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Chiral ethylene-bridged flavinium salts: the stereoselectivity of flavin-10a-hydroperoxide formation and the effect of substitution on the photochemical properties

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ABSTRACT

A series of chiral non-racemic N^1,N^{10}-ethylene bridged flavinium salts **4** was prepared using enantiomerically pure 2-substituted 2-aminoethanols (R = isopropyl, phenyl, benzyl, 4-methoxybenzyl, 4-benzyloxybenzyl) derived from amino acids as the sole source of chirality. The flavinium salts were shown to form 10a-hydroperoxy- and 10a-methoxy-adducts with moderate to high diastereoselectivity depending on the ethylene bridge substituent originating from the starting amino acid. High diastereoselectivities (*dr* values from 80:20 to >95:5) were observed for flavinium salts bearing benzyl substituents attached to the ethylene bridge. The benzyl group preferred the face-to-face (*syn*) orientation relative to the flavinium unit; thereby effectively preventing nucleophilic attack from one side. This conformation was found to be the most stable according to the DFT calculations. Consequently, the presence of benzyl groups causes intermolecular fluorescence quenching resulting in a significant decrease in the fluorescence quantum yield from 11% for **4a** bearing an isopropyl substituent to 0.3% for **4c** containing a benzyl group and to a value lower than 0.1% for the benzyloxybenzyl derivative **4e**.

1. Introduction

Flavin-dependent monooxygenases promote the insertion of an oxygen atom into a variety of biological substrates and xenobiotics.[1] The oxidative process is mediated by flavin co-factor **Fl** (FAD or FMN, see Scheme 1A) forming (upon reduction with NADPH, and the subsequent reaction with oxygen) flavin-4a-hydroperoxide **Fl-OOH**, which introduces one oxygen atom into the substrate molecule. After oxygen transfer, the co-factor is regenerated via the elimination of water (Scheme 1A).[2] Many of these enzymes, e.g. Baeyer–Villiger (B.V.) monooxygenases, have been found to oxidize prochiral substrates, cyclic ketones to lactones and sulfides to sulfoxides with high stereoselectivities.[3,4] Thus, several biocatalytic procedures with flavin-monooxygenases have been developed for these reactions and some of them have even been transformed into valuable technologies.[5]

In parallel, artificial flavin systems have been under investigation for chemoselective and stereoselective sulfoxidation and B.V. oxidation reactions.[6,7] In these procedures, instead of natural unsubstituted **FlOOH**, 5-ethylflavin-4a-hydroperoxide **5-EtFlOOH**, formed from 5-ethylflavinium salts **5-EtFl$^+$X$^-$**, were employed because of their significantly higher stability outside an enzyme (Scheme 1B).[8] Only very recently, has artificial unsubstituted **FlOOH** been utilized in oxidation reactions, which was allowed because of its intramolecular stabilization via a tripeptide unit.[9]

There is also a difference in the formation of hydroperoxide between biological and artificial systems. Unlike enzymes, artificial oxidative species are mostly generated using hydrogen peroxide as a stoichiometric oxidant, which undergoes addition to the flavinium catalyst (Scheme 1B). The biomimetic procedure involving the reduction of 5-alkylflavinium salt **5-EtFl$^+$X$^-$** to **5-EtFlH$_2$** using a sacrificial reducing agent followed by reaction with molecular oxygen has also been described for artificial monooxygenation, however, it has not been used in a stereoselective fashion to date.[6]

Leaving aside B.V. oxidations, in which the reaction is significantly influenced by the Criegee intermediate breaking down,[1c] the stereoselectivity of monooxygenation is controlled by two sequential steps: (i) The formation of hydroperoxide and (ii) the stereoselective transfer of an oxygen atom from the hydroperoxy group onto the substrate (Fig. 1). Both these steps must occur stereoselectively to produce one enantiomer of the sulfoxide in

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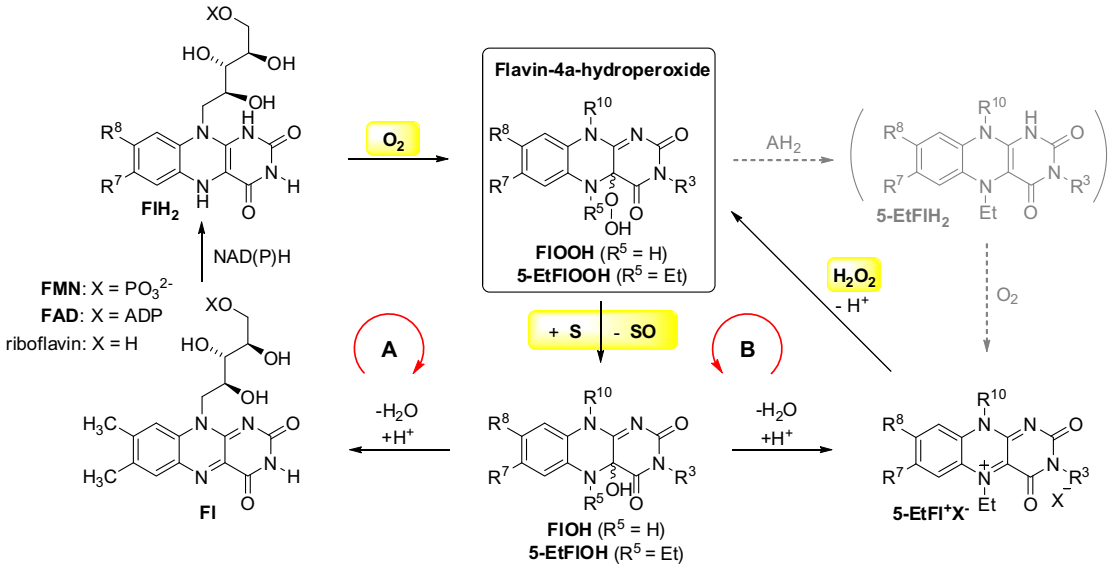


Scheme 1. Mechanism of monooxygenations promoted by flavin-4a-hydroperoxide and its generation in biological (A) and artificial (B) systems.

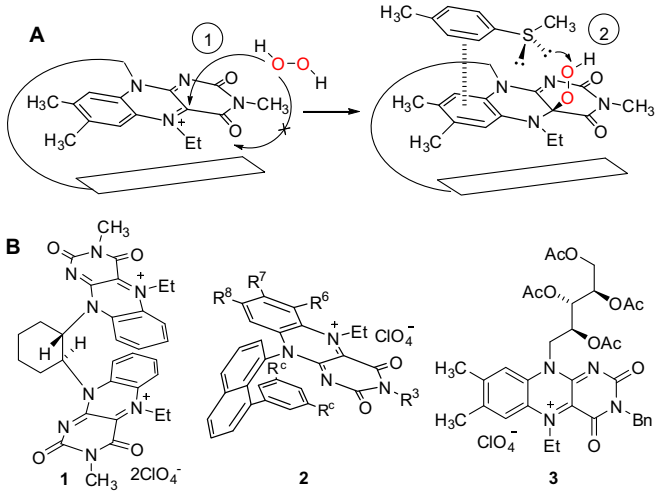
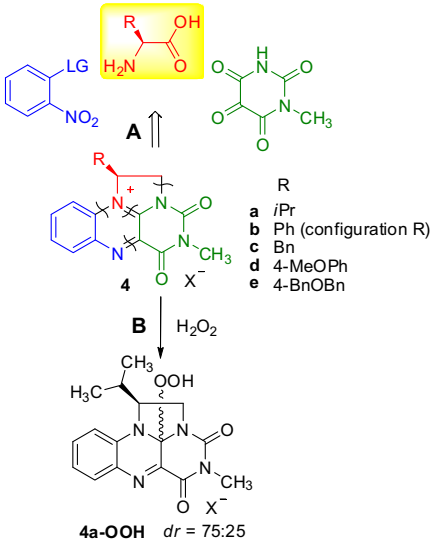


Figure 1. Origin of stereoinduction in monooxygenations mediated by flavinium salts shown on an example of sulfoxidation (A) and structures of selected chiral flavinium salts (B).



Scheme 2. Retrosynthesis of ethylene-bridged flavinium salts **4** (A) and the structure of flavin-10a-hydroperoxide **4a-OOH** (B).

excess. In enzymes, the stereoselectivity is controlled by the topography of the active site containing a chiral environment created by various amino acid residues. In artificial systems, two approaches have been applied: (i) Mimicking the binding site with a chiral cavity comprised of a cyclodextrin covalently bound to a flavin subunit[7b,10] or (ii) the introduction of a 'cap' allowing access of hydrogen peroxide from only one side (see catalysts **1** and **2**).[11] The second step, the transfer of oxygen, is believed to be controlled by π–π interactions between an aromatic substrate and flavin hydroperoxide (Fig. 1A). Catalysts **1** and **2** have been shown to catalyze the B.V. oxidation of phenylcyclobutanones[11c] and the sulfoxidation of aromatic sulfides[11a] with observed enantioselectivities up to 61 and 74%, respectively. Interestingly, a simple 5-ethyltetraacetylriboflavinium salt **3** was found to form a hydroxy adduct (a model of hydroperoxide) in 29% *de,* which was subsequently reflected by the stereoselective H_2O_2-sulfoxidation of methyl *p*-tolyl sulfide catalyzed by **3** (30% *ee*).[12]

In our preliminary communication,[13] we found that the chiral 1,10-ethylene-bridged flavinium salt **4a** bearing an amino acid residue (R = isopropyl) attached to the ethylene bridge can be straightforwardly prepared from valine (Scheme 2A). Salt **4a** is able to catalyze sulfoxidation reactions using hydrogen peroxide in a similar manner to that observed with 5-alkylflavinium salts (Scheme 2). This oxidation occurs through flavin-10a-hydroperoxide **4a-OOH** formed via the addition of hydrogen peroxide to **4a**.[14] Interestingly **4a-OOH** was found to be formed with *dr* = 75:25.

Having in mind their simple synthesis allowing the easy introduction of an amino acid residue and the ability to form adducts (e.g. hydroperoxides), salts **4** seem to be suitable models to study the effect of covalently attached amino-acid residues on the diastereoselectivity of hydrogen peroxide adduct formation. Herein, we report our investigation on flavins **4** with aromatic residues known to accompany flavin co-factors in various enzymes.[15] Besides their effect on adduct formation, we also observed the strong effect of the side chain structure on the spectroscopic properties of **4**. We believe these findings will help to design new efficient flavinium catalysts as well as to elucidate the

stereoselectivity of monooxygenation reactions mediated by flavoenzymes.

2. Results and discussion

2.1. Synthesis of the flavinium salts

Flavinium salts **4** were prepared using the methodology firstly published by Sayre et al.[16] with modifications recently described by our group for salt **4a**.[13] The synthesis commenced from 1-fluoro-2-nitrobenzene and the corresponding 2-amino alcohol (Scheme 3). The amino alcohols **5a** and **5b** were commercially available or prepared via the reduction of the corresponding amino acid (**5c**) using $NaBH_4/I_2$ in dry tetrahydrofuran[17] or the reduction of the corresponding *N*-protected amino acid esters (**5c** and **5d**); (see Experimental section). In contrast to the synthesis of simple *N*-hydroxyethyl-2-nitroanilines usually starting from 1-bromo- or 1-chloro-2-nitrobenzene,[16] more reactive 1-fluoro-2-nitrobenzene was necessary for derivatives branched on the carbon atom close to the nitrogen. The reaction time strongly depended on the steric hindrance of the substituent ranging from 1 h for **6b** (R = phenyl) to 20 h for the benzyloxybenzyl derivative **6e**. DABCO was found to be a more suitable base than potassium carbonate, which was originally used, preventing the competitive *O*-arylation of the amino ethanol substrates. In the presence of potassium carbonate, the formation of the *O*-aryl derivative in 13% yield was observed in the reaction of 1-fluoro-2-nitrobenzene with (*S*)-valinol **5a**.

