DOI: 10.1002/ejoc.200700602

Synthesis of Benzoazocines from Substituted Tetrahydroisoquinolines and Activated Alkynes in a Tetrahydropyridine Ring Expansion

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Keywords: Azocine / Tetrahydroisoquinolines / Activated alkynes / Tandem transformation / Ring expansion

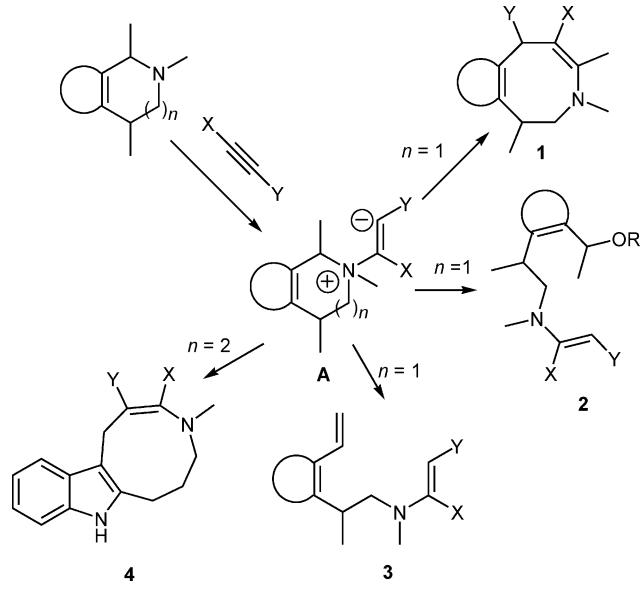
Tetrahydroisoquinolines underwent tandem piperidine ring enlargement in the presence of activated alkynes in acetonitrile or methanol, producing tetrahydrobenzo[*d*]azocines in high yields.

Introduction

Nitrogen heterocycles are structural elements of many natural alkaloids and drug candidates.[1] Among them, eight-membered (azocine) and larger N-containing fused-ring systems occupy a prominent place and deserve more investigation efforts from the point of view of organic chemistry. Alkaloids and drugs containing benzoazocine fragments in their structures exhibit extensive evidence of different activities: inhibition of α-glucosidase,[2] acetylcholinesterase,[3] antinociception activity,[4] antitumor activity,[5] antiinsectan activity,[6] and inhibition of HIV-1 replication.[7] Known synthetic routes towards the benzoazocine system include ring-closing metathesis,[8] intramolecular catalytic Friedel–Crafts reactions,[9] and palladium-catalyzed heteroannulation,[10] but only a few of these are really effective.[11]

Recently, we have reported a novel method for the synthesis of tetrahydropyrrolo[2,3-*d*]azocines,[12] tetrahydroazocino[4,5-*b*]- and -[5,4-*b*]indoles,[13] and hexahydroazonino[5,6-*b*]indoles.[14] It is based on the enlargement of either the tetrahydropyridine or hexahydroazepine fragments in tetrahydropyrrolo[3,2-*c*]pyridines, tetrahydro-β- and -γ-carbolines, or tetrahydroazepino[3,4-*b*]- and -[4,3-*b*]-indoles in the presence of activated alkynes. These reactions proceed via the intermediate zwitterion **A** (Scheme 1), resulting from the Michael addition of the tertiary nitrogen atom to the activated alkynes.

The pathways of the further nucleophilic transformations of the zwitterion **A** are presumably defined by the reactivity of the anionic center, the electronic effects of the substituent



Scheme 1.

or the fused aromatic system, and the nature of the solvent. In aprotic solvents tetrahydropyrrolopyridines produce pyrrolo[2,3-*c*]azocines **1**, but in the case of methyl-substituted tetrahydropyridine fragments, mixtures of azocines and 3-vinylpyrroles **3** (the products of Hofmann degradation) are formed, while tetrahydrocarbolines under the same conditions smoothly form azocino[4,5-*b*]- and -[5,4-*b*]indoles **1**. If the reaction is carried out in methanol, the tandem transformation of the tetrahydropyridine ring takes place and the formation of alkoxyalkyl-substituted pyrroles and indoles **2** occurs. Absolutely unexpectedly, tetrahydroazepino[4,3-*b*]indoles in the presence of activated alkynes give azonino[5,6-*b*]indoles **4** in high yields both in acetonitrile and in methanol (Scheme 1).

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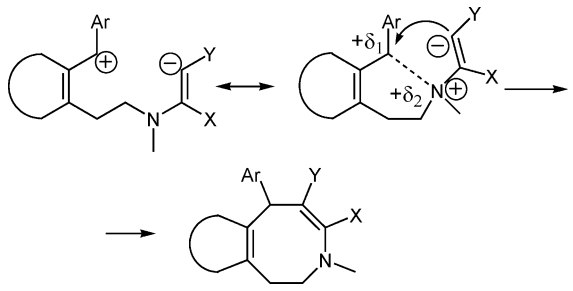
Analysis of the data obtained earlier allowed us to consider the transformation of the tetrahydropyridine ring to be an S_N process. On the basis of this presumption we think that electron-donating effects both of the fused fragment and of the substituents attached to the C-1 atom should diminish the partial positive charge ($+\delta_1$) appearing on the C-1 atom in the intermediate zwitterion **A** and facilitate the cleavage of the C-1–N bond, thus favoring the formation of azocines. It is obvious that the steric effects of the substituents at the C-1 and N atoms should also affect the formation of the intermediate zwitterion **A** (Scheme 2).



Scheme 2.

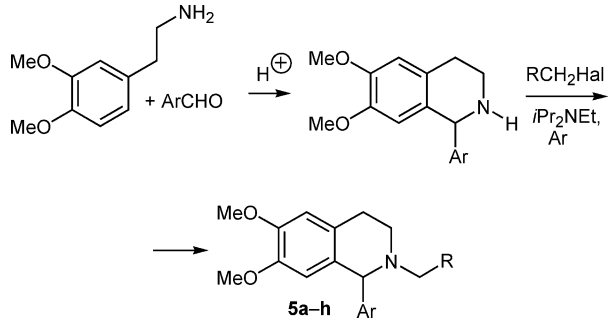
The driving force behind the ring-expansion process is still not determined, due to the lack of experimental material. This paper reports on the behavior of tetrahydroisoquinolines as a new representative of the annulated tetrahydropyridine (THPy) family in this reaction. We have recently published preliminary results on the behavior of 1-aryltetrahydroisoquinolines[15] in this reaction, and we now report on expanded research on the reactivity of isoquinolines with different substituents attached to the phenyl ring, C-1 atom, and nitrogen atom.

To obtain more information on the reaction scope and limitations, we studied the transformations of 2-substituted 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **5** in the presence of methyl propiolate, acetylacetylene, *p*-tosylacetylene, and dimethyl acetylenedicarboxylate (DMAD) in methanol or acetonitrile.

The presence of a 1-phenyl substituent in isoquinolines **5** would most probably favor the loosening of the C-1–N bond in the intermediate zwitterion **A**, thus facilitating the subsequent nucleophilic attack of the anionic center on the C-1 atom and the formation of benzoazocines. Therefore, the process shown in Scheme 2 ought to depend on the reactivity of the nucleophilic center rather than on the solvent nucleophilic assistance.

Results and Discussion

The starting *N*-ethyl- and *N*-benzyl-substituted isoquinolines **5a**–**h** were obtained by Pictet–Spengler condensation of 2-(3,4-dimethoxyphenyl)ethylamine and the appropriate aldehydes, followed by *N*-alkylation of the intermediate NH-isoquinolines with ethyl iodide or benzyl bromides in the presence of Hünig's base (Scheme 3).[16] The synthesis of 1-aryltetrahydroisoquinolines described in the literature[17] was unsuccessful in our case: after the addition of the cyclizing agent (usually HCl), hydrolysis of the corresponding Schiff base occurred and none of the desired products was obtained. Modification of the method to use H_3PO_4 instead of HCl avoided this problem. The modified, base-catalyzed alkylation protocol allowed the use of DMF to be avoided, thus simplifying the isolation procedure. In some cases, however, this method was unsuccessful, giving very low yields of the target products (Table 1).



Scheme 3.

Table 1. Yields and melting points of tetrahydroisoquinolines **5a**–**h**.

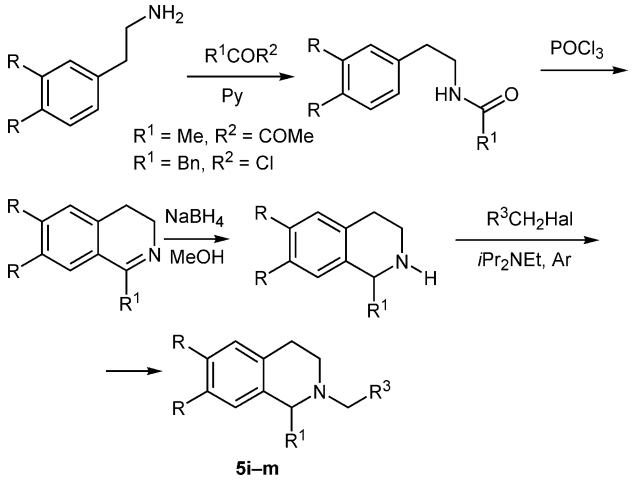
Compound	Ar	R	Yield [%]	M.p. [°C]
5a	*p*-MeO-C_6H_4	Me	75	64–66
5b	*p*-F-C_6H_4	Me	69	54–55
5c	*p*-F_3C-C_6H_4	Me	77	85–86
5d	*p*-O_2N-C_6H_4	Me	52	71–73
5e	*o*-F-C_6H_4	Me	81	69–70
5f	*p*-MeO-C_6H_4	*p*-MeO_2C-C_6H_4	65	141–142
5g	*p*-MeO-C_6H_4	*p*-F-C_6H_4	56	145–146
5h	*p*-MeO-C_6H_4	*p*-Me-C_6H_4	53	139–140

Isoquinolines **5i**–**m** were synthesized by the well-known Bischler–Napieralski reaction[18] starting from the appropriate amines, anhydrides, or acid chlorides and the reduction of the intermediate dihydroisoquinolines, followed by *N*-alkylation of the NH-isoquinolines with ethyl iodide or benzyl bromides (Scheme 4, Table 2).[16]

Aryl-substituted isoquinolines **5a**–**e** reacted with terminal alkynes at 25 °C in either methanol or acetonitrile, giving benzo[*d*]azocines **8**–**26** in high yields (Table 3). It was demonstrated that the rates of reactions of isoquinolines **5a**, **5b**, **5d**, and **5e** with activated alkynes in acetonitrile and methanol are almost equal. Generally, the yields in acetonitrile are higher than in methanol (Scheme 5).

The planes of the phenyl rings in the 1-aryl substituents in isoquinolines **5** are perpendicular to the dimethoxyphenyl fragment, so the intermediate zwitterion stabilization is possible only through the inductive effect.

The reactions between isoquinolines **5a**, **5b**, **5d**, or **5e** and DMAD in acetonitrile (also **5a** and **5d** in methanol and **5e** in DMSO) yielded benzoazocines **11**, **15**, **19**, and **23**. In the cases of the reactions of isoquinolines **5b** and **5e** with



Scheme 4.

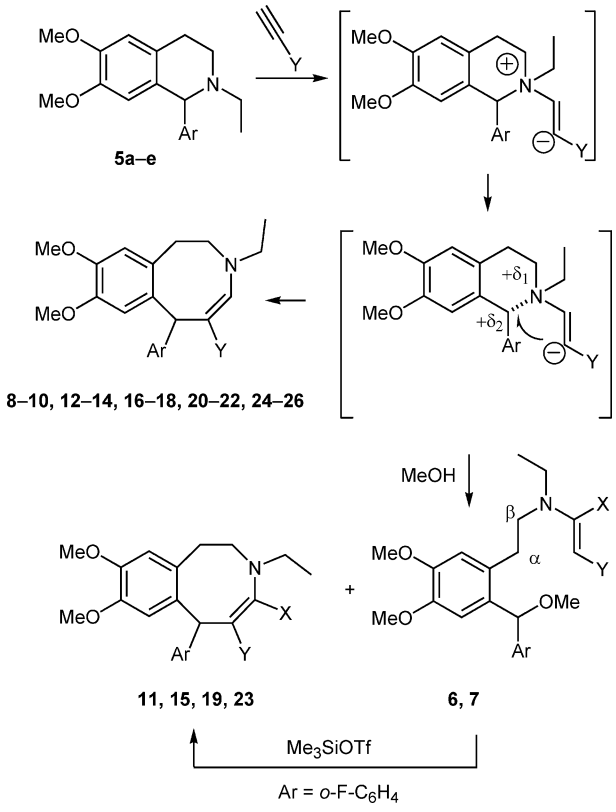
Table 2. Yields and melting points of tetrahydroisoquinolines **5i**–**m**.

Compound	R	R^1	R^2	Yield [%]	M.p. [°C]
5i	OMe	Bn	Me	65	–
5j	OMe	Me	Me	69	–
5k	H	Ph	Me	74	34–35
5l	OMe	Me	*p*-Me-C_6H_4	64	78–79
5m	OMe	Bn	*p*-Me-C_6H_4	53	88–89

Table 3. Yields of tetrahydrobenzo[*d*]azocines **8**–**26** and diarylmethanes **6** and **7**.

