode. STOE X-Area software was used for cell refinement and data reduction. Data collection and image processing were performed with X-Area 1.67 (STOE & Cie GmbH, Darmstadt, Germany, 2013). Intensity data were scaled with LANA (part of X-Area) in order to minimize the differences in intensities of symmetry-equivalent reflections (multiscan method).

3.1.1. Synthesis of 2-Alkyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **3a–d**

Phosphorus chloride was added dropwise in a volume of 10 mL to anthranilic acids **1a–c** (0.0146 mol), which was then added in 1 equivalent excess of (0.0146 mol) 1-alkylpiperidine-4-one **2a,b**. Next, the reaction was stirred for 4 h at 100 $^\circ\text{C}$ and controlled by TLC in an ethyl acetate—hexane (1:1) system on Silufol plates. After cooling, the resulting solution was neutralized with dilute NaOH solution to pH = 9–10, and the product was extracted with CH_2Cl_2 . The organic phase was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The product was obtained by crystallization from diethyl ether.

2-benzyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (3a). Light-yellow crystals, yield 92%, m.p. = 120–121 $^\circ\text{C}$. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.16 (1H, dd, $J = 8.3, 1.4$ Hz), 8.00 (1H, dd, $J = 8.5, 1.1$ Hz), 7.69 (1H, ddd, $J = 8.3, 6.8, 1.4$ Hz), 7.55 (1H, ddd, $J = 8.2, 6.9, 1.2$ Hz), 7.42 (2H, d, $J = 7.0$ Hz), 7.37 (2H, t, $J = 7.6$ Hz), 7.31 (1H, t, $J = 7.3$ Hz), 3.93 (2H, s), 3.82 (2H, s), 3.24 (2H, t, $J = 5.9$ Hz), 2.90 (2H, t, $J = 6.0$ Hz). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 157.4, 147.5, 139.9, 138.1, 129.9, 129.4(2C), 129.1, 128.8(2C), 127.7, 127.1, 127.0, 125.4, 123.9, 62.8, 54.5, 49.9, 34.0. HRMS (MALDI+) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{ClN}_2$ in form of $[\text{M} + \text{H}]^+$ ion 309.1159, found: 309.1176.

2-benzyl-8-bromo-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (3b). Brown crystals, yield 86%. m.p. = 138–139 $^\circ\text{C}$. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.32 (1H, d, $J = 2.3$ Hz), 7.85 (1H, d, $J = 8.8$ Hz), 7.75 (1H, dd, $J = 8.9, 2.2$ Hz), 7.41 (2H, d, $J = 7.5$ Hz), 7.37 (2H, t, $J = 7.4$ Hz), 7.32 (1H, d, $J = 7.1$ Hz), 3.92 (2H, s), 3.82 (2H, s), 3.21 (2H, t, $J = 6.0$ Hz), 2.90 (2H, t, $J = 5.9$ Hz). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 157.8, 145.8, 138.5, 133.3, 130.6(2C), 129.2(2C), 128.6(2C), 127.6, 126.4, 126.1(2C), 121.0, 62.6, 54.3, 49.6, 33.8. HRMS (MALDI+) m/z calcd for $\text{C}_{19}\text{H}_{16}\text{BrClN}_2$ in form of $[\text{M} + \text{H}]^+$ ion 387.0264, found: 387.0280. The observed characterization data (^1H) were consistent with those previously reported in the literature [46].

2-methyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (3c). Light-yellow crystals, yield 68%, m.p. = 94–95 °C. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.18 (1H, dd, *J* = 8.4, 0.9 Hz), 8.00 (1H, dd, *J* = 8.4, 0.6 Hz), 7.70 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.56 (1H, ddd, *J* = 8.2, 6.8, 1.2 Hz), 3.84 (2H, s), 3.28 (2H, t, *J* = 6.0 Hz), 2.87 (2H, t, *J* = 6.0 Hz), 2.58 (3H, s). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 156.6, 147.2, 139.5, 129.8, 128.9, 126.8, 126.6, 125.1, 123.7, 56.0, 52.5, 46.1, 33.8. HRMS (MALDI+) *m/z* calcd for C₁₃H₁₃ClN₂ in form of [M + H]⁺ ion 233.0846, found: 233.0831.

2-methyl-8-nitro-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (3d). Yellow crystals, yield 75%, m.p. = 172–173 °C. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 9.10 (1H, d, *J* = 2.5 Hz), 8.43 (1H, dd, *J* = 9.2, 2.5 Hz), 8.09 (1H, d, *J* = 9.2 Hz), 3.88 (2H, s), 3.31 (2H, t, *J* = 5.9 Hz), 2.92 (2H, t, *J* = 6.0 Hz), 2.61 (3H, s). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 161.2, 149.4, 146.0, 141.3, 131.1, 128.9, 124.6, 123.5, 121.3, 56.0, 52.2, 46.1, 34.2. HRMS (MALDI+) *m/z* calcd for C₁₃H₁₂ClN₃O₂ in form of [M + H]⁺ ion 278.0696, found: 278.0704.

3.1.2. Synthesis of 2-Vinyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **4a,b** and 1-Vinyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **4c**

To a solution of 0.2 g of benzonaphthyridines **3a,b** in 5 mL of methanol with 0.5 mL of formic acid was added a 1.2 equivalent of activated alkyne. The reaction was kept at room temperature for 10 days. Compounds **4a,b** spontaneously fell out of the reaction mass in the form of crystals and were released by filtration.

To a solution of 0.2 g of benzonaphthyridines **3d** in 5 mL of trifluoroethanol with 0.5 mL was added a 1.2 equivalent of activated alkyne. The reaction was kept at room temperature for 15 days. The product was obtained by crystallization from diethyl ether.

Methyl (2E)-3-(10-chloro-3,4-dihydrobenzo[*b*][1,6]naphthyridin-2(1H)-yl)prop-2-enoate (4a). White crystals, yield 59%. m.p. = 171–172 °C. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.21 (1H, dd, *J* = 8.4, 1.4 Hz), 8.02 (1H, d, *J* = 8.5 Hz), 7.76 (1H, ddd, *J* = 8.3, 6.8, 1.4 Hz), 7.63 (1H, d, *J* = 6.4 Hz), 7.65–7.61 (2H, m), 4.89 (1H, d, *J* = 13.2 Hz), 4.57 (2H, s), 3.71 (3H, s), 3.70–3.69 (2H, m), 3.27 (2H, t, *J* = 6.0 Hz). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 169.8, 155.5, 151.4, 147.4, 130.5, 129.1, 129.1, 127.6, 125.3, 123.8, 86.5, 50.9. HRMS (MALDI+) *m/z* calcd for C₁₆H₁₅ClN₂O₂ in form of [M + H]⁺ ion 303.0900, found: 303.0911.

Methyl (2E)-3-(8-bromo-10-chloro-3,4-dihydrobenzo[*b*][1,6]naphthyridin-2(1H)-yl)prop-2-enoate (4b). Yellow crystals, yield 67%. m.p. = 194–195 °C. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.36 (1H, d, *J* = 2.1 Hz), 7.88 (1H, d, *J* = 9.0 Hz), 7.81 (1H, dd, *J* = 9.0, 2.1 Hz), 7.62 (1H, d, *J* = 13.1 Hz), 4.90 (1H, d, *J* = 13.1 Hz), 4.56 (2H, s), 3.71 (3H, s), 3.69 (2H, m), 3.26 (2H, t, *J* = 6.0 Hz). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 169.8, 156.1, 151.3, 146.0, 134.1, 130.9, 126.4, 126.1, 121.8, 86.8, 50.9. HRMS (MALDI+) *m/z* calcd for C₁₆H₁₄BrClN₂O₂ in form of [M + H]⁺ ion 381.0005, found: 381.0014.