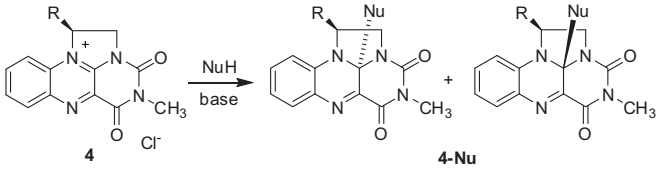
The reduction of nitroanilines was performed via catalytic hydrogenation with the exception of derivatives **6b** and **6e**, which were reduced using hydrazine/$FeCl_3$ to avoid debenzylation. Formation of the flavin skeleton via the reaction of the oxygen-sensitive diamine **7** with alloxane proved to be the most difficult step of the synthesis and required optimization. We found that the slow addition of the solution of diamine in AcOH to a hot solution of at least two equivalents of alloxane gave flavins **8** in satisfactory yields. The presence of boric acid usually used in flavin synthesis was not necessary in this method. The yields of flavins **8** strongly depended on their substitution ranging from 47% for **8e** containing the bulky benzyloxybenzyl group up to 91% for **8b** bearing a phenyl substituent. Despite our great efforts, we did not succeed in the synthesis of the flavin derived from *tert*-leucine. The 3-methyl derivatives **9** were prepared via the alkylation of **8** using methyl iodide in dry acetone in the presence of potassium carbonate. It should be noted that the prepared flavins **7** and **8** (except phenyl derivatives **7b** and **8b**) looks in ^{1}H NMR spectra like a mixture of diastereomers due to restricted rotation around N^{10}—C bond. The synthesis of flavinium salts **4** was completed with the reaction of the 10-(2-hydroxyethyl)flavins **9** with $SOCl_2$ under an argon atmosphere.

2.2. Diastereoselectivity of the nucleophile addition reaction

Upon the addition of hydrogen peroxide into a solution of **4a** in CD_3CN, a 75:25 mixture of diastereomeric hydroperoxides **4a-OOH** was formed (see scheme in Table 1). In this experiment, potassium carbonate was present as a base providing the complete transformation of the flavinium salt to hydroperoxide. The reaction was performed directly in the NMR cuvette because of the limited stability of the hydroperoxide. To elucidate the effect of various substituents on the ethylene bridge on the diastereoselectivity of hydroperoxide formation, we performed the same experiment with the other salts **4** (see Table 1). Interestingly, similar diastereoselectivities were observed for the methoxy adducts **4-OCD$_3$** formed after the addition of trimethylamine into a solution of **4** in CD_3OD (Table 1).

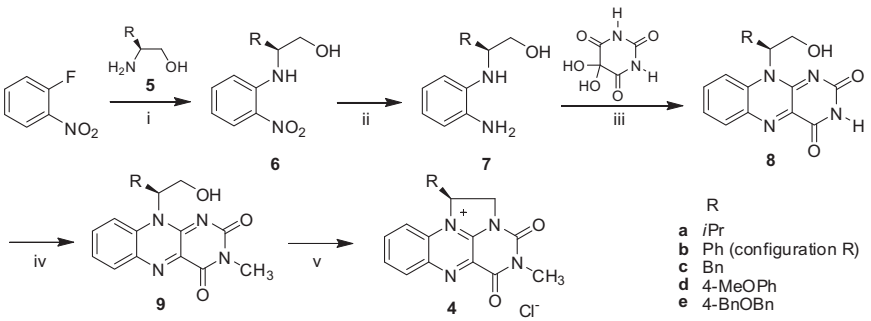
Unfortunately, the structure of flavin-hydroperoxides **4-OOH** and deuterated methoxy adducts **4-OCD$_3$** did not allow determination of their configuration using the NMR technique. For this purpose, the methoxy adducts **4-OCH$_3$** has been found to be more suitable allowing to study the relative position of the substituent on the ethylene bridge and methoxy group using NOE experiments (Fig. 2A). The methoxy adduct was prepared via a simple addition of sodium methoxide to a methanolic solution of the salts **4a**. Importantly, exactly 1 equivalent of sodium methoxide had to be added to avoid the destruction of the flavin skeleton. Then, the solvents were carefully evaporated, the residue was dried *in vacuo*,

Table 1
Diastereoselectivity of the reaction of flavinium salts **4** with hydrogen peroxide (Nu = OOH) and CD_3OD (Nu = OCD_3).



Flavinium salt	R	Ratio of diastereoisomers[a]	
		4-OOH[b]	**4-OCD$_3$**[c]
4a[d]	*i*Pr	75:25	75:25
4b	Ph	60:40	60:40
4c	Bn	80:20	90:10
4d	*p*-MeOBn	90:10	95:5
4e	*p*-BnOBn	>95:5	>95:5

[a] The ratios of diastereoisomers were determined by ^{1}H NMR.
[b] Base: potassium carbonate, solvent: CD_3CN.
[c] Base: Et_3N, solvent: CD_3OD.
[d] Ref. 13.



Scheme 3. Synthesis of flavinium salts **4**. (i) DABCO, *n*-butanol, reflux, 80–97%; (ii) H_2, Pd(C), methanol, 82–99% for **6a**, **6c** and **6d** or N_2H_4, $FeCl_3$, active coal, methanol, 82–90% for **6b** and **6e**; (iii) acetic acid, 70 °C, 47–91%; (iv) CH_3I, K_2CO_3, acetone, reflux, 90–95%; (v) $SOCl_2$, dichloromethane, rt, 89–97%.

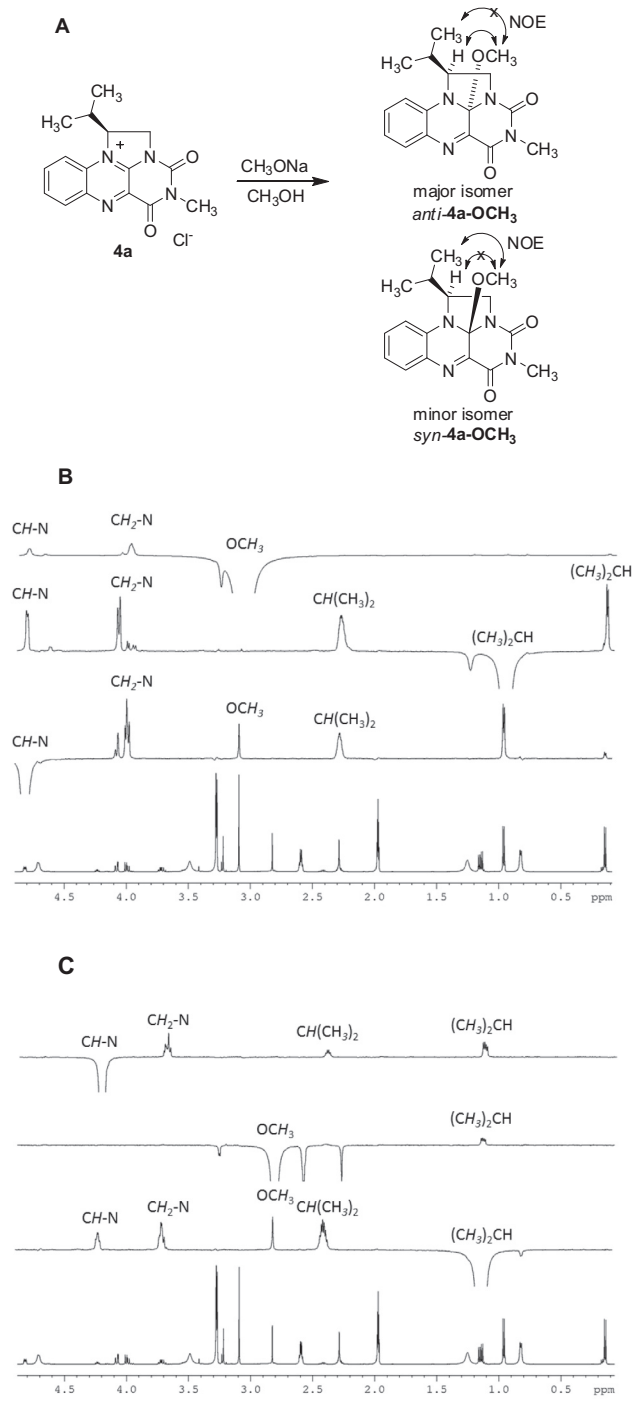


Figure 2. Formation of two diastereomers of **4a** adduct with methanol (A) and NOE spectra of major (B) and minor (C) stereoisomer.

dissolved in CD_3CN and the NOE spectra were measured immediately. The spectra clearly suggested that the methoxy group of the major diastereomer was in the *anti*-position relative to substituent on the ethylene bridge (Fig. 2B) and *vice versa* for the minor diastereomer (Fig. 2C).

The diastereoselectivity of the nucleophilic addition reaction strongly depends on the substitution on the ethylene-bridge (Table 1). The phenyl substituent in **4b** provides lower diastereoselectivities being less sterically demanding compared to the isopropyl group in **4a** (Fig. 3A,B). On the other hand, the stereoselectivities were significantly higher for salts **4c**–**e** possessing benzyl groups reaching an almost quantitative formation of the *anti*-isomer for **4e** (no signals of *syn*-**4e-OOH** or *syn*-**4e-OCD3** were observed in the ^{1}H NMR spectrum). This can be explained by the fact that the attachment of the phenyl ring via a flexible methylene bridge allows its face-to-face orientation relative to the flavinium unit and thus, prevents nucleophilic attack from one face (Fig. 3C). This conformation can be stabilized via cation-π interactions, which are known to be the origin of the stereoselective processes in many organocatalytic or supramolecular systems.[18] This effect was even more pronounced when an electron-rich 4-methoxyphenyl was introduced on the ethylene-bridge in **4**. The highest diastereoselectivities were achieved with derivative **4e** bearing a benzyloxybenzyl group allowing even more effective interactions between the substituent and flavinium core.

2.3. DFT calculations

To support the hypothesis on the induction of diastereoselectivity via the face-to-face oriented phenyl substituent in **4c**, the preferential conformation of the pendant phenyl ring relative to the flavin plane was estimated using DFT methods. By changing the dihedral angle between the flavin and phenyl ring, three minima and transition states were located using the BMK[19] DFT functional and Def2-SVP basis set with GD3 empirical dispersion[20] to take into account the long-range weak interactions and CPCM[21] solvent model for acetonitrile (Fig. 4).[‡]

True minima and transition states were localized at a higher level of theory to obtain more accurate energies. Different DFT functionals were used to confirm the previous results (BMK, B3LYP,[22] M06-2X[23] and CAM-B3LYP[24]) with the Def2-TZVP basis set, GD3 empirical dispersion and CPCM model for acetonitrile. The face-to-face conformation of **4c** was the most favourable (Table 2, Fig. 5), which was in accordance with our proposed origin of the diastereoselective nucleophilic addition. In the most stable conformation, the phenyl groups seem to be directed towards the pyrimidine ring (MIN1), close to the 10a-position and hindering the position to be attacked by the nucleophile from that side, rather than towards the benzene ring (MIN3) or in 'staggered conformation' (MIN2).

2.4. Fluorescence of the flavinium salts

Upon excitation with light at about 400 nm (for the absorption maxima, see Table 3), the flavinium salts **4** exhibit fluorescence with a maximum at about 490 nm. The quantum yield of the fluorescence for **4a** possessing an aliphatic side chain was approx. 11%, which was higher when compared to neutral alloxazines (1–3%)[25] but lower when compared with isoalloxazines (20–30%).[26] Interestingly, the normalized intensity of the fluorescence, as well as the fluorescence quantum yield, strongly depends on the substitution of the ethylene-bridge (Fig. 6A); it is significantly decreased going from **4a** to **4e** because of intramolecular quenching with an aromatic substituent. Similarly, like the stereoselectivity of the nucleophile addition reaction, the efficiency of fluorescence quenching depends on the flexibility of the aromatic substituent **4b** *vs* **4c**, and oxidation potential of the substituents, **4c** *vs* **4d**. In the most stable conformation of **4c**, estimated using DFT calculations, quenching was expected to be very efficient. For comparison, the intermolecular quenching of the fluorescence of **4a** with anisole was measured showing a huge excess (10 000 equiv. relative to flavin **4**) was necessary to decrease the fluorescence intensity on the level of that found for **4c** (Fig. 6B).

[‡] Rotation of the methyl group in the 3-position of the flavin ring was not considered in the calculations.