Compound	Ar	X	Y	Yield [%]
6	*o*-F-C_6H_4	CO_2Me	CO_2Me	–
7	*p*-F-C_6H_4	CO_2Me	CO_2Me	42
8	*p*-MeO-C_6H_4	H	CO_2Me	75 (MeOH)
				90 (MeCN)
9	*p*-MeO-C_6H_4	H	COMe	85 (MeCN)
10	*p*-MeO-C_6H_4	H	*p*-Ts	31 (MeCN)
11	*p*-MeO-C_6H_4	CO_2Me	CO_2Me	55 (MeOH)
				70 (MeCN)
12	*p*-F-C_6H_4	H	CO_2Me	77 (MeOH)
				88 (MeCN)
13	*p*-F-C_6H_4	H	COMe	73 (MeCN)
14	*p*-F-C_6H_4	H	*p*-Ts	42 (MeCN)
15	*p*-F-C_6H_4	CO_2Me	CO_2Me	29
16	*p*-O_2N-C_6H_4	H	CO_2Me	66 (MeOH)
				79 (MeCN)
17	*p*-O_2N-C_6H_4	H	COMe	43 (MeCN)
18	*p*-O_2N-C_6H_4	H	*p*-Ts	87 (MeCN)
19	*p*-O_2N-C_6H_4	CO_2Me	CO_2Me	27 (MeOH)
				51 (MeCN)
20	*o*-F-C_6H_4	H	CO_2Me	88 (MeOH)
				77 (MeCN)
21	*o*-F-C_6H_4	H	COMe	87 (MeCN)
22	*o*-F-C_6H_4	H	*p*-Ts	65 (MeCN)
23	*o*-F-C_6H_4	CO_2Me	CO_2Me	19 (MeOH)
				36 (MeCN)
24	*p*-F_3C-C_6H_4	H	CO_2Me	88 (MeCN)
25	*p*-F_3C-C_6H_4	H	COMe	76 (MeCN)
26	*p*-F_3C-C_6H_4	H	*p*-Ts	67 (MeCN)

DMAD in methanol the formation of two products was observed: along with the azocines **15** and **23**, diarylmethanes **6** and **7** were also formed. The latter compounds were



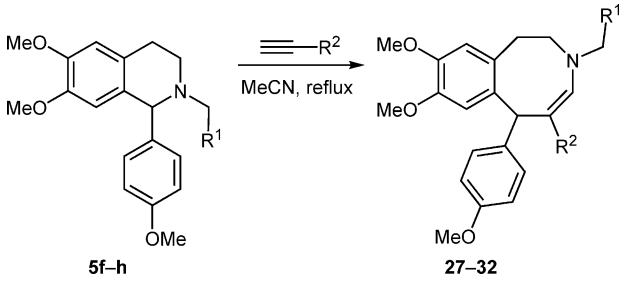
Scheme 5.

the result of the cleavage process involving one molecule of methanol. The formation of the diarylmethane **6** was only demonstrated with the aid of NMR analysis (ratio 1:1), whereas compounds **7** and **23** were isolated. We attribute this result both to steric hindrance and to the lower nucleophilic activity of the anionic center in the intermediate zwitterion, since the negative charge is delocalized between two ester groups. Compound **6** was converted into azocine **23** by treatment with trimethylsilyl triflate.

In the case of the *N*-benzyl-substituted isoquinolines **5f**–**h**, the reactions with activated alkynes in acetonitrile (methyl propiolate or *p*-tosylacetylene) became possible only with the use of an excess of the corresponding alkyne and required more forcing reaction conditions (reflux). This can most probably be explained by the steric hindrance of the *N*-benzyl and 1-aryl substituents preventing the formation of the intermediate zwitterion and the subsequent nucleophilic attack. Nevertheless, the target azocines **27**–**32** were isolated in good preparative yields (Scheme 6, Table 4).

To see whether the presence of the methoxy groups in the isoquinolines was mandatory for the transformation of the tetrahydropyridine ring, we examined the reaction behavior of isoquinoline **5k** (Scheme 7) with methyl propiolate, acetylacetylene, and *p*-tosylacetylene in acetonitrile. The reactions proceeded smoothly, giving azocines **33**–**35** in good yields (Table 5).

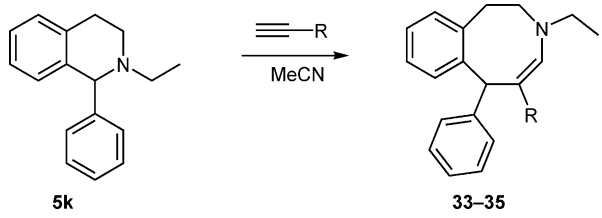
The ease of transformation of 1-aryl-substituted tetrahydroisoquinolines **5a**–**h** into benzoazocines **8**–**32** encour-



Scheme 6.

Table 4. Yields of tetrahydrobenzo[*d*]azocines **27**–**32**.

Compound	R^1	R^2	Yield [%]
27	*p*-MeO_2C-C_6H_4	CO_2Me	50 (MeCN)
28	*p*-MeO_2C-C_6H_4	*p*-Ts	83 (MeCN)
29	*p*-F-C_6H_4	CO_2Me	37 (MeCN)
30	*p*-F-C_6H_4	*p*-Ts	81 (MeCN)
31	*p*-Me-C_6H_4	CO_2Me	43 (MeCN)
32	*p*-Me-C_6H_4	*p*-Ts	54 (MeCN)

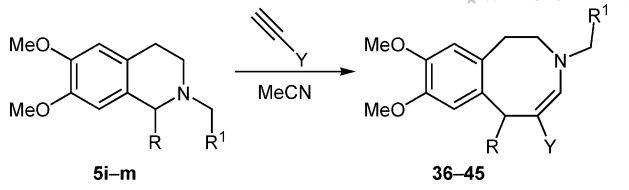


Scheme 7.

Table 5. Yields of tetrahydrobenzo[*d*]azocine **33**–**35**.

Compound	R	Yield [%]
33	CO_2Me	50 (MeCN)
34	COMe	45 (MeCN)
35	*p*-Ts	82 (MeCN)

aged us to apply this approach to isoquinolines containing 1-benzyl or 1-methyl substituents. Isoquinolines **5i**–**m** (Scheme 8) reacted with activated alkynes at room temperature to yield benzoazocines **36**–**45** in 35–87% yields (Table 6). We had also expected the formation of vinyl-substituted benzenes – possible products of the Hofmann degradation reaction. Indeed, the formation of vinylic byproducts was registered (NMR analysis of the reaction mixture), but none of them was isolated individually. In the case of the *N*-benzyl-substituted isoquinoline **5m**, the reactions required excesses of the alkynes to proceed.



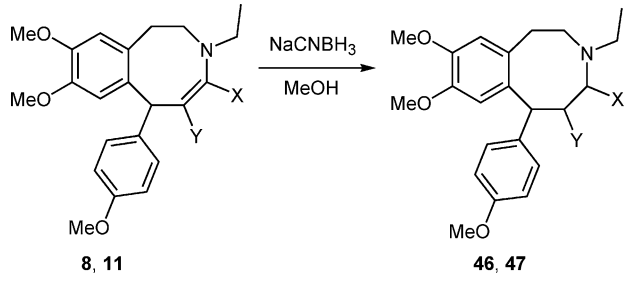
Scheme 8.

Table 6. Yields of tetrahydrobenzo[*d*]azocines **36**–**45**.

Compound	R	R^1	Y	Yield [%]
36	Me	Me	CO_2Me	31 (MeCN)
37	Me	Me	*p*-Ts	40 (MeCN)
38	Me	*p*-Me-C_6H_4	CO_2Me	50 (MeCN)
39	Me	*p*-Me-C_6H_4	*p*-Ts	54 (MeCN)
40	Bn	Me	CO_2Me	60 (MeCN)
41	Bn	Me	COMe	55 (MeCN)
42	Bn	Me	*p*-Ts	65 (MeCN)
43	Bn	*p*-Me-C_6H_4	CO_2Me	83 (MeCN)
44	Bn	*p*-Me-C_6H_4	COMe	78 (MeCN)
45	Bn	*p*-Me-C_6H_4	*p*-Ts	64 (MeCN)

The structures of the compounds **8**–**45** were confirmed by their NMR spectroscopic data. The ^1H NMR spectra have signals corresponding to all the protons of the molecules, with reasonable chemical shifts and coupling constant values. The ^1H NMR spectra of benzoazocines **8**–**10**, **12**–**14**, **16**–**18**, **20**–**22**, and **24**–**45** all have similar characteristic signals: the enamine protons resonate as singlets at δ = 7.40–7.60 ppm.

Benzoazocines **8** and **11** were reduced to the corresponding hexahydrobenzoazocines **46** and **47** by treatment with $NaCNBH_3$ in methanol (Scheme 9, Table 7).



Scheme 9.

Table 7. Yields of hexahydrobenzo[*d*]azocines **46** and **47**.

Compound	X	Y	Yield [%]
46	H	CO_2Me	80
47	CO_2Me	CO_2Me	62

Hexahydrobenzoazocine **46** was isolated as a mixture of two diastereoisomers (1:4 ratio), whereas benzoazocine **47**, according to its spectroscopic data, was formed as a single diastereoisomer. The stereochemistry of compounds **46** and **47** was determined on the basis of the spin-spin coupling constants of the 6-H and 5-H atoms. Thus, for the major isomer of **46** the 6-H atom resonates as a doublet with J = 12.0 Hz, such a high vicinal coupling constant value indi-

cating a pseudoaxial orientation of 6-H and 5-H, whereas for the minor isomer 6-H appears as a doublet with J = 3.8 Hz, indicating a pseudoequatorial orientation of 6-H and 5-H. In compound **47** the 6-H atom resonates at δ = 4.99 ppm as a doublet with J = 11.4 Hz, also showing a pseudoaxial orientation of the 6-H and 5-H atoms.

The three-dimensional structure of compound **47** was also investigated by X-ray diffraction. A monocrystal was obtained by recrystallisation from an ethyl acetate/hexane mixture by slow concentration at room temperature, and the refined X-ray crystal structure of **47** is shown in Figure 1. The conformation of the eight-membered ring is a twisted chair-boat, in which atoms C(2), C(4), C(1), C(9), N(1), C(10), and C(11) form the chair fragment, whereas atoms C(3), C(2), C(4), C(1), C(9), N(1), and C(1) form the boat fragment. The X-ray structure confirmed our presumption that 6-H and 5-H are pseudoaxially oriented.

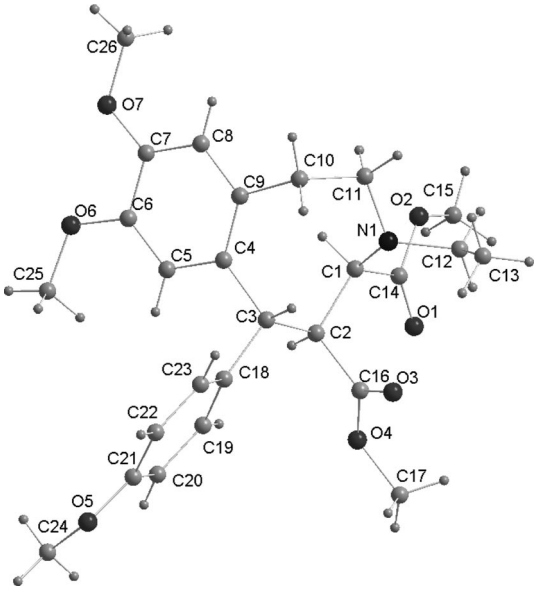


Figure 1. X-ray crystal structure of **47**.

Conclusions

We presented a new one-step procedure for the synthesis of tetrahydrobenzo[*d*]azocines, starting from readily available tetrahydroisoquinolines. This reaction could represent a new and powerful tool for the construction of fused azocine derivatives.

Experimental Section

General Remarks: All solvents were distilled and dried before use; methyl propiolate, acetylacetylene and DMAD were purchased from Acros Organics and were used without any additional purification. *p*-Tosylacetylene was synthesized by a literature procedure.[19] Column chromatography was performed with aluminum oxide 60 from Fluka. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 25 °C or in [D_6]DMSO solution at 40 °C with a Bruker WM 400 NMR spectrometer operating at 400 and 100 MHz, respectively; peak positions are given in ppm (δ) with tetramethylsilane as the internal standard. For the proton indexes for compounds **6** and **7** see Scheme 5. A ^{1}H-^{1}H COSY experiment was used for the assignment of the signals in the spectra of **46**. Mass spectra were obtained by the EI technique (Finnigan-MAT 95 XL Engine) or the ESI method (Agilent 1100 Series LC/MSD Trap System VL). IR spectra were recorded with a Perkin–Elmer Spectrum One instrument. Only noteworthy IR absorptions [cm^{-1}] are listed. Melting points were determined in a capillary tube and are uncorrected.

General Procedure for the Synthesis of Tetrahydroisoquinolines: In a flask fitted with a Dean–Stark apparatus, the amine (0.06 mmol), the aldehyde (0.065 mmol), and toluene (70 mL) were mixed and the reaction mixture was heated at reflux for 3–4 h. The reaction mixture was allowed to cool to room temperature, and phosphoric acid (85%, 50 mL) was added. The resulting mixture was heated at reflux for 3 h and then allowed to cool to room temperature. The organic layer was decanted. The residue was poured onto ice, and the pH was adjusted to 9–10 (NaOH). The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give the target isoquinolines.

