



Cite this: *RSC Adv.*, 2018, 8, 38598

Received 5th October 2018
 Accepted 8th November 2018

DOI: 10.1039/c8ra08241c

rsc.li/rsc-advances

Synthesis and fluorescent properties of boroisoquinolines, a new family of fluorophores†

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First representatives of a new family of isoquinolines, so called boroisoquinolines, were synthesized and characterized. The synthesis was based on the insertion of the difluoroboranyl group into the 1-methylidene-3,4-dihydroisoquinoline core. The optimization of the 2-difluoroboranyl-3,4-dihydroisoquinoline-1(2*H*)-ylidene core led to efficient fluorescence in a range of 400–600 nm with outstanding (>100 nm) Stokes shifts. The compounds might be suitable for reversible or irreversible labelling of proteins, particularly the cannabinoid receptor CB₂.

Introduction

The isoquinoline core is represented in a large number of biologically active compounds containing alkaloids and also synthetic heterocycles (Fig. 1). The alkaloids can be found widely in various plants^{1–4} and marine invertebrates.⁵ A well-known pharmacologically significant compound is papaverine (1) that was isolated from opium poppies (*Papaver somniferum*) and was used as a smooth muscle relaxant.⁶ Other biologically active representatives are the members of the berberine (2) family that were isolated from various herbs.^{7,8} These plants (*e.g.* *Coptis chinensis*) have been used in traditional Chinese medicine for the treatment of infections, skin problems and diabetes.^{9–12} Among the latter compounds palmatine (3) should be mentioned as a widely used tetracyclic isoquinoline against, among others, hypertension and inflammation.¹³ From a marine sponge *Jaspis* sp. also, more complex isoquinoline natural products were isolated such as jasioquinoline A and B (4a and 4b, respectively) that possess anticancer activity.¹⁴ Ripasudil (5, Glanatec®) activates the Rho-kinase, hence it is used in the treatment of glaucoma and increased eye-pressure.^{15,16} Furthermore, many isolated or synthesized isoquinoline derivatives exhibit a vast spectrum of biological activities including anti-HIV,¹⁷ antitubercular,¹⁸ antiplasmodial,¹⁹ anti-Alzheimer's²⁰ and antifungal effects²¹ and some representatives are non-competitive

AMPA [2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid] receptor antagonists.²² In addition, the commercially available drug solifenacin (Vesicare®, 6), a 1-aryl-tetrahydroisoquinoline derivative shows competitive cholinergic receptor antagonist effect used in the treatment of contraction of overactive bladder.^{23,24} Members of the 2'-(3,3-dimethyl-3,4-dihydroisoquinoline-1-ylidene)-1-ethane-1-one family (7) should be mentioned as non-toxic and specific nanomolar CB₂ agonist, while other derivatives of this family can inhibit phosphodiesterase 7 (PDE7). On this basis, these compounds might be considered as preventive or treating agents for asthma, autoimmune diseases, rheumatoid arthritis, Crohn's disease or carcinomatous pain.^{25–28} Besides the pharmaceutical applications, isoquinoline derivatives were also utilized as chiral ligands for catalytic asymmetric reactions²⁹ or as electrophosphorescent iridium complexes.³⁰ Boranyl (8) and related compounds containing nitrogen–boron–oxygen structural element (NBO-complexes) are a recently developed family of fluorescent molecules (Fig. 2). The photophysical properties of several known NBO-complexes are summarized in Table 1. These compounds were designed to overcome the drawbacks of BODIPY's *e.g.* small Stokes-shift, difficult industrial synthesis.³¹ The synthesis of boranyl is usually starting from an imino compound containing a hydroxyl or an enolizable oxo group at the γ -position. The parent compounds are reacted with a trisubstituted borane, mostly BF₃ or B(aryl)₃ resulting in a disubstituted borane group inserted between the nitrogen and the oxygen atom. The photophysical characterization of these compounds showed acceptable Stokes-shifts with good ϵ and Φ values (Table 1, entry 1).³² It was observed that in the case of borobenzothiazoles³³ (9) a push–pull system between a disubstituted amino and a nitrile group was required for an outstanding Stokes-shift (149–170 nm, entry 2), but the quantum yield of the compounds was weak. Minuti and co-workers designed boranyl for biological application by the ring opening of isoxazoles to 10 equipped with an acetylene tail in order to the click

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† Electronic supplementary information (ESI) available: Experimental, spectroscopy and XRD data. For experimental procedures and compound characterization. CCDC 1854624 and 1854625. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra08241c