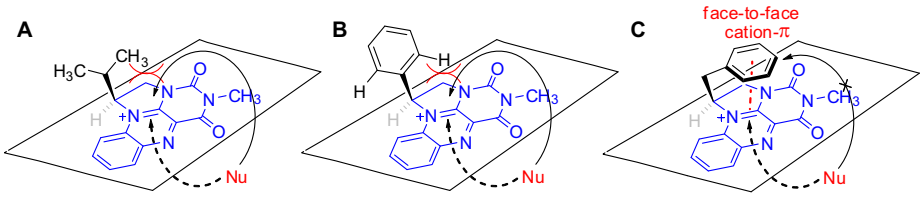


Figure 3. Proposed origin of diastereoselectivities in adduct formation with **4a** (A), **4b** (B) and **4c** (C).

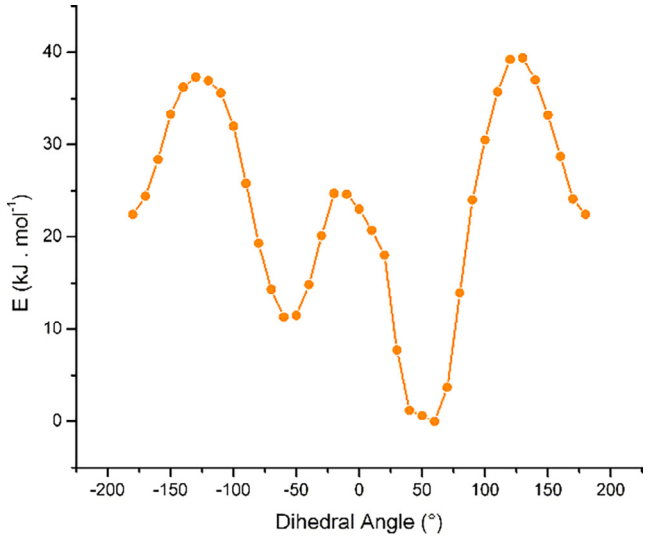


Figure 4. Energy of rotation of the pendant phenyl ring as a function of dihedral angle.

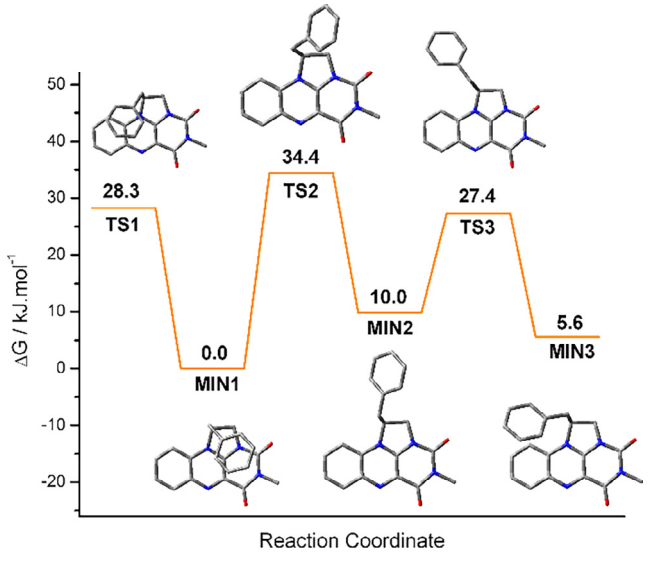


Figure 5. Reaction coordinate showing geometries of minima and transition states at BMK/Def2-TZVP level of theory.

Table 3
Fluorescence quantum yields of salts **4a**–**e** in acetonitrile.

Entry	Flavinium salt	λ_{ex} [nm] (ε [L mol^{-1} dm^{-1}])	c(**4**) × 10^6 [mol L^{-1}]	λ_{ex} [nm]	Φ_F [%]
1	**4a**	406 (550)	2.5	364	11.3
2	**4b**	400 (597)	2.1	364	1.64
3	**4c**	409 (604)	2.1	364	0.33
4	**4d**	394 (667)	2.3	364	0.19
5	**4e**	405 (651)	2.2	364	<0.1

3. Conclusions

The environments of the flavin co-factor in enzymes are comprised of amino acid residues and usually influence the reactivity of the flavin moiety from the point of view of both the regioselectivity as well as stereoselectivity. Herein, we have shown the flavinium salts **4** can serve as a simplified and readily available co-factor model with an amino acid residue covalently bound to the flavin unit. We have demonstrated that the substituent on the ethylene-bridge significantly influences the diastereoselectivity of the corresponding flavin-10a-hydroperoxide **4-OOH** and 10a-methoxyflavin **4-OCH$_3$** (**4-OCD$_3$**) formation achieving almost solely the formation of one diastereomer (dr > 95:5) when **4e** reacts with H_2O_2 or methanol. The reason of this phenomenon was supported by DFT calculations showing flavins **4** with a benzyl substituent prefer a face-to-face (*syn*) orientation relative to the flavinium unit and thus, effectively prevents nucleophile attack from one face. These findings will be helpful in the design of new flavin organocatalysts used for the stereoselective oxidation reactions and complement the very recent and highly important finding that covalently attached tripeptides can stabilize artificial flavin hydroperoxide **FlOOH** formed from neutral flavin.[9] Noteworthy, our finding that **4a** emits light upon excitation with visible light clearly demonstrates the potential application of ethylene-bridged flavinium salts in photocatalysis.

4. Experimental

The melting point temperature data are uncorrected. NMR Spectra were recorded on Varian Mercury Plus 300 (299.97 MHz for ^{1}H and 75.44 MHz for ^{13}C), Bruker Avance DRX 500 spectrometer (500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C), and Bruker 600

Table 2
Summary of Gibbs free energies of rotation and dihedral angles.

	BMK		M06-2X		CAM-B3LYP		B3LYP	
	ΔG [kJ mol^{-1}]	Dih. Angle [°]	ΔG [kJ mol^{-1}]	Dih. Angle [°]	ΔG [kJ mol^{-1}]	Dih. Angle [°]	ΔG [kJ mol^{-1}]	Dih. Angle [°]
MIN1	0.00	58.3	0.00	58.0	0.00	57.6	0.00	57.4
TS2	34.43	125.1	30.01	123.0	25.82	121.9	26.14	122.6
MIN2	9.95	−179.8	9.70	−179.5	5.84	−179.6	6.85	−179.4
TS3	27.36	−127.5	24.78	−127.7	21.39	−129.4	23.96	−130.0
MIN3	5.57	−58.0	6.48	−59.1	5.69	−61.3	5.57	−60.4
TS1	28.26	−14.4	26.72	−10.9	25.47	−9.4	24.54	−9.6

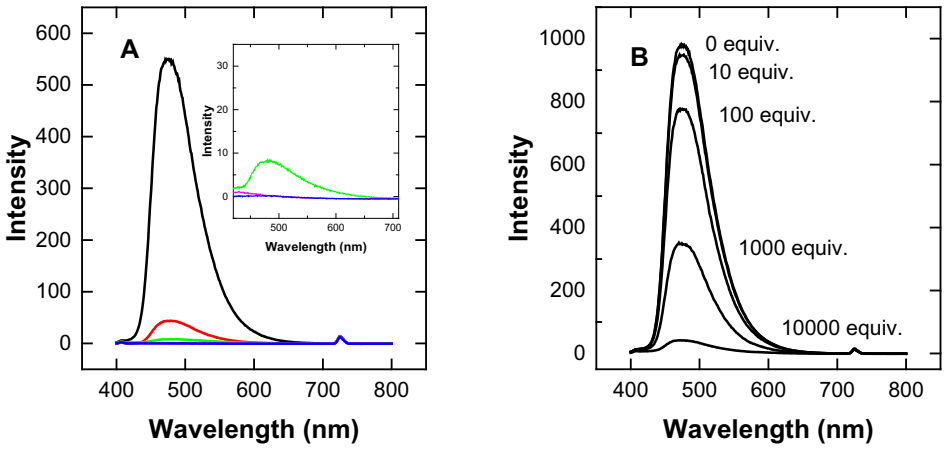


Figure 6. Fluorescence spectra of flavinium salts **4a** (black), **4b** (red), **4c** (green), **4d** (purple) and **4e** (blue) (c(**4**) = 1.10^{-5} mol L^{-1}, acetonitrile, λ_{ex} = 364 nm) (A) and intermolecular quenching of **4a** fluorescence by anisole (B).

Avance^{III} spectrometer (600.13 MHz for ^{1}H and 150.92 MHz for ^{13}C). The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard or to residual solvent peak. High-resolution mass spectra were obtained on an LTQ Orbitrap Velos (Thermo Fisher Scientific), equipped with an orbitrap mass analyzer. The mass spectrometer was operated in ESI mode (ESI source temperature 250 °C, potential 3000 V) and in APCI mode (APCI source temperature 250 °C, spray current 4.0 μA) with a mass range from 200 to 2000 a.m.u. Optical rotations were measured on Perkin-Elmer M-241 digital polarimeter. All reagents were purchased from commercial sources and used without any treatment unless otherwise indicated. TLC analyses were carried out on DC Alufolien Kieselgel 60H F254 (Merck). Preparative column chromatography was performed on silica gel Kieselgel 60, 0.040–0.063 mm (Merck). Elemental analyses were performed on a Perkin–Elmer 240 analyser. Preparative HPLC was carried out on an Agilent 1100 Series instrument.

4.1. Synthesis of alcohols 5d and 5e

4.1.1. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-hydroxyphenyl)propanoate 10a

To the suspension of (*S*)-tyrosine (5.00 g, 27.60 mmol) in dry methanol (100 mL), thionyl chloride (10 mL) was added dropwise. Reaction mixture was heated under argon atmosphere for 3 h and then evaporated. Dry methanol (100 mL), Boc_2O (9.44 g, 43.30 mmol) and triethylamine (9.10 g, 90.10 mmol) were added, the mixture was stirred under an argon atmosphere for 20 h and finally, solvents were evaporated. Residue was diluted with water (50 mL), pH was adjusted to 4 by 2 M aqueous HCl and the mixture was extracted with ethyl acetate (5 × 50 mL). Collected organic layers were washed with brine, dried over $MgSO_4$ and evaporated. After column chromatography ($CHCl_3$/MeOH 100:3), 8.15 g (quant.) of **10a** was obtained, m p 105.4–107.5 °C, $[\alpha]_D^{25}$ = +4.0 (c 0.379, MeOH) [ref.[27] m p 102–104 °C, $[\alpha]_D^{20}$ = +8.8 (c 1.7, MeOH)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H, (C**H**$_3$)$_3$), 2.87–3.08 (m, 2H, C**H**$_2$Ar), 3.71 (s, 3H, C**H**$_3$O), 4.47–4.60 (m, 1H, C**H**N), 5.03 (d, J = 7.9 Hz, 1H, N**H**), 6.10 (s, 1H, O**H**), 6.72 (d, J = 8.2 Hz, 2H, ArH), 6.95 (d, J = 8.5 Hz, 2H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5, 37.8, 52.5, 54.9, 80.5, 115.7, 127.7, 130.6, 155.4, 155.6, 172.9 ppm.

4.1.2. (2*S*)-2-Amino-3-(4-methoxyphenyl)propan-1-ol 5d

A mixture of ester **10a** (24.45 g, 82.80 mmol), K_2CO_3 (22.90 g, 165.70 mmol) and methyl iodide (35.00 g, 246.58 mmol) in dry acetone (250 mL) was heated to reflux for 10 h. After evaporation of solvents, the residue was diluted with water (100 mL) and extracted with ethyl acetate (100 mL + 3 × 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated. After evaporation of solvent and column chromatography ($CHCl_3$/MeOH 100 : 1), 25.61 g (98%) of methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-methoxyphenyl)propanoate **10b** was obtained as a colorless oil, $[\alpha]_D^{25}$ = +1.3 (c 0.614, MeOH) [ref.[28] mp 49–50 °C, $[\alpha]_D^{20}$ = +5.9 (c 2.5, MeOH)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H, (C**H**$_3$)$_3$), 2.92–3.10 (m, 2H, C**H**$_2$Ar), 3.70 (s, 3H, C**H**$_3$O), 3.78 (s, 3H, C**H**$_3$OAr), 4.47–4.58 (m, 1H, C**H**N), 4.96 (d, J = 7.6 Hz, 1H, N**H**), 6.82 (d, J = 8.8 Hz, 2H, ArH), 7.03 (d, J = 8.8 Hz, 2H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5, 37.7, 52.4, 54.8, 55.4, 80.1, 114.2, 128.2, 130.5, 155.3, 158.9, 172.7 ppm.