General Synthetic Procedure for the Synthesis of Benzo[*d*]azocines 8–26 and 33–45: DMAD, methyl propiolate, acetylacetylene, or *p*-tosylacetylene (1.2 mmol) was added to a solution of one of the isoquinoline derivatives **5a**–**e** or **5i**–**m** (1 mmol) in methanol or acetonitrile (15 mL). The reaction mixture was stirred at 25 °C (TLC monitoring). The solvent was evaporated under reduced pressure, and the residue was recrystallized (ethyl acetate/hexane) to give benzoazocines **8**–**26**, **35**, **37**, or **39**–**45** or diarylmethane **7**. In the cases of benzoazocines **33**, **34**, **36**, **38** they were purified by column chromatography with mixtures of ethyl acetate/hexane as eluent (1:40 for **33** and **34** or 1:15 for **36** and **38**). In the case of the reaction between isoquinoline **5e** and DMAD in methanol, a mixture (1:1 according to ^{1}H NMR spectroscopic data) of the azocine **23** and the diarylmethane **6** was formed. This mixture (0.15 g) was dissolved in acetonitrile (10 mL) and a few drops of trimethylsilyl triflate were added. The reaction mixture was kept at room temperature for a week (TLC monitoring). The solvent was evaporated under reduced pressure, and the resulting residue was purified by column chromatography with ethyl acetate as eluent to give benzoazocine **23**.

Dimethyl (2*E*)-2-[(Ethyl)(2-{2-[(4-fluorophenyl)(methoxy)methyl]-4,5-dimethoxyphenyl}ethyl)amino]but-2-enedioate (7): Yield 205 mg (42%) in methanol, white crystals, m.p. 118–120 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.1 Hz, 3 H, –CH_2–CH_3), 2.59 (dd, J = 4.5, J = 16.2 Hz, 1 H, CH_2-α), 2.75–2.85 (m, 2 H, –CH_2–CH_3 and CH_2-α), 2.99 (qd, J = 7.1, J = 14.3 Hz, 1 H, –CH_2–CH_3), 3.23 (ddd, J = 1.9, J = 7.5, J = 15.3 Hz, 1 H, CH_2-β), 3.30–3.36 (m, 1 H, CH_2-β), 3.75 (s, 3 H, CH–OCH_3), 3.82 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, CO_2CH_3), 3.90 (s, 3 H, OCH_3), 3.92–3.93 (m, 4 H, OCH_3 and =CH), 5.86 (s, 1 H, CH–OCH_3), 6.63 (s, 1 H, CH-Ar), 6.83 (s, 1 H, CH-Ar), 6.94 (t, J = 8.6 Hz, 2 H, CH-Ar), 7.05–7.08 (m, 2 H, CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1732, 1681, 1605 cm^{-1}. EI MS: m/z (%) = 489 (20) [M]$^+$, 457 (20), 398 (30), 386 (100), 371 (12), 354 (17), 339 (12), 327 (11), 309 (5), 240 (95), 200 (20), 183 (13), 169 (10), 111 (30), 98 (5), 80 (7), 72 (70), 59 (15), 52 (13), 39 (20). $C_{26}H_{32}FNO_7$ (489.22): calcd. C 63.79, H 6.59, N 2.86; found C 63.68, H 6.56, N 2.96.

Methyl 3-Ethyl-8,9-dimethoxy-6-(4-methoxyphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (8): Yield 308 mg (75%) in methanol (90% in acetonitrile), white crystals, m.p. 100–102 °C

(ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.76–2.87 (m, 3 H, CH_2-1 and CH_2-2), 3.16 (qd, J = 7.2, J = 14.1 Hz, 2 H, –CH_2–CH_3), 3.49–3.58 (m, 1 H, CH_2-2), 3.74 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 5.80 (s, 1 H, 6-H), 6.63 (s, 1 H, 7-H), 6.78–6.80 (m, 3 H, 2 × CH-Ar and 10-H), 7.02 (d, J = 7.4 Hz, 2 H, 2 × CH-Ar), 7.68 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 36.7, 48.6, 51.4, 54.9, 55.7, 55.7 56.0, 97.1, 114.2, 116.2, 116.2, 117.0, 117.1, 127.1, 129.6, 132.4, 139.4, 147.1, 147.5, 152.9, 153.1, 157.5, 170.4 ppm. IR (KBr): $\tilde{\nu}$ = 1670, 1577 cm^{-1}. EI MS: m/z (%) = 411 (20) $[M]^+$, 354 (20), 340 (35), 282 (10), 176 (20), 164 (50), 151 (20), 135 (14), 121 (60), 91 (15), 72 (40), 58 (100), 56 (50), 42 (30). $C_{24}H_{29}NO_5$ (411.20): calcd. C 70.05, H 7.10, N 3.40; found C 70.04, H 7.12, N 3.39.

1-[3-Ethyl-8,9-dimethoxy-6-(4-methoxyphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-yl]ethan-1-one (9): Yield 336 mg (85%) in acetonitrile, white crystals, m.p. 146–147 °C (ethyl acetate/hexane). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.13 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.34 (s, 3 H, COCH_3), 2.86 (m, 3 H, CH_2-1 and CH_2-2), 3.22 (dq, J = 1.5, J = 7.2 Hz, 2 H, –CH_2–CH_3), 3.60 (m, 1 H, CH_2-2), 3.76 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.11 (s, 1 H, 6-H), 6.63 (s, 1 H, 7-H), 6.74 (s, 1 H, 10-H), 6.77 (d, J = 8.4 Hz, 2 H, 2 × CH-Ar), 6.92 (d, J = 8.4 Hz, 2 H, 2 × CH-Ar), 7.51 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1610, 1582 cm^{-1}. EI MS: m/z (%) = 395 (15) $[M]^+$, 295 (25), 281 (15), 58 (100), 43 (30). $C_{24}H_{29}NO_4$ (395.21): calcd. C 72.89, H 7.39, N 3.54; found C 72.91, H 7.40, N 3.52.

3-Ethyl-8,9-dimethoxy-6-(4-methoxyphenyl)-5-[(4-methylphenyl)-sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (10): Yield 157 mg (31%), white crystals, m.p. 185–186 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.1 Hz, 3 H, –CH_2–CH_3), 2.38 (s, 3 H, CH_3–Ar), 2.71 (dd, J = 5.5, J = 15.1 Hz, 1 H, CH_2-1), 2.80–2.88 (m, 2 H, CH_2-1 and –CH_2–CH_3), 3.21–3.27 (m, 2 H, CH_2-2 and –CH_2–CH_3), 3.38 (s, 3 H, OCH_3), 3.52–3.62 (m, 1 H, CH_2-2), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.89 (s, 1 H, 6-H), 5.57 (s, 1 H, 7-H), 6.58 (s, 1 H, 10-H), 6.78 (d, J = 8.5 Hz, 2 H, 2 × CH-Ar), 7.18 (d, J = 8.5 Hz, 2 H, 2 × CH-Ar), 7.23 (d, J = 7.6 Hz, 2 H, 2 × CH-Ar), 7.68–7.70 (m, 3 H, 2 × CH-Ar and 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1614 cm^{-1}. EI MS: m/z (%) = 507 (5) $[M]^+$, 353 (23), 352 (100), 351 (57), 350 (15), 336 (33), 324 (12), 307 (10), 295 (10), 294 (12), 283 (97), 263 (10), 244 (20), 219 (25), 189 (12), 176 (14), 165 (27), 164 (30), 160 (12), 145 (46), 121 (50), 102 (14), 91 (93), 77 (14), 65 (30), 58 (35), 57 (27), 42 (10). $C_{29}H_{33}NO_5S$ (507.21): calcd. C 68.61, H 6.55, N 2.76; found C 68.75, H 6.47, N 2.80.

Dimethyl 3-Ethyl-8,9-dimethoxy-6-(4-methoxyphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-4,5-dicarboxylate (11): Yield 258 mg (55%) in methanol (70% in acetonitrile), white crystals, m.p. 188–190 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.1 Hz, 3 H, –CH_2–CH_3), 2.58 (ddd, J = 0.7, J = 5.3, J = 7.0 Hz, 1 H, CH_2-1), 2.71–2.81 (m, 2 H, –CH_2–CH_3 and CH_2-1), 2.96 (qd, J = 7.2, J = 14.3 Hz, 1 H, –CH_2–CH_3), 3.19 (ddd, J = 1.8, J = 7.0, J = 15.1 Hz, 1 H, CH_2-2), 3.36–3.44 (m, 1 H, CH_2-2), 3.72 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 5.82 (s, 1 H, 6-H), 6.60 (s, 1 H, 7-H), 6.77 (d, J = 8.4 Hz, 2 H, 2 × CH-Ar), 6.80 (s, 1 H, 10-H), 6.99 (d, J = 8.4 Hz, 2 H, 2 × CH-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 34.2, 45.6, 50.3, 50.9, 51.6, 53.3, 55.1, 55.8, 55.8, 102.4, 113.4 (2 C), 114.1, 116.6, 127.3 (2 C), 129.6, 131.2, 137.0, 147.0, 147.3, 155.6, 157.5, 167.3, 169.8 ppm. IR (KBr): $\tilde{\nu}$ = 1728, 1678, 1558 cm^{-1}. EI MS: m/z (%) = 469 (5) $[M]^+$, 410 (10), 398 (100), 382 (15), 350 (20), 339 (25), 283 (15), 59 (12). $C_{26}H_{31}NO_7$ (469.21): calcd. C 66.51, H 6.65, N 2.98; found C 66.53, H 6.63, N 3.00.

Methyl 3-Ethyl-6-(4-fluorophenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (12): Yield 307 mg (77%) in methanol (351 mg, 88% in acetonitrile), white crystals, m.p. 95–97 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.74–2.87 (m, 3 H, 2 × CH_2-1 and CH_2-2), 3.13–3.23 (m, 2 H, –CH_2–CH_3), 3.42–3.50 (m, 1 H, CH_2-2), 3.75 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.81 (s, 1 H, 6-H), 6.64 (s, 1 H, 7-H), 6.77 (s, 1 H, 10-H), 6.93 (t, J = 8.7 Hz, 2 H, 2 × CH-Ar), 7.05–7.12 (m, 2 H, 2 × CH-Ar), 7.67 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 36.9, 48.7, 49.0, 51.3, 51.9, 55.9, 56.0, 98.0, 115.0 (d, $^2J_{C,F}$ = 21 Hz, 2 C), 116.0, 116.6, 127.6 (d, $^3J_{C,F}$ = 7 Hz, 2 C), 128.7, 132.2, 142.8 (d, $^4J_{C,F}$ = 3 Hz), 147.0, 147.6, 152.8, 161.0 (d, $^1J_{C,F}$ = 234 Hz), 170.8 ppm. IR (KBr): $\tilde{\nu}$ = 1670, 1605 cm^{-1}. EI MS: m/z (%) = 399 (72) $[M]^+$, 384 (11), 370 (17), 354 (10), 342 (10), 341 (23), 340 (100), 329 (20), 328 (70), 312 (7), 295 (9), 270 (12), 240 (7), 183 (7), 164 (12), 133 (5), 109 (6), 59 (5). $C_{23}H_{26}FNO_4$ (399.18): calcd. C 69.16, H 6.56, F 4.76, N 3.51; found C 69.15, H 6.58, F 4.74, N 3.52.

1-[3-Ethyl-6-(4-fluorophenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]azocin-5-yl]ethan-1-one (13): Yield 280 mg (73%) in acetonitrile, white crystals, m.p. 131–132 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.33 (s, 3 H, $COCH_3$), 2.75–2.91 (m, 3 H, 2 × CH_2-1 and CH_2-2), 3.22 (dq, J = 1.2, J = 7.1 Hz, 2 H, –CH_2–CH_3), 3.45–3.55 (m, 1 H, CH_2-2), 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.12 (s, 1 H, 6-H), 6.62 (s, 1 H, 7-H), 6.72 (s, 1 H, 10-H), 6.70 (t, J = 8.7 Hz, 2 H, 2 × CH-Ar), 6.94–6.98 (m, 2 H, 2 × CH-Ar), 7.50 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 25.1, 36.6, 46.5, 49.0, 52.1, 55.8, 56.0, 113.2, 114.9, 115.0 (d, $^2J_{C,F}$ = 21 Hz, 2 C), 116.7, 127.5 (d, $^3J_{C,F}$ = 7 Hz, 2 C), 128.5, 132.1, 142 (d, $^3J_{C,F}$ = 3 Hz), 147.0, 147.6, 154.9, 160.0 (d, $^1J_{C,F}$ = 240 Hz), 194.4 ppm. IR (KBr): $\tilde{\nu}$ = 1574, 1503 cm^{-1}. EI MS: m/z (%) = 383 (7) $[M]^+$, 340 (13), 312 (10), 283 (5), 269 (7), 218 (10), 183 (6), 133 (8), 109 (5), 72 (13), 58 (100), 43 (35). $C_{23}H_{26}FNO_3$ (383.45): calcd. C 72.04, H 6.83, N 3.65; found C 72.12, H 6.52, N 3.60.