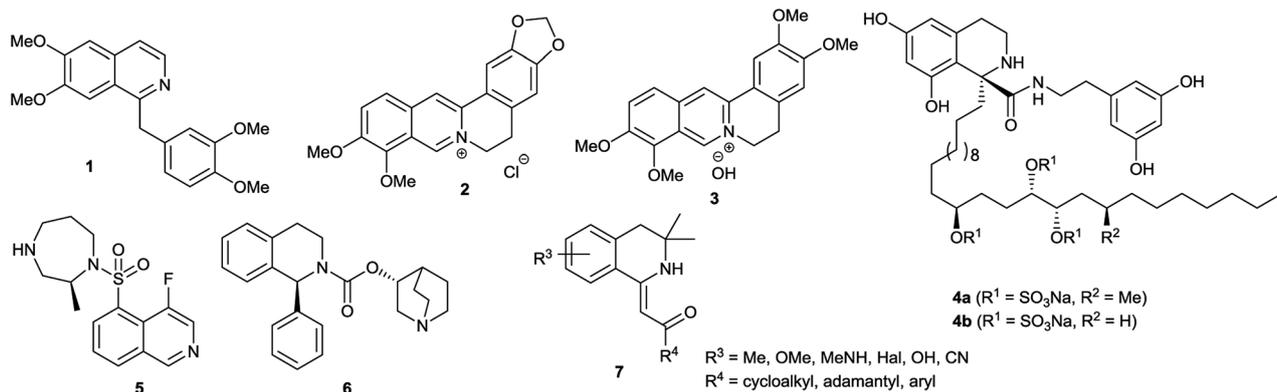


Fig. 1 Structures of pharmaceutically active isoquinoline derivatives.

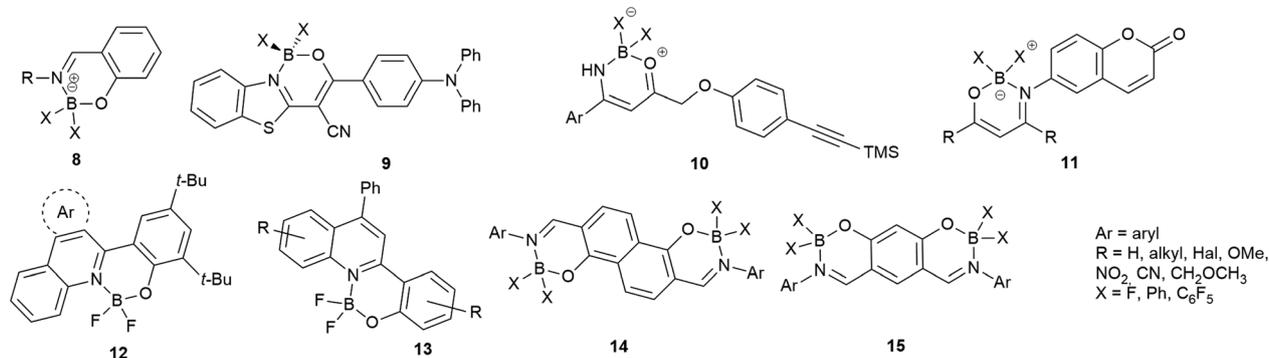


Fig. 2 Boranyles (8) and related compounds containing nitrogen–boron–oxygen structural element (NBO-complexes, 9–15).

labeling of azidoproteins.³⁴ Only one member of the boranyles derived from coumarins (11) showed weak fluorescence but on the contrary, the phosphorescence of those was remarkable (Table 1, entry 3).³⁵ Boroquinolines (12, 13) were synthesized from salicylic aldehyde, aniline and phenylacetylene, showing a Stokes-shift of 80–200 nm and green fluorescence (Table 1, entries 4, 5).^{36,37} From naphthalene dialdehyde multiboranyles (14) were synthesized, but the larger molecule size caused lower fluorescence.³⁸ Nevertheless, a nice red shift was obtained with a wide range of quantum yield (Table 1, entry 6). Related compounds, so called polyboranyles (15) were designed from *m*-phthalic aldehyde exhibiting large Stokes-shift with medium molar absorptivity and quantum yield (Table 1, entry 7).³⁹

As a continuation of our efforts on the field of developing biologically interesting isoquinoline derivatives,⁴⁰ the objective of our work was the synthesis of new fluorescent members of the 2'-(3,4-dihydroisoquinoline-1-ylidene)-1-ethan-1-one (7) family equipped with BR₂ groups.