(3E)-4-(10-chloro-2-methyl-8-nitro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridin-1-yl)but-3-en-2-one (4c). White crystals, yield 62%. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 9.13 (1H, d, *J* = 2.2 Hz), 8.49 (1H, dd, *J* = 9.2, 2.5 Hz), 8.13 (1H, d, *J* = 9.2 Hz), 6.82 (1H, dd, *J* = 16.0, 7.0 Hz), 6.04 (1H, d, *J* = 15.9 Hz), 4.86 (1H, d, *J* = 6.9 Hz), 3.41–3.34 (1H, m), 3.27–3.22 (1H, m), 3.16 (1H, dd, *J* = 4.8, 2.4 Hz), 3.03–2.99 (1H, m), 2.60 (3H, s), 2.26 (3H, s). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 197.8, 161.2, 149.5, 146.0, 143.0, 140.9, 134.6, 131.0, 128.8, 124.7, 123.9, 121.5, 62.0, 45.6, 42.4, 31.4, 27.7. HRMS (MALDI+) *m/z* calcd for C₁₇H₁₆ClN₃O₃ in form of [M + H]⁺ ion 346.0958, found: 346.0981.

3.1.3. Synthesis of 2-Alkyl-10-chloro-1-phenylethynyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **5a–h**

A solution of **3a,c** (0.5 g) in 10 mL of THF was cooled to 0 °C, then a 1.5 equivalent excess of DIAD (diisopropylazodicarboxylate) was added. The mixture was stirred at room temperature for 1 h. After cooling it again to 0 °C, a 3 equivalent excess of the appropriate phenylacetylene and CuI catalyst were added. The reaction was stirred at room temperature and controlled by TLC in an ethyl acetate-hexane (1:5) system on Silufol plates. The product was separated by column chromatography.

2-benzyl-10-chloro-1-phenylethynyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthridine (5a). Colorless crystals, yield 24%. m.p. = 139–140 °C. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.22 (1H, d, *J* = 8.3 Hz), 8.01 (1H, d, *J* = 8.3 Hz), 7.72 (1H, t, *J* = 7.6 Hz), 7.57 (1H, t, *J* = 7.7 Hz), 7.50–7.43 (4H, m), 7.38 (2H, t, *J* = 7.5 Hz), 7.34–7.28 (4H, m), 5.31 (1H, s), 4.09 (1H, d, *J* = 13.0 Hz), 3.91 (1H, d, *J* = 13.1 Hz), 3.35–3.41 (1H, m), 3.31 (1H, td, *J* = 11.5, 3.6 Hz), 3.18 (1H, dd, *J* = 16.6, 3.6 Hz), 3.08 (1H, dd, *J* = 11.6, 6.7 Hz). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 156.7, 147.6, 140.6, 138.0, 131.9(2C), 130.2, 129.2(2C), 128.8, 128.6(2C), 128.4(2C), 128.3, 127.6, 126.9, 125.3, 124.2(2C), 122.8, 87.5, 84.3, 59.4, 52.8, 44.8, 33.4. IR spectrum (KBr), ν/cm⁻¹: 2223.1 (C≡C). HRMS (MALDI+) *m/z* calcd for C₂₇H₂₁ClN₂ in form of [M + H]⁺ ion 409.1471, found: 409.1483.

2-benzyl-10-chloro-1-(3-methoxyphenyl)ethynyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthridine (5b). Oil, yield 35%. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.21 (1H, d, *J* = 8.4 Hz), 8.01 (1H, d, *J* = 8.5 Hz), 7.71 (1H, t, *J* = 7.7 Hz), 7.57 (1H, t, *J* = 7.8 Hz), 7.47 (2H, d, *J* = 7.4 Hz), 7.37 (2H, t, *J* = 7.5 Hz), 7.31 (1H, t, *J* = 7.3 Hz), 7.20 (1H, t, *J* = 8.0 Hz), 7.05 (1H, d, *J* = 7.6 Hz), 6.96 (1H, s), 6.86 (1H, dd, *J* = 8.2, 2.6 Hz), 5.30 (1H, s), 4.08 (1H, d, *J* = 13.1 Hz), 3.90 (1H, d, *J* = 13.1 Hz), 3.78 (3H, s), 3.41–3.34 (1H, m), 3.30 (1H, td, *J* = 11.6, 3.6 Hz), 3.18 (1H, dd, *J* = 16.4, 3.1 Hz), 3.07 (1H, dd, *J* = 11.5, 6.8 Hz). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 159.4, 156.7, 138.0, 130.3, 129.5, 129.2(2C), 128.8, 128.7(2C), 127.6, 127.5, 127.0, 125.4, 124.6(2C), 124.2, 123.8, 116.9(2C), 115.0, 87.5, 84.1, 59.4, 55.4, 52.9, 44.8, 33.3. IR spectrum (KBr), ν/cm⁻¹: 2222.9 (C≡C). HRMS (MALDI+) *m/z* calcd for C₂₈H₂₃ClN₂O in form of [M + H]⁺ ion 439.1577, found: 439.1558.

10-chloro-2-methyl-1-phenylethynyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthridine (5c). Oil, yield 32%. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.23 (1H, d, *J* = 8.4 Hz), 8.01 (1H, d, *J* = 8.3 Hz), 7.72 (1H, t, *J* = 7.6 Hz), 7.58 (1H, t, *J* = 7.6 Hz), 7.39 (2H, dd, *J* = 7.4, 2.2 Hz), 7.25 (3H, m), 5.30 (1H, s), 3.41 (1H, ddd, *J* = 17.4, 11.7, 7.3 Hz), 3.28 (1H, td, *J* = 11.8, 4.2 Hz), 3.18 (1H, dd, *J* = 17.3, 4.1 Hz), 2.98 (1H, dd, *J* = 12.0, 7.3 Hz), 2.69 (3H, s). IR spectrum (KBr), ν/cm⁻¹: 2225.8 (C≡C). HRMS (MALDI+) *m/z* calcd for: C₂₁H₁₇ClN₂ in form of [M + H]⁺ ion 333.1159, found: 333.1142.

10-chloro-2-methyl-1-[3-(methoxyphenyl)ethynyl]-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthridine (5d). Oil, yield 85%. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.23 (1H, d, *J* = 8.5 Hz), 8.04 (1H, d, *J* = 8.4 Hz), 7.73 (1H, t, *J* = 7.7 Hz), 7.59 (1H, t, *J* = 7.7 Hz), 7.17 (1H, t, *J* = 8.0 Hz), 6.99 (1H, d, *J* = 7.7 Hz), 6.91 (1H, s), 6.84 (1H, dd, *J* = 8.5, 2.6 Hz), 5.35 (1H, s), 3.75 (3H, s), 3.49 (1H, ddd, *J* = 18.2, 11.8, 7.3 Hz), 3.34 (1H, td, *J* = 11.9, 4.5 Hz), 3.23 (1H, dd, *J* = 17.5, 4.3 Hz), 3.05 (1H, dd, *J* = 12.1, 7.2 Hz), 2.74 (3H, s). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 159.3, 155.4, 147.4, 140.9, 130.6, 129.5, 128.7, 127.2, 125.4, 124.5(2C), 124.2, 123.4, 116.8, 115.2, 88.1, 82.8, 55.4, 54.6, 46.9, 43.1, 32.6. IR spectrum (KBr), ν/cm⁻¹: 2216.1 (C≡C). HRMS (MALDI+) *m/z* calcd for: C₂₂H₁₉ClN₂O in form of [M + H]⁺ ion 363.1264, found: 363.1281.