3-Ethyl-6-(4-fluorophenyl)-8,9-dimethoxy-5-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (14): Yield 208 mg (42%) in acetonitrile, white crystals, m.p. 201–202 °C (ethyl acetate/hexane). ^{1}H (400 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.38 (s, 3 H, CH_3–Ar), 2.68 (dd, J = 5.2, J = 14.7 Hz, 1 H, CH_2-1), 2.78–2.88 (m, 2 H, –CH_2–CH_3 and CH_2-1), 3.20–3.28 (m, 2 H, –CH_2–CH_3 and CH_2-2), 3.40 (s, 3 H, OCH_3), 3.42–3.55 (m, 1 H, CH_2-2), 3.83 (s, 3 H, OCH_3), 4.92 (s, 1 H, 6-H), 5.62 (s, 1 H, 7-H), 6.58 (s, 1 H, 10-H), 6.92 (t, J = 8.7 Hz, 2 H, 2 × CH-Ar), 7.22–7.24 (m, 4 H, 4 × CH-Ar), 7.66–7.69 (m, 3 H, 2 × CH-Ar and 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1624 cm^{-1}. EI MS: m/z (%) = 495 (7) $[M]^+$, 341 (23), 340 (100), 339 (17), 324 (13), 312 (5), 283 (97), 207 (15), 183 (8), 133 (12), 109 (8), 91 (25), 58 (7). $C_{28}H_{30}FNO_4S$ (495.60): calcd. C 67.86, H 6.10, N 2.83; found C 67.91, H 6.06, N 2.85.

Dimethyl 3-Ethyl-6-(4-fluorophenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]azocine-4,5-dicarboxylate (15): Yield 133 mg (29%), white crystals, m.p. 132–134 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.1 Hz, 3 H, –CH_2–CH_3), 2.59 (ddd, J = 2.0, J = 5.9, J = 16.0 Hz, 1 H, CH_2-1), 2.75–2.87 (m, 2 H, –CH_2–CH_3 and CH_2-1), 2.99 (qd, J = 7.1, J = 14.2 Hz, 1 H, –CH_2–CH_3), 3.23 (ddd, J = 2.0, J = 7.3, J = 15.1 Hz, 1 H, CH_2-2), 3.30–3.39 (m, 1 H, CH_2-2), 3.75 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 5.86 (s, 1 H, 6-H), 6.63 (s, 1 H, 7-H), 6.83 (s, 1 H, 10-H), 6.94 (d, J = 8.7 Hz, 2 H, 2 × CH-Ar), 7.05–7.08 (m, 2 H, 2 × CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1731, 1683, 1563 cm^{-1}. EI MS: m/z (%) = 457 (29) $[M]^+$, 426 (5), 398 (27), 387 (23), 386 (100), 370 (20), 354 (17), 327 (10), 271 (5),

183 (7), 109 (95), 72 (46), 59 (11), 42 (7). $C_{25}H_{28}FNO_6$ (457.49): calcd. C 65.63, H 6.17, N 3.06; found C 65.67, H. 6.12, N 3.10.

Methyl 3-Ethyl-8,9-dimethoxy-6-(4-nitrophenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (16): Yield 281 mg (66%) in methanol (336 mg, 79% in acetonitrile), yellow crystals, m.p. 79–80 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.2 Hz, 3 H, –CH_2–*CH_3*), 2.74 (dd, J = 5.1, J = 14.7 Hz, 1 H, CH_2-1), 2.83–2.95 (m, 2 H, –*CH_2*–CH_3 and CH_2-1), 3.11–3.33 (m, 3 H, –*CH_2*–CH_3 and 2 × CH_2-2), 3.76 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.92 (s, 1 H, 6-H), 6.65 (s, 1 H, 7-H), 6.77 (s, 1 H, 10-H), 7.29 (d, J = 8.8 Hz, 2 H, 2 × CH-Ar), 7.70 (s, 1 H, 4-H), 8.12 (d, J = 8.8 Hz, 2 H, 2 × CH-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 36.7, 48.8, 49.6, 51.4, 52.0, 55.9, 56.0, 97.0, 115.1, 116.5, 123.7 (2 C), 127.1 (2 C), 128.3, 130.9, 146.0, 147.3, 147.8, 152.9, 155.3, 170.6 ppm. IR (KBr): $\tilde{\nu}$ = 1735, 1670, 1607, 1518 cm^{-1}. EI MS: *m*/*z* (%) = 426 (65) $[M]^+$, 397 (14), 367 (100), 355 (92), 339 (10), 322 (17), 297 (31), 267 (5), 244 (5), 218 (33), 205 (23), 176 (27), 164 (62), 151 (27), 121 (23), 91 (17), 71 (50), 58 (87), 56 (63), 42 (35). $C_{23}H_{26}N_2O_6$ (426.46): calcd. C 64.78, H 6.15, N 6.57; found C 64.65, H 6.10, N 6.48.

1-[3-Ethyl-8,9-dimethoxy-6-(4-nitrophenyl)-1,2,3,6-tetrahydrobenzo-[*d*]azocin-5-yl]ethan-1-one (17): Yield 176 mg (43%) in acetonitrile, yellow crystals, m.p. 90–91 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.3 Hz, 3 H, –CH_2–*CH_3*), 2.39 (s, 3 H, $COCH_3$), 2.80 (dd, J = 5.6, J = 15.0 Hz, 1 H, CH_2-1), 2.89–2.99 (m, 2 H, CH_2-1 and CH_2-2), 3.26 (q, J = 7.3 Hz, 2 H, –*CH_2*–CH_3), 3.32–3.40 (m, 1 H, CH_2-2), 3.86 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.31 (s, 1 H, 6-H), 6.68 (s, 1 H, 7-H), 6.75 (s, 1 H, 10-H), 7.21 (d, J = 8.7 Hz, 2 H, 2 × CH-Ar), 7.29 (s, 1 H, 4-H), 8.11 (d, J = 8.7 Hz, 2 H, 2 × CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1737, 1583 cm^{-1}. EI MS: *m*/*z* (%) = 410 (16) $[M]^+$, 367 (25), 339 (12), 218 (8), 189 (5), 164 (5), 58 (100), 43 (50). $C_{23}H_{26}N_2O_5$ (410.46): calcd. C 67.30, H 6.38, N 6.82; found C 67.41, H 6.43, N 6.90.

3-Ethyl-8,9-dimethoxy-5-[(4-methylphenyl)sulfonyl]-6-(4-nitrophenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine (18): Yield 454 mg (87%) in acetonitrile, yellow crystals, m.p. 229–231 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.2 Hz, 3 H, –CH_2–*CH_3*), 2.40 (s, 3 H, *CH_3*–Ar), 2.66 (dd, J = 4.9, J = 14.9 Hz, 1 H, CH_2-1), 2.83–2.93 (m, 2 H, CH_2-1 and CH_2-2), 3.21–3.29 (m, 3 H, CH_2-2 and –*CH_2*–CH_3), 3.39 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.95 (s, 1 H, 6-H), 5.58 (s, 1 H, 7-H), 6.59 (s, 1 H, 10-H), 7.24–7.26 (m, 2 H, 2 × CH-Ar), 7.47 (d, J = 7.7 Hz, 2 H, 2 × CH-Ar), 7.68 (d, J = 8.4 Hz, 2 H, 2 × CH-Ar), 7.71 (s, 1 H, 4-H), 8.11 (d, J = 8.4 Hz, 2 H, 2 × CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1613, 1520 cm^{-1}. EI MS: *m*/*z* (%) = 522 (3) $[M]^+$, 367 (100), 351 (7), 218 (13), 207 (15), 189 (9), 176 (7), 164 (13), 151 (5), 115 (6), 105 (10), 91 (35), 77 (70), 65 (15), 58 (43), 44 (12). $C_{28}H_{30}N_2O_6S$ (522.61): calcd. C 64.35, H 5.79, N 5.36; found C 64.27, H 5.86, N 5.31.

Dimethyl 3-Ethyl-8,9-dimethoxy-6-(4-nitrophenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-4,5-dicarboxylate (19): Yield 130 mg (27%) in methanol (247 mg, 51% in acetonitrile), yellow crystals, m.p. 228–229 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.1 Hz, 3 H, –CH_2–*CH_3*), 2.57 (dd, J = 5.5, J = 16.5 Hz, 1 H, CH_2-1), 2.77–2.91 (m, 2 H, –*CH_2*–CH_3 and CH_2-1), 3.01 (qd, J = 7.1, J = 14.2 Hz, 1 H, –*CH_2*–CH_3), 3.15–3.30 (m, 2 H, 2 × CH_2-2), 3.76 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 5.96 (s, 1 H, 6-H), 6.65 (s, 1 H, 7-H), 6.83 (s, 1 H, 10-H), 7.29 (d, J = 8.6 Hz, 2 H, 2 × CH-Ar), 8.12 (d, J = 8.6 Hz, 2 H, 2 × CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1729, 1681, 1560 cm^{-1}. EI MS: *m*/*z* (%) = 484 (31) $[M]^+$, 453 (5), 425 (933), 413 (100), 381 (14), 355 (7), 298 (10), 252 (5), 189 (6), 164 (17), 72 (85), 71 (30), 59 (17), 44 (23). $C_{25}H_{28}N_2O_8$ (484.50): calcd. C61.97, H 5.83, N 5.78; found C 62.03, H 5.89, N 5.83.

Methyl 3-Ethyl-6-(*o*-fluorophenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (20): Yield 351 mg (88%) in methanol (307 mg, 77% in acetonitrile), white crystals, m.p. 88–90 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, J = 7.2 Hz, 3 H, –CH_2–*CH_3*), 2.82–2.86 (m, 2 H, 2 × CH_2-1), 2.90–2.96 (m, 1 H, CH_2-2), 3.16 (qd, J = 7.2, J = 14.1 Hz, 2 H, –*CH_2*–CH_3), 3.60–3.68 (m, 1 H, CH_2-2), 3.74 (s, 3 H, OCH_3), 3.86 (s, 6 H, 2 × OCH_3), 5.96 (s, 1 H, 6-H), 6.60 (s, 1 H, 7-H), 6.78 (s, 1 H, 10-H), 6.94 (dd, J = 7.9, J = 11.6 Hz, 1 H, CH-Ar), 7.01 (t, J = 7.1 Hz, 1 H, CH-Ar), 7.12–7.16 (m, 2 H, 2 × CH-Ar), 7.61 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 36.6, 45.8, 49.5, 51.4, 55.9, 55.9, 98.0, 114.7, 115.6, 123.6 (d, $^2J_{C,F}$ = 23 Hz), 127.4 (d, $^3J_{C,F}$ = 8 Hz), 128.5 (d, $^3J_{C,F}$ = 8 Hz), 129.3, 133.4 (d, $^2J_{C,F}$ = 22 Hz), 135.7, 136.1, 146.7, 147.6, 152.2, 159.2, 159.0 (d, $^1J_{C,F}$ = 270 Hz), 170.1 ppm. IR (KBr): $\tilde{\nu}$ = 1672, 1605 cm^{-1}. EI MS: *m*/*z* (%) = 399 (70) $[M]^+$, 370 (12), 340 (100), 328 (95), 295 (20), 270 (35), 218 (40), 164 (60), 142 (65), 109 (35), 71 (20), 58 (60). $C_{23}H_{26}FNO_4$ (399.18): calcd. C 69.16, H 6.56, N 3.51; found C 69.13, H 6.58, N 3.53.

1-[3-Ethyl-6-(*o*-fluorophenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]azocin-5-yl]ethan-1-one (21): Yield 333 mg (87%) in acetonitrile, white crystals, m.p. 149–151 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.2 Hz, 3 H, –CH_2–*CH_3*), 2.32 (s, 3 H, $COCH_3$), 2.83–2.87 (m, 2 H, CH_2-1), 2.95–3.00 (m, 1 H, CH_2-2), 3.22 (q, J = 7.2 Hz, 2 H, –*CH_2*–CH_3), 3.67–3.75 (m, 1 H, CH_2-2), 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.28 (s, 1 H, 6-H), 6.59 (s, 1 H, 7-H), 6.75 (s, 1 H, 10-H), 6.91 (dd, J = 8.2, J = 11.5 Hz, 1 H, CH-Ar), 6.98–7.07 (m, 2 H, 2 × CH-Ar), 7.10–7.15 (m, 1 H, CH-Ar), 7.45 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 15.2, 25.8, 35.9, 43.3, 49.0, 51.9, 55.7, 56.0, 111.1, 115.7 (d, $^3J_{C,F}$ = 10 Hz), 116.3 (d, $^2J_{C,F}$ = 22 Hz), 124.4 (d, $^4J_{C,F}$ = 3 Hz), 128.1 (d, $^3J_{C,F}$ = 9 Hz), 129.4, 129.9, 130.0, 132.8, 133.7 (d, $^2J_{C,F}$ = 11 Hz), 146.8, 147.5, 155.7, 160.3 (d, $^1J_{C,F}$ = 246 Hz), 193.2 ppm. IR (KBr): $\tilde{\nu}$ = 1623, 1571 cm^{-1}. EI MS: *m*/*z* (%) = 383 (38) $[M]^+$, 384 (9), 354 (7), 341 (24), 340 (100), 327 (9), 326 (44), 325 (5), 324 (7), 313 (12), 312 (50), 311 (5), 297 (18), 296 (20), 218 (11), 196 (95), 164 (11), 133 (6), 109 (5), 72 (7), 58 (63), 43 (9). $C_{23}H_{26}FNO_3$ (383.19): calcd. C 72.04, H 6.83, N 3.65; found C 72.06, H 6.82, N 3.63.

