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Fused Azolium Salts XVIII [1]. Synthesis and Reactivity of a Novel Fused Heteroaromatic System: [1,2,3]Triazolo[1,5-*b*]isoquinolinium Salts

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Summary. Oxidative cyclization of 3-isoquinolyl ketone hydrazones afforded the novel tricyclic heteroaromatic [1,2,3]triazolo[1,5-*b*]isoquinolinium salts. The reactivity of the ring system towards nucleophiles proved to be regioselective. Secondary amines induced ring opening of the pyridine moiety, forming a triazolyl substituted benzaldehyde derivative; sodium borohydride afforded partially reduced derivatives of the parent compound.

Keywords. Triazolium salt; Ring closure; Regiospecificity, Ring opening; Indole synthesis.

Kondensierte Azoliumsalze, 18. Mitt. [1]**. Synthese und Reaktivität eines neuen kondensierten heteroaromatischen Systems: [1,2,3]Triazolo[1,5-*b*]isochinoliniumsalze**

Zusammenfassung. Die oxidierende Cyclisierung von 3-Isochinolylketonhydrazonen ergab die neuen tricyclischen [1,2,3]Triazolo[1,5-*b*]isochinoliniumsalze. Die Reaktivität des Ringsystems gegenüber Nukleophilen erwies sich regioselektiv. Bei Reaktion mit sekundären Aminen trat Öffnung des Pyridinringes ein; die Reaktion mit Natriumborhydrid führte zu partiell reduzierten Derivaten der Ausgangsverbindung.

Introduction

In continuation of our studies on fused azolium salts [1], the synthesis and the investigation of the reactivity of the hitherto unknown linearly fused heteroaromatic system of [1,2,3]triazolo[1,5-*b*]isoquinolinium salts attracted our interest. In this paper we report their synthesis and discuss some reactions of these new compounds.

Results and Discussion

Commercially available 3-cyanoisoquinoline (**1**) was transformed to various ketones (**3**) with *Grignard* reagents (**2**). The ketones in turn reacted with *p*-

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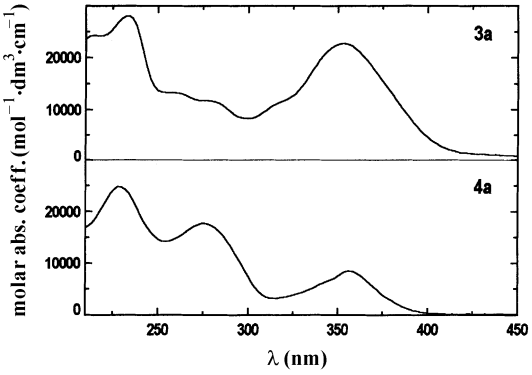


Fig. 1. Comparison of the UV spectra (acetonitrile, 25°C) of hydrazone **4a** and triazolium salt **5a**

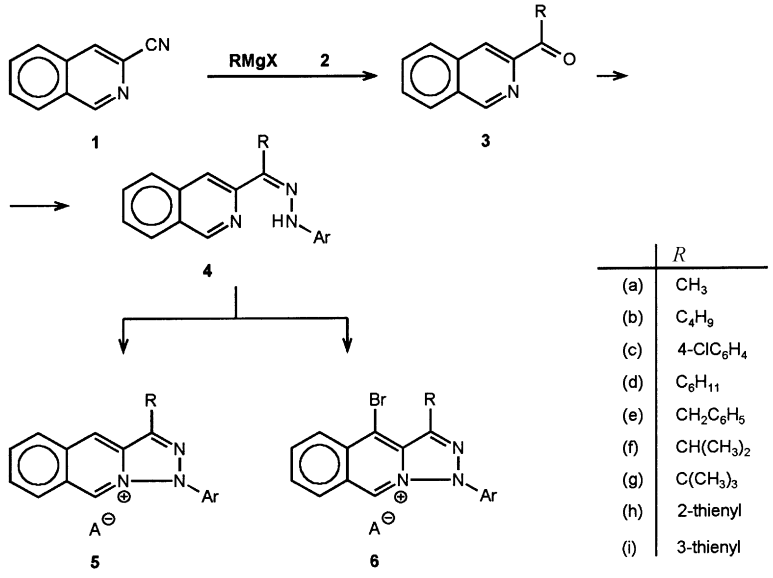
bromophenylhydrazine to give the corresponding hydrazones **4**. Inspection of the ^{1}H NMR spectra of **4** revealed that the majority of these compounds were obtained as pure geometric isomers and proved to be *E* isomers; only in some cases (*e.g.* **4d**, **f**, and **i**) the *Z* isomer was formed. In this respect, the NH shift seemed to be of diagnostic importance: in the *Z* isomers (*i.e.* those containing the NH group in a chelate form), the δ value of this proton is larger than 12 ppm, whereas that of the *E* derivatives amounts to less than 8 ppm.

In order to achieve the desired ring closure of the appropriate isoquinolyl ketone arylhydrazones (**4**), a well established synthetic path (oxidative cyclization) was applied [1]. Treatment of compounds **4** with *N*-bromosuccinimide (*NBS*) or 2,4,4,6-tetrabromo-cyclohexa-2,5-dien-1-one (*TBB*) afforded the novel linearly fused heteroaromatic [1,2,3]triazolo[1,5-*b*]isoquinolinium salts **5**. The spectroscopic characteristics of **5** support the formation of the extended heteroaromatic system: the blue shift of the first maximum and the disappearance of the absorbance at 260 nm in the UV (Fig. 1) indicate the change of the chromophore, whereas the appearance of two downfield shifted singlets of H-4 and H-9 in the ^{1}H NMR spectrum of the product reveals the formation of the positively charged heteroaromatic cation.