To the ice-cooled solution of ester **10b** (6.68 g, 21.60 mmol) in dry THF (100 mL), $LiBH_4$ (2.40 g, 108.0 mmol) was added in several portions. Reaction was stirred at rt for 20 min and then heated to 50 °C for 2 h. After cooling to rt, solvent was evaporated and the residue was diluted with saturated aqueous solution of ammonium chloride (80 mL) and extracted with ethyl acetate (60 mL + 4 × 40 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated. It was obtained 5.80 g (95%) of *tert*-butyl [(1*S*)-2-hydroxy-1-(4-methoxybenzyl)]ethyl carbamate **10c** as a colorless oil, $[\alpha]_D^{25}$ = −19.2 (c 0.426, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9H, (C**H**$_3$)$_3$), 2.76 (d, J = 7.0 Hz, 2H, C**H**$_2$Ar), 3.46–3.66 (m, 2H, C**H**$_2$OH), 3.76 (s, 3H, C**H**$_3$O), 3.76–3.85 (m, 1H, C**H**N), 4.86 (d, J = 7.6 Hz, 1H, N**H**), 6.82 (d, J = 7.6 Hz, 2H, ArH), 7.11 (d, J = 8.2 Hz, 2H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6, 36.7, 54.0, 55.5, 64.3, 79.9, 114.2, 130.1, 130.5, 156.5, 158.5 ppm.

A mixture of carbamate **10c** (5.78 g, 20.54 mmol), KOH (20.00 g) and 2-methoxyethanol (150 mL) was heated to reflux for 10 h. After evaporation of solvents, the residue was diluted with water (50 mL) and extracted with dichloromethane (100 mL + 3 × 30 mL). The organic layers were combined, washed with brine and dried over $MgSO_4$. After evaporation of the solvent and crystallization (hexane/dichloromethane), 3.00 g (81%) of **5d** was obtained as white crystals, mp 100.9–103.8 °C, $[\alpha]_D^{25}$ = −19.0 (c 0.385, MeOH) [ref.[29] mp 111.0–112.5 °C, $[\alpha]_D^{20}$ = −13.2 (c 0.05, MeOH)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (br s, 2H, N**H**$_2$), 2.40–2.53 (m, 1H, C**H**$_2$Ar), 2.66–2.83 (br s, 1H, C**H**$_2$Ar), 2.98–3.20 (br s, 1H, C**H**N), 3.30–3.48 (br s, 1H, C**H**$_2$OH), 3.50–3.70 (br s, 1H, C**H**$_2$OH), 3.78 (s, 3H, C**H**$_3$O), 6.84 (d, J = 8.5 Hz, 2H, ArH), 7.10 (d, J = 8.5 Hz, 2H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.3, 54.0, 55.5, 66.5, 114.2, 130.4, 130.9, 158.4 ppm.

4.1.3. (2*S*)-2-Amino-3-[4-(benzyloxy)phenyl]propan-1-ol 5e

A mixture of ester **10a** (8.15 g, 27.6 mmol), K_2CO_3 (5.72 g, 41.4 mmol), benzyl bromide (5.66 g, 33.1 mmol) in dry acetone (250 mL) was heated to reflux for 22 h and evaporated. Residue was diluted with water (100 mL) and extracted with ethyl acetate (100 mL + 3 × 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated. After evaporation of the solvents and column chromatography ($CHCl_3$), 8.22 g (77%) of methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-(benzyloxy) phenyl]propanoate **10d** was obtained mp 53.2–58.8 °C, $[\alpha]_D^{25}$ = +1.5 (*c* 0.777, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9H, (C**H**$_3$)$_3$), 2.95–3.12 (m, 2H, C**H**$_2$Ar), 3.71 (s, 3H, C**H**$_3$O), 4.50–4.60 (m, 1H, C**H**N), 5.00 (d, *J* = 7.8 Hz, 1H, N**H**), 5.03 (s, 2H, OC**H**$_2$Ph), 6.90 (d, *J* = 8.5 Hz, 2H, ArH), 7.04 (d, *J* = 8.5 Hz, 2H, ArH), 7.28–7.45 (m, 5H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6, 37.7, 52.4, 54.8, 70.2, 80.1, 115.1, 127.7, 128.2, 128.5, 128.8, 130.6, 137.2, 155.4, 158.1, 172.7 ppm.

To the ice-cooled solution of ester **10d** (5.86 g, 15.20 mmol) in dry THF (80 mL), $LiBH_4$ (1.70 g, 76.47 mmol) was added in several portions. Reaction was stirred at rt for 20 min and then slowly heated to 50 °C for 2 h. After cooling to rt, the solvent was evaporated and residue was diluted with saturated solution of ammonium chloride (60 mL) and extracted with ethyl acetate (50 mL + 3 × 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated. It was obtained 5.22 g (96%) of *tert*-butyl (1*S*)-2-hydroxy-1-[4-(benzyloxy)benzyl]ethylcarbamate **10e** as white crystals, mp 105.1–108.5 °C, $[\alpha]_D^{25}$ = −23.3 (*c* 0.403, MeOH) [ref.[30] mp 108 °C, $[\alpha]_D^{20}$ = −17 (*c* 1.0, MeOH)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H, (C**H**$_3$)$_3$), 2.70–2.80 (m, 2H, C**H**$_2$-Ar), 3.48–3.70 (m, 2H, C**H**$_2$OH), 3.74–3.88 (m, 1H, C**H**N), 4.76 (d, *J* = 7.9 Hz, 1H, N**H**), 5.04 (s, 2H, OC**H**$_2$Ph), 6.91 (d, *J* = 8.8 Hz, 2H, ArH), 7.12 (d, *J* = 8.5 Hz, 2H, ArH), 7.29–7.46 (m, 5H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6, 36.8, 54.1, 64.6, 70.3, 80.0, 115.2, 127.7, 128.2, 128.8, 130.5, 130.6, 137.3, 155.0, 157.8 ppm.

The reaction mixture of carbamate **10e** (2.03 g, 5.69 mmol), KOH (5.00 g) and 2-methoxyethanol (100 mL) was heated to reflux for 10 h and then evaporated. The residue was diluted with water (50 mL) and extracted with dichloromethane (50 mL + 3 × 20 mL). The organic layers were combined, washed with brine and dried over $MgSO_4$. After evaporation of solvent and crystallization (hexane/dichloromethane), 1.32 g (90%) of **5e** was obtained as white crystals, mp 106.6–110.3 °C, $[\alpha]_D^{25}$ = −23.7 (*c* 0.342, MeOH) [ref.[31] m p 96–97 °C, $[\alpha]_D^{25}$ = −12 (*c* 0.04, MeOH)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (br s, 3H, O**H**+N**H**$_2$), 2.47 (dd, *J* = 13.5, 8.5 Hz, 1H, C**H**$_2$Ar), 2.75 (dd, *J* = 13.5, 5.0 Hz, 1H, C**H**$_2$Ar), 3.00–3.14 (m, 1H, C**H**N), 3.36 (dd, *J* = 10.5, 7.3 Hz, 1H, C**H**$_2$OH), 3.63 (dd, *J* = 10.5, 4.1 Hz, 1H, C**H**$_2$OH), 5.03 (s, 1H, OC**H**$_2$Ph), 6.92 (d, *J* = 8.5 Hz, 2H, ArH), 7.10 (d, *J* = 8.5 Hz, 2H, ArH), 7.29–7.47 (m, 5H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.3, 54.5, 66.6, 70.3, 115.2, 127.7, 128.2, 128.8, 130.4, 131.1, 137.3, 157.7 ppm.

4.2. Preparation of (*o*-nitrophenyl)aminoalcohols 6

4.2.1. General procedure

A solution of aminoalcohol (20 mmol), *o*-fluoronitrobenzene (50 mmol) and DABCO (70 mmol) in *n*-butanol (40 mL) was heated to reflux under argon atmosphere until all starting material disappear (monitored by TLC). Solvent was evaporated and reaction mixture was dissolved in water (50 mL) and toluene (50 mL). pH was adjusted to 1 by 2 M aqueous HCl. The organic layer was separated and the aqueous layer was extracted with toluene (3 × 30 mL). The Organic layers were combined, washed with brine and dried over $MgSO_4$. After evaporation of solvent and column chromatography (chloroform/methanol 100:1), aminoalcohols **6** were obtained.

4.2.2. (*S*)-3-Methyl-2-[(2-nitrophenyl)amino]butan-1-ol 6a

Aminoalcohol **6a** was prepared from (*S*)-valinol (2.06 g, 20 mmol), *o*-fluoronitrobenzene (7.06 g, 50 mmol) and DABCO (7.85 g, 70 mmol). After heating (6 h) 3.77 g (84%) of **6a** was obtained as a red oil, $[\alpha]_D^{25}$ = +164.1 (*c* 0.460, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.9 Hz, 3H, (C**H**$_3$)$_2$CH), 1.03 (d, *J* = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 1.70 (br s, 1H, O**H**), 1.96–2.14 (m, 1H, (CH$_3$)$_2$C**H**), 3.55–3.67 (m, 1H, C**H**N), 3.74 (dd, *J* = 11.1, 6.0 Hz, 1H, C**H**$_2$OH), 3.83 (dd, *J* = 11.1, 4.8 Hz, 1H, C**H**$_2$OH), 6.62 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H, ArH), 6.98 (d, *J* = 8.7 Hz, 1H, ArH), 7.40 (ddd, *J* = 8.7, 6.9, 1.2 Hz, 1H, ArH), 8.15 (dd, *J* = 9.0, 1.5 Hz, 1H, ArH), 8.21 (br d, *J* = 8.7 Hz, 1H, N**H**) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 19.7, 30.0, 60.1, 63.4, 114.7, 115.7, 127.3, 132.3, 136.5, 146.4 ppm.

4.2.3. (*R*)-2-[(2-Nitrophenyl)amino]-2-phenylethanol 6b

Aminoalcohol **6b** was prepared from (*R*)-phenylglycinol (2.06 g, 15.01 mmol), *o*-fluoronitrobenzene (5.29 g, 37.50 mmol) and DABCO (5.89 g, 52.50 mmol). After heating (1.5 h), 3.09 g (80%) of **6b** was obtained as a red oil, $[\alpha]_D^{25}$ = +1924.1 (*c* 0.406, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (br s, 1H, O**H**), 3.93 (dd, *J* = 10.8, 6.0 Hz, 1H, C**H**$_2$OH), 4.04 (dd, *J* = 11.1, 4.2 Hz, 1H, C**H**$_2$OH), 4.72 (dd, *J* = 10.5, 6.0 Hz, 1H, C**H**N), 6.61–6.66 (m, 2H, ArH), 7.24–7.40 (m, 6H, ArH), 8.18 (dd, *J* = 9.0, 1.5 Hz, 1H, ArH), 8.75 (br d, *J* = 5.1 Hz, 1H, N**H**) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 59.5, 67.3, 115.3, 116.2, 126.8, 127.0, 128.4, 129.4, 136.3, 138.9, 144.8 ppm.

4.2.4. (*S*)-2-[(2-Nitrophenyl)amino]-3-phenylpropan-1-ol 6c

Aminoalcohol **6c** was prepared from (*S*)-fenylalaninol (2.87 g, 19 mmol), *o*-fluoronitrobenzene (8.04 g, 57 mmol) and DABCO (7.85 g, 70 mmol). After heating (2 h), 4.25 g (82%) of **6c** was obtained as red oil, $[\alpha]_D^{25}$ = −1268.4 (*c* 0.446, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (br s, 1H, O**H**), 2.95 (dd, *J* = 13.5, 6.7 Hz, 1H, C**H**$_2$Ph), 3.04 (dd, *J* = 13.8, 6.7 Hz, 1H, C**H**$_2$Ph), 3.71 (dd, *J* = 11.1, 5.0 Hz, 1H, C**H**$_2$OH), 3.79 (dd, *J* = 11.1, 4.7 Hz, 1H, C**H**$_2$OH), 3.92–4.04 (m, 1H, C**H**N), 6.62 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, ArH), 6.89 (d, *J* = 8.8 Hz, 1H, ArH), 7.18–7.33 (m, 5H, ArH), 7.37 (ddd, *J* = 9.2, 8.5, 1.8 Hz, 1H, ArH), 8.13 (dd, *J* = 8.8, 1.8 Hz, 1H, ArH), 8.24 (br d, *J* = 7.9 Hz, 1H, N**H**) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.9, 55.8, 63.6, 114.4, 115.8, 127.0, 127.3, 128.9, 129.5, 132.5, 136.4, 137.6, 145.2 ppm.