10-chloro-2-methyl-1-[4-(methoxyphenyl)ethynyl]-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthridine (5e). Oil, yield 88%. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.23 (1H, d, *J* = 8.3 Hz), 8.01 (1H, d, *J* = 8.4 Hz), 7.72 (1H, ddd, *J* = 8.3, 6.9, 1.4 Hz), 7.58 (1H, ddd, *J* = 8.2, 6.8, 1.2 Hz), 7.33 (2H, d, *J* = 8.9 Hz), 6.79 (2H, d, *J* = 8.9 Hz), 5.28 (1H, s), 3.77 (3H, s), 3.46–3.34 (1H, m), 3.28 (1H, td, *J* = 11.7, 4.3 Hz), 3.18 (1H, dd, *J* = 17.4, 3.4 Hz), 2.97 (1H, dd, *J* = 11.9, 7.3 Hz), 2.68 (3H, s). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 159.7, 156.1, 147.6, 140.4, 133.3(2C), 130.2, 128.9, 127.6, 126.9, 125.4, 124.3, 114.9, 113.9(2C), 87.5, 82.3, 55.4, 54.7, 46.9, 43.2, 33.1. IR spectrum (KBr), ν/cm⁻¹: 2222.3 (C≡C). HRMS (MALDI+) *m/z* calcd for: C₂₂H₁₉ClN₂O in form of [M + H]⁺ ion 363.1264, found: 363.1279.

2-benzyl-10-chloro-1-[4-(trifluoromethyl)phenyl]ethynyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthridine (5f). Oil, yield 61%. ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.24 (1H, d, *J* = 8.6 Hz), 8.05 (1H, d, *J* = 8.6 Hz), 7.75 (1H, t, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.7 Hz), 7.42 (2H, *J* = 8.5 Hz), 7.12 (2H, d, *J* = 8.4 Hz), 5.34 (1H, s), 3.52–3.46 (1H, m), 3.33–3.26 (1H, m), 3.23 (1H, dd, *J* = 17.4, 4.1 Hz), 3.05 (1H, dd, *J* = 12.2, 7.4 Hz), 2.73 (3H, s). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 155.5, 149.2, 133.5(2C), 130.6, 128.7, 127.32, 125.4, 124.3(2C), 121.4, 121.3, 120.9(2C), 119.6, 86.8, 84.2, 60.5, 54.6, 47.0, 43.1, 32.6. IR spectrum (KBr),

ν/cm^{-1} : 2221.2 ($-\text{C}\equiv\text{C}-$). HRMS (MALDI+) m/z calcd for: $\text{C}_{22}\text{H}_{16}\text{ClN}_2\text{F}_3$ in form of $[\text{M} + \text{H}]^+$ ion 401.1032, found: 401.1041.

10-chloro-1-[4-fluorophenyl]ethynyl]-2-methyl-1,2,3,4-tetrahydrobenzo[b][1,6]-naphthyridine (5g). Oil, yield 44%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.23 (1H, d, $J = 8.4$ Hz), 8.03 (1H, d, $J = 8.5$ Hz), 7.73 (1H, t, $J = 7.3$ Hz), 7.59 (1H, t, $J = 7.6$ Hz), 7.40–7.35 (2H, m), 6.99–6.93 (2H, m), 5.31 (1H, s), 3.45 (1H, ddd, $J = 17.4, 11.7, 7.3$ Hz), 3.29 (1H, td, $J = 11.8, 4.4$ Hz), 3.20 (1H, dd, $J = 17.4, 4.3$ Hz), 3.02 (1H, dd, $J = 11.9, 7.2$ Hz), 2.71 (3H, s). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 163.3, 161.6, 155.6, 147.3, 140.5, 133.7, 133.6, 130.2, 128.6, 126.9, 125.1, 124.0, 118.5, 115.5, 115.4, 86.6, 83.0, 54.5, 46.8, 42.9, 32.6. IR spectrum (KBr), ν/cm^{-1} : 2227.1 ($-\text{C}\equiv\text{C}-$). IR spectrum (KBr), ν/cm^{-1} : 2227.1 ($-\text{C}\equiv\text{C}-$). HRMS (MALDI+) m/z calcd for $\text{C}_{21}\text{H}_{16}\text{ClFN}_2$ in form of $[\text{M} + \text{H}]^+$ ion 351.1064, found: 351.1049.

10-chloro-1-[4-chlorophenyl]ethynyl]-2-methyl-1,2,3,4-tetrahydrobenzo[b][1,6]-naphthyridine (5h). Oil, yield 59%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.24 (1H, dd, $J = 8.5, 0.9$ Hz), 8.11 (1H, d, $J = 8.4$ Hz), 7.78 (1H, ddd, $J = 8.3, 6.9, 1.4$ Hz), 7.63 (1H, ddd, $J = 8.3, 6.9, 1.2$ Hz), 7.32 (2H, d, $J = 8.7$ Hz), 7.25 (2H, d, $J = 6.7$ Hz), 5.44 (1H, s), 3.67–3.58 (1H, m), 3.45–3.36 (1H, m), 3.32 (1H, dd, $J = 17.8, 4.4$ Hz), 3.17 (1H, m), 2.81 (3H, s). IR spectrum (KBr), ν/cm^{-1} : 2223.0 ($-\text{C}\equiv\text{C}-$). HRMS (MALDI+) m/z calcd for: $\text{C}_{21}\text{H}_{16}\text{Cl}_2\text{N}_2$ in form of $[\text{M} + \text{H}]^+$ ion 367.0769, found: 367.0780.

3.1.4. Synthesis of Compounds 6a–f

The appropriate tetrahydrobenzobenzonaphthyridines **5c,d,f,g** were dissolved in isopropanol at room temperature and cooled for 10 min in the freezer, then a 1.2 equivalent of activated alkyne was added and the mixture was stored in the refrigerator for 1 week. The reaction was controlled by TLC in an ethyl acetate/n-hexane 1:1 system on Silufol plates. The product was separated by column chromatography.

Methyl (2E)-3-{10-chloro-1-[4-fluorophenyl]ethynyl]-2-methyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridin-1-yl}prop-2-enoate (6a). Oil, yield 27%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.26 (1H, d, $J = 8.6, 1.4, 0.6$ Hz), 7.99 (1H, d, $J = 8.5, 0.6$ Hz), 7.74 (1H, t, $J = 7.6$ Hz), 7.56 (1H, t, $J = 7.6$ Hz), 7.44 (2H, dd, $J = 8.8, 5.3$ Hz), 7.00 (2H, t, $J = 8.7$ Hz), 6.83 (1H, d, $J = 15.6$ Hz), 6.50 (1H, d, $J = 15.6$ Hz), 3.76 (3H, s), 3.53–3.49 (1H, m), 3.17–3.12 (2H, m), 3.07–3.03 (1H, m), 2.53 (3H, s). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 166.9, 163.8, 162.1, 156.5, 147.5, 142.8, 134.1, 134.1, 131.0, 128.9, 128.7, 127.4, 126.4, 125.2, 124.7, 124.6, 118.8, 116.0, 88.3, 83.46, 63.6, 52.1, 48.0, 40.0, 35.1. IR spectrum (KBr), ν/cm^{-1} : 2224.3 ($-\text{C}\equiv\text{C}-$); 1724 (C = O). HRMS (MALDI+) m/z calcd for: $\text{C}_{25}\text{H}_{20}\text{ClFN}_2\text{O}_2$ in form of $[\text{M} + \text{H}]^+$ ion 435.1276, found: 435.1261.