3-Ethyl-6-(*o*-fluorophenyl)-8,9-dimethoxy-5-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (22): Yield 322 mg (65%) in acetonitrile, white crystals, m.p. 202–204 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.1 Hz, 3 H, –CH_2–*CH_3*), 2.39 (s, 3 H, *CH_3*–Ar), 2.62 (dd, J = 5.4, J = 15.8 Hz, 1 H, CH_2-1), 2.68–2.78 (m, 1 H, CH_2-1), 2.98 (dd, J = 7.4, J = 15.8 Hz, 1 H, CH_2-2), 3.18–3.28 (m, 2 H, –*CH_2*–CH_3), 3.42 (s, 3 H, OCH_3), 3.73–3.79 (m, 4 H, OCH_3 and CH_2-2), 5.06 (s, 1 H, 6-H), 5.71 (s, 1 H, 7-H), 6.74 (s, 1 H, 10-H), 6.84 (dd, J = 8.1, J = 11.0 Hz, 1 H, CH-Ar), 7.09 (t, J = 8.1 Hz, 1 H, CH-Ar), 7.15–7.20 (m, 1 H, CH-Ar), 7.24 (d, J = 7.8 Hz, 2 H, 2 × CH-Ts), 7.62 (t, J = 8.1 Hz, 1 H, CH-Ar), 7.68 (s, 1 H, 4-H), 7.70 (d, J = 7.8 Hz, 2 H, 2 × CH-Ts) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 15.1, 21.4, 35.4, 46.8, 49.7, 51.8, 55.0, 55.7, 102.8, 114.3, 115.3, 115.9, (d, $^2J_{C,F}$ = 22 Hz), 124.2 (d, $^4J_{C,F}$ = 4 Hz), 127.9 (2 C), 128.5, 129.1 (d, $^3J_{C,F}$ = 8 Hz), 130.1 (2 C), 131.5, 131.7 (d, $^3J_{C,F}$ = 3 Hz), 131.9 (d, $^2J_{C,F}$ = 10 Hz), 140.7, 142.8, 146.8, 146.9, 153.2, 160.5 (d, $^1J_{C,F}$ = 242 Hz) ppm. IR (KBr): $\tilde{\nu}$ = 1728, 1608 cm^{-1}. EI MS: *m*/*z* (%) = 495 (15) $[M]^+$, 340 (100), 324 (5), 207 (20), 164 (10), 133 (15), 109 (20), 91 (85), 77 (15), 65 (57), 58 (45), 39 (20). $C_{28}H_{30}FNO_4S$ (495.19): calcd. C 67.86, H 6.10, N 2.83; found C 67.90, H 6.12, N 2.82.

Dimethyl 3-Ethyl-6-(*o*-fluorophenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]azocine-4,5-dicarboxylate (23): Yield 87 mg (19%) in methanol (164 mg, 36% in acetonitrile), white crystals, m.p. 148–150 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.63 (ddd, J = 2.8, J = 5.7, J = 9.0 Hz, 1 H, CH_2-1), 2.71–2.80 (m, 1 H, CH_2-1), 2.82–2.94 (m, 2 H, –CH_2–CH_3), 3.33 (ddd, J = 2.8, J = 7.1, J = 14.9 Hz, 1 H, CH_2-2), 3.50–3.60 (m, 1 H, CH_2-2), 3.73 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 5.97 (s, 1 H, 6-H), 6.59 (s, 1 H, 7-H), 6.83 (s, 1 H, 10-H), 6.95 (dd, J = 8.5, J = 11.4 Hz, 1 H, CH-Ar), 7.02 (t, J = 7.3 Hz, 1 H, CH-Ar), 7.09–7.12 (m, 1 H, CH-Ar), 7.15–7.17 (m, 1 H, CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1735, 1681, 1559 cm^{-1}. EI MS: m/z (%) = 457 (5) $[M]^+$, 456 (25), 455 (100), 424 (20), 394 (45), 336 (10), 28 (12). $C_{25}H_{28}FNO_6$ (457.19): calcd. C 65.63, H 6.17, N 3.06; found C 65.65, H 6.15, N 3.07.

Methyl 3-Ethyl-8,9-dimethoxy-6-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (24): Yield 395 mg (88%) in acetonitrile, white crystals, m.p. 122–124 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.75 (dd, J = 5.7, J = 14.5 Hz, 1 H, CH_2-1), 2.83–2.92 (m, 2 H, CH_2-1 and CH_2-2), 3.17 (qd, J = 7.2, J = 13.8 Hz, 2 H, –CH_2–CH_3), 3.30–3.40 (m, 1 H, CH_2-2), 3.76 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.89 (s, 1 H, 6-H), 6.65 (s, 1 H, 7-H), 6.77 (s, 1 H, 10-H), 7.24 (d, J = 8.0 Hz, 2 H, 2 × CH-Ar), 7.50 (d, J = 8.0 Hz, 2 H, 2 × CH-Ar), 7.71 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 36.8, 48.9, 49.3, 51.6, 51.9, 55.9, 56.0, 97.3, 114.9, 116.5, 124.4 (q, $^1J_{C,F}$ = 275 Hz), 125.2 (q, $^3J_{C,F}$ = 4 Hz, 2 C), 126.5 (2 C), 127.7 (q, $^2J_{C,F}$ = 32 Hz), 128.6, 131.4, 147.1, 147.6, 151.4, 153.2, 171.0 ppm. IR (KBr): $\tilde{\nu}$ = 1680, 1588 cm^{-1}. EI MS: m/z (%) = 449 (63) $[M]^+$, 450 (17), 434 (12), 420 (13), 418 (8), 392 (5), 391 (24), 390 (100), 379 (17), 378 (73), 374 (5), 362 (7), 347 (5), 346 (6), 345 (10), 333 (7), 321 (15), 320 (20), 319 (10), 305 (5), 304 (8), 290 (10), 234 (6), 232 (5), 220 (5), 218 (10), 164 (16), 58 (5). $C_{24}H_{26}F_3NO_4$ (449.19): calcd. C 64.13, H 5.83, N 3.13; found C 64.14, H 5.87, N 3.12.

1-[3-Ethyl-8,9-dimethoxy-6-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-yl]-1-ethan-1-one (25): Yield 329 mg (76%) in acetonitrile, white crystals, m.p. 126–128 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.0 Hz, 3 H, –CH_2–CH_3), 2.36 (s, 3 H, $COCH_3$), 2.79 (dd, J = 5.4, J = 15.0 Hz, 1 H, CH_2-1), 2.90 (qd, J = 7.0, J = 13.6 Hz, 2 H, –CH_2–CH_3), 3.24 (dd, J = 6.7, J = 13.8 Hz, 2 H, CH_2-1 and CH_2-2), 3.37–3.46 (m, 1 H, CH_2-2), 3.83 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.24 (s, 1 H, 6-H), 6.65 (s, 1 H, 7-H), 6.73 (s, 1 H, 10-H), 7.14 (d, J = 7.8 Hz, 2 H, 2 × CH-Ar), 7.48 (d, J = 7.8 Hz, 2 H, 2 × CH-Ar), 7.53 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.2, 20.3, 31.7, 42.4, 44.2, 47.5, 51.3, 51.4, 107.9, 109.9, 111.8, 120.6 (q, $^3J_{C,F}$ = 4 Hz, 2 C), 121.7 (2 C), 122.8 (q, $^2J_{C,F}$ = 32 Hz), 123.5 (q, $^1J_{C,F}$ = 280 Hz), 123.6, 126.6, 142.3, 142.9, 146.7, 150.6, 189.7 ppm. IR (KBr): $\tilde{\nu}$ = 1613, 1571 cm^{-1}. EI MS: m/z (%) = 433 (47) $[M]^+$, 414 (9), 404 (7), 391 (24), 390 (100), 376 (12), 374 (6), 363 (13), 362 (50), 348 (6), 347 (21), 346 (23), 345 (5), 334 (6), 333 (18), 321 (7), 320 (8), 319 (20), 290 (6), 275 (5), 219 (6), 218 (13), 202 (6), 164 (9), 72 (7), 58 (72), 43 (11). $C_{24}H_{26}F_3NO_3$ (433.19): calcd. C 66.50, H 6.05, N 3.23; found C 66.59, H 6.01, N 3.21.

3-Ethyl-8,9-dimethoxy-5-[(4-methylphenyl)sulfonyl]-6-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine (26): Yield 365 mg (67%), white crystals, m.p. 154–155 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.39 (s, 3 H, CH_3–Ar), 2.67 (dd, J = 4.9, J = 15.2 Hz, 1 H, CH_2-1), 2.86 (qd, J = 7.2, J = 13.8 Hz, 2 H, –CH_2–CH_3), 3.20–3.29 (m, 2 H, CH_2-1 and CH_2-2), 3.32–3.42 (m, 4 H, OCH_3 and CH_2-2), 3.83 (s, 3 H, OCH_3), 4.96 (s, 1 H, 6-H), 5.61 (s, 1 H, 7-H), 6.59 (s, 1 H, 10-H), 7.24 (d, J = 7.9 Hz, 2 H, 2 × CH-Ar), 7.40 (d, J = 8.3 Hz, 2 H, 2 × CH-Ar), 7.50 (d, J = 8.3 Hz, 2 H, 2 × CH-Ar), 7.68 (d, J = 7.9 Hz, 2 H, 2 × CH-Ar), 7.70 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 21.3, 37.1, 48.8, 49.8, 51.9, 55.2, 55.8, 104.5, 115.1, 115.4, 124.2 (q, ^1J = 275 Hz), 125.3 (q, ^4J = 3 Hz, 2 C), 127.2 (2 C), 127.7 (2 C), 127.8 (q, ^2J = 32 Hz, 2 C), 129.5 (2 C), 129.7, 139.8, 142.6, 147.1, 147.2, 150.0, 151.5 ppm. IR (KBr): $\tilde{\nu}$ = 1611 cm^{-1}. EI MS: m/z (%) = 545 (5) $[M]^+$, 390 (100), 374 (5), 319 (5), 229 (20), 207 (23), 178 (5), 164 (18), 151 (5), 91 (30), 65 (7), 58 (35), 44 (18). $C_{29}H_{30}F_3NO_4S$ (545.18): calcd. C 63.84, H 5.54, N 2.57; found C 63.85, H 5.58, N 2.56.

Methyl 3-Ethyl-6-phenyl-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (33): Yield 161 mg (50%) in acetonitrile, white crystals, m.p. 108–109 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.80–2.97 (m, 3 H, 2 × CH_2-1 and CH_2-2), 3.08–3.22 (m, 2 H, –CH_2–CH_3), 3.51–3.61 (m, 1 H, CH_2-2), 3.74 (s, 3 H, OCH_3), 6.00 (s, 1 H, 6-H), 7.12–7.30 (m, 9 H, Ar), 7.67 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 14.9, 37.4, 49.0, 49.7, 51.3, 52.0, 97.8, 125.3, 126.2 (2 C), 126.3, 127.2, 128.3 (2 C), 131.7, 133.6, 137.0, 140.0, 147.0, 152.9, 170.9 ppm. IR (KBr): $\tilde{\nu}$ = 1675, 1605 cm^{-1}. EI MS: m/z (%) = 321 (78) $[M]^+$, 306 (12), 290 (15), 262 (100), 230 (13), 202 (27), 178 (24), 158 (15), 144 (11), 128 (15), 115 (27), 103 (7), 91 (28), 77 (13), 59 (17), 42 (6). $C_{21}H_{23}NO_2$ (321.41): calcd. C 78.47, H 7.21, N 4.36; found C 78.51, H 7.17, N 4.42.

1-(3-Ethyl-6-phenyl-1,2,3,6-tetrahydrobenzo[*d*]azocin-5-yl)ethan-1-one (34): Yield 137 mg (45%) in acetonitrile, white crystals, m.p. 135–137 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.34 (s, 3 H, $COCH_3$), 2.84–3.01 (m, 3 H, 2 × CH_2-1 and CH_2-2), 3.20 (q, J = 7.2 Hz, 2 H, –CH_2–CH_3), 3.56–3.68 (m, 1 H, CH_2-2), 6.31 (s, 1 H, 6-H), 7.03 (d, J = 7.6 Hz, 2 H, 2 × CH-Ar), 7.10–7.28 (m, 7 H, 7 × CH-Ar), 7.50 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1622, 1571 cm^{-1}. EI MS: m/z (%) = 305 (56) $[M]^+$, 290 (5), 276 (21), 262 (67), 234 (32), 217 (14), 202 (28), 191 (22), 178 (23), 165 (15), 146 (17), 128 (12), 115 (28), 91 (26), 77 (17), 58 (65), 43 (100). $C_{21}H_{23}NO$ (305.42): calcd. C 82.58, H 7.59, N 4.59; found C 82.67, H 7.58, N 4.61.