Two unexpected problems arose in the course of this preparative route:

(1) The synthesis of the hydrazones **4** can be carried out both in a neutral organic solvent and in acetic acid. Although traces of acetic acid could never be removed entirely from the product obtained by the acidic method, we routinely applied this method because the yield was higher and the impurity did not affect the subsequent ring closure reaction. However, in the case of the reaction of **3d**, **e**, **f** with 4-bromophenylhydrazine we found that isoquinolylindoles **7–9** were formed instead of the expected hydrazones **4**. These compounds are obviously products of a *Fischer* type indole synthesis derived from the primarily formed hydrazones **4 d**, **e**, **f**. They can exist in the hydro form (**7** and **9**) or in the heteroaromatic from (**8**), depending on whether C-3 of the indole moiety bears a hydrogen available for the tautomerism.

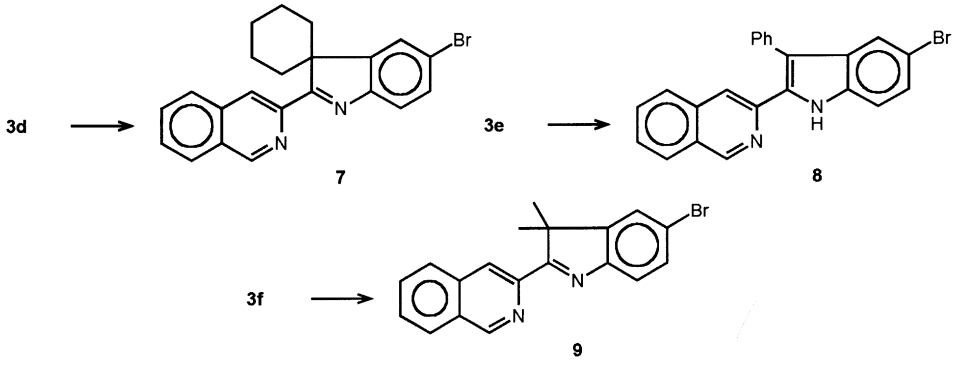
(2) Unlike our earlier observations with the analogous triazolopyridazinium and tetrazoloisoquinolinium ring systems [2, 3] we experienced that, in some cases,



	R
(a)	CH_3
(b)	C_4H_9
(c)	4-ClC_6H_4
(d)	C_6H_{11}
(e)	$CH_2C_6H_5$
(f)	$CH(CH_3)_2$
(g)	$C(CH_3)_3$
(h)	2-thienyl
(i)	3-thienyl

Ar = 4-BrC_6H_4

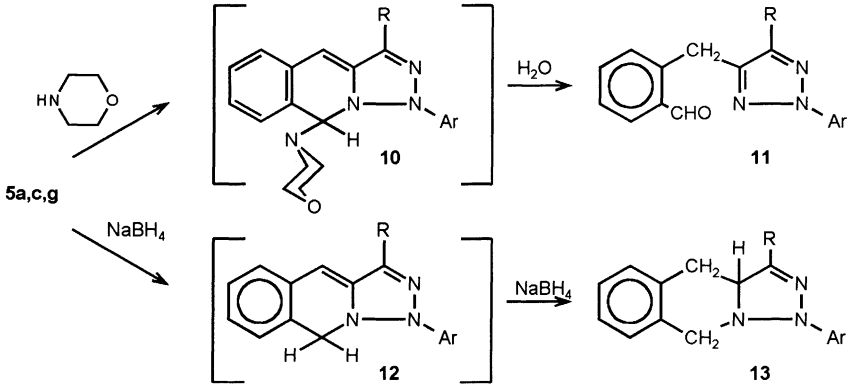
Scheme 1



Scheme 2

an excessive bromination at C-4 takes place during the ring closure (presence of **6** as an impurity was detected in the NMR spectrum of the crude product), which apparently is due to the high reactivity of this position towards electrophiles. In order to avoid this undesired side reaction, in some cases (*e.g.* for $R = CH_3$ and C_4H_9) ring closure had to be carried out at low temperatures using exactly three molar equivalents of the reagent. This is the minimal amount of the reagent needed because the primarily formed ring closed bromide salt rapidly takes up one molecule of bromine to form the perbromide salt.

Investigation of the reactivity of the linearly fused tricyclic salts **5** revealed that – according to our expectations – this ring system reacts with nucleophiles



$Ar = 4\text{-}BrC_6H_4$; R : (a) CH_3 (c) $4\text{-}ClC_6H_4$ (g) $(CH_3)_3C$

Scheme 3

selectively at position 9. Thus, when a solution of **5a**, **5c**, or **5g** ($A = BF_4$) in acetonitrile was treated with morpholine at room temperature, the colour of the reaction mixture turned deep yellow or red, and work-up of the mixture by addition of water afforded the aldehydes **11**. The course of the reaction leading to these compounds can be rationalized by the formation of the intermediate **10** which first undergoes cycloreversion; a subsequent hydrolytic step removes the morpholino group to yield the final product **11**.

A different behaviour was observed when the triazolium salts **5a**, **5c**, and **5g** ($A = BF_4$) reacted with sodium borohydride. Although the nucleophilic attack of the hydride anion is expected to afford the same type of intermediate as above (**12**), a rapid subsequent reduction took place at C-3a–C-4, preventing the cycloreversion reaction observed with **10** and affording the tricyclic compound **13**.

The high regioselectivity of the new linearly fused tricyclic triazolium salts **5** ($A = BF_4$) towards nucleophiles seems to be in good accordance with our earlier findings with related heteroaromatic salts [3, 4, 5]. Further study of the reactivity of this ring system is in progress.

Experimental

Melting points were determined with a Büchi apparatus; NMR spectra were recorded on Varian VXR-200 and Varian Unity Inova 400 spectrometers; mass spectra were measured on an MS-902 spectrometer (EI technique, resolution: 10000).

General procedure for the synthesis of **3a–h**

To a stirred solution of 15.4 g (0.1 mol) 3-cyanoisoquinoline (**1**; Sigma-Aldrich) in 350 ml dry ether, a solution of the appropriate *Grignard* reagent (0.12 mol) in 150 ml of dry ether was added dropwise at 0°C. Stirring was continued at 0°C for 2 h, and the reaction mixture was kept at 5°C for 12 h. After pouring on ice containing 10 g ammonium chloride, the mixture was acidified with 20% sulfuric acid ($pH = 1$), thoroughly shaken, and neutralized with 20% sodium hydroxide solution. The aqueous layer was separated and extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was dissolved in dichloromethane, filtered through alumina, and evaporated to dryness. **3f** and **3g** were purified by vacuum distillation.