Results and discussion

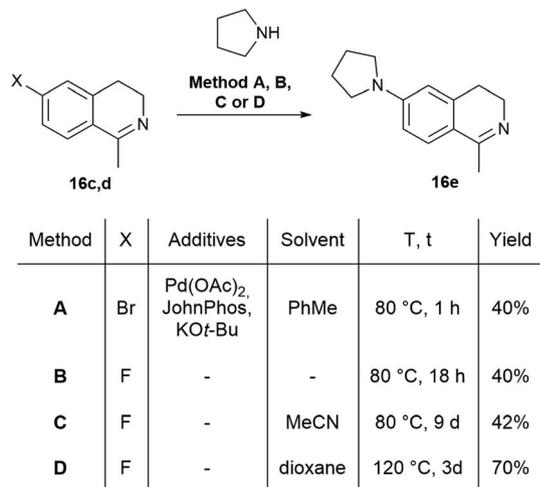
The fluorescent molecules were envisaged to be obtained by the acylation of dihydroisoquinolines followed by the incorporation of a boranyl group. Initially, the starting 7-methoxy (16a), 6,7-dimethoxy (16b), 7-bromo (16c) and 7-fluoro-3,4-dihydroisoquinoline (16d) have been synthesized by slight

Table 1 Photophysical properties of NBO-complexes

Entry	Solvent	$\lambda_{\text{absz}}^{\text{max}}$ [nm]	$\lambda_{\text{em}}^{\text{max}}$ [nm]	Stokes-shift [nm]	ϵ [M ⁻¹ cm ⁻¹]	Φ_{F} [–]
1	CH ₂ Cl ₂	344–387	380–432	14–68	13100–67200	0.22–0.73
2	MeCN	442–450	599–612	149–170	—	0.004–0.008
3	THF/dioxane	331	420	89	33660	—
4	CHCl ₃	385–417	523–543	126–145	8317–11482	0.18–0.32
5	CHCl ₃	288–385	467–538	82–201	14300–38500	0–0.22
6	CH ₂ Cl ₂	495–589	457–609	37–183	17300–148700	0–0.56
7	CH ₂ Cl ₂	495–589	533–683	38–101	13100–44500	0–0.81

^a Only one member showed fluorescence.





Scheme 1 The synthesis of 1-methyl-7-pyrrolidine-1-yl-3,4-dihydroisoquinoline (**16e**).

modification of literature procedures.^{41,42} In most cases, the corresponding phenylacetone nitriles were transformed to phenylethylamines using borane in THF,⁴³ followed by the acylation with acetyl chloride. The ring closure was achieved with a modified Bischler–Napieralski reaction after Larsen using oxalyl chloride in the presence of FeCl₃ and the subsequent reaction with sulphuric acid in MeOH.⁴⁴ In the case of 7-pyrrolidinyl-1-methyl-3,4-dihydroisoquinoline (**16e**), the pyrrolidine group was inserted either with Buchwald–Hartwig reaction of **16c** or with the aromatic nucleophilic substitution of **16d** (Scheme 1).

The Buchwald–Hartwig coupling was performed in the presence of Pd(OAc)₂, JohnPhos and KOt-Bu in toluene leading to **16e** in a yield of 40% (Scheme 1, Method A).⁴⁵ In order to improve the outcome, several substitution reactions were tried using **16d** (Method B, C and D).^{46,47} The best result was obtained reacting **16d** with 6 equiv. of pyrrolidine in dioxane at 120 °C in a sealed tube for 3 days resulting in **16e** in a yield of 70% (Method D). Notably, for the purification of **16e** steam distillation and normal phase flash chromatography was required.

The synthesis of the 1-methylidene-1,2,3,4-tetrahydroisoquinolines (**17**) was accomplished by the slight modification of the method of Dannhardt *et al.* using BuLi or lithium-diisopropylamide (LDA) to deprotonate the methyl group of the 1-methyl-3,4-dihydroisoquinolines (**16a–e**) derivatives followed by the addition of the appropriate ester (Scheme

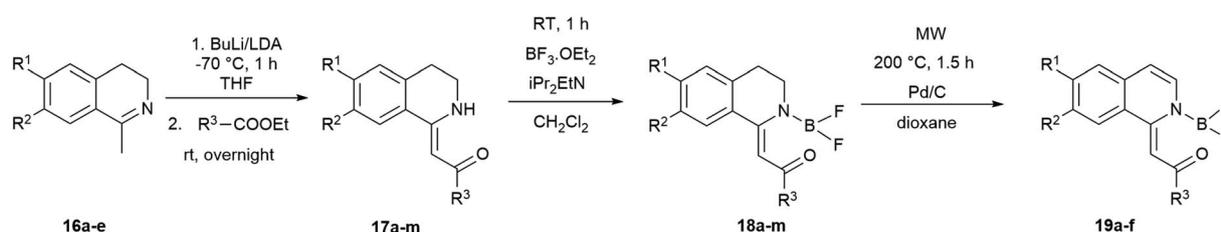
Table 2 Results for the synthesis of 1-methylidene-1,2,3,4-tetrahydroisoquinolines (**17**) and borisoquinolines **18**, **21**