3-Ethyl-5-[(4-methylphenyl)sulfonyl]-6-phenyl-1,2,3,6-tetrahydrobenzo[*d*]azocine (35): Yield 342 mg (82%) in acetonitrile, brownish crystals, m.p. 192–193 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.44 (s, 3 H, CH_3–Ar), 2.74 (dd, J = 5.7, J = 15.4 Hz, 1 H, CH_2-1), 2.79–2.95 (m, 2 H, CH_2-1 and CH_2-2), 3.24 (qd, J = 7.2, J = 14.1 Hz, 2 H, –CH_2–CH_3), 3.55 (ddd, J = 5.7, J = 12.1, J = 15.4 Hz, 1 H, CH_2-2), 5.07 (s, 1 H, 6-H), 6.00 (d, J = 7.4 Hz, 1 H, 7-H), 6.79–6.83 (m, 1 H, CH-Ar), 7.05–7.11 (m, 2 H, 2 × CH-Ar), 7.20–7.25 (m, 5 H, 5 × CHAr), 7.64 (d, J = 8.2 Hz, 2 H, 2 × CH-Ar), 7.67 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1614 cm^{-1}. EI MS: m/z (%) = 417 (11) $[M]^+$, 263 (17), 262 (100), 261 (55), 246 (7), 232 (10), 217 (8), 205 (15), 204 (23), 203 (17), 191 (12), 178 (70), 165 (5), 158 (13), 147 (7), 141 (5), 128 (8), 115 (12), 105 (5), 91 (43), 77 (7), 65 (18), 56 (15), 51 (7). $C_{26}H_{27}NO_2S$ (417.56): calcd. C 74.79, H 6.52, N 3.35; found C 74.83, H 6.62, N 3.44.

Methyl 3-Ethyl-8,9-dimethoxy-6-methyl-1,2,3,6-tetrahydrobenzo[*d*]-azocine-5-carboxylate (36): Yield 99 mg (31%) in acetonitrile, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 1.52 (d, J = 7.5 Hz, 3 H, 6-CH_3), 3.08 (ddd, J = 6.1, J = 10.0, J = 16.3 Hz, 1 H, CH_2-1), 3.16–3.27 (m, 3 H, CH_2-1 and –CH_2–CH_3), 3.58 (ddd, J = 4.8, J = 6.1, J = 15.2 Hz, 1 H, CH_2-2), 3.64–3.68 (m, 4 H, OCH_3 and CH_2-2), 3.82 (s, 3 H, OCH_3),

3.85 (s, 3 H, OCH_3), 4.57 (q, J = 7.5 Hz, 1 H, 6-H), 6.55 (s, 1 H, 7-H), 6.74 (s, 1 H, 10-H), 7.50 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1728, 1689 cm^{-1}. EI MS: m/z (%) = 319 (50) $[M]^+$, 304 (100), 288 (20), 272 (15), 260 (60), 248 (84), 323 (10), 218 (16), 215 (20), 203 (17), 191 (44), 190 (24), 175 (20), 164 (30), 160 (15), 145 (10), 128 (8), 115 (16), 91 (7), 77 (6), 58 (8), 42 (6), 29 (10). $C_{18}H_{25}NO_4$ (319.39): calcd. C 67.69, H 7.89, N 4.39; found C 67.73, H 7.93, N 4.43.

3-Ethyl-8,9-dimethoxy-6-methyl-5-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (37): Yield 166 mg (40%) in acetonitrile, brownish crystals, m.p. 139–140 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 1.59 (d, J = 7.2 Hz, 2 H, 6-CH_3), 2.43 (s, 3 H, CH_3–Ar), 2.99–3.09 (m, 1 H, CH_2-1), 3.21–3.30 (m, 3 H, CH_2-1 and –CH_2–CH_3), 3.43–3.52 (m, 4 H, OCH_3 and CH_2-2), 3.76–3.85 (m, 5 H, OCH_3, 6-H and CH_2-2), 5.60 (s, 1 H, 7-H), 6.50 (s, 1 H, 10-H), 7.27 (d, J = 8.1 Hz, 2 H, 2 × CH-Ar), 7.57 (s, 1 H, 4-H), 7.71 (d, J = 8.1 Hz, 2 H, 2 × CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1613 cm^{-1}. EI MS: m/z (%) = 415 (12) $[M]^+$, 400 (5), 260 (100), 233 (100), 215 (14), 203 (11), 191 (15), 174 (5), 164 (10), 145 (7), 130 (5), 115 (10), 105 (7), 91 (35), 77 (7), 65 (18), 58 (16), 51 (6), 39 (13). $C_{23}H_{29}NO_4S$ (415.54): calcd. C 66.48, H 7.03, N 3.37; found C 66.54, H 7.07, N 3.30.

Methyl 8,9-Dimethoxy-6-methyl-3-(4-methylbenzyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (38): Yield 198 mg (50%) in acetonitrile, yellow viscous oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, J = 7.5 Hz, 3 H, 6-CH_3), 2.33 (s, 3 H, CH_3–Ar), 2.75 (ddd, J = 6.6, J = 10.1, J = 17.0 Hz, 1 H, CH_2-1), 3.06–3.08 (m, 1 H, CH_2-1), 3.54 (ddd, J = 4.3, J = 6.6, J = 15.4 Hz, 1 H, CH_2-2), 3.66–3.73 (m, 4 H, CH_2-2 and OCH_3), 3.76 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.23 (d, J = 14.8 Hz, 1 H, CH_2–Ar), 4.35 (d, J = 14.8 Hz, 1 H, CH_2–Ar), 4.60 (q, J = 7.5 Hz, 1 H, 6-H), 6.21 (s, 1 H, 7-H), 6.72 (s, 1 H, 10-H), 6.89 (d, J = 7.9 Hz, 2 H, 2 × CH-Ar), 7.07 (d, J = 7.9 Hz, 2 H, 2 × CH-Ar), 7.67 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1670, 1584 cm^{-1}. EI MS: m/z (%) = 395 (15) $[M]^+$, 380 (14), 364 (5), 336 (12), 290 (27), 276 (95), 258 (6), 248 (53), 234 (8), 215 (14), 203 (10), 191 (30), 175 (9), 164 (28), 147 (13), 134 (10), 128 (6), 115 (10), 105 (100), 91 (12), 77 (35), 65 (7), 59 (10), 42 (12). $C_{24}H_{29}NO_4$ (395.49): calcd. C 72.89, H 7.39, N 3.54; found C 72.96, H 7.43, N 3.46.

8,9-Dimethoxy-6-methyl-3-(4-methylbenzyl)-5-[(4-methylphenyl)-sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (39): Yield 265 mg (54%) in acetonitrile, brownish crystals, m.p. 152–153 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (d, J = 7.7 Hz, 3 H, 6-CH_3), 2.34 (s, 3 H, CH_3–Ar), 2.41 (s, 3 H, CH_3–Ar), 2.64–2.74 (m, 1 H, CH_2-1), 3.05 (dd, J = 5.4, J = 16.5 Hz, 1 H, CH_2-1), 3.44 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.78–3.88 (m, 3 H, 2 × CH_2-2 and 6-H), 4.29 (d, J = 15.1 Hz, 1 H, CH_2–Ar), 4.40 (d, J = 15.1 Hz, 1 H, CH_2–Ar), 5.57 (s, 1 H, 7-H), 6.16 (s, 1 H, 10-H), 6.89 (d, J = 7.6 Hz, 2 H, 2 × CH-Ar), 7.07 (d, J = 7.6 Hz, 2 H, 2 × CH-Ar), 7.26–7.29 (m, 2 H, 2 × CH-Ar), 7.72–7.74 (m, 3 H, 2 × CH-Ar and 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1614 cm^{-1}. EI MS: m/z (%) = 491 (3) $[M]^+$, 336 (50), 296 (5), 238 (10), 217 (80), 164 (7), 106 (37), 105 (100), 91 (16), 77 (17), 65 (7), 51 (95), 39 (7). $C_{29}H_{33}NO_4S$ (491.64): calcd. C 70.85, H 6.77, N 2.85; found C 70.91, H 6.73, N 2.93.

Methyl 6-Benzyl-3-ethyl-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]-azocine-5-carboxylate (40): Yield 237 mg (60%) in acetonitrile, viscous yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, J = 6.5 Hz, 3 H, –CH_2–CH_3), 3.09–3.31 (m, 7 H, –CH_2–CH_3, CH_2-1, CH_2-2, and CH_2–Ar), 3.65–3.68 (m, 7 H, CH_2–Ar and 2 × OCH_3), 3.82 (s, 3 H, OCH_3), 4.66 (t, J = 7.1 Hz, 1 H, 6-H), 6.44 (br. s, 1 H, 7-H), 6.55 (s, 1 H, 10-H), 7.11–7.12 (m, 3 H, CH-Ar), 7.16–7.19 (m, 2 H, CH-Ar), 7.52 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1677, 1609 cm^{-1}. ESI MS: m/z = 396 $[M + 1]^+$. $C_{24}H_{29}NO_4$ (395.49): calcd. C 72.89, H 7.39, N 3.54; found C 72.93, H 7.31, N 3.62.

1-(6-Benzyl-3-ethyl-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[*d*]azocin-5-yl)ethan-1-one (41): Yield 208 mg (55%) in acetonitrile, white crystals, m.p. 152–153 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3 H, –CH_2–CH_3), 2.17 (s, 3 H, $COCH_3$), 3.03–3.18 (m, 3 H, 2 × CH_2-1 and CH_2-2), 3.26–3.36 (m, 3 H –CH_2–CH_3 and CH_2-2), 3.64 (m, 4 H, OCH_3 and CH_2–Ar), 3.66 (m, 4 H, OCH_3 and CH_2–Ar), 4.85 (dd, J = 5.2, J = 8.4 Hz, 1 H, 6-H), 6.37 (br. s, 1 H, 7-H), 6.54 (s, 1 H, 10-H), 7.07–7.17 (m, 5 H, Ar), 7.38 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1623, 1574 cm^{-1}. EI MS: m/z (%) = 379 (3) $[M]^+$, 288 (100), 244 (5), 218 (7), 189 (10), 175 (15), 144 (13), 91 (25), 65 (10), 43 (35). $C_{24}H_{29}NO_3$ (379.49): calcd. C 75.96, H 7.70, N 3.69; found C 76.07, H 7.78, N 3.72.

6-Benzyl-3-ethyl-8,9-dimethoxy-5-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (42): Yield 319 mg (65%) in acetonitrile, white crystals, m.p. 173–174 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3 H, –CH_2–CH_3), 2.34 (s, 3 H, CH_3–Ar), 3.02–3.11 (m, 2 H, CH_2-1), 3.17 (s, 3 H, OCH_3), 3.26–3.43 (m, 4 H, –CH_2–CH_3 and CH_2–Ar), 3.49–3.57 (m, 1 H, CH_2-2), 3.64–3.69 (m, 1 H, CH_2-2), 3.79 (s, 3 H, OCH_3), 3.83–3.96 (m, 1 H, 6-H), 5.06 (s, 1 H, 7-H), 6.51 (s, 1 H, 10-H), 6.94 (d, J = 7.5 Hz, 2 H, 2 × CH-Ar), 7.07–7.14 (m, 3 H, 3 × CH-Ar), 7.21 (d, J = 8.0 Hz, 2 H, 2 × CH-Ar), 7.62 (s, 1 H, 4-H), 7.71 (d, J = 8.0 Hz, 2 H, 2 × CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1614, 1514 cm^{-1}. EI MS: m/z (%) = 491 (3) $[M]^+$, 400 (100), 244 (23), 230 (19), 219 (40), 189 (12), 175 (10), 145 (11), 130 (7), 91 (37). $C_{29}H_{33}NO_4S$ (491.21): calcd. C 70.85, H 6.77, N 2.85; found C 70.69, H 6.89, N 2.87.

General Synthetic Procedure for the Synthesis of Benzo[*d*]azocines 43–45: *p*-Tosylacetylene (2 mmol) or methyl propiolate (acetylacetylene) (5 mmol) was added to a solution of the isoquinoline derivative **5m** (1 mmol) in acetonitrile. The mixture was stirred at room temperature (TLC monitoring). The solvent was evaporated under reduced pressure, and the residue was recrystallized (ethyl acetate/hexane) to give benzoazocines **43**–**45**.

Methyl 6-Benzyl-8,9-dimethoxy-3-(4-methylbenzyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (43): Yield 372 mg (79%) in acetonitrile, white crystals, m.p. 136–138 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, CH_3–Ar), 2.83–2.95 (m, 1 H, CH_2-1), 3.11–3.18 (m, 2 H, CH_2-1 and CH_2-2), 3.24–3.30 (m, 1 H, CH_2-2), 3.70–3.76 (m, 8 H, 2 × OCH_3 and 6-CH_2–Ar), 3.78 (s, 3 H, OCH_3), 4.27 (d, J = 14.8 Hz, 1 H, N–CH_2–Ar), 4.38 (d, J = 14.8 Hz, 1 H, N–CH_2–Ar), 4.70 (dd, J = 5.9, J = 8.6 Hz, 1 H, 6-H), 6.49 (s, 1 H, 10-H), 6.49 (br. s, 1 H, 7-H), 6.94 (d, J = 7.5 Hz, 2 H, 2 × CH-Ar), 7.08–7.28 (m, 7 H, CH-Ar), 7.69 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 21.0, 36.3, 43.3, 46.5, 51.1, 52.3, 55.6, 55.8, 62.1, 101.4, 114.5, 114.9, 125.6, 127.6 (2 C), 127.9 (2 C), 128.8, 128.9 (2 C), 129.2 (2 C), 132.7, 134.4, 137.3, 141.5, 146.3, 147.0, 152.6, 170.1 ppm. IR (KBr): $\tilde{\nu}$ = 1666, 1603 cm^{-1}. EI MS: m/z (%) = 471 (5) $[M]^+$, 440 (50), 380 (35), 175 (5), 105 (100), 79 (12), 65 (6). $C_{30}H_{33}NO_4$ (471.58): calcd. C 76.41, H 7.05, N 2.97; found C 76.54, H 6.99, N 3.02.