Methyl 3-isoquinolyl ketone (**3a**; $C_{11}H_9NO$)

The *Grignard* reagent was prepared from methyl iodide; yield: 8.5 g (50%); m.p.: 84–86°C; the crude product (Ref. [6]: m.p.: 92–92.8°C) proved to be suitable for further conversions; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.28$ (s, 1H, H-1), 8.47 (s, 1H, H-4), 8.07–7.96 (m, 2H, H-5, 8), 7.81–7.69 (m, 2H, H-6, 7), 2.83 (s, 3H, H-Me) ppm.

n-Butyl 3-isoquinolyl ketone (**3b**; $C_{14}H_{15}NO$)

The *Grignard* reagent was prepared from *n*-butyl bromide; yield: 14.5 g (40.0%); m.p.: 58–59°C; ^{1}H NMR (200 MHz, $CDCl_3$); $\delta = 9.27$ (s, 1H, H-1), 8.46 (s, 1H, H-4), 8.05–7.96 (m, 2H, H-5, 6), 7.79–7.66 (m, 2H, H-6, 7), 3.31 (t, $J = 7.4$ Hz, 2H, CH_2), 1.76 (m, 2H, CH_2), 1.44 (m, 2H, CH_2), 0.96 (t, $J = 7.3$ Hz, 3H, CH_3) ppm; $C_{14}H_{15}NO$ (213.28); calcd.: C 78.84, H 7.09, N 6.57; found: C 78.93, H 6.98, N 6.76.

4-p-Chlorophenyl 3-isoquinolyl ketone (**3c**; $C_{16}H_{10}ClNO$)

The *Grignard* reagent was prepared from 4-bromochlorobenzene; m.p.: 127–128°C (Ref. [7]: m.p.: 125–127°C); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.32$ (s, 1H, H-1), 8.49 (s, 1H, H-4), 8.10–7.98 (m, 2H, H-5, 8), 8.09–7.45 (AA′BB′, 4H, H-aryl), 7.83–7.91 (m, 2H, H-6, 7) ppm.

Cyclohexyl 3-isoquinolyl ketone (**3d**; $C_{16}H_{17}NO$)

The *Grignard* reagent was prepared from cyclohexyl chloride; the crude product (m.p.: 81–82°C, Ref. [8]: m.p.: 85–87°C, yield: 12.6 g (52.6%)) proved to be suitable for further conversions; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.28$ (s, 1H, H-1), 8.46 (s, 1H, H-4), 8.07–7.96 (m, 2H, H-5, 8), 7.80–7.67 (m, 2H, H-6, 7), 3.97 (m, 1H, H-1′), 2.00–1.25 (m, 10H, H-cyclohexyl) ppm.

Benzyl 3-isoquinolyl ketone (**3e**; $C_{17}H_{13}NO$)

The *Grignard* reagent was prepared from benzyl bromide; this compound has been reported earlier without complete analytical characterization [9]; yield: 12.6 g (51.1%); m.p.: 77°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.31$ (s, 1H, H-1), 8.49 (s, 1H, H-4), 8.08–7.93 (m, 2H, H-5, 8), 7.79–7.19 (m, 2H, H-6, 7), 7.42–7.23 (m, 5H, H-phenyl), 4.66 (s, 2H, H-CH_2) ppm; $C_{17}H_{13}NO$ (247.30); calcd.: C 82.57, H 5.30, N 5.66; found: C 82.41, H 5.07, N 5.46.

Isopropyl 3-isoquinolyl ketone (**3f**; $C_{13}H_{11}NO$)

The *Grignard* reagent was prepared from isopropyl bromide; yield: 12.3 g (61.9%); colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.28$ (s, 1H, H-1), 8.49 (s, 1H, H-4), 8.04 (dd, $J = 7$ Hz, 1.5 Hz, 1H, H-8), 7.98 (dd, $J = 7$ Hz, 1.5 Hz, 1H, H-5) 7.76 (ddd, $J = 7$ Hz, 7 Hz, 1.5 Hz, 1H, H-7), 7.72 (ddd, $J = 7$ Hz, 7 Hz, 1.5 Hz, 1H, H-6), 4.22 (qq, $J = 7$ Hz, 1H, CH); 1.27 (d, $J = 7$ Hz, 6H, CH_3) ppm; $C_{13}H_{11}NO$ (197.24); calcd.: C 79.17, H 5.62, N 7.10; found: C 79.16, H 5.87, N 7.01.

t-Butyl 3-isoquinolyl ketone (**3g**; $C_{14}H_{13}NO$)

The *Grignard* reagent was prepared from *t*-butyl chloride; yield: 11.5 g (52.5%); colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.23$ (s, 1H, H-1), 8.36 (s, 1H, H-4), 8.02 (dd, $J = 7$ Hz, 1.5 Hz, 1H, H-8), 7.96 (dd, $J = 7$ Hz, 1.5 Hz, 1H, H-5), 7.75 (ddd, $J = 7$ Hz, 7 Hz, 1.5 Hz, 1H, H-7), 7.70 (ddd, $J = 7$ Hz, 7 Hz, 1.5 Hz, 1H, H-6), 1.53 (s, 9H, CH_3) ppm; $C_{14}H_{13}NO$ (211.27); calcd.: C 79.59, H 6.20, N 6.63; found: C 79.34, H 6.37, N 6.66.

2-Thienyl 3-isoquinolyl ketone (**3h**; $C_{14}H_9NOS$)

The *Grignard* reagent was prepared from 2-bromothiophene; yield: 19.6 g (81.9%); m.p.: 120–122°C (Refs. [10, 11]: m.p.: 124°C); the crude product proved to be suitable for further conversions.