#	R ¹	R ²	R ³	17 ^a [%]	18 ^a [%]	19 ^a [%]	
1	a	MeO	H	Me	46	77	73
2	b	MeO	MeO	Me	50	78	70
3	c	MeO	H	Ph	45	70	77
4	d	MeO	MeO	Ph	53	88	89
5	e	MeO	H	2-Thienyl	58	50	52
6	f	MeO	MeO	2-Thienyl	48	85	48
7	g	MeO	H	C ₆ F ₅	12	85	—
8	h	MeO	MeO	C ₆ F ₅	57	89	—
9	i	MeO	H	4-O ₂ N-C ₆ H ₄	5	—	—
10	j	MeO	MeO	4-O ₂ N-C ₆ H ₄	54 (3) ^b	49	—
11	k	MeO	H	Me	41 (26) ^b	78	—
12	l	Py ^c	H	Ph	72 (27) ^b	97	—
13	m	Py ^c	H	C ₆ F ₅	20 (16) ^b	81	—

^a Isolated yields. ^b Yields with LDA, results with BuLi are in parentheses. ^c Pyrrolidine-1-yl.

2).⁴⁸ Heterocycles **17a–h** were isolated in moderate yields (12–65%, Table 2, entries 1–8). In the case of 4-nitrobenzoic acid ethyl ester, the products (**17i,j**) could be isolated in traces with BuLi (3–5%), but using LDA the yield of **17j** was raised to 54% (Table 2, entries 9, 10). Changing the methoxy group on the isoquinoline to pyrrolidine also lowered the yields (16–27%) possibly due to the interaction of the pyrrolidine nitrogen with the BuLi. The use of a larger amount of BuLi, or changing the base to *sec*-BuLi or BuLi-TMEDA did not give better results, but again, the application of LDA led to a significant raise in the isolated yields (20–72%, Table 2, entries 11–13).

The difluoro-borisoquinoline structure (**18**) was constructed by reacting compounds **17** with boron trifluoride diethyl etherate in the presence of 5 equiv. of diisopropylethylamine (DIPEA) in dichloromethane (Scheme 2).³² In order to synthesize fully aromatic derivatives with respect to its expected advantageous effect on the fluorescence, compounds **18a–f** were dehydrogenated with Pd/C in dioxane at 200 °C for 90 min (Scheme 2). Borisoquinolines **19a–f** were isolated in good yields (48–89%, Table 2, entries 1–6). In the case of **18k–m**, the pyrrolidine ring was aromatized during the reaction, a selective oxidation could not be developed. Dehydrogenating derivatives with C₆F₅ substituent produced only degradation products that could be detected by HPLC-MS with loss of various fluorine atoms. In the case of **18j**, the nitro group was converted to amino function, and decomposition products were observed.



Scheme 2 Synthesis of 1-methylidene-1,2,3,4-tetrahydroisoquinolines (**17**) and borisoquinolines **18** and **19**.



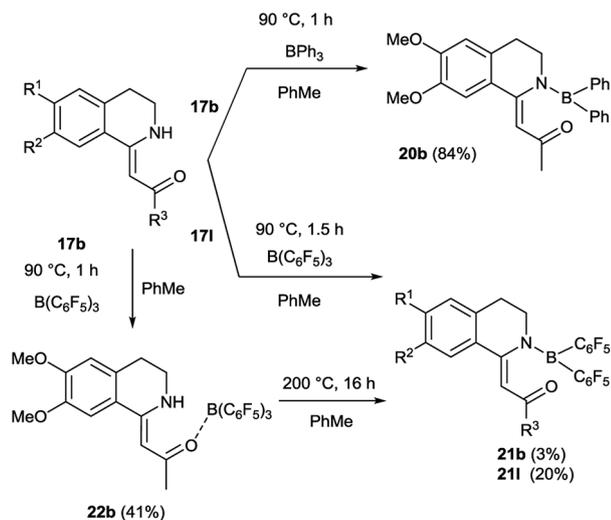
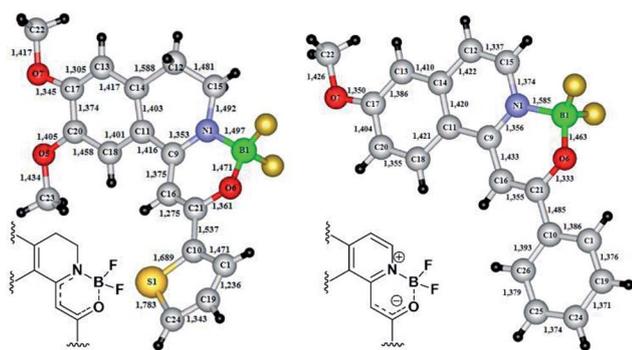
Scheme 3 Synthesis of boraisoquinolines **20**, **21**, **22**.Fig. 3 X-ray structures of boraisoquinolines **18f** and **19c**.