1-[6-Benzyl-8,9-dimethoxy-3-(4-methylbenzyl)-1,2,3,6-tetrahydrobenzo[*d*]azocin-5-yl]ethan-1-one (44): Yield 378 mg (83%) in acetonitrile, white crystals, m.p. 159–161 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, $COCH_3$), 2.35 (s, 3 H, CH_3–Ar), 2.78–2.90 (m, 1 H, CH_2-1), 3.03–3.24 (m, 3 H, CH_2-1 and CH_2-2), 3.60–3.66 (m, 4 H, OCH_3 and 6-CH_2–Ar), 3.76 (s, 3 H, OCH_3), 3.82–3.93 (m, 1 H, 6-CH_2–Ar), 4.31 (d, J = 14.9 Hz, 1

H, N–CH_2–Ar), 4.39 (d, J = 14.9 Hz, 1 H, N–CH_2–Ar), 4.85 (dd, J = 5.0, J = 8.7 Hz, 1 H, 6-H), 6.24 (s, 1 H, 10-H), 6.38 (br. s, 1 H, 7-H), 6.92 (d, J = 7.9 Hz, 2 H, 2×CH-Ar), 7.09–7.19 (m, 7 H, CH-Ar), 7.54 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 21.0, 36.3, 43.2, 46.4, 51.0, 52.3, 55.3, 55.8, 62.1, 114.5, 115.3, 115.5, 125.6, 127.6 (2 C), 127.9 (2 C), 128.6, 128.9 (2 C), 129.3 (2 C), 132.5, 133.9, 137.6, 141.6, 146.3, 147.0, 154.7, 195.1 ppm. IR (KBr): $\tilde{\nu}$ = 1574, 1515 cm^{-1}. EI MS: m/z (%) = 455 (3) [M]$^+$, 364 (100), 258 (5), 174 (7), 105 (73), 91 (15), 79 (10), 43 (14). $C_{30}H_{33}NO_3$ (455.59): calcd. C 79.09, H 7.30, N 3.07; found C 780.3, H 7.35, N 3.02.

6-Benzyl-8,9-dimethoxy-3-(4-methylbenzyl)-5-[(4-methylphenyl)-sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (45): Yield 363 mg (64%) in acetonitrile, white crystals, m.p. 182–183 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3–Ar), 2.36 (s, 3 H, CH_3–Ar), 2.73–2.82 (m, 1 H, CH_2-1), 3.05–3.09 (m, 1 H, CH_2-1), 3.19–3.26 (m, 4 H, OCH_3 and CH_2-2), 3.37 (dd, J = 2.1, J = 12.8 Hz, 1 H, CH_2-2), 3.46–3.53 (m, 1 H, 6-CH_2–Ar), 3.71–3.73 (m, 4 H, OCH_3 and 6-CH_2–Ar), 3.87–3.96 (m, 1 H, 6-H), 4.34 (d, J = 14.8 Hz, 1 H, N–CH_2–Ar), 4.44 (d, J = 14.8 Hz, 1 H, N–CH_2–Ar), 5.05 (s, 1 H, 7-H), 6.19 (s, 1 H, 10-H), 6.92–6.96 (m, 4 H, CH-Ar), 7.09–7.13 (m, 5 H, CH-Ar), 7.23–7.25 (m, 2 H, 2×CH-Ar), 7.73 (d, J = 8.2 Hz, 2 H, 2×CH-Ar), 7.79 (s, 1 H, 4-H) ppm. IR (KBr): $\tilde{\nu}$ = 1616 cm^{-1}. EI MS: m/z (%) = 567 (3) [M]$^+$, 476 (30), 188 (5), 105 (100), 91 (12), 65 (5), 43 (11). $C_{35}H_{37}NO_4S$ (567.74): calcd. C 74.04, H 6.57, N 2.47; found C 74.10, H 6.65, N 2.39.

General Synthetic Procedure for the Synthesis of Benzo[*d*]azocines 27–32: *p*-Tosylacetylene (3 mmol) or methyl propiolate (11 mmol) was added to a solution of the isoquinoline derivative **5f**–**h** (1 mmol) in acetonitrile. The mixture was heated at reflux (TLC monitoring). The solvent was evaporated under reduced pressure, and the residue was recrystallized (ethyl acetate/hexane) to give benzoazocines **27**–**32**.

Methyl 8,9-Dimethoxy-3-[4-(methoxycarbonyl)benzyl]-6-(4-methoxyphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (27): Yield 265 mg (50%) in acetonitrile, white crystals, m.p. 160–161 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (ddd, J = 7.2, J = 12.9, J = 16.3 Hz, 1 H, CH_2-1), 2.59 (dd, J = 4.7, J = 16.3 Hz, 1 H, CH_2-1), 2.78 (dd, J = 7.2, J = 15.5 Hz, 1 H, CH_2-2), 3.58–3.66 (m, 1 H, CH_2-2), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.24 (d, J = 15.3 Hz, 1 H, CH_2–Ar), 4.44 (d, J = 15.3 Hz, 1 H, CH_2–Ar), 5.83 (s, 1 H, 6-H), 6.19 (s, 1 H, 7-H), 6.77–6.79 (m, 3 H, 10-H and 2×CH-Ar), 6.99–7.02 (m, 4 H, 4×CH-Ar), 7.82 (s, 1 H, 4-H), 7.90 (d, J = 8.4 Hz, 2 H, 2×CH-Ar) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 36.6, 48.7, 50.6, 51.6, 52.3, 55.2, 55.7, 56.0, 61.7, 99.9, 113.7 (2 C), 115.0, 116.4, 127.1 (2 C), 127.8 (2 C), 128.6, 129.6, 130.1 (2 C), 132.2, 139.0, 142.7, 146.7, 147.5, 153.3, 157.5, 166.7, 170.9 ppm. IR (KBr): $\tilde{\nu}$ = 1719, 1659, 1600 cm^{-1}. EI MS: m/z (%) = 531 (30) [M]$^+$, 500 (10), 472 (50), 382 (53), 364 (50), 350 (20), 340 (72), 307 (10), 282 (27), 237 (12), 178 (20), 164 (30), 149 (87), 136 (40), 121 (100), 105 (20), 90 (30), 77 (17), 59 (17), 44 (28). $C_{31}H_{33}NO_7$ (531.60): calcd. C 70.04, H 6.26, N 2.63; found C 69.97, H 6.29, N 2.71.

Methyl 4-({8,9-Dimethoxy-6-(4-methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-1,6-dihydrobenzo[*d*]azocin-3(2*H*)-yl}methyl)-benzoate (28): Yield 520 mg (83%) in acetonitrile, white crystals, m.p. 184–185 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37–2.45 (m, 4 H, CH_3-Ts, CH_2-1), 2.50–2.59 (m, 1 H, CH_2-1), 2.78 (dd, J = 7.8, J = 15.4 Hz, 1 H, CH_2-2), 3.42 (s, 3 H, OCH_3), 3.60–3.65 (m, 1 H, CH_2-2), 3.74 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.32 (d, J = 15.4 Hz, 1 H, CH_2–Ar), 4.52 (d, J = 15.4 Hz, 1 H, CH_2–Ar), 4.96 (s, 1 H, 6-H), 5.64 (s, 1 H, 7-H), 6.21 (s, 1 H, 10-H), 6.77 (d, J = 8.2 Hz, 2 H, 2×CH-Ar), 7.04 (d, J = 7.9 Hz, 2 H, 2×CH-Ar), 7.15 (d, J = 7.7 Hz, 2 H, 2×CH-Ar), 7.25–7.29 (m, 2 H, 2×CH-Ar), 7.68 (d, J = 7.7 Hz, 2 H, 2×CH-Ar), 7.82 (s, 1 H, 4-H), 7.93 (d, J = 8.2 Hz, 2 H, 2×CH-Ar) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 21.4, 36.5, 49.2, 50.1, 52.6, 55.1, 55.3, 55.4, 59.7, 106.1, 114.0 (2 C), 115.7, 115.8, 127.9 (2 C), 128.0 (2 C), 128.4 (2 C), 128.8, 129.2, 129.7 (2 C), 130.0 (2 C), 130.5, 137.5, 140.6, 142.9, 144.0, 146.8, 146.9, 152.9, 157.9, 166.4 ppm. IR (KBr): $\tilde{\nu}$ = 1716, 1613 cm^{-1}. EI MS: m/z (%) = 627 (2) [M]$^+$, 472 (35), 444 (10), 340 (5), 322 (53), 308 (7), 295 (25), 280 (12), 264 (17), 249 (10), 221 (7), 190 (11), 165 (15), 149 (91), 121 (83), 91 (65), 77 (20), 55 (15), 44 (30). $C_{36}H_{37}NO_7S$ (627.75): calcd. C 68.88, H 5.94, N 2.23; found C 68.97, H 5.86, N 2.31.

Methyl 3-(4-Fluorobenzyl)-8,9-dimethoxy-6-(4-methoxyphenyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (29): Yield 181 mg (37%) in acetonitrile, white crystals, m.p. 117–119 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (ddd, J = 6.8, J = 13.2, J = 16.1 Hz, 1 H, CH_2-1), 2.58 (dd, J = 5.4, J = 16.1 Hz, 1 H, CH_2-1), 2.79 (dd, J = 6.8, J = 15.4 Hz, 1 H, CH_2-2), 3.58 (ddd, J = 5.4, J = 13.2, J = 15.4 Hz, 1 H, CH_2-2), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.16 (d, J = 14.7 Hz, 1 H, CH_2–Ar), 4.36 (d, J = 14.7 Hz, 1 H, CH_2–Ar), 5.84 (s, 1 H, 6-H), 6.19 (s, 1 H, 7-H), 6.77–6.79 (m, 3 H, 10-H and 2×CH-Ar), 6.90–6.93 (m, 4 H, 4×CH-Ar), 7.02 (d, J = 8.0 Hz, 2 H, 2×CH-Ar), 7.83 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.4, 48.6, 50.2, 51.4, 55.2, 55.7, 55.9, 61.2, 99.6, 113.7 (2 C), 115.0, 115.2 (d, $^2J_{C,F}$ = 22 Hz, 2 C), 116.6, 127.1 (2 C), 128.7, 129.2 (d, $^3J_{C,F}$ = 8 Hz, 2 C), 132.4, 133.2 (d, $^4J_{C,F}$ = 3 Hz), 139.1, 146.7, 147.5, 153.3, 157.5, 162.1 (d, $^1J_{C,F}$ = 246 Hz), 170.9 ppm. IR (KBr): $\tilde{\nu}$ = 1677, 1605 cm^{-1}. EI MS: m/z (%) = 491 (13) [M]$^+$, 432 (17), 382 (15), 350 (10), 340 (20), 121 (13), 109 (100), 83 (12), 59 (7). $C_{29}H_{30}FNO_5$ (491.55): calcd. C 70.86, H 6.15, N 2.85; found C 70.90, H 6.12, N 2.93.

3-(4-Fluorobenzyl)-8,9-dimethoxy-6-(4-methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (30): Yield 475 mg (81%) in acetonitrile, white crystals, m.p. 112–113 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39–2.44 (m, 4 H, CH_2-1 and CH_3-Ts), 2.53 (dd, J = 5.2, J = 15.8 Hz, 1 H, CH_2-1), 2.78 (dd, J = 6.4, J = 15.4 Hz, 1 H, CH_2-2), 3.40 (s, 3 H, OCH_3), 3.60 (ddd, J = 5.2, J = 13.6, J = 15.8 Hz, 1 H, CH_2-2), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.22 (d, J = 15.0 Hz, 1 H, CH_2–Ar), 4.25 (d, J = 15.0 Hz, 1 H, CH_2–Ar), 4.94 (s, 1 H, 6-H), 5.60 (s, 1 H, 7-H), 6.21 (s, 1 H, 10-H), 6.78 (d, J = 8.9 Hz, 2 H, 2×CH-Ar), 6.95–6.96 (m, 4 H, 4×CH-Ar), 7.15 (d, J = 8.1 Hz, 2 H, 2×CH-Ar), 7.70 (d, J = 8.1 Hz, 2 H, 2×CH-Ar), 7.83 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 36.8, 49.2, 49.9, 55.1, 55.2, 55.6, 60.9, 106.9, 113.7 (2 C), 115.1, 115.2, 115.3 (d, $^2J_{C,F}$ = 21 Hz, 2 C), 127.8 (2 C), 127.8 (2 C), 128.4, 129.3 (d, $^3J_{C,F}$ = 8 Hz, 2 C), 129.4 (2 C), 130.7, 132.9 (d, $^4J_{C,F}$ = 3 Hz), 137.4, 139.9, 142.5, 146.7, 146.9, 151.8, 157.9, 162.1 (d, $^1J_{C,F}$ = 247 Hz) ppm. IR (KBr): $\tilde{\nu}$ = 1614 cm^{-1}. EI MS: m/z (%) = 587 (3) [M]$^+$, 432 (7), 295 (8), 145 (11), 121 (18), 109 (100), 91 (23), 65 (6). $C_{34}H_{34}FNO_5S$ (587.70): calcd. C 69.48, H 5.83, N 2.38; found C 69.55, H 5.90, N 2.29.