3-Thienyl 3-isoquinolyl ketone (**3i**; $C_{14}H_9NOS$)

To a stirred solution of 7.9 g (0.03 mol) 3-bromothiophene in 20 ml dry ether, to a solution of *n*-butyllithium in hexane (16.5 ml, 2 *M*, 0.033 mol) was added dropwise under argon at −70°C. After stirring for 15 min, 3-cyanoisoquinoline (**1**, 4.6 g, 0.03 mol) in 40 ml ether was added. The stirred reaction mixture was allowed to warm up to room temperature and was kept at 5°C for 12 h. Water (20 ml) was added under ice-cooling, and the mixture was acidified with 10% hydrochloric acid ($pH = 1$). After stirring for 1 h, the mixture was neutralized with solid sodium hydrogencarbonate. The layers were separated, and the aqueous phase was extracted with ether. The combined organic extracts were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was recrystallized from isopropyl alcohol.

Yield: 12.7 g (53%); m.p.: 86–87°C. (Refs. [10, 11]: m.p.: 89–90°C); $C_{14}N_9NOS$ (239.30); calcd.: C 70.27, H 3.79, N 5.85; found: C 70.16, H 3.87, N 6.06.

General procedure for the synthesis of 3-isoquinolyl ketone arylhydrazones **4a–i**

To a solution of 3-isoquinolyl ketones **4a–i** (0.04 mol) in 70 ml chloroform, a solution of 4-bromophenylhydrazine hydrochloride (8.9 g, 0.044 mol) and sodium acetate (3.6 g, 0.044 mol) in ethanol (70 ml) was added at room temperature. After stirring for 12 h, H_2O was added, and the mixture was extracted with chloroform. The organic layer was evaporated, the residue was triturated with hot methanol, and the precipitate was filtered off and recrystallized from ethanol.

(E)-Methyl 3-isoquinolyl ketone 4-bromophenylhydrazone (**4a**; $C_{17}H_{14}BrN_3$)

Yield: 8.1 g (59.6%); m.p.: 183–187°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.20$ (s, 1H, H-1), 8.41 (s, 1H, H-4), 7.91 (dd, $J = 8.5$ Hz, 8.5 Hz, 2H, H-5, 8), 7.67 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.54 (s, N-H), 7.54 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.42–7.12 (AA′BB′, 4H, H-aryl), 2.47 (s, 3H, CH_3) ppm; $C_{17}H_{14}BrN_3$ (340.22); calcd.: C 60.02, H 4.15, N 12.35; found: C 59.87, H 4.01, N 12.17.

(E)-n-Butyl 3-isoquinolyl ketone 4-bromophenylhydrazone (**4b**; $C_{20}H_{18}BrN_3$)

Yield: 10.7 g (70.0%); m.p.: 185–187°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.21$ (s, 1H, H-1), 8.40 (s, 1H, H-4), 7.91 (dd, $J = 8.5$ Hz, 8.5 Hz, 2H, H-5, 8), 7.67 (s, N-H), 7.66 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.55 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.42–7.10 (AA′BB′, 4H, H-aryl), 3.02 (m, 2H, CH_2), 1.64–1.42 (m, 4H, CH_2), 0.96 (m, 3H, CH_3) ppm; $C_{20}H_{20}BrN_3$ (382.30); calcd.: C 62.83, H 5.27, N 10.99; found: C 62.56, H 5.28, N 10.87.

4-p-Chlorophenyl 3-isoquinolyl ketone 4-bromophenyl hydrazone (**4c**; $C_{22}H_{15}ClBrN_3$)

Yield: 10.0 g (85.8%); m.p.: 138–141°C (mixture of *E* and *Z* isomers); ^{1}H NMR (400 MHz, $CDCl_3$, (*E*)-**4c**): $\delta = 9.17$ (s, 1H, H-1), 8.20 (s, 1H, H-4), 7.94 (d, $J = 8.5$ Hz, 1H, H-8), 7.88 (d, $J = 8.5$ Hz, 1H, H-5), 7.77 (s, N-H), 7.68 (dd, $J = 8.5$ Hz, 8.5 Hz, 1H, H-7), 7.58 (dd, $J = 8.5$ hz, 8.5 Hz, 1H, H-6), 7.59–7.36 (AA′BB′, 4H, H-chlorophenyl), 7.36–7.06 (AA′BB′, 4H, H-bromophenyl) ppm; $C_{22}H_{15}BrClN_3$ (436.74); calcd.: C 60.50, H 3.46, N 9.62; found: C 60.61, H 3.51, N 9.52.

(Z)-Cyclohexyl 3-isoquinolyl ketone 4-bromophenyl hydrazone (**4d**; $C_{22}H_{22}BrN_3$)

Yield: 12.7 g (78.1%); m.p.: 176–178°C; ^{1}H NMR (400 MHz, $CDCl_3$); $\delta = 13.05$ (s, N-H), 9.28 (s, 1H, H-1), 8.00 (d, $J = 8.15$ Hz, 1H, H-8), 7.90 (d, $J = 8.15$ Hz, 1H, H-5), 7.84 (s, 1H, H-4), 7.73 (dd, $J = 8.5$ Hz, 8.5 Hz, 1H, H-7), 7.63 (dd, $J = 8.5$ Hz, 8.5 Hz, 1H, H-6), 7.34–7.07 (AA′BB′, 4H, H-aryl), 2.93 (m, 1H, H-1′), 2.04–1.30 (m, 10H, H-cyclohexyl) ppm; $C_{22}H_{22}BrN_3$ (408.34); calcd.: C 64.71, H 5.43, N 10.29; found: C 64.48, H 5.35, N 10.07.

(E)-Benzyl 3-isoquinolyl ketone 4-bromophenyl hydrazone (**4e**; $C_{23}H_{18}BrN_3$)

Yield: 11.5 g (68.3%); m.p.: 188–189°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.22$ (s, 1H, H-1), 8.52 (s, 1H, H-4), 7.94 (dd, $J = 8.5$ Hz, 8.5 Hz, 2H, H-5, 6), 7.74 (s, N-H), 7.68 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.56 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.35–6.97 (AA′BB′, 4H, H-bromophenyl), 7.33–7.19 (m, 5H, H-phenyl), 4.54 (s, 2H, CH_2) ppm; $C_{23}H_{18}BrN_3$ (416.32); calcd.: C 66.36, H 4.36, N 10.09; found: C 66.14, H 4.22, N 9.86.