Table 3 Representative bond lengths and bond angles

18f		19c	
Bond length (Å)	Bond angle (°)	Bond length (Å)	Bond angle (°)
B1–N1 = 1.497	C21–O6–B1 = 119.0	B1–N1 = 1.585	C21–O6–B1 = 119.0
B1–O6 = 1.471	C9–N1–C15 = 125.4	B1–O6 = 1.463	C9–N1–C15 = 125.4
N1–C9 = 1.353	C15–N1–B1 = 114.6	N1–C9 = 1.365	C15–N1–B1 = 114.6
C9–C16 = 1.375	N1–C9–C11 = 112.8	N1–C9 = 1.379	N1–C9–C11 = 112.8
C16–C21 = 1.275	O6–C21–C10 = 107.8	N1–C15 = 1.374	O6–C21–C10 = 107.8
O6–C21 = 1.361	C10–C21–C16 = 128.6	C15–C12 = 1.337	C10–C21–C16 = 128.6
N1–C15 = 1.492	F3–B1–F4 = 107.5	C9–C16 = 1.433	F3–B1–F4 = 107.5
	F3–B1–N1 = 108.6	C16–C21 = 1.355	F3–B1–N1 = 108.6
	C9–N1–B1 = 119.5		C9–N1–B1 = 119.5
	N1–C9–C16 = 120.6		N1–C9–C16 = 120.6
	N1–C15–C12 = 110.8		N1–C15–C12 = 110.8
	C9–C16–C21 = 121.1		C9–C16–C21 = 121.1
	O6–C21–C16 = 123.5		O6–C21–C16 = 123.5
	F3–B1–O6 = 105.8		F3–B1–O6 = 105.8
	F4–B1–O6 = 109.8		F4–B1–O6 = 109.8
	F4–B1–N1 = 114.4		F4–B1–N1 = 114.4
	O6–B1–N1 = 110.3		O6–B1–N1 = 110.3

We aimed to synthesize further boranyl derivatives using triaryl boranes. A diphenyl-boraisoquinoline (**20b**) was prepared in a yield of 84% by refluxing **17b** with triphenylborane in toluene at 90 °C (Scheme 3).³¹ In the case of $\text{B}(\text{C}_6\text{F}_5)_3$ as the borulating agent, the formation of the desired bis(perfluorophenyl)-boraisoquinoline was observed depending on the starting compound either in a one-step reaction in toluene at 90 °C leading to **21b** in a yield of 20%, or in a two-step procedure through the heating of tris(perfluorophenyl)-boraisoquinoline intermediate **22b** at 200 °C resulting in **21b** in a poor yield (3%) (Scheme 3).

In the cases of **18f** and **19c** the exact structure of the new heterocyclic family members was elucidated by single crystal X-ray diffraction measurements (Fig. 3). From the crystal structures it could be concluded, that until the nitrogen atom of **18f** has pyramidal conformation, in **19c** the nitrogen is planar. The bond lengths proved the boron–nitrogen bonding and the boron–oxygen coordination. The proposed electron-distribution and bonding in the NBO containing ring is shown on the figures next to the crystal structures. Representative bond lengths and bond angles are shown in Table 3. The detailed XRD data and ORTEP figures can be found in the ESI.†

The synthesis was followed by the extensive photophysical analysis of the new boraisoquinolines. The absorbance and fluorescence spectra were measured for compounds **18a–h, k–m**, **19a–f**, **20b**, **21b, l** and **22b** (Table 4) in acetonitrile. It should be noted, that the nitro group of **18j** was disadvantageous for the fluorescence, as the intensity was measured in the range of the noise.