4.2.5. (2*S*)-3-(4-Methoxyphenyl)-2-[(2-nitrophenyl)amino]propan-1-ol 6d

Aminoalcohol **6d** was prepared from (2*S*)-2-amino-3-(4-methoxyphenyl)propan-1-ol (2.00 g, 11.04 mmol), *o*-fluoronitrobenzene (4.67 g, 33.11 mmol) and DABCO (5.00 g, 44.57 mmol). After heating (14 h), 3.24 g (97%) of **6d** was obtained as a red oil, $[\alpha]_D^{25}$ = −539.0 (*c* 0.497, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (dd, *J* = 5.9, 5.3 Hz, 1H, O**H**), 2.89 (dd, *J* = 14.1, 6.7 Hz, 1H, C**H**$_2$Ar), 2.98 (dd, *J* = 14.1, 6.7 Hz, 1H, C**H**$_2$Ar), 3.65–3.84 (m, 2H, C**H**$_2$OH), 3.77 (s, 3H, C**H**$_3$O), 3.84–3.98 (m, 1H, C**H**N), 6.61 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, ArH), 6.82 (d, *J* = 8.8 Hz, 2H, ArH), 6.89 (d, *J* = 8.5 Hz, 1H, ArH), 7.15 (d, *J* = 8.8 Hz, 2H, ArH), 7.38 (ddd, *J* = 9.1, 8.5, 1.8 Hz, 1H, ArH), 8.12 (dd, *J* = 8.5, 1.5 Hz, 1H, ArH), 8.22 (br, d, *J* = 8.5 Hz, 1H, N**H**) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.0, 55.5, 56.0, 63.6, 114.3, 114.4, 115.8, 127.3, 129.4, 130.5, 132.3, 136.5, 145.3, 158.7 ppm.

4.2.6. (2*S*)-3-[4-(Benzyloxy)phenyl]-2-[(2-nitrophenyl)amino] propan-1-ol 6e

Aminoalcohol **6e** was prepared from (2*S*)-2-amino-3[4-(benzyloxy)phenyl]propan-1-ol (1.00 g, 3.89 mmol), *o*-fluoronitrobenzene (1.64 g, 11.62 mmol) and DABCO (2.00 g, 17.83 mmol). After heating (20 h), 1.43 g (97%) of **6e** was obtained as a red oil, $[\alpha]_D^{25}$ = −499.2 (*c* 0.624, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (br, s, 1H, O**H**), 2.90 (dd, *J* = 14.1, 6.7 Hz, 1H, C**H**$_2$Ar), 2.98 (dd, *J* =

13.8, 6.7 Hz, 1H, C**H**$_2$Ar), 3.64–3.83 (m, 2H, C**H**$_2$OH), 3.85–3.98 (m, 1H, C**H**N), 5.03 (s, 2H, C**H**$_2$Ph), 6.62 (dd, *J* = 8.5, 8.2 Hz, 1H, ArH), 6.89 (d, *J* = 8.2 Hz, 1H, ArH), 6.91 (d, *J* = 8.5 Hz, 2H, ArH), 7.16 (d, *J* = 8.5 Hz, 2H, ArH), 7.45–7.29 (m, 6H, ArH), 8.14 (dd, *J* = 8.5, 1.5 Hz, 1H, ArH), 8.23 (br d, *J* = 7.9 Hz, 1H, N**H**) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.0, 55.9, 63.6, 70.2, 114.4, 115.3, 115.8, 127.3, 127.8, 128.2, 128.8, 129.7, 130.6, 132.4, 136.5, 137.2, 145.3, 157.9 ppm.

4.3. Preparation of (o-aminophenyl)aminoalcohols 7

4.3.1. General procedure

Suspension of (*o*-nitrophenyl)aminoalcohol **6** (10 mmol) and palladium on carbon (10%, 0.1 g) in methanol (20 mL) was stirred under a hydrogen atmosphere (1 bar) at r.t for 2 h. The solids were filtered out and crude product was directly used for the preparation of alloxazine **8**.

4.3.2. (*S*)-2-[(2-Aminophenyl)amino]-3-methylbutan-1-ol 7a

Prepared by general procedure from **6a** (1.01 g, 4.50 mmol). 0.86 g (99 %) of **7a** was obtained as a dark oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.9 Hz, 3H, (C**H**$_3$)$_2$CH), 1.02 (d, *J* = 6.9 Hz, 3H, (C**H**$_3$)$_2$CH), 1.87–2.04 (m, 1H, (CH$_3$)$_2$C**H**), 2.94 (br s, 3H, N**H**$_2$+N**H**+O**H**), 3.26–3.34 (m, 1H, C**H**NH), 3.58 (dd, *J* = 11.1, 6.9 Hz, 1H, C**H**$_2$OH), 3.73 (dd, *J* = 10.8, 3.6 Hz, 1H, C**H**$_2$OH), 6.65–6.85 (m, 4H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 19.3, 29.6, 60.4, 62.0, 113.3, 117.6, 118.7, 121.0, 134.1, 137.6 ppm.

4.3.3. (*R*)-2-[(2-Aminophenyl)amino]-2-fenylethanol 7b

The suspension of **6b** (2.98 g, 11.55 mmol), $FeCl_3$.6 H_2O (0.20 g), active coal (0.20 g) and hydrazine monohydrate (1.8 mL, 37.08 mmol) in methanol (80 mL) was stirred under reflux for 12 h. After the filtration and evaporation of solvent, the crude product was dissolved in methanol (30 mL) and precipitated by the addition of water (about 1 mL). It was obtained 2.16 g (82%) of **7b** as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (br s, 2H, N**H**$_2$), 1.83 (br s, 1H, O**H**), 3.93 (dd, *J* = 11.1, 6.0 Hz, 1H, C**H**$_2$OH), 4.03 (dd, *J* = 11.1, 4.5 Hz, 1H, C**H**$_2$OH), 4.72 (m, 1H, C**H**N), 6.60–6.66 (m, 2H, ArH), 7.23–7.40 (m, 6H, ArH), 8.18 (dd, *J* = 9.0, 1.8 Hz, 1H, ArH), 8.74 (br d, *J* = 5.1 Hz, 1H, N**H**) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 60.3, 67.7, 114.3, 116.9, 119.3, 121.0, 126.9, 127.8, 129.0, 134.6, 136.8, 140.3 ppm.

4.3.4. (*S*)-2-[(2-Aminophenyl)amino]-3-phenylpropan-1-ol 7c

Prepared by general procedure from **6c** (2.62 g, 9.63 mmol). 2.10 g (90 %) of **7c** was obtained as a dark oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85 (dd, *J* = 13.5, 7.3 Hz, 1H, C**H**$_2$Ph), 2.97 (dd, *J* = 13.8, 5.6 Hz, 1H, C**H**$_2$Ph), 3.24 (br s, 2H, N**H**+O**H**), 3.48–3.54 (m, 1H, C**H**$_2$OH), 3.67–3.76 (m, 2H, C**H**N+C**H**$_2$OH), 6.70–6.88 (m, 4H, ArH), 7.19–7.35 (m, 5H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.9, 55.8, 63.6, 114.4, 115.8, 127.1, 127.3, 129.0, 129.5, 136.4, 137.5, 145.2 ppm.

4.3.5. (2*S*)-2-[(2-Aminophenyl)amino]-3-(4-methoxyphenyl) propan-1-ol 7d

Prepared by general procedure from **6d** (2.57 g, 8.48 mmol). 2.07 g (90 %) of **7d** was obtained as a pink oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.78 (dd, *J* = 13.8, 7.3 Hz, 1H, C**H**$_2$Ar), 2.89 (dd, *J* = 13.8, 5.6 Hz, 1H, C**H**$_2$Ar), 3.00–3.40 (br s, 3H, N**H**$_2$+O**H**), 3.49 (dd, *J* = 10.6, 5.0 Hz, 1H, C**H**$_2$OH), 3.59–3.68 (m, 1H, C**H**N), 3.71 (dd, *J* = 10.5, 3.5 Hz, 1H, C**H**$_2$OH), 3.79 (s, 3H, C**H**$_3$O), 6.70–6.83 (m, 4H, ArH), 6.85 (d, *J* = 8.2 Hz, 2H, ArH), 7.12 (d, *J* = 8.5 Hz, 2H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.8, 55.5, 56.4, 63.2, 114.2, 114.3, 117.4, 119.8, 121.0, 130.4, 130.5, 135.4, 136.4, 158.4 ppm.

4.3.6. (2*S*)-2-[(2-Aminophenyl)amino]-3-[4-(benzyloxy)phenyl] propan-1-ol 7e

The mixture of **6e** (1.08 g, 2.86 mmol), $FeCl_3 \times 6H_2O$ (50 mg), hydrazine hydrate (0.42 mL, 8.58 mmol), active coal (100 mg) and methanol (50 mL) was stirred under argon atmosphere under reflux for 24 h. After filtration and evaporation of solvent, 0.90 g (90%) of **7e** was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (dd, *J* = 13.5, 7.0 Hz, 1H, C**H**$_2$Ar), 2.90 (dd, *J* = 13.8, 5.3 Hz, 1H, C**H**$_2$Ar), 3.00–3.40 (br s, 3H, N**H**$_2$+O**H**), 3.51 (dd, *J* = 10.8, 4.1 Hz, 1H, C**H**$_2$OH), 3.60–3.78 (m, 2H, C**H**$_2$OH+C**H**N), 5.05 (s, 2H, C**H**$_2$Ph), 6.70–6.87 (m, 4H, ArH), 6.93 (d, *J* = 7.0 Hz, 2H, ArH); 7.13 (d, *J* = 7.0 Hz, 2H, ArH), 7.30–7.48 (m, 5H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.9, 56.5, 63.3, 70.3, 114.5, 115.2, 117.4, 119.9, 121.0, 127.8, 128.2, 128.9, 130.6, 130.8, 135.6, 136.4, 137.3, 157.7 ppm.

4.4. Preparation of 10-(1-alkyl-2-hydroxyethyl)isoalloxazines 8

4.4.1. General procedure

To the warm solution (60–70 °C) of alloxane monohydrate (20 mmol) in glacial acetic acid (100 mL), solution of diamine **7** (5 mmol) in glacial acetic acid (20 mL) was added dropwise under an argon atmosphere. Reaction mixture was stirred for 20 min, acetic acid was evaporated and product was purified by column chromatography (chloroform/methanol 100:3) and by crystallization.

4.4.2. (3*H*)-10-[(1*S*)-1-(Hydroxymethyl)-2-methylpropyl]benzo [*g*]pteridin-2,4-dione 8a

Prepared by general procedure from alloxane (4.45 g, 27.78 mmol) and diamine **7a** (1.80 g, 9.26 mmol). 1.49 g (54%) of **8a** was obtained as yellow crystals (chloroform/methanol). ^{1}H NMR (300 MHz, DMSO-d_6): mixture of diastereomers A and B in ratio A/B = 2.5:1. (Diastereomer A) δ = 0.67 (d, *J* = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 1.11 (d, *J* = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 3.00–3.17 (m, 1H, (CH$_3$)$_2$C**H**), 3.82 (dd, *J* = 11.7, 3.6 Hz, 1H, C**H**$_2$OH), 4.55 (dd, *J* = 11.7, 8.4 Hz, 1H, C**H**$_2$-OH), 4.80–4.88 (m, 1H, C**H**N), 7.60 (dd, *J* = 7.8, 7.5 Hz, 1H, ArH), 7.88 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H, ArH), 8.10 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 8.27 (d, *J* = 9.0 Hz, 1H, ArH), 11.42 (s, 1H, N**H**) ppm. (Diastereomer B) δ = 0.65 (d, *J* = 5.1 Hz, 3H, (C**H**$_3$)$_2$CH), 1.18 (d, *J* = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 2.59–2.74 (m, 1H, (CH$_3$)$_2$C**H**), 3.98 (dd, *J* = 12.0, 3.9 Hz, 1H, C**H**$_2$OH), 4.15 (dd, *J* = 12.0, 8.4 Hz, 1H, C**H**$_2$OH), 5.90–6.08 (m, 1H, C**H**N), 7.60 (dd, *J* = 7.8, 7.5 Hz, 1H, ArH), 7.83 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H, ArH), 8.12 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 8.27 (d, *J* = 9.0 Hz, 1H, ArH), 11.44 (s, 1H, N**H**) ppm. For $C_{15}H_{14}N_4O_3$ (300.31) calculated: C 59.99, H 5.37, N 18.66, found: C 60.08, H 5.55, N 18.36. HR-MS (ESI): calculated for $C_{15}H_{15}N_4O_3^+$ (M+H$^+$): 301.12952, found: 301.12975.