(Z)-Isopropyl 3-isoquinolyl ketone 4-bromophenyl hydrazone (**4f**; $C_{19}H_{16}BrN_3$)

Yield: 12.2 g (82.5%); m.p.: 155–157°C; ^{1}H NMR (400 MHz, $CDCl_3$); $\delta = 13.12$ (s, N-H), 9.00 (s, 1H, H-1), 8.00 (d, $J = 8.5$ Hz, 1H, H-8), 7.89 (d, $J = 8.5$ Hz, 1H, H-5), 7.89 (s, 1H, H-4), 7.73 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.64 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.37–7.09 (AA′BB′, 4H, H-aryl), 3.34 (m, 1H, CH), 1.35 (d, $J = 6.7$ Hz, 6H, CH_3) ppm; $C_{19}H_{18}BrN_3$ (368.28); calcd.: C 61.97, H 4.93, N 11.41; found: C 61.86, H 4.95, N 11.32.

(E)-t-Butyl 3-isoquinolyl ketone 4-bromophenyl hydrazone (**4g**; $C_{20}H_{18}BrN_3$)

Yield: 12.3 (80.3%); m.p.: 140–144°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.40$ (s, 1H, H-1), 8.06 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-8), 7.88 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-5), 7.78 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.70 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.64 (s, N-H), 7.30 (s, 1H, H-4), 7.26–6.82 (AA′BB′, 4H, H-aryl), 1.31 (s, 9H, CH_3) ppm; $C_{20}H_{20}BrN_3$ (382.30); calcd.: C 62.83, H 5.27, N 10.99; found: C 62.70, H 5.17, N 10.74.

2-Thienyl 3-isoquinolyl ketone 4-bromophenyl hydrazone (**4h**, $C_{20}H_{14}BrN_3$)

Yield: 9.2 (55.9%); m.p.: 117–121°C (mixture of *E* and *Z* isomers); ^{1}H NMR (400 MHz, $CDCl_3$, (*Z*)-**4h**): $\delta = 12.15$ (s, N-H), 9.38 (s, 1H, H-1), 8.08 (s, 1H, H-4), 8.06 (d, $J = 8.5$ Hz, 1H, H-8), 7.86 (d, $J = 8.5$ Hz, 1H, H-5), 7.75 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.69 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.36–7.09 (AA′BB′, 4H, H-bromophenyl), 7.32 (dd, $J = 5$ Hz, 1 Hz, 1H, H-5′), 7.14 (dd, $J = 3.8$ Hz, 1 Hz, 1H, H-3′), 7.04 (dd, $J = 5$ Hz, 3.8 Hz, 1H, H-4′) ppm; $C_{20}H_{14}BrN_3S_1$ (408.32); calcd.: C 58.83, H 3.46, N 10.29; found: C 59.17, H 3.49, N 11.33.

(Z)-3-Thienyl 3-isoquinolyl ketone 4-bromophenyl hydrazone (**4i**; $C_{20}H_{14}BrN_3$)

Yield: 14 g (81.7%); m.p.: 125–126°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.47$ (s, N-H), 9.40 (s, 1H, H-1), 8.06 (d, $J = 8.5$ Hz, 1H, H-8), 7.92 (s, 1H, H-4), 7.83 (d, $J = 8.5$ Hz, 1H, H-5), 7.74 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.69 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.51 (dd, $J = 5$ Hz, 1 Hz, 1H, H-4′), 7.42 (dd, $J = 2.9$ Hz, 1 Hz, 1H, H-2′), 7.39 (dd, $J = 5$ Hz, 2.9 Hz, 1H, H-5′), 7.36–7.11 (AA′BB′, 4H, H-bromophenyl) ppm; $C_{20}H_{14}BrN_3S$ (408.32); calcd.: C 58.83, H 3.46, N 10.29; found: C 59.81, H 3.52, N 10.22.

Table 1. Experimental conditions for the ring closure reactions affording **5**; *NBS*: N-bromosuccinimide, *TBB*: 2,4,4,6-tetrabromo-cyclohexa-2,5-diene-1-one

	R	Reagent	Solvent	*T* (°C)	*t* (h)
5a	CH_3	*NBS*	ethyl acetate	−17	3
5b	*n*-C_4H_9	*NBS*	ethyl acetate	0	2
5c	4-Cl-C_6H_4	*TBB*	CH_2Cl_2	r.t.	0.5
5f	$CH(CH_3)_2$	*TBB*	CH_2Cl_2	0	1.5
5g	*tert*.-C_4H_9	*TBB*	CH_2Cl_2	0	1
5h	2-thienyl	*NBS*	ethyl acetate	−20	1.5
5i	3-thienyl	*NBS*	ethyl acetate	−17	1

General procedure for the ring closure of **4** *to [1,2,3]triazolo[1,5-b]isoquinolinium salts* **5a–c**, **f–i**

To a stirred solution of hydrazone **4** in the appropriate solvent, the ring closure reagent (3 equivalents) was added in portions at the temperature given in Table 1. Stirring was continued; after the reaction time given in Table 1, ether was added, and the precipitate formed was filtered off. The yellow crystals were suspended in nitromethane, cyclohexene was added at room temperature (except **5a** which was treated at 0°C), and the mixture was stirred for 30 min. Ether was added again, and the resultant precipitate was filtered off to yield crude bromide salts (**5**, $A = Br$). Conversion into the terafluoroborate salts **5** ($A = BF_4$) was carried out by addition of an aqueous solution of NH_4BF_4 to the hot solution of the bromide salt in aqueous ethanol. The precipitate was filtered off and recrystallized from acetonitrile/ether.