Methyl (2E)-3-{10-chloro-1-[3-methoxyphenyl]ethynyl]-2-methyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridin-1-yl}prop-2-enoate (6b). Oil, yield 22%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.27 (1H, d, $J = 8.1$ Hz), 7.99 (1H, d, $J = 8.3$ Hz), 7.73 (1H, t, $J = 7.6$ Hz), 7.57 (1H, t, $J = 7.7$ Hz), 7.21 (1H, t, $J = 8.0$ Hz), 7.07 (1H, d, $J = 7.6$ Hz), 6.98 (1H, s), 6.88 (1H, dd, $J = 8.2, 2.7$ Hz), 6.83 (1H, d, $J = 15.6$ Hz), 6.51 (1H, d, $J = 15.6$ Hz), 3.79 (3H, s), 3.75 (3H, s), 3.51 (1H, ddd, $J = 17.9, 12.0, 6.1$ Hz), 3.20–3.12 (2H, m), 3.05 (1H, ddd, $J = 11.7, 6.1, 1.9$ Hz), 2.53 (3H, s). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 166.7, 159.4, 156.3, 147.3, 142.6, 130.7, 130.2, 129.5, 129.4, 128.6, 128.5, 127.1, 128.8, 126.2, 124.9, 124.5, 123.4, 116.9, 115.1, 89.0, 83.3, 63.4, 60.5, 55.4, 51.9, 47.8. IR spectrum (KBr), ν/cm^{-1} : 2224.3 ($-\text{C}\equiv\text{C}-$); 1724 (C = O). HRMS (MALDI+) m/z calcd for $\text{C}_{26}\text{H}_{23}\text{ClN}_2\text{O}_3$ in form of $[\text{M} + \text{H}]^+$ ion 447.1476, found: 447.1460.

(3E)-4-[10-chloro-2-methyl-1-(phenylethynyl)-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridin-1-yl]but-3-en-2-one (6c). White crystals, yield 37%, m.p. = 154–155 °C. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.28 (1H, d, $J = 8.5$ Hz), 8.01 (1H, d, $J = 8.5$ Hz), 7.75 (1H, ddd, $J = 8.3, 6.8, 1.3$ Hz), 7.58 (1H, ddd, $J = 8.3, 6.8, 1.2$ Hz), 7.47 (2H, dd, $J = 7.4, 1.9$ Hz), 7.32–7.30 (3H, m), 6.73 (1H, d, $J = 16.1$ Hz), 6.63 (1H, d, $J = 16.1$ Hz), 3.59–3.47 (1H, m), 3.24–3.11 (2H, m), 3.06 (1H, ddd, $J = 13.1, 6.1, 2.5$ Hz), 2.53 (3H, s), 2.31 (3H, s). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 198.6, 156.0, 147.1, 146.2, 142.4, 134.2(2C), 131.8(2C), 130.6, 128.6, 128.5, 128.3(2C), 127.0(2C), 126.0, 124.3, 122.2, 89.3, 82.9, 63.5, 47.7, 39.6, 34.7. IR spectrum (KBr),

ν/cm^{-1} : 2219.3 ($-\text{C}\equiv\text{C}-$); 1675.5 ($\text{C}=\text{O}$). HRMS (MALDI+) m/z calcd for: $\text{C}_{25}\text{H}_{21}\text{ClN}_2\text{O}$ in form of $[\text{M} + \text{H}]^+$ ion 401.1421, found: 401.1411.

(3E)-4-(10-chloro-1-[(3-methoxyphenyl)ethynyl]-2-methyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridin-1-yl)but-3-en-2-one (6d). Oil, yield 34%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.28 (1H, ddd, $J = 8.5, 1.3, 0.6$ Hz), 8.01 (1H, dd, $J = 8.5, 0.6$ Hz), 7.75 (1H, ddd, $J = 8.4, 6.8, 1.4$ Hz), 7.58 (1H, ddd, $J = 8.3, 6.8, 1.2$ Hz), 7.21 (1H, ddd, $J = 8.2, 7.6, 0.4$ Hz), 7.07 (1H, ddd, $J = 7.6, 1.4, 1.0$ Hz), 6.97 (1H, dd, $J = 2.7, 1.3$ Hz), 6.88 (1H, ddd, $J = 8.4, 2.6, 1.0$ Hz), 6.72 (1H, d, $J = 16.1$ Hz), 6.62 (1H, d, $J = 16.1$ Hz), 3.79 (3H, s), 3.53 (1H, ddd, $J = 16.0, 11.6, 6.2$ Hz), 3.23–3.11 (2H, m), 3.06 (1H, ddd, $J = 13.4, 6.2, 2.8$ Hz), 2.53 (3H, s), 2.31 (3H, s). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 166.8, 159.5, 156.3, 147.3, 142.7, 130.8, 129.5, 128.7, 128.6, 127.1, 126.2, 125.0, 124.6, 124.5, 123.5, 122.1, 116.9, 115.2, 111.8, 89.0, 83.3, 63.4, 60.5, 55.4, 51.9, 47.8. IR spectrum (KBr), ν/cm^{-1} : 2219.3 ($-\text{C}\equiv\text{C}-$); 1723.8 ($\text{C}=\text{O}$). HRMS (MALDI+) m/z calcd for: $\text{C}_{26}\text{H}_{23}\text{ClN}_2\text{O}_2$ in form of $[\text{M} + \text{H}]^+$ ion 431.1526, found: 431.1539.

(3E)-4-(10-chloro-2-methyl-1-[4-(trifluoromethyl)phenyl]ethynyl)-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridin-1-yl)but-3-en-2-one (6e). Oil, yield 42%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.28 (1H, d, $J = 8.5$ Hz), 8.01 (1H, d, $J = 8.5$ Hz), 7.76 (1H, t, $J = 7.7$ Hz), 7.64–7.55 (1H, m), 7.49 (2H, d, $J = 8.4$ Hz), 7.16 (2H, d, $J = 8.8$ Hz), 6.69 (1H, d, $J = 16.1$ Hz), 6.62 (1H, d, $J = 16.1$ Hz), 3.56–3.50 (1H, m), 3.17 (2H, m), 3.07 (1H, m), 2.52 (3H, s), 2.31 (3H, s). IR spectrum (KBr), ν/cm^{-1} : 2220.9 ($-\text{C}\equiv\text{C}-$); 1721.4 ($\text{C}=\text{O}$). HRMS (MALDI+) m/z calcd for: $\text{C}_{26}\text{H}_{20}\text{ClF}_3\text{N}_2\text{O}$ in form of $[\text{M} + \text{H}]^+$ ion 469.1295, found: 469.1301.

Methyl 5-(4-chloro-2-ethenylquinolin-3-yl)-4-(4-fluorobenzyl)-1-methyl-1H-pyrrole-3-carboxylate (7). Oil, yield 3%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.07 (1H, d, ddd, $J = 8.5, 1.4, 0.7$ Hz), 7.99 (1H, d, $J = 8.5$ Hz), 7.69 (1H, ddd, $J = 8.4, 6.9, 1.4$ Hz), 7.56 (1H, ddd, $J = 8.3, 6.9, 1.1$ Hz), 7.25 (1H, s), 7.07–7.04 (2H, m), 6.74 (2H, t, $J = 8.8$ Hz), 6.68 (1H, dd, $J = 16.7, 10.6$ Hz), 6.32 (1H, dd, $J = 16.8, 2.0$ Hz), 5.42 (1H, dd, $J = 10.6, 1.9$ Hz), 4.40 (2H, s), 3.60 (3H, s), 3.46 (3H, s). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 165.0, 155.6, 133.7, 132.0, 132.0, 130.9, 130.9, 130.3(2C), 129.9, 128.2(2C), 127.7(2C), 126.9, 125.7, 124.5, 124.5, 124.5, 122.4, 114.5, 114.3, 51.0, 35.5, 26.8. HRMS (MALDI+) m/z calcd for: $\text{C}_{25}\text{H}_{20}\text{ClFN}_2\text{O}_2$ in form of $[\text{M} + \text{H}]^+$ ion 435.1276, found: 435.1268.