Regarding the different boranyles, although λ^{max} -s of the di- or triarylboranyl derivatives (**20b**, **21b, l**, **22b**, Table 4, entries 7, 13–15) were uniformly higher than those of the difluoroboranyl, the Stokes-shift did not raise or even decreased. This observation has led to the conclusion that the fluoro derivatives should be developed further and this was supported by sterical



Table 4 Photophysical properties of the borisoquinolines

Entry	R ¹ ^a	R ²	R ³	BX	$\lambda_{\text{abs}}^{\text{max}}$ [nm]	$\lambda_{\text{exc}}^{\text{max}}$ [nm]	$\lambda_{\text{em}}^{\text{max}}$ [nm]	$\Delta\lambda$ [nm]	
1	18a	MeO	H	Me	BF ₂	328		390	62
2	18b	MeO	MeO	Me	BF ₂	321	339	431	110
3	18k	Py	H	Me	BF ₂	383	379	450	67
4	18c	MeO	H	Ph	BF ₂	357		411	54
5	18d	MeO	MeO	Ph	BF ₂	361	380	483	122
6	18l	Py	H	Ph	BF ₂	408	406	537	129
7	21l	Py	H	Ph	B(C ₆ F ₅) ₂	417	415	544	127
8	18e	MeO	H	2-Thienyl	BF ₂	374		437	63
9	18f	MeO	MeO	2-Thienyl	BF ₂	383		448	65
10	18g	MeO	H	C ₆ F ₅	BF ₂	334	343	435	101
11	18h	MeO	MeO	C ₆ F ₅	BF ₂	334	356	537	203
12	18m	Py	H	C ₆ F ₅	BF ₂	411	410	565	154
13	20b	MeO	MeO	Me	BPh ₂	337	387	453	116
14	21b	MeO	MeO	Me	B(C ₆ F ₅) ₂	346	372	440	94
15	22b	MeO	MeO	Me	B(C ₆ F ₅) ₃	357	368	465	108
16	19a	MeO	H	Me	BF ₂	355		410	55
17	19b	MeO	MeO	Me	BF ₂	371		415	45
18	19c	MeO	H	Ph	BF ₂	378	372	487	109
19	19d	MeO	MeO	Ph	BF ₂	396		458	62
20	19e	MeO	H	2-Thienyl	BF ₂	401		471	70
21	19f	MeO	MeO	2-Thienyl	BF ₂	410		480	70

^a Py = pyrrolidine-1-yl.

factors too, namely it is presumed, that the extensive diarylboranyl group would be less favoured in a binding pocket of a protein than the smaller difluoroboranyl group.

On the isoquinoline ring electron donating substituents were chosen for the substitution envisioning that the electron donation will raise the fluorescence. This assumption was confirmed as the 6-methoxy derivatives showed the weakest fluorescence intensity and the lowest λ^{max} -s, while the insertion of a second methoxy group or changing the methoxy to pyrrolidinyl initiated significant increase in intensity and also λ^{max} -s (Table 4, entries 1–3, 4–6 and 10–12; representative spectra for **18c,d,l** shown on Fig. 4) leading the fluorescence into the >500 nm range. In order to prove the electron donating effect of the pyrrolidine substituent, the fluorescence spectrum of **18l** was measured in the presence of HCl (1 equiv.) (Fig. 4, grey spectrum) and a significant decrease of the fluorescence intensity was observed.

The pyrrolidine substituent caused strikingly good fluorescence λ^{max} -s depending on the substituent on the carbonyl

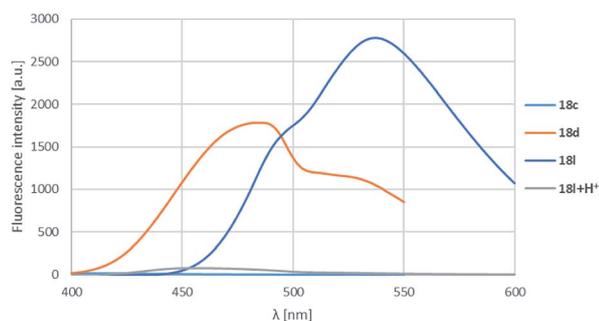


Fig. 4 R¹, R² substituent effects for borisoquinoline **18**.

group. It was found that the electron donating methyl group (**18k**) performed best, and as the electron withdrawal was increasing from the phenyl (**18l**) to the perfluorophenyl (**18m**) substituent, the fluorescence was shifted to the yellow range, but the intensity decreased significantly (Table 4, entries 3, 6, 12, Fig. 5).

The effect of the dehydrogenation was also studied, and it was found that in the case of the 6-methoxy derivatives (**18a,c,e** and **19a,c,e**) the extension of the aromatic system was advantageous for the λ^{max} -s and the Stokes-shifts (Table 4, entries 1 and 16, 4 and 18, 8 and 20). It should be noted, that by **19c** a remarkable Stokes-shift (115 nm) was measured (Table 4, entry 18). Meanwhile, in the case of the 6,7-dimethoxyborisoquinolines, the oxidized species were better only for the thienyl derivative (**18f** and **19f**, Table 4, entries 9 and 21).