1-(4-Bromophenyl)-3-methyl[1,2,3]triazolo[1,5-b]isoquinolinium tetrafluoroborate (**5a**; $A = BF_4$; $C_{17}H_{13}BBrF_4N_3$)

Starting from **4a** (3.4 g, 10 mmol), 1.7 g (41%) of **5a** were obtained. M.p.: 204–205°C; ^{1}H NMR (400 MHz, CD_3CN+*TFA*): $\delta = 9.87$ (s, 1H, H-9), 9.13 (s, 1H, H-4), 8.39 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-8), 8.31 (dd, $J = 8.5$ Hz, 1,5 Hz, 1H, H-5), 8.06 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 8.00 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.98–7.71 (AA′BB′, 4H, H-aryl), 2.91 (s, 3H, CH_3) ppm; $C_{17}H_{13}BBrF_4N_3$ (426.02); calcd.: C 47.93, H 3.08, N 9.86; found: C 46.34, H 2.97, N 9.62.

1-(4-Bromophenyl)-3-n-butyl[1,2,3]triazolo[1,5-b]isoquinolinium tetrafluoroborate (**5b**; $A = BF_4$; $C_{20}H_{19}BBrF_4N_3$)

Starting from **4b** (3.8 g, 10 mmol), 2.5 g (53%) of **5b** were obtained. M.p.: 143–146°C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 10.00$ (s, 1H, H-9), 9.13 (s, 1H, H-4), 8.38 (d, $J = 8.5$ Hz, 1H, H-8), 8.28 (d, $J = 8.5$ Hz, 1H, H-5), 8.04 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.99 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.98–7.69 (AA′BB′, 4H, H-aryl), 3.30 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 1.02 (m, 3H, CH_3) ppm; $C_{20}H_{19}BBrF_4N_3$ (468.10); calcd.: C 51.32, H 4.09, N 9.98; found: C 51.12, H 4.07, N 9.76.

1-(4-Bromophenyl)-3-(4-chlorophenyl)[1,2,3]triazolo[1,5-b]isoquinolinium tetrafluoroborate (**5c**; $A = BF_4$; $C_{22}H_{14}BBrClF_4N_3$)

Starting from **4c** (4.3 g, 10 mmol), 3.7 g (70%) of **5c** were obtained. M.p.: 206–208°C; ^{1}H NMR (400 MHz, CD_3CN+*TFA*): $\delta = 9.91$ (s, 1H, H-9), 9.39 (s, 1H, H-4), 8.45 (d, $J = 8.5$ Hz, 1H, H-8),

8.34 (d, $J = 8.5$ Hz, 1H, H-5), 8.21–7.74 (AA′BB′, 4H, H-chlorophenyl), 8.09 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 8.03 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 8.02–7.81 (AA′BB′, 4H, H-bromophenyl) ppm; $C_{22}H_{14}BBrClF_4N_3$ (522.53); calcd.: C 50.57, H 2.70, N 8.04; found: C 50.76, H 2.71, N 7.93.

1-(4-Bromophenyl)-3-isopropyl[1,2,3]triazolo[1,5-b]isoquinolinium tetrafluoroborate (**5f**; $A = BF_4$; $C_{19}H_{17}BBrF_4N_3$)

Starting from **4f** (3.7 g, 10 mmol), 2.5 g (55%) of **5f** were obtained. M.p.: 164–167°C; ^{1}H NMR (400 MHz, CD_3CN+*TFA*): $\delta = 9.87$ (s, 1H, H-9), 9.19 (s, 1H, H-4), 8.40 (d, $J = 8.5$ Hz, 1H, H-8), 8.30 (d, $J = 8.5$ Hz, 1H, H-5), 8.06 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.99 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.99–7.71 (AA′BB′, 4H, H-aryl), 3.78 (m, 1H, CH), 1.60 (d, $J = 7$ Hz, 6H, CH_3) ppm; $C_{19}H_{17}BBrF_4N_3$ (454.07); calcd.: C 50.26, H 3.77, N 9.25; found: C 50.03, H 3.49, N 9.12.

1-(4-Bromophenyl)-3-tert.–butyl[1,2,3]triazolo[1,5-b]isoquinolinium tetrafluoroborate (**5g**; $A = BF_4$; $C_{20}H_{19}BBrF_4N_3$)

Starting from **4g** (3.8 g, 10 mmol), 2.8 g (60%) of **5g** were obtained. M.p.: 221–223°C; ^{1}H NMR (400 MHz, CD_3CN+*TFA*): $\delta = 9.84$ (s, 1H, H-9), 9.31 (s, 1H, H-4), 8.44 (d, $J = 8.5$ Hz, 1H, H-8), 8.28 (d, $J = 8.5$ Hz, 1H, H-5, H-5), 8.06 (dd, $J = 8.5$ Hz, 8.5 Hz, 1H, H-7), 7.98 (dd, $J = 8.5$ Hz, 8.5 Hz, 1H, H-6), 8.00–7.73 (AA′BB′, 4H, H-aryl), 1.70 (s, 9H, CH_3) ppm; $C_{20}H_{19}BBrF_4N_3$ (468.10); calcd.: C 51.32, H 4.09, N 9.98; found: C 51.26, H 4.15, N 9.13.

1-(4-Bromophenyl)-3(2-thienyl)[1,2,3]triazolo[1,5-b]isoquinolinium tetrafluoroborate (**5h**; $A = BF_4$; $C_{20}H_{13}BBrF_4N_3S$)

Starting from **4h** (0.82 g, 2 mmol), 0.23 g (23%) of **5h** were obtained M.p.: 205–206°C; ^{1}H NMR (400 MHz, CD_3CN+*TFA*): $\delta = 9.91$ (s, 1H, H-9), 9.45 (s, 1H, H-4), 8.49 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-8), 8.33 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-5), 8.11 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 8.04 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 8.03–7.79 (AA′BB′, 4H, H-aryl), 8.20 (dd, $J = 5$ Hz, 1 Hz, 1H, H-5′), 7.85 (dd, $J = 4$ Hz, 1 Hz, 1H, H-3′), 7.44 (dd, $J = 5$ Hz, 4 Hz, 1H, H-4′) ppm; $C_{20}H_{13}BBrF_4N_3S$; calcd.: C 48.62, H 2.65, N 8.50; found: C 48.89, H 2.67, N 8.68.