3.1.5. Synthesis of 2-Benzyl-10-chloro-1-(indol-3-yl)-1,2,3,4-tetrahydrobenzo[b][1,6]-naphthyridines **8a–d**

A solution of **3a** (0.5 g) in 10 mL of THF was cooled to 0 °C, then a 1.2 equivalent excess of DIAD (diisopropylazodicarboxylate) was added. The mixture was stirred at room temperature for 1 h. After cooling it again to 0 °C, a 1.5 equivalent excess of the appropriate indole was added. The reaction was stirred at room temperature and controlled by TLC in an ethyl acetate/hexane (1:1) system on Silufol plates. The product was separated by column chromatography.

2-benzyl-10-chloro-1-(5-methoxy-1H-indol-3-yl)-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine (8a). Yellow foamed oil, yield 61%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.17 (1H, d, $J = 7.6$ Hz), 8.08 (1H, d, $J = 8.4$ Hz), 8.03 (1H, s), 7.74 (1H, ddd, $J = 8.4, 6.9, 1.3$ Hz), 7.57 (1H, ddd, $J = 8.1, 6.9, 1.0$ Hz), 7.44 (2H, d, $J = 7.2$ Hz), 7.37 (2H, t, $J = 7.5$ Hz), 7.33–7.29 (1H, m), 7.20 (1H, d, $J = 8.7$ Hz), 7.01 (1H, d, $J = 2.4$ Hz), 6.84 (1H, dd, $J = 8.7, 2.5$ Hz), 6.36 (1H, d, $J = 2.5$ Hz), 5.76 (1H, s), 4.00 (1H, d, $J = 13.2$ Hz), 3.79 (3H, s), 3.65 (1H, d, $J = 13.2$ Hz), 3.44–3.33 (2H, m), 3.09–3.05 (1H, m), 3.03–2.99 (1H, m). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 157.5, 154.2, 147.5, 141.9, 139.2, 131.4, 130.0(2C), 129.6, 129.3(2C), 128.8, 128.6(2C), 127.8, 127.4, 126.9(2C), 125.0, 124.2, 115.3, 112.9, 111.9, 101.3, 57.5, 55.9, 42.5, 29.1. HRMS (MALDI+) m/z calcd for: $\text{C}_{28}\text{H}_{24}\text{ClN}_3\text{O}$ in form of $[\text{M} + \text{H}]^+$ ion 454.1686, found: 454.1669.

2-benzyl-10-chloro-1-(1H-indol-3-yl)-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine (8b). Compound was isolated in mixture with hydrazine **9**. Yellow foamed oil, yield 48%. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.31 (1H, s), 8.22 (1H, s), 8.16 (1H, d, $J = 8.3$ Hz), 8.08 (1H, d, $J = 8.4$ Hz), 7.73 (1H, t, $J = 7.7$ Hz), 7.62 (1H, d, $J = 8.0$ Hz), 7.56 (1H, t, $J = 7.6$ Hz),

7.41 (1H, d, $J = 7.5$ Hz), 7.38–7.33 (2H, m), 7.34–7.28 (3H, m), 7.19 (1H, t, $J = 7.6$ Hz), 7.15–7.09 (2H, m), 6.42 (1H, s), 5.84 (1H, s), 4.01 (1H, d, $J = 13.3$ Hz), 3.61 (1H, d, $J = 13.2$ Hz), 3.39 (1H, ddd, $J = 18.4, 11.8, 7.3$ Hz), 3.26 (1H, td, $J = 12.5, 5.0$ Hz), 3.10 (1H, dd, $J = 17.9, 4.8$ Hz), 2.94 (1H, dd, $J = 13.1, 7.3$ Hz). HRMS (MALDI+) m/z calcd for: $C_{27}H_{22}ClN_3$ in form of $[M + H]^+$ ion 424.1581, found: 424.1591.

2-benzyl-10-chloro-1-(5-chloro-1H-indol-3-yl)-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (8c). Compound was isolated in mixture with hydrazine **9**. Yellow foamed oil, yield 51%. 1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.34 (1H, s), 8.17–8.16 (2H, m), 8.08 (1H, d, $J = 8.4$ Hz), 7.75 (1H, ddd, $J = 8.3, 6.7, 1.4$ Hz), 7.61–7.56 (2H, m), 7.54 (1H, d, $J = 2.1$ Hz), 7.42–7.39 (5H, m), 7.35–7.33 (2H, m), 7.24 (2H, d, $J = 8.6$ Hz), 7.14 (2H, dd, $J = 8.6, 2.0$ Hz), 6.38 (1H, d, $J = 2.4$ Hz), 5.73 (1H, s), 3.97 (1H, d, $J = 13.1$ Hz), 3.62 (1H, d, $J = 13.1$ Hz), 3.39 (1H, ddd, $J = 18.4, 12.0, 7.2$ Hz), 3.29 (1H, td, $J = 12.7, 4.9$ Hz), 3.06 (1H, dd, $J = 17.9, 4.8$ Hz), 3.01 (1H, dd, $J = 13.4, 7.1$ Hz). HRMS (MALDI+) m/z calcd for: $C_{27}H_{21}Cl_2N_3$ in form of $[M + H]^+$ ion 458.1191, found: 458.1183.

2-benzyl-10-chloro-1-(5-bromo-1H-indol-3-yl)-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (8d). Compound was isolated in mixture with hydrazine **9**. Yellow foamed oil, yield 69%. 1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.18 (1H, s), 8.17 (1H, dd, $J = 8.3, 1.3$ Hz), 8.08 (1H, d, $J = 8.5$ Hz), 7.77–7.72 (2H, m), 7.69 (1H, s), 7.58 (1H, ddd, $J = 8.3, 6.8, 1.2$ Hz), 7.42 (3H, d, $J = 4.4$ Hz), 7.37–7.33 (1H, m), 7.27 (1H, d, $J = 1.9$ Hz), 7.19 (1H, d, $J = 8.6$ Hz), 6.34 (1H, s), 5.72 (1H, s), 3.96 (1H, d, $J = 13.0$ Hz), 3.62 (1H, d, $J = 13.0$ Hz), 3.39 (1H, ddd, $J = 18.1, 12.0, 7.2$ Hz), 3.30 (1H, td, $J = 12.7, 4.9$ Hz), 3.06 (1H, dd, $J = 17.9, 4.8$ Hz), 3.02 (1H, dd, $J = 13.3, 7.1$ Hz). HRMS (MALDI+) m/z calcd for: $C_{27}H_{21}BrClN_3$ in form of $[M + H]^+$ ion 502.0686, found: 502.0678.

3.1.6. Synthesis of 1-[2-Benzyl-6-chloro-5-(indol-3-yl)-2,5-dihydro-1H-azepino[3,4-*b*]quinolin-4-yl]ethanones **10a,b**

The appropriate compounds **8a,d** were dissolved in isopropanol at room temperature and cooled for 10 min in the freezer, then a 1.2 equivalent of activated alkyne was added and the mixture was stored in the refrigerator for 1 week. The reaction was controlled by TLC in an ethyl acetate/hexane 1:1 system on Silufol plates. The compound spontaneously fell out of the reaction mass in the form of crystals and was released by filtration.