4.4.3. (3*H*)-10-[(1*R*)-1-Phenyl-2-hydroxyethyl]benzo[*g*]pteridin-2,4-dione 8b

Prepared by general procedure from alloxane (4.21 g, 26.28 mmol) and diamine **7b** (1.50 g, 6,57 mmol). 2.00 g (91%) of **8b** was obtained as yellow crystals, mp 198.2–202.0 °C (benzene/methanol), $[\alpha]_D^{25}$ = −214.6 (*c* 0.512; MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.21–4.43 (m, 1H, C**H**$_2$OH), 4.52–4.69 (m, 1H, C**H**$_2$-OH), 5.23–5.38 (m, 1H, C**H**N), 7.20–7.45 (m, 6H, ArH), 7.46–7.68 (m, 2H, ArH), 8.10 (d, *J* = 8.1 Hz, 1H, ArH), 11.49 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 49.3, 60.8, 118.9, 126.4, 127.0, 128.0, 129.0, 129.5, 132.8, 134.4, 136.1, 137.2, 139.8, 156.3, 160.5 ppm. For $C_{18}H_{14}N_4O_3$ (334.33) calculated: C 64.66, H 4.22, N 16.76, found: C 64.53, H 4.12, N 16.41. HR-MS (ESI): calculated for $C_{18}H_{15}N_4O_3^+$ (M+H$^+$): 335.11387, found: 335.11393.

4.4.4. (3*H*)-10-[(1*S*)-1-Benzyl-2-hydroxyethyl]benzo[*g*]pteridin-2,4-dione 8c

Prepared by general procedure from alloxane (5.55 g, 34.66 mmol) and diamine **7c** (2.10 g, 8.66 mmol). 2.20 g (73%) of **8c** was obtained as yellow crystals (benzene/methanol). ^{1}H NMR (300 MHz, $CDCl_3$): mixture of diastereomers A and B, in ratio A/B = 3.7:1. (Diastereomer A) δ = 3.18–3.30 (m, 1H, C**H**$_2$Ph), 3.72–3.96 (m, 1H, C**H**$_2$Ph+C**H**$_2$OH), 4.60–4.74 (m, 1H, C**H**$_2$OH), 4.93–5.03 (m, 1H, O**H**), 5.40–5.52 (m, 1H, C**H**N), 6.94–7.09 (m, 3H, ArH), 7.01–7.23 (m, 2H, ArH), 7.48 (dd, *J* = 7.6, 7.3 Hz, 1H, ArH), 7.71 (dd, *J* = 7.9, 7.6 Hz, 1H, ArH), 7.85 (d, *J* = 9.1 Hz, 1H, ArH), 7.97 (d, *J* = 7.9 Hz, 1H, ArH), 11.53 (s, 1H, N**H**) ppm. (Diastereomer B) δ = 3.18–3.30 (m, 1H, C**H**$_2$Ph), 3.50–3.62 (m, 1H, C**H**$_2$Ph), 3.84–3.96 (m, 1H, C**H**$_2$OH), 4.18–4.31 (m, 1H, C**H**$_2$OH), 5.12–5.20 (m, 1H, O**H**), 6.50–6.62 (m, 1H, C**H**N), 6.94–7.09 (m, 3H, ArH), 7.01–7.23 (m, 2H, ArH), 7.63 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 7.90 (dd, *J* = 8.8, 7.6 Hz, 1H, ArH), 8.11 (d, *J* = 7.9 Hz, 1H, ArH), 8.30 (d, *J* = 8.8 Hz, 1H, ArH); 11.43 (s, 1H, N**H**) ppm. For $C_{19}H_{16}N_4O_3$ (348.36) calculated: C 65.51, H 4.63, N 16.08; found: C 65.56, H 4.69, N 15.91. HR-MS (ESI): calculated for $C_{20}H_{19}N_4O_4^+$ (M+H$^+$): 349.12952, found: 349.12968.

4.4.5. (3*H*)-10-[(1*S*)-2-Hydroxy-1-(4-methoxybenzyl)ethyl]benzo-[*g*]pteridin-2,4-dione 8d

Prepared by general procedure from alloxane (8.00 g, 49.97 mmol) and diamine **7d** (2.02 g, 7.41 mmol). 1.87 g (67%) of **8d** was obtained as yellow crystals (benzene/methanol). ^{1}H NMR (300 MHz, DMSO-d_6): mixture of diastereomers A and B in ratio A/B = 3.3:1. (Diastereomer A) δ = 3.08–3.23 (m, 1H, C**H**$_2$Ar), 3.56 (s, 3H, C**H**$_3$O), 3.65–3.78 (m, 1H, C**H**$_2$Ar), 3.77–3.94 (m, 1H, C**H**$_2$OH), 4.54–4.70 (m, 1H, C**H**$_2$OH), 4.94 (dd, *J* = 6.2, 6.2 Hz, 1H, O**H**), 5.32–5.47 (m, 1H, C**H**N), 6.62 (d, *J* = 8.2 Hz, 2H, ArH), 7.06 (d, *J* = 8.5 Hz, 2H, ArH), 7.50 (dd, *J* = 7.6, 7.3 Hz, 1H, ArH), 7.73 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 7.87 (d, *J* = 9.1 Hz, 1H, ArH), 7.98 (d, *J* = 7.9 Hz, 1H, ArH), 11.50 (s, 1H, N**H**) ppm. (Diastereomer B) δ = 3.08–3.28 (m, 1H, C**H**$_2$Ar), 3.66 (s, 3H, C**H**$_3$O), 3.65–3.78 (m, 1H, C**H**$_2$Ar), 3.77–3.94 (m, 1H, C**H**$_2$OH), 4.16–4.27 (m, 1H, C**H**$_2$OH), 5.11 (dd, *J* = 6.2, 6.2 Hz, 1H, O**H**), 6.53–6.58 (m, 1H, C**H**N), 6.77 (d, *J* = 8.2 Hz, 2H, ArH), 7.09 (d, *J* = 8.5 Hz, 2H, ArH), 7.63 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 7.89 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 8.10 (d, *J* = 7.3 Hz, 1H, ArH), 8.28 (d, *J* = 8.8 Hz, 1H, ArH), 11.45 (s, 1H, N**H**) ppm. For $C_{20}H_{18}N_4O_4$ (378.38) calculated: C 63.48, H 4.79, N 14.81, found: C 63.56, H 4.62, N 14.45. HR-MS (ESI): calculated for $C_{20}H_{18}N_4O_4$-Na^+ (M+Na$^+$): 401.12203, found: 401.12228.

4.4.6. (3*H*)-10-{(1*S*)-1-[4-(Benzyloxy)benzyl]-2-hydroxyethyl}benzo[*g*]pteridin-2,4-dione 8e

Prepared by general procedure from alloxane (4.00 g, 24.98 mmol) and diamine **7e** (0.90 g, 2.58 mmol). 0.55 g (47%) of **8e** was obtained as orange crystals (dichloromethane). ^{1}H NMR (300 MHz, DMSO-d_6): mixture of diastereomers A and B in ratio A/B = 3.4:1. (Diastereomer A) δ = 3.15 (dd, *J* = 13.5, 5.3 Hz, 1H, C**H**$_2$-Ar), 3.65–3.76 (m, 1H, C**H**$_2$Ar), 3.80–3.90 (m, 1H, C**H**$_2$OH), 4.57–4.69 (m, 1H, C**H**$_2$OH), 4.91 (s, 2H, C**H**$_2$Ph), 4.95 (dd, *J* = 6.5, 6.5 Hz, 1H, O**H**), 5.34–5.47 (m, 1H, C**H**N), 6.69 (d, *J* = 8.5 Hz, 2H, ArH), 7.07 (d, *J* = 8.8 Hz, 2H, ArH), 7.24–7.44 (m, 5H, Ph), 7.50 (dd, *J* = 7.6, 7.3 Hz, 1H, ArH), 7.72 (dd, *J* = 7.6, 7.0 Hz, 1H, ArH), 7.86 (d, *J* = 8.8 Hz, 1H, ArH), 7.99 (d, *J* = 7.9 Hz, 1H, ArH), 11.51 (s, 1H, NH) ppm. (Diastereomer B) δ = 3.10–3.24 (m, 1H, C**H**$_2$Ar), 3.56–3.94 (m, 2H, C**H**$_2$Ar+C**H**$_2$OH), 4.10–4.28 (m, 1H, C**H**$_2$OH), 5.00 (s, 2H, C**H**$_2$Ph), 5.12 (dd, *J* = 5.6, 5.6 Hz, 1H, O**H**), 6.44–6.56 (m, 1H, C**H**N), 6.86 (d, *J* = 8.5 Hz, 2H, ArH), 7.10 (d, *J* = 8.5 Hz, 2H, ArH), 7.24–7.44 (m, 5H, Ph), 7.63 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 7.90 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 8.11 (d, *J* = 7.9 Hz, 1H, ArH), 8.28 (d, *J* = 8.8 Hz, 1H, ArH), 11.47 (s, 1H, N**H**) ppm. For $C_{26}H_{22}N_4O_4$ (454.48) calculated: C 68.71, H 4.88, N 12.33, found: C 68.66, H 4.95, N 12.07. HR-MS (ESI): calculated for $C_{26}H_{22}N_4O_4Na^+$ (M+Na$^+$): 477.15333, found: 477.15318.

4.5. Preparation of 3-methylisoalloxazines 9

4.5.1. General procedure

The solution of isoalloxazine **8** (0.60 mmol), methyl iodide (16 or 32 mmol) and anhydrous potassium carbonate (0.90 mmol) in dry acetone (10 mL) was heated to reflux under an argon atmosphere until all 3*H*-isoalloxazine disappeared (monitored by TLC). After evaporation of solvent, the crude product was immediately purified by column chromatography (chloroform/methanol 100:1) and by crystallization. Alternatively, the cooled reaction mixture was poured to 5% aqueous HCl (20 mL), solvents were evaporated and reaction mixture was extracted with dichloromethane (3 × 10 mL), dried over $MgSO_4$ and purified by column chromatography.

4.5.2. 10-[(1*S*)-1-(Hydroxymethyl)-2-methylpropyl]-3-methylbenzo[*g*]pteridin-2,4-dione 9a

Prepared by general procedure from isoalloxazine **8a** (0.45 g, 1.50 mmol) and methyl iodide (2 mL, 31.99 mmol). 0.42 g (90%) of **9a** was obtained as yellow crystals (cryst. benzene/methanol). ^{1}H NMR (300 MHz, DMSO-d_6): mixture of diastereomers A and B in ratio A/B = 2.3:1. (Diastereomer A) δ = 0.66 (d, *J* = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 1.12 (d, *J* = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 3.04–3.20 (m, 1H, (CH$_3$)$_2$C**H**), 3.27 (s, 3H, C**H**$_3$N), 3.78–3.90 (m, 1H, C**H**$_2$OH), 4.50–4.62 (m, 1H, C**H**$_2$OH), 4.77 (dd, *J* = 6.5, 6.0 Hz, 1H, O**H**), 4.84–4.93 (m, 1H, C**H**N), 7.63 (dd, *J* = 8.1, 7.2 Hz, 1H, ArH), 7.90 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H, ArH), 8.12 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 8.30 (d, *J* = 8.7 Hz, 1H, ArH) ppm. (Diastereomer B) δ = 0.64 (d, *J* = 6.0 Hz, 3H, (C**H**$_3$)$_2$CH), 1.19 (d, *J* = 6.3 Hz, 3H, (C**H**$_3$)$_2$CH), 2.62–2.74 (m, 1H, (CH$_3$)$_2$C**H**), 3.30 (s, 3H, C**H**$_3$N), 3.94–4.04 (m, 1H, C**H**$_2$OH), 4.10–4.22 (m, 1H, C**H**$_2$OH), 4.99 (dd, *J* = 6.5, 6.0 Hz, 1H, O**H**), 5.98–6.08 (m, 1H, C**H**N), 7.63 (dd, *J* = 8.1, 7.2 Hz, 1H, ArH), 7.85 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H, ArH), 8.17 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 8.30 (d, *J* = 8.7 Hz, 1H, ArH) ppm. For $C_{16}H_{18}N_4O_3$ (314.34) calculated: C 61.13, H 5.77, N 17.82, found: C 61.56, H 5.47, N 17.23. HR-MS (ESI): calculated for $C_{16}H_{19}N_4O_3$ (M+H$^+$): 315.14517, found: 315.14528.