1-(4-Bromophenyl)-3(3-thienyl)[1,2,3]triazolo[1,5-b]isoquinolinium tetrafluoroborate (**5i**; $A = BF_4$; $C_{20}H_{13}BBrF_4N_3S$)

Starting from **4i** (0.41 g, 1 mmol), 0.2 g (40%) of **5i** were obtained. M.p.: 188–189°C; ^{1}H NMR (400 MHz, CD_3CN+*TFA*): $\delta = 9.84$ (s, 1H, H-9), 9.40 (s, 1H, H-4), 8.44 (dd, $J = 2.9$ Hz, 1.2 Hz, 1H, H-2′), 8.42 (d, $J = 8.5$ Hz, 1H, H-8), 8.28 (d, $J = 8.5$ Hz, 1H, H-5), 8.06 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.99 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.98–7.75 (AA′BB′,4H, H-aryl), 7.87 (dd, $J = 5$ Hz, 1.2 Hz, 1H, H-4′), 7.76 (dd, $J = 5$ Hz, 2.9 Hz, 1H, H-5′) ppm; $C_{20}H_{13}BBrF_4N_3S$ (494.11); calcd.: C 48.62, H 2.65, N 8.50; found: C 48.78, H 2.67, N 8.66.

General procedure for the synthesis of indoles **7–9**

A solution of 3-isoquinolyl ketone **3d–f** (12.5 mmol), 4-bromophenylhydrazine hydrochloride (2.8 g, 15 mmol), and sodium acetate (0.54 g, 15 mmol) in 40 ml acetic acid was refluxed for 3 h. After cooling, the pale yellow precipitate was filtered off and recrystallized from acetonitrile.

3-(5′-Bromo-3′H-spiro[cyclohexan-1,3′-indol]-2′-yl)isoquinoline (**7**; $C_{22}H_{19}BrN_2$)

Yield: 3.4 g (69.3%); m.p.: 185–187°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.32$ (s, 1H, H-1), 8.84 (s, 1H, H-4), 8.02 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-8), 8.01 (d, $J = 2$ Hz, 1H, H-4′), 7.96 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-5), 7.72 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.66 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.63 (d, $J = 8$ Hz, 1H, H-7′), 7.54 (dd, $J = 8$ Hz, 2 Hz, 1H, H-6′), 3.18 (m, 2H, CH_2), 2.05–1.67 (m, 6H, CH_2), 1.36 (d, 2H, CH_2) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 183.18$ (C-2′), 152.80, 151.11, 149.12, 146.83 (C-3,4a,7′a), 135.88, 128.76, (C-8a,3′a), 130.50, 128.42, 127.80, 127.77, 127.33, 122.38, 121.32 (C-4, 5, 6, 7, 8, 4′, 6′, 7′), 118.90 (C-5′), 59.66 (C-3′), 30.10 (C-cyclohexyl-2,6), 24.92 (C-cyclohexyl-4), 21.94 (C-cyclohexyl-3,5) ppm; $C_{22}H_{19}BrN_2$(391.31); calcd.: C 67.53, H 4.89, N 7.16; found: C 67.68, H 4.91, N 7.17.

3-(5-Bromo-3-phenyl-1H-indol-2′-yl)isoquinoline (**8**; $C_{23}H_{15}BrN_2$)

Yield: 2.8 g (55.7%); m.p.: 175–178°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.46$ (s, 1H, NH), 9.19 (s, 1H, H-1), 7.92 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-8), 7.69 (s, 1H, H-4), 7.65 (d, $J = 2$ Hz, 1H, H-4′), 7.58 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.56–7.41 (m, 7H, H-5, 6, phenyl), 7.34 (d, $J = 8$ Hz, 1H, H-7′), 7.30 (dd, $J = 8$ Hz, 1.5 Hz, 1H, H-6′) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 151.78$ (C-1), 143.32, 136.01, 134.79, 134.08, 133.19, 131.28, 127.58, 115.55, 113.40 (C-3,4a,8a,2′,3′,3′a, 5′,7′a,phenyl-1), 130.45, 129.02 (C-phenyl-2,3,5,6), 130.88, 127.60, 127.40, 127.33, 127.08, 125.98, 122.20, 118.47, 112.77 (C-4,5,6,7,8,4′,6′,7′,C-phenyl-4) ppm; $C_{23}H_{15}BrN_2$ (399.29); calcd.: C 69.19, H 3.79, N 7.02; found: C 69.16, H 3.77, N 7.06.

*3-(5-Bromo-3,3-dimethyl-3H-indol-2′-yl)isoquinoline (***9**; $C_{19}H_{15}BrN_2$)

Yield: 2.5 g (56.0%); m.p.: 146–149°C; $C_{19}H_{15}BrN_2$ (351.25); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.32$ (s, 1H, H-1), 8.83 (s, 1H, H-4), 8.02 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-8), 7.98 (dd, $J = 8.5$ Hz, 1.5 Hz, 1H, H-5), 7.73 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-7), 7.67 (ddd, $J = 8.5$ Hz, 8.5 Hz, 1.5 Hz, 1H, H-6), 7.60 (d, $J = 8$ Hz, 1H, H-7′), 7.52 (d, $J = 2$ Hz, 1H, H-4′), 7.50 (dd, $J = 8$ Hz, 2 Hz, 1H, H-6′), 1.77 (s, 6H, CH_3) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 184.18$ (C-2′), 151.93 (C-1), 152.55, 150.72, 146.64 (C-3,4a,7′a), 136.16, 129.25 (C-8a,3′a), 130.97, 130.89, 128.82, 128.12, 127.71, 125.03, 122.55, 121.08 (C-4,5,6,7,8,4′,6′,7′), 120.16 (C-5′), 55.26 (C-3′), 24.19 (C-methyl) ppm; $C_{19}H_{15}BrN_2$ (351.25); calcd.: C 64.97, H 4.30, N 7.98; found: C 65.02, H 4.40, N 8.14.