1-[(4E)-3-benzyl-7-chloro-6-(5-methoxy-1H-indol-3-yl)-1,2,3,6-tetrahydroazocino[4,5-*b*]quinolin-5-yl]ethanone (10a). White crystals, yield 87%, m.p. = 147–149 °C. 1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.33 (1H, s), 8.30 (1H, dd, $J = 8.3, 1.3$ Hz), 7.94 (1H, d, $J = 8.4$ Hz), 7.76 (1H, s), 7.72 (1H, ddd, $J = 8.4, 6.9, 1.4$ Hz), 7.61 (1H, ddd, $J = 8.3, 6.9, 1.2$ Hz), 7.21 (1H, s), 7.18 (1H, d, $J = 8.8$ Hz), 7.15–7.10 (1H, m), 7.03 (2H, t, $J = 7.7$ Hz), 6.74 (1H, dd, $J = 8.8, 2.5$ Hz), 6.71 (2H, d, $J = 7.4$ Hz), 6.61 (1H, s), 4.31 (1H, d, $J = 15.0$ Hz), 4.22 (1H, d, $J = 15.0$ Hz), 4.22–4.18 (1H, m), 3.47 (3H, s), 3.30 (1H, ddd, $J = 16.9, 10.9, 7.4$ Hz), 3.17–3.11 (2H, m), 2.42 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 195.0, 174.5, 171.2, 160.4, 156.5, 153.6, 136.0, 132.3, 132.0, 129.7, 128.7(2C), 128.6, 127.9(2C), 127.3(2C), 127.0, 126.3, 125.9, 125.1(2C), 122.4, 119.3, 112.0, 101.3, 61.8, 60.4, 55.4, 51.0, 39.8, 36.5. IR spectrum (KBr), ν/cm^{-1} : 1695.7 (C = O). HRMS (MALDI+) m/z calcd for: $C_{32}H_{28}ClN_3O_2$ in form of $[M + H]^+$ ion 522.1948, found: 522.1956.

1-[(4E)-3-benzyl-7-chloro-6-(5-bromo-1H-indol-3-yl)-1,2,3,6-tetrahydroazocino[4,5-*b*]quinolin-5-yl]ethanone (10b). White crystals, yield 82%, m.p. = 136–137 °C. 1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.32 (1H, s), 8.30 (1H, d, $J = 8.4$ Hz), 7.94 (1H, d, $J = 8.8$ Hz), 7.78–7.69 (2H, m), 7.62 (1H, t, $J = 7.6$ Hz), 7.24 (1H, s), 7.22–7.14 (2H, m), 7.15 (1H, t, $J = 7.4$ Hz), 7.06 (2H, t, $J = 7.6$ Hz), 6.72 (2H, d, $J = 7.4$ Hz), 6.61 (1H, s), 4.32 (1H, d, $J = 15.0$ Hz), 4.24 (1H, d, $J = 15.0$ Hz), 4.16–4.09 (1H, m), 3.31 (1H, ddd, $J = 16.7, 10.6, 7.1$ Hz), 3.17–3.11 (2H, m), 2.42 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 194.7, 159.9, 156.1, 146.4, 143.3, 135.8, 135.3, 131.7, 129.7, 128.7, 128.6(2C), 127.8(2C), 127.6, 127.2(2C), 127.0, 125.8, 125.1, 124.9, 122.6, 121.9, 119.7, 112.7, 112.6, 61.8, 50.7, 40.0, 35.9, 25.4. IR spectrum (KBr), ν/cm^{-1} : 1700.3 (C = O). HRMS (MALDI+) m/z calcd for: $C_{31}H_{25}BrClN_3O$ in form of $[M + H]^+$ ion 570.0948, found: 570.0969.

3.2. Biochemical Assays

MAO Inhibition

All reagents were purchased from Sigma Aldrich (Milan, Italy). The fluorometric assay was performed as previously described [17] using human recombinant enzymes from baculovirus-infected insect cells, following the formation of fluorescing 4-hydroxyquinoline from the MAO substrate, kynuramine. Assays were performed in triplicate in 96-well plates (Greiner Bio-One GmbH, Frickenhausen, Germany) using an Infinite M1000 multiplate reader (Tecan, Cernusco sul Naviglio (MI), Italy). Results were expressed as mean \pm SEM. IC₅₀ values were obtained by nonlinear regression using Prism software (GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, CA, USA).

4. Conclusions

As a major outcome of this study, novel functionalized 2-alkyl-10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **3** were synthesized for the first time, specifically 1-phenylethynyl derivatives **5** and 1-indol-3-yl derivatives **8**. Moreover, the interaction of these compounds with activated alkynes was studied, revealing that the substituent in the first position played a key role in these reactions and either Stevens rearrangement products or azocino[4,5-*b*]quinolines were formed.

The 1-phenylethynyl derivatives **5c–h** were discovered as MAO inhibitors, showing selectivity toward the human MAO B isoform and potency in the low micromolar range. In particular, the 4-F derivative **5g** achieved an IC₅₀ of 1.35 μ M in vitro, which was almost equipotent with pargyline (IC₅₀ 2.69), a known MAO B irreversible inhibitor that was taken as the positive control. MAO B inhibitors are typically used in the treatment of early symptoms of PD [47], while their efficacy in decreasing oxidative stress may provide neuroprotective effects in the treatment of AD [48]. In this context, compound **5g** deserves further optimization studies for improving its pharmacological potential as an effective agent for the treatment of neurodegenerative syndromes.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules28041662/s1>, Figures S1–S48: Copies of ¹H and ¹³C NMR spectra. Table S1: Crystal data and structure refinement for **5a**.

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References

1. Lowe, P.A. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, UK, 1984; Volume 1.
2. Devadoss, T.; Sowmya, V.; Bastati, R. Synthesis of 1,6-Naphthyridine and Its Derivatives: A Systematic Review. *ChemistrySelect* **2021**, *15*, 3610–3641. [[CrossRef](#)]