The effect of various solvents for the absorbance, excitation and fluorescence was also investigated on borisoquinoline **18l**

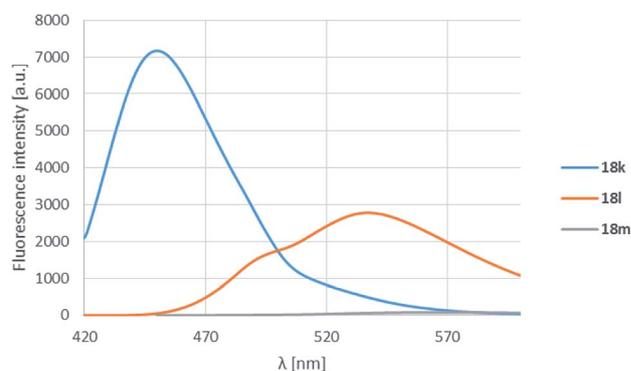


Fig. 5 R³ substituent effect for borisoquinolines **18**.



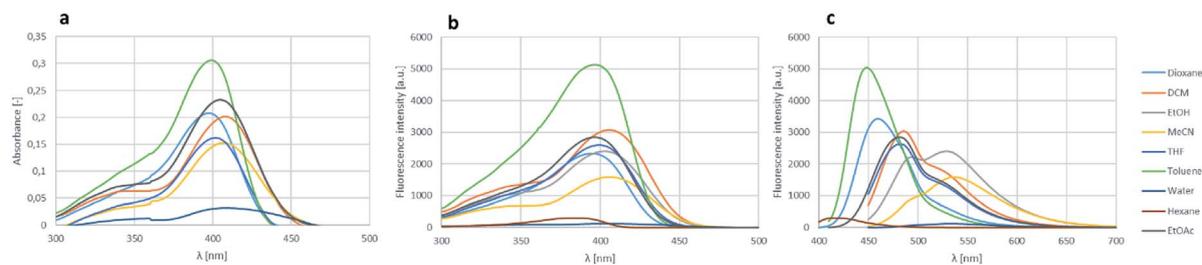


Fig. 6 Solvent screen for the absorbance (a), excitation (b) and fluorescence (c) of **18l**.

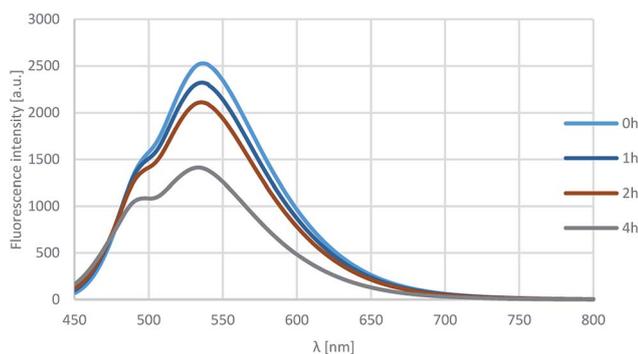


Fig. 7 Results of the photostability test.

(Fig. 6). The solvent screen contained hexane, toluene, ethyl acetate, dichloromethane, dioxane, tetrahydrofuran, ethanol, acetonitrile and water. It could be concluded, that the absorbance and excitation spectra remained similar in the different solvents, the absorption maximum was not shifting significantly (Fig. 6a and b, respectively). It should be noted, that the largest intensity was reached in toluene, ethanol, ethyl acetate and dioxane, while in water (or PBS buffer) the absorbance was practically ceased because of aggregation of the molecules. Meanwhile the solvents seemed to influence the fluorescence more significantly (Fig. 6b).

The measured intensities were similar for the different solvents than those by the absorbance measurements, but in most solvents except MeCN and EtOH the fluorescence maximum decreased to the range under 500 nm narrowing the

room between the excitation and the fluorescence. The loss of absorbance and fluorescence in aqueous medium might be an advantage targeting a protein in an aprotic environment *e.g.* in the cell membrane, if the fluorescence gets enhanced reaching the target, while stay hidden in the aqueous environment outside the membrane.

Furthermore, the photostability of compound **18l** was investigated by measuring the fluorescence in acetonitrile after 0, 1, 2 and 4 h of irradiation with 360 nm light. As shown on Fig. 7, the fluorescence intensity was still around 60% after 4 h, that corresponds to outstanding photostability.

Compounds showing outstanding Stokes-shift were studied forward measuring molar absorptivity (ϵ) and quantum yield (Φ_F) (Table 5). It was found, that some of the borisoquinolines, particularly **18b** and **18l** showed more than 0.3 (entries 1, 4) and a remarkable quantum yield of 0.84 belonged to **18k** (entry 2). On the contrary, the fully aromatic **19c** (entry 10) and the perfluorophenyl derivatives (**18g,h,m**; entries 6–8) has lower Φ_F than 0.1, that might be explained with the dissipation of the electrons on the extended aromatic system, and the large, shielding substituents on the boron atom, respectively. Notably, the pyrrolidine substituent was advantageous for the ϵ and Φ_F , but the larger substituents on either the carbonyl group or the boron atom decreased the above values, presumably because of the too extended electron system.