General procedure for the synthesis of the ring opened products **11a**, **c**, **g**

To a stirred solution of 0.88 (5 mmol) morpholine in aqueous acetonitrile (2 ml water and 6 ml acetonitrile), a solution of **5a**, **c**, **g** ($A = BF_4$, 0.5 mmol) in acetonitrile (20 ml) was added dropwise. After stirring for 2 h H_2O was added, and the mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (alumina; *n*-hexane:ethyl acetate = 5:1).

2-(2-(4-Bromophenyl)-4-methyl-[1,2,3]-triazol-5-ylmethyl)benzaldehyde
(**11a**; $C_{17}H_{14}BrN_3O$)

Yield: 72 mg (40.0%); m.p.: 90–92°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 10.30$ (s, 1H, CHO), 7.86–7.38 (m, 3H, H-4, 5, 6), 7.81–7.47 (AA′BB′, 4H, H-bromophenyl), 7.24 (d, $J = 8$ Hz, 1H, H-3), 4.50 (s, 2H, CH_2), 2.25 (s, 3H, CH_3) ppm; HRMS: *m/z*: calcd.: 355.032, found: 355.032.

2-(2-(4-Bromophenyl)-4-(4-chlorophenyl)[1,2,3]-triazol-5-ylmethyl)benzaldehyde
(**11c**; $C_{22}H_{15}BrClN_3O$)

Yield: 60 mg (26.6%); m.p.: 119–120°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.27$ (s, 1H, CHO), 7.93–7.38 (AA′BB′, 4H, H-bromophenyl), 7.88 (m, 1H, H-6), 7.64–7.56 (AA′BB′, 4H, H-chlorophenyl), 7.52–7.45 (m, 2H, H-4, 5), 7.19 (m, 1H, H-3), 4.76 (s, 2H, CH_2) ppm; HRMS: *m*/*z*: calcd.: 451.008, found: 451.010.

2-(2-(4-Bromophenyl)-4-dimethylethyl-[1,2,3]-triazol-5-yl)benzaldehyde
(**11g**; $C_{20}H_{20}BrN_3O$)

Yield: 105 mg (53.0%); colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 10.28$ (s, 1H, CHO), 7.92–7.40 (m, 3H, H-4, 5, 6), 7.94–7.48 (AA′BB′, 4H, H-bromophenyl), 7.17 (d, $J = 8$ Hz, 1H, H-3), 4.72 (s, 2H, CH_2), 1.40 (s, 9H, CH_3) ppm; HRMS: *m*/*z*: calcd.: 397.078, found: 397.077.

General procedure for the synthesis of 1,3a,4,9-tetrahydro[1,2,3]triazolo[1,5-b]isoquinolines
13a,**c**,**g**

To a stirred solution of **5a**,**c**,**g** ($A = $ Br, 0.5 mmol) in 5 ml methanol, sodium borohydride (94 mg, 2.5 mmol) was added. After stirring for 2 h at room temperature, 10 ml H_20 were added, and stirring was continued for 30 min. The reaction mixture was extracted with CH_2Cl_2, the organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was recrystallized from acetonitrile.

1-(4-Bromophenyl)-3-methyl-1,3a,4,9-tetrahydro[1,2,3]triazolo[1,5-b]isoquinoline
(**13a**; $C_{17}H_{16}BrN_3$)

Yield: 140 mg (81.6%); m.p.: 137°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.14 (AA′BB′, 4H, H-bromophenyl), 7.28–7.15 (m, 4H, H-5, 6, 7, 8), 4.64 (m, 1H, H-3a), 4.02 (d, $J = 14.5$ Hz, 1H, H-9α), 3.93 (d, $J = 14.5$ Hz, 1H, H-9β), 3.10 (dd, $J = 15$ Hz, 6 Hz, 1H, H-4α), 2.96 (dd, $J = 15$ Hz, 4 Hz, 1H, H-4β), 1.87 (d, $J = 1.2$ Hz, 3H, H-CH_3) ppm; $C_{17}H_{16}BrN_3$ (342.24); calcd.: C 59.66, H 4.71, N 12.28; found: C 59.91, H 4.78, N 12.38.

1-(p-Bromophenyl)-3-(4-chlorophenyl)-1,3a,4,9-tetrahydro[1,2,3]triazolo[1,5-b]isoquinoline
(**13c**; $C_{22}H_{17}BrClN_3$)

Yield: 190 mg (85.9%); m.p.: 157–158°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$–7.22 (AA′BB′, 4H, H-bromophenyl), 7.40–7.36 (AA′BB′, 4H, H-chlorophenyl), 7.26–7.16 (m, 3H, H-5, 6, 7), 7.97 (d, 1H, H-8), 5.29 (m, 1H, H-3a), 4.10 (d, $J = 14.5$ Hz, 1H, H-9α), 4.03 (d, $J = 14.5$ Hz, 1H, H-9β), 3.16 (dd, $J = 15$ Hz, 6 Hz, 1H, H-4α), 3.08 (dd, $J = 15$ Hz, 4.5 Hz, 1H, H-4β) ppm; $C_{22}H_{17}BrClN_3$ (438.75); calcd.: C 60.23, H 3.91, N 9.58; found: C 60.17, H 3.86, N 9.46.

1-(p-Bromophenyl)-3-tert.–butyl-1,3a,4,9-tetrahydro[1,2,3]triazolo[1,5-b]isoquinoline
(**13g**; $C_{20}H_{22}BrN_3$)

Yield: 130 mg (67.8%); m.p.: 76–78°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.18 (AA′BB′, 4H, H-bromophenyl), 7.26–7.15 (m, 4H, H-aryl), 4.63 (m, 1H, H-3a), 4.04 (s, 2H, H-9α, 9β) 3.22 (dd, $J = 15$ Hz, 7 Hz, 1H, H-4α), 3.16 (dd, $J = 15$ Hz, 6 Hz, 1H, H-4β), 1.26 (s, 9H, CH_3) ppm; $C_{20}H_{22}BrN_3$ (384.32); calcd.: C 62.51, H 5.77, N 10.93; found: C 62.59, H 5.63, N 10.87.

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