4.5.3. 10-[(1*R*)-1-Phenyl-2-hydroxyethyl]-3-methylbenzo[*g*]pteridin-2,4-dione 9b

Prepared by general procedure from isoalloxazine **8b** (0.33 g, 0.99 mmol) and methyl iodide (2 mL, 31.99 mmol). 0.32 g (92%) of **9b** was obtained as yellow oil, $[\alpha]_D^{25}$ = −161.5° (*c* = 0.502, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.34 (s, 3H, C**H**$_3$N), 4.02–4.16 (m, 1H, C**H**$_2$OH), 4.60–4.74 (m, 1H, C**H**$_2$OH), 4.75–4.88 (m, 1H, C**H**N), 7.15–7.23 (m, 6H, ArH), 7.41–7.57 (m, 2H, ArH), 8.15 (d, *J* = 8.5 Hz, 1H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8, 61.2, 77.5, 118.3, 126.3, 126.5, 128.4, 129.5, 132.5, 133.3, 134.8, 135.7, 136.7, 136.7, 151.0, 156.0, 159.9 ppm. For $C_{19}H_{16}N_4O_3$ (348.36) calculated: C 65.51, H 4.63, N 16.08, found: C 65.46, H 4.65, N 16.01. HR-MS (ESI): calculated for $C_{19}H_{17}N_4O_3^+$ (M+H$^+$): 349.12952, found: 349.12987.

4.5.4. 10-[(1*S*)-1-Benzyl-2-hydroxyethyl]-3-methylbenzo[*g*]pteridin-2,4-dione 9c

Prepared by general procedure from isoalloxazine **8c** (0.23 g, 0.66 mmol) and methyl iodide (1 mL, 15.99 mmol). 0.22 g (92%) of **9c** was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): mixture of diastereomers A and B in ratio A/B = 3.5:1. (Diastereomer A) δ = 3.32 (s, 3H, C**H**$_3$N), 3.74–3.96 (m, 2H, C**H**$_2$Ph), 4.60–4.72 (m, 1H, C**H**$_2$OH), 4.94 (dd, *J* = 6.5, 6.4 Hz, 1H, C**H**$_2$OH), 5.40–5.53 (m, 1H, C**H**N), 6.92–7.26 (m, 5H, ArH), 7.49 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 7.72 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH), 7.84 (d, *J* = 8.8 Hz, 1H, ArH),

8.01 (d, J = 7.9 Hz, 1H, ArH) ppm. (Diastereomer B) δ = 3.25 (s, 3H, C**H**$_3$N), 3.74–3.96 (m, 2H, C**H**$_2$Ph), 4.17–4.30 (m, 1H, C**H**$_2$OH), 5.13 (dd, J = 5.9, 5.0 Hz, 1H, C**H**$_2$OH), 6.50–6.63 (m, 1H, C**H**N), 6.92–7.26 (m, 5H, ArH), 7.65 (dd, J = 7.3, 7.3 Hz, 1H, ArH), 7.92 (dd, J = 8.8, 5.0 Hz, 1H, ArH), 8.16 (d, J = 9.1 Hz, 1H, ArH), δ = 8.33 (d, J = 8.8 Hz, 1H, ArH) ppm. For $C_{20}H_{18}N_4O_3$ (362.38) calculated: C 66.29, H 5.01, N 15.46, found: C 66.32, H 5.30, N 14.98. HR-MS (ESI): calculated for $C_{20}H_{19}N_4O_3^+$ (M+H$^+$): 363.14517, found: 363.14536.

4.5.5. 10-[(1*S*)-2-Hydroxy-1-(4-methoxybenzyl)ethyl]-3-methylbenzo[*g*]pteridin-2,4-dione 9d

Prepared by general procedure from isoalloxazine **8d** (1.08 g, 2.86 mmol) and methyl iodide (2 mL, 31.99 mmol). 1.12 g (95%) of **9d** was obtained as yellow crystals (cryst. methanol). ^{1}H NMR (300 MHz, DMSO-d_6): mixture of diastereomers A and B in ratio A/B = 3.3:1. (Diastereomer A) δ = 3.12–3.21 (m, 1H, C**H**$_2$Ar), 3.30 (s, 3H, C**H**$_3$N), 3.55 (s, 3H, C**H**$_3$O), 3.74 (dd, J = 13.5, 10.0 Hz, 1 H; C**H**$_2$Ar), 3.83–3.93 (m, 1H, C**H**$_2$OH), 4.58–4.70 (m, 1H, C**H**$_2$OH), 4.93 (dd, J = 6.2, 6.2 Hz, 1H, O**H**), 5.36–5.48 (m, 1H, C**H**N), 6.61 (d, J = 8.5 Hz, 2H, ArH), 7.07 (d, J = 8.5 Hz, 2H, ArH), 7.51 (dd, J = 7.6, 7.3 Hz, 1H, ArH), 7.74 (dd, J = 7.9, 7.3 Hz, 1H, ArH), 7.87 (d, J = 8.8 Hz, 1H, ArH), 8.03 (d, J = 7.9 Hz, 1H, ArH) ppm. (Diastereomer B) δ = 3.12–3.21 (m, 1H, C**H**$_2$Ar), 3.25 (s, 3H, C**H**$_3$N), 3.65 (s, 3H, C**H**$_3$O), 3.83–3.94 (m, 2H, C**H**$_2$Ar+C**H**$_2$OH), 4.18–4.28 (m, 1H, C**H**$_2$-OH), 5.13 (dd, J = 5.3, 5.0 Hz, 1H, O**H**), 6.46–6.60 (m, 1H, C**H**N), 6.78 (d, J = 8.5 Hz, 2H, ArH), 7.10 (d, J = 8.5 Hz, 2H, ArH), 7.64 (dd, J = 7.9, 7.6 Hz, 1H, ArH), 7.91 (dd, J = 8.0, 7.6 Hz, 1H, ArH), 8.15 (d, J = 7.6 Hz, 1H, ArH), 8.32 (d, J = 8.8 Hz, 1H, ArH) ppm. For $C_{21}H_{20}N_4O_4$ (392.41) calculated: C 64.28, H 5.14, N 14.28, found: C 64.22, H 5.24, N 14.19. HR-MS (ESI): calculated for $C_{21}H_{20}N_4O_4$-Na$^+$ (M+Na$^+$): 415.13768, found: 415.13740.

4.5.6. 10-{(1*S*)-1-[4-(Benzyloxy)benzyl]-2-hydroxyethyl}-3-methylbenzo[*g*]pteridin-2,4-dion 9e

Prepared by general procedure from isoalloxazine **8e** (0.42 g, 0.92 mmol) and methyl iodide (1 mL, 15.99 mmol). 0.40 g (92%) of **9e** was obtained as yellow crystals (cryst. dichloromethane). ^{1}H NMR (300 MHz, DMSO-d_6): mixture of diastereomers A and B in ratio A/B = 3.5:1. (Diastereomer A) δ = 3.15 (dd, J = 13.5, 4.7 Hz, 1H, C**H**$_2$Ar), 3.30 (s, 3H, C**H**$_3$N), 3.74 (dd, J = 13.5, 9.1 Hz, 1H, C**H**$_2$Ar), 3.82–4.14 (m, 1H, C**H**$_2$OH), 4.58–4.70 (m, 1H, C**H**$_2$OH), 4.90 (s, 2H, OC**H**$_2$Ph), 4.93 (dd, J = 6.4, 6.4 Hz, 1H, O**H**), 5.34–5.48 (m, 1H, C**H**N), 6.68 (d, J = 8.5 Hz, 2H, ArH), 7.07 (d, J = 8.5 Hz, 2H, ArH), 7.22–7.42 (m, 5H, Ph), 7.52 (dd, J = 7.6, 7.3 Hz, 1H, ArH), 7.72 (dd, J = 8.8, 7.0 Hz, 1H, ArH), 7.86 (d, J = 8.8 Hz, 1H, ArH), 8.03 (d, J = 7.9 Hz, 1H, ArH) ppm. (Diastereomer B) δ = 3.10–3.24 (m, 1H, C**H**$_2$Ar), 3.25 (s, 3H, C**H**$_3$N), 3.56–3.94 (m, 2H, C**H**$_2$Ar+C**H**$_2$OH), 4.16–4.28 (m, 1H, C**H**$_2$OH), 5.00 (s, 2H, OC**H**$_2$Ph), 5.13 (dd, J = 5.6, 5.6 Hz, 1H, O**H**), 6.46–6.78 (m, 1H, C**H**N), 6.86 (d, J = 8.5 Hz, 2H, ArH), 7.15 (d, J = 8.5 Hz, 2H, ArH), 7.22–7.42 (m, 5H, Ph), 7.65 (dd, J = 7.6, 7.3 Hz, 1H, ArH), 7.91 (dd, J = 7.6, 7.6 Hz, 1H, ArH), 8.16 (d, J = 7.9 Hz, 1H, ArH), 8.31 (d, J = 8.8 Hz, 1H, ArH) ppm. For $C_{27}H_{24}N_4O_4$ (468.50) calculated: C 69.22, H 5.16, N 11.96, found: C 69.01, H 5.37, N 10.78. HR-MS(ESI): calculated for $C_{27}H_{24}N_4O_4Na^+$ (M+Na$^+$): 491.16898, found: 491.16857.

4.6. Preparation of alloxazinium salts 4

4.6.1. General procedure

Thionyl chloride (1 mL) was added to the solution of isoalloxazine **8** (0.3 mmol) in dry dichloromethane (5 mL) and the reaction mixture was stirred at dark for 24 h under an argon atmosphere. After addition of hexane (3–8 mL), salt **4** was precipitated and collected by filtration.

4.6.2. (1*S*)-(5*H*)-1,2-Dihydro-5-methyl-1-(1-methylethyl)-4,6-dioxobenzo[*g*]imidazo-[1,2,3-*ij*]pteridin-12-ium chloride 4a

Prepared by general procedure from isoalloxazine **9a** (100 mg, 0.32 mmol). 101 mg (95%) of **4a** was obtained as yellow crystals, mp 157.6–164.3 °C, $[\alpha]_D^{25}$ = −195.0 (c 0.502, methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.73 (d, J = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 1.15 (d, J = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH), 2.78–2.92 (m, 1H, (CH$_3$)$_2$C**H**), 4.40 (s, 3H, C**H**$_3$N), 4.61 (dd, J = 11.4, 10.5 Hz, 1H, C**H**$_2$N), 4.78 (dd, J = 11.4, 4.5 Hz, 1H, C**H**$_2$N), 6.04–6.15 (m, 1H, C**H**N$^+$), 8.13 (dd, J = 8.1, 7.2 Hz, 1H, ArH), 8.35 (dd, J = 7.8, 7.8 Hz, 1H, ArH), 8.52 (d, J = 8.7 Hz, 1H, ArH), 8.63 (d, J = 8.1 Hz, 1H, ArH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.5, 18.7, 29.4, 29.9, 46.7, 69.4, 118.6, 128.7, 131.7, 133.5, 135.0, 138.8, 140.4, 143.3, 147.5, 158.3 ppm . For $C_{16}H_{17}ClN_4O_2$ 2H$_2$O (368.82) calculated: C 52.10, H 5.74, N 15.19, found: C 51.77, H 5.97, N 15.20. HR-MS (ESI) calculated for $C_{16}H_{17}N_4O_2^+$: (M−Cl$^+$): 297.13460, found: 297.13475.