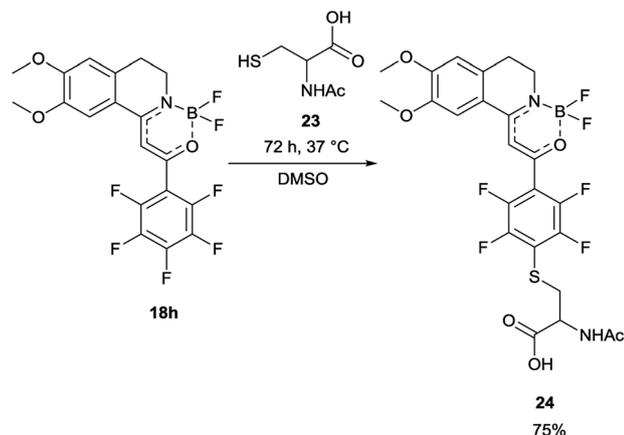
In order to find a possible biological application, compound **18h** was reacted with *N*-acetylcysteine (**23**), as a thiol-surrogate in DMSO at 37 °C. The full conversion was reached after 72 h and the adduct was isolated in a yield of 75% (Scheme 4). It was

Table 5 Molar absorptivity and quantum yield for selected borisoquinolines

Entry		$\lambda_{\text{abs}}^{\text{max}}$ [nm]	$\lambda_{\text{exc}}^{\text{max}}$ [nm]	$\lambda_{\text{em}}^{\text{max}}$ [nm]	$\Delta\lambda$ [nm]	ϵ ($\lambda_{\text{abs}}^{\text{max}}$) [$\times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$]	Φ_F^a [–]
1	18b	321	339	431	110	2.20	0.32
2	18k	383	379	450	67	5.47	0.84
3	18d	361	380	483	122	3.06	0.18
4	18l	408	406	537	129	3.58	0.35
5	21l	417	415	544	127	3.71	0.17
6	18g	334	343	435	101	2.75	0.0024
7	18h	334	356	537	203	2.31	0.022
8	18m	411	410	565	154	2.55	0.037
9	22b	357	368	465	108	3.16	0.11
10	19c	378	372	487	109	2.47	0.016

^a Quantum yields relative to quinin sulfate (dyes **18b,g, 22b**) or to Coumarin 153 (dyes **18k,d,l,g,h,m, 19c, 21l, 22b**).





Scheme 4 Reaction of **18h** with *N*-acetylcysteine (**23**), as thiol-surrogate.

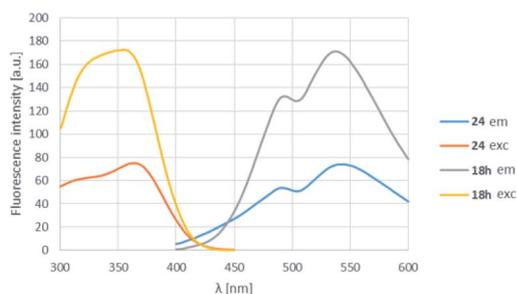


Fig. 8 The change of the excitation and fluorescence spectra in the reaction of **18h** with *N*-acetylcysteine (**23**).

proven, that the thiol group reacted with a fluorine atom on the aromatic ring. The photophysical properties of the conjugate were investigated, and although the intensity of the fluorescence was decreased, the shape of the excitation and fluorescence curve and the Stokes-shift remained similar (Fig. 8). Although the reaction conditions are not yet compatible with the conditions in human cells, this preliminary result projects that after careful optimization these compounds might be applicable for the covalent labelling of cysteines in proteins.

Conclusions

A new family of fluorophores, namely boroisoquinolines was developed, synthesized from 1-methyl-3,4-dihydroisoquinolines in a two or three step synthesis. The photophysical properties of the small library were extensively studied, and outstanding Stokes shifts with good molar absorptivity values were observed. Some of the dyes (**18b**,**k**,**l**) showed appreciable to excellent quantum yields with good photostability. The solvent screening results indicated low fluorescence in aqueous medium that might serve as an advantage using the compounds in aprotic conditions *e.g.* in cell membranes. We believe that upon further optimization these fluorescent dyes might be good choices for visualization of the labelling of the appropriate proteins (*e.g.* CB₂).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

P. Á-B. is grateful for the postdoctoral fellowship of the Hungarian Academy of Sciences and the Hungarian Science Foundation (OTKA PD124598).

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