Methyl 8,9-Dimethoxy-6-(4-methoxyphenyl)-3-(4-methylbenzyl)-1,2,3,6-tetrahydrobenzo[*d*]azocine-5-carboxylate (31): Yield 210 mg (43%) in acetonitrile, white crystals, m.p. 122–124 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3–Ar), 2.40–2.50 (m, 1 H, CH_2-1), 2.60 (dd, J = 5.1, J = 15.5 Hz, 1 H,

CH_2-1), 2.81 (dd, J = 7.0, J = 15.5 Hz, 1 H, CH_2-2), 3.58 (m, 1 H, CH_2-2), 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.17 (d, J = 14.8 Hz, 1 H, CH_2–Ar), 4.35 (d, J = 14.8 Hz, 1 H, CH_2–Ar), 5.84 (s, 1 H, 6-H), 6.26 (s, 1 H, 7-H), 6.78–6.80 (m, 3 H, 10-H and 2 × CH-Ar), 6.87 (d, J = 7.7 Hz, 2 H, 2 × CH-Ar), 7.02–7.07 (m, 4 H, 4 × CH-Ar), 7.86 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 36.4, 48.6, 49.8, 51.3, 55.2, 55.6, 55.9, 61.4, 98.9, 113.7 (2 C), 115.2, 116.5, 127.1 (2 C), 127.6 (2 C), 128.8, 129.1 (2 C), 132.5, 134.2, 137.3, 139.2, 146.6, 147.4, 153.5, 157.4, 171.0 ppm. IR (KBr): 1670, 1605 cm^{-1}. EI MS: m/z (%) = 487 (10) $[M]^+$, 428 (21), 382 (30), 340 (17), 281 (70), 192 (7), 151 (5), 121 (15), 105 (100), 79 (13), 59 (50). $C_{30}H_{33}NO_5$ (487.58): calcd. C 73.90, H 6.82, N 2.87; found C 73.99, H 6.77, N 2.95.

8,9-Dimethoxy-6-(4-methoxyphenyl)-3-(4-methylbenzyl)-5-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydrobenzo[*d*]azocine (32): Yield 315 mg (54%) in acetonitrile, white crystals, m.p. 165–166 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3–Ar), 2.41 (s, 3 H, CH_3–Ar), 2.43–2.56 (m, 2 H, CH_2-1), 2.79 (dd, J = 6.1, J = 15.4 Hz, 1 H, CH_2-2), 3.39 (s, 3 H, OCH_3), 3.57 (ddd, J = 6.1, J = 12.8, J = 15.4 Hz, 1 H, CH_2-2), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.25 (d, J = 14.8 Hz, 1 H, CH_2–Ar), 4.40 (d, J = 14.8 Hz, 1 H, CH_2–Ar), 4.93 (s, 1 H, 6-H), 5.58 (s, 1 H, 7-H), 6.24 (s, 1 H, 10-H), 6.77 (d, J = 8.9 Hz, 2 H, 2 × CH-Ar), 6.89 (d, J = 7.9 Hz, 2 H, 2 × CH-Ar), 7.07 (d, J = 7.5 Hz, 2 H, 2 × CH-Ar), 7.24–7.26 (m, 2 H, 2 × CH-Ar), 7.69 (d, J = 7.9 Hz, 2 H, 2 × CH-Ar), 7.84 (s, 1 H, 4-H) ppm. IR (KBr): 1620 cm^{-1}. EI MS: m/z (%) = 583 (3) $[M]^+$, 428 (53), 322 (15), 295 (10), 206 (13), 165 (70), 155 (5), 145 (6), 121 (20), 105 (100), 91 (21), 77 (13), 65 (7). $C_{35}H_{37}NO_5S$ (583.74): calcd. C 72.01, H 6.39, N 2.40; found C 72.11, H 6.44, N 2.37.

Methyl 3-Ethyl-8,9-dimethoxy-6-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydrobenzo[*d*]azocine-5-carboxylate (46): $NaCNBH_3$ (104 mg, 1.66 mmol) and a few drops of acetic acid, as catalyst, were added to a solution of benzo[*d*]azocine **8** (340 mg, 0.83 mmol) in methanol (20 mL). The reaction mixture was heated at reflux (TCL monitoring). The solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate (3 × 25 mL). The solvent was evaporated under reduced pressure to give hexahydrobenzo[*d*]azocine **46** (275 mg, 80%) as a viscous yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 6.3 Hz, 2.4 H, –CH_2–CH_3 maj), 1.06 (t, J = 6.3 Hz, 0.6 H, –CH_2–CH_3 min), 2.10 (dd, J = 2.5, J = 15.0 Hz, 0.8 H, CH_2-1 maj), 2.25 (br. d, J = 13.4 Hz, 0.2 H, CH_2-1 min), 2.42–2.61 (m, 2 H, –CH_2–CH_3), 2.63–2.74 (m, 1 H, 2-CH_2), 2.76–2.85 (m, 1 H, 5-H), 2.88–2.97 (m, 2 H, 4-CH_2), 3.02–3.12 (m, 1 H, CH_2-1), 3.33–3.47 (m, 1 H, CH_2-2), 3.58 (s, 2.4 H, CO_2CH_3 maj), 3.68 (s, 0.6 H, CO_2CH_3 min), 3.59 (s, 2.4 H, OCH_3 maj), 3.70 (s, 0.6 H, OCH_3 min), 3.78 (br. s, 3 H, 8-OCH_3), 3.85 (s, 2.4 H, 9-OCH_3 maj), 3.88 (s, 0.6 H, 9-OCH_3 min), 4.94 (d, J = 12.0 Hz, 0.8 H, 6-H maj), 5.01 (d, J = 3.8 Hz, 0.2 H, 6-H min), 6.39 (s, 0.8 H, 7-H maj), 6.42 (s, 0.2 H, 7-H min), 6.62 (s, 0.8 H, 10-H maj), 6.65 (s, 0.2 H, 10-H min), 6.86 (br. d, J = 8.0 Hz, 2 H, CH-Ar), 7.19 (d, J = 8.0 Hz, 1.6 H, CH-Ar maj), 7.25 (d, J = 8.0 Hz, 0.4 H, CH-Ar min) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ maj (min) = 11.7 (12.7), 36.7 (37.3), 43.3 (43.7), 51.4 (49.9), 52.3 (51.1), 54.2 (53.3), 55.1, 55.2, 55.7, 55.8, 55.8, 111.4 (112.1), 112.5 (113.2), 113.7 (2 C), 129.0 (129.2, 2 C), 132.7 (131.6), 134.3 (133.6), 135.3 (135.1), 147.2 (146.6), 147.5 [157.8 (157.5), 174.2 (173.6) ppm. IR (KBr): $\tilde{\nu}$ = 1743 cm^{-1}. EI MS: m/z (%) = 413 (30) $[M]^+$, 411 (6), 356 (5), 354 (8), 283 (13), 282 (6), 271 (5), 296 (5), 234 (8), 220 (10), 208 (14), 207 (100), 206 (13), 192 (23), 165 (5), 164 (6), 147 (9), 121 (10), 72 (9), 58 (5). $C_{24}H_{31}NO_5$ (413.51): calcd. C 69.71, H 7.56, N 3.39; found C 69.78, H 7.47, N 3.30.

Dimethyl 3-Ethyl-8,7-dimethoxy-6-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydrobenzo[*d*]azocine-4,5-dicarboxylate (47): $NaCNBH_3$ (165 mg, 2.63 mmol) and a few drops of acetic acid, as catalyst, were added to a solution of benzo[*d*]azocine **11** (350 mg, 0.75 mmol) in methanol (20 mL). The reaction mixture was heated at reflux (TCL monitoring). The solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate (3 × 25 mL). The solvent was evaporated under reduced pressure to give hexahydrobenzo[*d*]azocine **47** (221 mg, 62%); white crystals, m.p. 130–131 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, J = 6.9 Hz, 3 H, –CH_2–CH_3), 2.54 (qd, J = 6.9, J = 13.9 Hz, 1 H, –CH_2–CH_3), 2.62 (dd, J = 3.7, J = 13.3 Hz, 1 H, CH_2-1), 2.67–2.78 (m, 1 H, CH_2-1), 2.83 (qd, J = 6.9, J = 13.9 Hz, 1 H, –CH_2–CH_3), 3.23–3.37 (m, 4 H, 2 × CH_2-2, 4-H, and 5-H), 3.51 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.99 (d, J = 11.4 Hz, 1 H, 6-H), 6.46 (s, 1 H, 7-H), 6.59 (s, 1 H, 10-H), 6.84 (d, J = 8.7 Hz, 2 H, 2 × CH-Ar), 7.26 (d, J = 8.7 Hz, 2 H, 2 × CH-Ar) ppm. IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1}. EI MS: m/z (%) = 471 (12) $[M]^+$, 412 (10), 295 (7), 233 (15), 220 (25), 207 (100), 192 (11), 165 (8), 142 (20), 130 (70), 121 (30), 82 (5), 72 (20), 56 (14), 45 (31). $C_{26}H_{33}NO_7$ (471.54): calcd. C 66.22, H 7.05, N 2.97; found C 66.01, H 7.12, N 3.04.

Crystal Structure Analysis for 47: $C_{26}H_{33}NO_7$, M_r = 471.54 g mol^{-1}, monoclinic, space group $P2_1/c$, a = 11.7535(11), b = 9.2742(13), c = 23.647(3) Å, β = 98.251(8)°, V = 2551.0(6) Å^3, Z = 4, ρ = 1.228 g cm^3, μ = 0.089 mm^{-1}, F(000) = 1008. A total of 8286 reflections (1.74° < θ < 30.00°), of which 7320 were unique [R(int.) = 0.0277], were collected with a Bruker-P4 diffractometer with use of monochromatized Mo-K_α radiation. The structure was solved with the program SHELXS-97 and refined by use of SHELXL-97 to R_1 = 0.065 and $wR(F^2)$ = 0.2024 for 7320 reflections with $I > 2\sigma(I)$; max./min. residual electron density 0.182/–0.385 e Å^{-3}. CCDC-646020 (for **47**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

The financial support of the Russian Foundation for Basic Research (grant #03-05-32211) is gratefully acknowledged.

[1] D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446.
[2] R. Worayuthakarn, N. Thasana, S. Ruchirawat, *Org. Lett.* **2006**, *25*, 5845–5848.
[3] Y. Ishihara, K. Hirai, M. Miyamoto, G. Goto, *J. Med. Chem.* **1994**, *37*, 2292–2299.
[4] M. P. Wentland, M. VanAlstina, R. Kucejko, R. Lou, D. J. Cohen, A. L. Parkhill, J. M. Bidlack, *J. Med. Chem.* **2006**, *49*, 5635–5639.
[5] M. Kambe, E. Arai, M. Suzuki, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2001**, *16*, 2575–2578.
[6] Y. Liu, W. W. McWhorter, C. Hadden, *Org. Lett.* **2003**, *3*, 333–335.
[7] M. Seto, K. Aikawa, Y. Aramaki, N. Kanzaki, K. Takashima, Y. Kuze, Y. Iizama, *J. Med. Chem.* **2006**, *49*, 2037–2048.
[8] a) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007; b) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238.
[9] a) J. R. Fuchs, R. L. Funk, *Org. Lett.* **2001**, *21*, 3349–3351; b) T. Ishikawa, S. Manabe, T. Aikawa, T. Kudo, S. Saito, *Org. Lett.* **2004**, *14*, 2361–2364.
[10] a) R. C. Larock, C. Tu, P. Pace, *J. Org. Chem.* **1998**, *63*, 6859–6866; b) B. M. Trost, M. K. Ameriks, *Org. Lett.* **2004**, *11*,

1745–1748; c) E. L. Crooper, A. J. P. White, A. Ford, K. K. Hii, *J. Org. Chem.* **2006**, *71*, 1732–1735.
[11] a) R. Worayuthakarn, N. Thasana, S. Ruchirawat, *Org. Lett.* **2006**, *25*, 5845–5848; b) Z. Ma, S. Dai, D. Yu, *Tetrahedron* **2006**, *47*, 4721–4724.
[12] A. V. Varlamov, T. N. Borisova, L. G. Voskressensky, L. N. Kulikova, T. A. Soklakova, A. I. Chernyshev, G. G. Alexandrov, *Tetrahedron Lett.* **2002**, *43*, 6767–6769.
[13] L. G. Voskressensky, T. N. Borisova, L. N. Kulikova, A. V. Varlamov, M. Catto, C. Altomare, A. Carotti, *Eur. J. Org. Chem.* **2004**, 3128–3135.
[14] L. G. Voskressensky, S. V. Akbulatov, T. N. Borisova, A. V. Varlamov, *Tetrahedron* **2006**, *62*, 12392–12397.
[15] L. G. Voskressensky, T. N. Borisova, A. V. Listratova, L. N. Kulikova, A. A. Titov, A. V. Varlamov, *Tetrahedron Lett.* **2006**, *47*, 4585–4589.
[16] J. L. Moore, S. M. Taylor, V. A. Soloshonok, *ARKIVOC* **2005**, *vi*, 287–292.
[17] G. K. Cheung, M. J. Earle, R. A. Faihurt, H. Heaney, K. F. Shuhaibar, S. C. Eyley, F. Ince, *Synlett* **1991**, *10*, 721–722.
[18] See, e.g.: a) W. M. Whaley, T. R. Govindachari, *Org. React.* **1951**, *6*, 74–150; b) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1996**, *61*, 824–825.
[19] L. Waykole, L. A. Paquette, *Org. Synth.* **1989**, *67*, 149.

Received: June 30, 2007
Published Online: October 16, 2007