3. Ghobadi, N.; Nazari, N.; Gholamzadeh, P. The Friedländer reaction: A powerful strategy for the synthesis of heterocycles. *Adv. Heterocycl. Chem.* **2020**, *132*, 85–134. [[CrossRef](#)]
4. Lavanya, M.; Lin, C.; Mao, J.; Thirumalai, D.; Aabaka, S.R.; Yang, X.; Mao, J.; Huang, Z.; Zhao, J. Synthesis and Anticancer Properties of Functionalized 1,6-Naphthyridines. *Top. Curr. Chem.* **2021**, *379*, 13. [[CrossRef](#)] [[PubMed](#)]
5. Wu, J.F.; Liu, M.M.; Huang, S.X.; Wang, Y. Design and synthesis of novel substituted naphthyridines as potential c-Met kinase inhibitors based on MK-2461. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3251–3255. [[CrossRef](#)]
6. Kiselev, E.; Dexheimer, T.; Pommier, Y.; Cushman, M. Design, synthesis, and evaluation of dibenzo[c,h][1,6]naphthyridines as topoisomerase I inhibitors and potential anticancer agents. *J. Med. Chem.* **2010**, *24*, 8716–8726. [[CrossRef](#)]
7. Galatsis, P.; Yamagata, K.; Wendt, J.A.; Connolly, C.J.; Mickelson, J.W.; Milbank, J.B.; Bove, S.E.; Knauer, C.S.; Brooker, R.M.; Augelli-Szafran, C.E.; et al. Synthesis and SAR comparison of regioisomeric aryl naphthyridines as potent mGlu5 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6525–6528. [[CrossRef](#)]
8. Cywin, C.L.; Zhao, B.P.; McNeil, D.W.; Hrapchak, M.; Prokopowicz, A.S., III; Goldberg, D.R.; Morwick, T.M.; Gao, A.; Jakes, S.; Kashem, M.; et al. Discovery and SAR of novel, Naphthyridines as potent inhibitors of spleen tyrosine kinase (SYK). *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1415–1418. [[CrossRef](#)]
9. Chan, L.; Jin, H.; Stefanac, T.; Lavallée, J.F.; Falardeau, G.; Wang, W. Discovery of 1,6-naphthyridines as a novel class of potent and selective human cytomegalovirus inhibitors. *J. Med. Chem.* **1999**, *42*, 3023–3025. [[CrossRef](#)]
10. Yu, H.-B.; Yang, F.; Sun, F.; Ma, G.-Y.; Gan, J.-H.; Hu, W.-Z.; Han, B.-N.; Jiao, W.-H.; Lin, H.-W. Cytotoxic Aaptamine Derivatives from the South China Sea Sponge *Aaptos aaptos*. *J. Nat. Prod.* **2014**, *77*, 2124. [[CrossRef](#)]
11. Pham, C.-D.; Hartmann, R.; Müller, W.E.G.; Voogd, N.D.; Lai, D.; Proksch, P. Aaptamine Derivatives from the Indonesian Sponge *Aaptos suberitoides*. *J. Nat. Prod.* **2013**, *76*, 103–106. [[CrossRef](#)]
12. Rajivgandhi, G.; Ramachandran, G.; Manoharan, N. Marine sponge alkaloid aaptamine enhances the anti-bacterial and anti-cancer activity against ESBL producing Gram negative bacteria and HepG 2 human liver carcinoma cells. *Biocatal. Agric. Biotech.* **2019**, *17*, 628–637. [[CrossRef](#)]
13. Rudys, S.; Luci, C.R.; Roth, E.P.; Cikotiene, I.; Padron, J.M. Antiproliferative activity of novel benzo[b][1,6]naphthyridines in human solid tumor cell lines. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1504–1506. [[CrossRef](#)]
14. Deady, L.W.; Rodemann, T.; Zhuang, L.; Baguley, B.C.; Denny, W.A. Synthesis and Cytotoxic Activity of Carboxamide Derivatives of Benzo[b][1,6]naphthyridines. *J. Med. Chem.* **2003**, *46*, 1049–1054. [[CrossRef](#)]
15. Fiorito, J.; Vendome, J.; Saeed, F.; Staniszewski, A.; Zhang, H.; Yan, S.; Deng, S.X.; Arancio, O.; Landry, D.W. Identification of a novel 1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine analogue as a potent phosphodiesterase 5 inhibitor with improved aqueous solubility for the treatment of Alzheimer's disease. *J. Med. Chem.* **2017**, *60*, 8858–8875. [[CrossRef](#)]
16. Purgatorio, R.; Kulikova, L.N.; Pisani, L.; Catto, M.; de Candia, M.; Carrieri, A.; Cellamare, S.; De Palma, A.; Beloglazkin, A.A.; Reza Raesi, G.; et al. Scouting around 1,2,3,4-Tetrahydrochromeno[3,2-c]pyridin-10-ones for Single- and Multitarget Ligands Directed towards Relevant Alzheimer's Targets. *ChemMedChem* **2020**, *15*, 1947–1955. [[CrossRef](#)]
17. Nevskaya, A.A.; Anikina, L.V.; Purgatorio, R.; Catto, M.; Nicolotti, O.; de Candia, M.; Pisani, L.; Borisova, T.N.; Miftyakhova, A.R.; Varlamov, A.V.; et al. Homobivalent lamellarin-like schiff bases: In vitro evaluation of their cancer cell cytotoxicity and multitargeting anti-Alzheimer's disease potential. *Molecules* **2021**, *26*, 359. [[CrossRef](#)]
18. Catto, M.; Berezin, A.A.; Lo Re, D.; Loizou, G.; Demetriades, M.; De Stradis, A.; Campagna, F.; Koutentis, P.A.; Carotti, A. Design, synthesis and biological evaluation of benzo[e][1,2,4]triazin-7(1H)-one and [1,2,4]-triazino[5,6,1-jk]carbazol-6-one derivatives as dual inhibitors of beta-amyloid aggregation and acetyl/butyryl cholinesterase. *Eur. J. Med. Chem.* **2012**, *58*, 84–97. [[CrossRef](#)]
19. Titov, A.A.; Kobzev, M.S.; Catto, M.; de Candia, M.; Gambacorta, N.; Denora, N.; Pisani, L.; Nicolotti, O.; Borisova, T.N.; Varlamov, A.V.; et al. Away from Flatness: Unprecedented Nitrogen-bridged Cyclopenta[a]indene Derivatives as Novel Anti-Alzheimer Multitarget Agents. *ACS Chem. Neurosci.* **2021**, *12*, 340–353. [[CrossRef](#)]
20. Samadi, A.; de los Ríos, C.; Bolea, I.; Chioua, M.; Iriepa, I.; Moraleda, I.; Bartolini, M.; Andrisano, V.; Gálvez, E.; Valderas, C.; et al. Multipotent MAO and cholinesterase inhibitors for the treatment of Alzheimer's disease: Synthesis, pharmacological analysis and molecular modeling of heterocyclic substituted alkyl and cycloalkyl propargyl amine. *Eur. J. Med. Chem.* **2012**, *52*, 251–262. [[CrossRef](#)]
21. Berlowitz, I.; Egger, K.; Cumming, P. Monoamine Oxidase Inhibition by Plant-Derived β -Carbolines; Implications for the Psychopharmacology of Tobacco and Ayahuasca. *Front. Pharmacol.* **2022**, *13*, 886408. [[CrossRef](#)]
22. Maleki, B.; Seresht, E.R.; Ebrahimi, Z. Friedlander synthesis of quinolines promoted by polymer-bound sulfonic acid. *Org. Prep. Proc. Int.* **2015**, *47*, 149–160. [[CrossRef](#)]
23. Chen, Q.P.; Deady, L.W. Synthesis of some benzo[b][1,6]naphthyridines and benzo[b][1,7]naphthyridines. *Austral. J. Chem.* **1993**, *46*, 987–993. [[CrossRef](#)]
24. Wolinska, E.; Paliakov, E.; Streckowski, L. Facile synthesis of 1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridines. *Heteroc. Commun.* **2009**, *15*, 63–66. [[CrossRef](#)]
25. Kumar, P.; Aggarwal, T.; Verma, A.K. Chemoselective Azidation of o-Alkynylaldehydes over [3+2] Cycloaddition and Subsequent Staudinger Reaction: Access to Benzonaphthyridines/Naphthyridines. *J. Org. Chem.* **2017**, *82*, 6388–6397. [[CrossRef](#)] [[PubMed](#)]
26. Ravi, M.; Chauhan, P.; Singh, S.; Kant, R.; Yadav, P.P. p-TsOH-promoted synthesis of (E)-6-phenyl-7-styryl-5,6-dihydrodibenzo[b,h][1,6]naphthyridines via cascade intramolecular aza-Michael addition/Friedlander condensation of 2'-aminochalcones in a SDS/H₂O system. *RSC Adv.* **2017**, *6*, 48774–48778. [[CrossRef](#)]

27. Voskressensky, L.G.; Borisova, T.N.; Listratova, A.; Vorobiev, I.V.; Varlamov, A.V.; Aleksandrov, G.G. First synthesis and x-ray crystal structure of hexahydrobenzo[b]pyrido[3,4,5-de]-1,6-naphthyridines. *J. Heteroc. Chem.* **2005**, *42*, 1207–1210. [[CrossRef](#)]
28. Voskressensky, L.G.; Vorobiev, I.V.; Borisova, T.N.; Kulikova, L.N.; Bolshov, A.V.; Varlamov, A.V. The first synthesis of tetrahydrobenzo[b]pyrrolo [2,1-f][1,6]naphthyridine by the Michael addition of butyn-2-one to 1-(2-methoxycarbonylviny)tetrahydrobenzo[b][1,6]naphthyridine. *Russ. Chem. Bull.* **2010**, *59*, 1063–1064. [[CrossRef](#)]
29. Voskressensky, L.G.; Vorobiev, I.V.; Borisova, T.N.; Varlamov, A.V. Synthesis and reactivity of a novel class of long-lived ammonium ylides: Derivatives of benzo[b]pyrrolo[2,1-f][1,6]naphthyridine. *J. Org. Chem.* **2008**, *73*, 4596–4601. [[CrossRef](#)]
30. Kulikova, L.N.; Borisov, R.S.; Voskressensky, L.G. Ring opening in 1,2,3,4-tetrahydrochromeno[3,2-c]pyridines under the action of electron-deficient alkynes. *Mendel. Comm.* **2017**, *27*, 640–641. [[CrossRef](#)]
31. Zheng, Q.H.; Meng, W.; Jiang, G.J.; Yu, Z.X. CuI-catalyzed C1-alkynylation of tetrahydroisoquinolines (THIQs) by A³ reaction with tunable iminium ions. *Org. Lett.* **2013**, *15*, 5928–5931. [[CrossRef](#)]
32. Liu, W.; Liu, S.; Jin, R.; Guo, H.; Zhao, J. Novel strategies for catalytic asymmetric synthesis of C1-chiral 1, 2, 3, 4-tetrahydroisoquinolines and 3, 4-dihydrotetrahydroisoquinolines. *Org. Chem. Front.* **2015**, *2*, 288–299. [[CrossRef](#)]
33. Zhao, H.; He, W.; Wei, L.; Cai, M. A highly efficient heterogeneous copper-catalyzed three-component coupling of tetrahydroisoquinolines, aldehydes and 1-alkynes. *Cat. Sci. Technol.* **2016**, *6*, 1488–1495. [[CrossRef](#)]
34. Singh, K.N.; Singh, P.; Kaur, A.; Singh, P. C-1 Alkynylation of N-methyltetrahydroisoquinolines through CDC: A direct access to phenethylisoquinoline alkaloids. *Synlett* **2012**, *23*, 760–764. [[CrossRef](#)]
35. Voskressensky, L.G.; Titov, A.A.; Kobzev, M.S.; Samavati, R.; Borisov, R.S.; Kulikova, L.N.; Varlamov, A.V. The first synthesis of 6-(phenylethynyl)-substituted tetrahydroazocino[5,4-b]indoles. *Chem. Heteroc. Comp.* **2016**, *52*, 68–70. [[CrossRef](#)]
36. Voskressensky, L.G.; Borisova, T.N.; Kulikova, L.N.; Dolgova, E.G.; Kleimenov, A.I.; Sorokina, E.A.; Titov, A.A.; Varlamov, A.V. Reaction of 1-substituted tetrahydro-β-carbolines with activated alkynes—a new original approach to the synthesis of tetrahydroazocino[5,4-b]indoles. *Chem. Heteroc. Comp.* **2007**, *43*, 587–598. [[CrossRef](#)]
37. Voskressensky, L.G.; Borisova, T.N.; Ovcharov, M.V.; Kulikova, L.N.; Sorokina, E.A.; Borisov, R.S.; Varlamov, A.V. Transformations of tetrahydro-pyrido[4,3-d]pyrimidines[b]-condensed with isoxazole, thiazole, thiadiazole, and triazole units under the action of activated alkynes. *Chem. Heteroc. Comp.* **2008**, *44*, 1510–1519. [[CrossRef](#)]
38. Voskressensky, L.G.; Kulikova, L.N.; Kleimenov, A.V.; Borisova, T.N.; Nikitina, E.V.; Listratova, A.V.; Varlamov, A.V. Interaction of 4-hydroxymethyl-2-(3,4-dimethoxybenzyl)isoindoline with methyl propiolate. *Chem. Heteroc. Comp.* **2009**, *45*, 372–374. [[CrossRef](#)]
39. Voskressensky, L.G.; Kulikova, L.N.; Gozun, S.V.; Khrustalev, V.N.; Borisova, T.N.; Listratova, A.V.; Ovcharov, M.V.; Varlamov, A.V. The reaction of tetrahydrochromeno[3,4-c]pyridines with activated alkynes. The first synthesis of tetrahydrochromeno[4,3-d]azocines. *Tetr. Lett.* **2011**, *52*, 4189–4191. [[CrossRef](#)]
40. Voskressensky, L.G.; Ovcharov, M.V.; Borisova, T.N.; Kulikova, L.N.; Listratova, A.V.; Borisov, R.S.; Varlamov, A.V. 2-Alkyl-4-oxohexahydropyrimido[4,5-d]- and -[5,4-d]azocines. *Chem. Heteroc. Comp.* **2011**, *47*, 222–228. [[CrossRef](#)]
41. Voskressensky, L.G.; de Candia, M.; Carotti, A.; Borisova, T.N.; Kulikova, L.N.; Varlamov, A.V.; Altomare, C. Investigation on the antiplatelet activity of pyrrolo[3,2-c]pyridine-containing compounds. *J. Pharm. Pharmacol.* **2003**, *55*, 323–332. [[CrossRef](#)]
42. Ciriaco, F.; Gambacorta, N.; Trisciuzzi, D.; Nicolotti, O. PLATO: A Predictive Drug Discovery Web Platform for Efficient Target Fishing and Bioactivity Profiling of Small Molecules. *Int. J. Mol. Sci.* **2022**, *8*, 5245. [[CrossRef](#)] [[PubMed](#)]
43. Ciriaco, F.; Gambacorta, N.; Alberga, D.; Nicolotti, O. Quantitative polypharmacology profiling based on a multifingerprint similarity predictive approach. *J. Chem. Inf. Model.* **2021**, *61*, 4868–4876. [[CrossRef](#)] [[PubMed](#)]
44. Montaruli, M.; Alberga, D.; Ciriaco, F.; Trisciuzzi, D.; Tondo, A.R.; Mangiatordi, G.F.; Nicolotti, O. Accelerating drug discovery by early protein drug target prediction based on multi-fingerprint similarity search. *Molecules* **2019**, *24*, 2233. [[CrossRef](#)] [[PubMed](#)]
45. Purgatorio, R.; de Candia, M.; Catto, M.; Rullo, M.; Pisani, L.; Denora, N.; Carrieri, A.; Nevskaya, A.A.; Voskressensky, L.G.; Altomare, C.D. Evaluation of Water-Soluble Mannich Base Prodrugs of 2,3,4,5-Tetrahydroazepino[4,3-b]indol-1(6H)-one as Multitarget-Directed Agents for Alzheimer’s Disease. *ChemMedChem* **2021**, *16*, 589–598. [[CrossRef](#)]
46. Landry, D.W.; Deng, S.; Arancio, O.; Fiorito, J.; Wasmuth, A. Phosphodiesterase Inhibitors and Uses Thereof. U.S. Patent 10,626,113 B2, 21 April 2020.
47. Binde, C.D.; Tvette, I.F.; Gasemyr, J.; Natvig, B.; Klemp, M. A multiple treatment comparison meta-analysis of monoamine oxidase type B inhibitors for Parkinson’s disease. *Br. J. Clin. Pharmacol.* **2018**, *84*, 1917–1927. [[CrossRef](#)]
48. Youdim, M.B.H. Monoamine oxidase inhibitors, and iron chelators in depressive illness and neurodegenerative diseases. *J. Neural. Transm.* **2018**, *125*, 1719–1733. [[CrossRef](#)]

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