4.6.3. (1*R*)-(5*H*)-1-Phenyl-1,2-dihydro-5-methyl-4,6-dioxobenzo[*g*]imidazo[1,2,3-*ij*]pteridin-12-ium chloride 4b

Prepared by general procedure from isoalloxazine **9b** (100 mg, 0.29 mmol). 94 mg (89%) of **4b** was obtained, mp 170.9–177.2 °C, $[\alpha]_D^{25}$ = +199.2 (c 0.128, methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.44 (s, 3H, C**H**$_3$N), 4.53 (dd, J = 11.4, 6.5 Hz, 1H, C**H**$_2$N), 5.19 (dd, J = 11.1, 11.1 Hz, 1H, C**H**$_2$N), 7.20 (dd, J = 10.5, 6.2 Hz, 1H, C**H**N$^+$), 7.43–7.50 (m, 3H, ArH), 7.68 (d, J = 8.5 Hz, 1H, ArH), 7.71–7.79 (m, 2H, ArH), 8.01 (dd, J = 8.2, 7.3 Hz, 1H, ArH), 8.14 (dd, J = 8.5, 7.3 Hz, 1H, ArH), 8.59 (d, J = 8.5 Hz, 1H, ArH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.5, 54.7, 67.1, 118.0, 128.3, 128.7, 130.3, 130.9, 131.6, 133.6, 135.2, 136.2, 138.8, 140.4, 143.6, 147.4, 158.2 ppm. For $C_{19}H_{15}ClN_4O_2$ 2H$_2$O (402.83) calculated: C 56.65, H 4.75, N 13.91, found: C 56.77, H 4.67, N 13.92. HR-MS (ESI): calculated for $C_{19}H_{15}N_4O_2^+$ (M−Cl$^+$) calculated: 331.11895, found: 331.11899.

4.6.4. (1*S*)-(5*H*)-1-Benzyl-1,2-dihydro-5-methyl-4,6-dioxobenzo[*g*]imidazo[1,2,3-*ij*]pteridin-12-ium chloride 4c

Prepared by general procedure from isoalloxazine **9c** (100 mg, 0.28 mmol), 93 mg (88%) of **4c** was obtained as yellow crystals, mp 147.5–151.4 °C, $[\alpha]_D^{25}$ = −242.5 (c 0.440, methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.27 (dd, J = 14.1, 9.4 Hz, 1H, C**H**$_2$Ph), 3.42 (s, 3H, C**H**$_3$N), 3.66 (dd, J = 13.8, 6.2 Hz, 1H, C**H**$_2$Ph), 4.48 (dd, J = 11.1, 3.2 Hz, 1H, C**H**$_2$N), 4.60 (dd, J = 10.8, 9.1 Hz, 1H, C**H**$_2$N), 6.42–6.54 (m, 1H, C**H**N$^+$), 7.30–7.40 (m, 5H, Ph), 8.05–8.12 (m, 1H, ArH), 8.18–8.23 (m, 2H, ArH), 8.60 (d, J = 8.2 Hz, 1H, ArH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.5, 38.4, 50.8, 65.6, 118.7, 128.4, 128.7, 129.6, 130.6, 131.6, 133.3, 135.2, 138.6, 140.4, 143.0, 147.6, 158.2 ppm. For $C_{20}H_{17}ClN_4O_2$ 2H$_2$O (416.86) calculated: C 57.62, H 5.08, N 13.44, found: C 57.70, H 4.99, N 13.51. HR-MS (ESI): calculated for $C_{20}H_{17}N_4O_2^+$ (M−Cl$^+$) calculated: 345.13460, found: 345.13472.

4.6.5. (1*S*)-(5*H*)-1,2-Dihydro-1-(4-methoxybenzyl)-5-methyl-4,6-dioxobenzo[*g*]imidazo-[1,2,3-*ij*]pteridin-12-ium chloride 4d

Prepared by general procedure from isoalloxazine **9d** (221 mg, 0.56 mmol). 224 mg (97%) of **4d** was obtained as yellow crystals, mp 143.5–146.7 °C, $[\alpha]_D^{25}$ = −362.2 (c 0.286, methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.21 (dd, J = 13.5, 9.1 Hz, 1H, C**H**$_2$Ar), 3.40 (s, 3H, C**H**$_3$N), 3.59 (dd, J = 13.8, 5.2 Hz, 1H, C**H**$_2$Ar), 3.73 (s, 3H, C**H**$_3$O), 4.45 (dd, J = 10.8, 2.6 Hz, 1H, C**H**$_2$N), 4.57 (dd, J = 10.8, 9.1 Hz, 1H, C**H**$_2$N), 6.35–6.48 (m, 1H, C**H**N$^+$), 6.88 (d, J = 8.5 Hz, 2H, ArH), 7.29 (d, J = 8.5 Hz, 2H, ArH), 8.02–8.13 (m, 1H, ArH), 8.16–8.28 (m, 2H, ArH), 8.58 (d, J = 8.2 Hz, 1H, ArH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.4, 37.5, 50.6, 55.9, 65.8, 115.0, 118.8, 126.9, 128.8, 131.5, 131.8, 133.2, 134.8, 138.5, 140.3, 143.0, 147.6, 158.2, 159.5 ppm. For $C_{21}H_{19}ClN_4O_3$ 2H$_2$O (446.88) calculated: C 56.44, H 5.19, N 12.54, found: C 56.48, H 5.12, N

12.42. HR-MS (ESI): calculated for $C_{21}H_{19}N_4O_3^+$ ($M-Cl^+$): 375.14517, found: 375.14534.

4.6.6. (1*S*)-(5*H*)-1-[4-(Benzyloxy)benzyl]-1,2-dihydro-5-methyl-4,6-dioxobenzo[*g*]imidazo-[1,2,3-*ij*]pteridin-12-ium chloride 4e

Prepared by general procedure from isoalloxazine **9e** (130 mg, 0.28 mmol). 120 mg (89%) of **4e** was obtained as yellow crystals, mp 139.8–144.5 °C, $[\alpha]_D^{25} = -403.3$ (*c* 0.091, methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.24 (dd, *J* = 13.5, 9.1 Hz, 1H, C**H$_2$**Ar), 3.39 (s, 3H, C**H$_3$**N), 3.59 (dd, *J* = 13.8, 6.2 Hz, 1H, C**H$_2$**Ar), 4.45 (dd, *J* = 10.8, 2.6 Hz, 1 H C**H$_2$**N), 4.57 (dd, *J* = 10.8, 9.1 Hz, 1H, C**H$_2$**N), 5.09 (s, 2H, OC**H$_2$**Ph), 6.36–6.49 (m, 1H, C**H**N$^+$), 6.96 (d, *J* = 8.5 Hz, 2H, ArH), 7.30 (d, *J* = 8.8 Hz, 2H, ArH), 7.30–7.47 (m, 5H, Ph), 8.03 (dd, *J* = 8.2, 7.0 Hz, 1H, ArH), 8.08–8.22 (m, 2H, ArH), 8.55 (d, *J* = 8.2 Hz, 1H, ArH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.4, 37.5, 50.7, 65.8, 69.8, 115.8, 118.8, 127.3, 128.4, 128.6, 128.8, 129.2, 131.4, 131.5, 133.1, 134.9, 137.7, 138.3, 140.3, 143.0, 147.7, 158.3, 158.6 ppm. For $C_{27}H_{23}ClN_4O_3$ $2H_2O$ (522.98) calculated: C 62.01, H 5.20, N 10.71, found: C 62.12, H 5.13, N 10.64. HR-MS (ESI): calculated for $C_{27}H_{23}N_4O_3^+$ ($M-Cl^+$): 451.17647, found: 451.17638.

4.7. Generation and synthesis of flavin-10a-adducts

4.7.1. Flavin-10a-hydroperoxides 4-OOH

Hydroperoxides **4-OOH** were prepared in a NMR tube by dissolving salt **4** (0.029 mmol) in CD_3CN (600 μL) and adding urea–H_2O_2 complex (0.127 mmol) and anhydrous K_2CO_3 (0.145 mmol). The mixture was sonicated for 10 min before analysis. Diastereoselectivity was determined from the ratio of signals of flavin-10a-hydroperoxides in ^{1}H NMR spectrum.

4.7.2. 10a-Methoxyflavins-d3 (4-OCD3)

Adducts **4-OCD$_3$** were prepared in a NMR tube by dissolving salt **4** (0.06 mmol) in CD_3OD (600 μL) and adding triethylamine (0.06 mmol). The mixture was sonicated for 10 min and the ^{1}H NMR spectrum was measured immediately. Diastereoselectivity was determined from the ratio of signals of isomeric **4-OCD$_3$** in ^{1}H NMR spectrum.

4.7.3. (1*S*)-1,2-Dihydro-10a-methoxy-5-methyl-1-(1-methylethyl)-4,6-dioxobenzo[*g*]imidazo[1,2,3-*ij*]pteridin 4a-OCH$_3$

A solution of sodium methoxide (795 μL; 75.36 mmol L^{-1}, prepared by dissolving of sodium (104 mg; 4.52 mmol) in dry methanol (60 mL) under argon) was added dropwise to the stirred solution of alloxazinium salt **4a** (20 mg, 0.0599 mmol) in dry methanol (1 mL) . Methanol was evaporated at low pressure without heating in dark. Residue was dissolved in CD_3CN (0.7 ml), decanted, transferred into a NMR tube and analyzed immediately. ^{1}H NMR (600 MHz, CD_3CN, *T* = 298 K): major isomer: δ = 0.14 (d, *J* = 6.8 Hz, 3H, C**H$_3$**), 0,96 (d, *J* = 7.0 Hz, 3H, C**H$_3$**), 2.25–2.32 (m, 1H, C**H**(CH$_3$)$_2$), 3.09 (s, 3H, C**H$_3$**O); 3.27 (s, 3H, C**H$_3$**N), 3.99 (dd, *J* = 11.9, 8.1 Hz, 1H, C**H$_2$**), 4.08 (dd, *J* = 11.9; 2.1 Hz, 1H, C**H$_2$**), 4.79–4.84 (m, 1H, C**H**N), 7.15 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH9), 7.28 (d, *J* = 8.2 Hz, 1H, ArH11), 7.51 (dd, *J* = 8.2, 7.3 Hz, 1H, ArH10), 7.76 (d, *J* = 8.0 Hz, 1H, ArH8). Minor isomer: δ = 0.17 (d, *J* = 6.8 Hz, 3H, C**H$_3$**), 0.96 (d, *J* = 6.8 Hz, 3H, C**H$_3$**), 2.37–2.45 (m, 1H, C**H**(CH$_3$)$_2$), 2.83 (s, 3H, C**H$_3$**O), 3,22 (s, 3H, C**H$_3$**N), 3.67–3.75 (m, 1H, C**H$_2$**), 4.21–4.25 (m, 1H, C**H$_2$**), 4.65–4.75 (m, 1H, C**H**N), 7.07 (dd, *J* = 7.6, 7.6 Hz, 1H, ArH9), 7.21 (d, *J* = 8.3 Hz, 1H, ArH11); 7.47 (dd, *J* = 8.2, 7.6 Hz, 1H, ArH10), 7.71 (d, 1H, *J* = 7.9 Hz, ArH8). ^{13}C NMR (150 MHz, CD_3CN): major isomer δ = 12.6 (**C**H$_3$), 17.5 (**C**H$_3$), 26.4 (**C**H(CH$_3$)$_2$), 43.7 (**C**H$_2$N), 47.6 (**C**H$_3$O), 48.8 (**C**H$_3$N), 63.0 (**C**HN), 88.2 (**C**-OCH$_3$),117.1 (C11), 121.0 (C9), 130.4 (C8), 131.4 (C10), 131.5 (ArC), 134.7 (ArC), 137.7 (ArC), 149.2 (CO), 160.5 (CO) ppm. Minor isomer δ = 13.5 (**C**H$_3$), 19.6 (**C**H$_3$), 33.6 (**C**H(CH$_3$)$_2$), 44.1 (**C**H$_2$N), 48.8 (**C**H$_3$N), 49.6 (**C**H$_3$O), 66.3 (**C**HN), 84.0 (**C**-OCH$_3$), 113.1 (C11), 120.1 (C9), 131.0 (C8)m, 132.1 (C10), 131,5 (ArC), 134.7 (ArC), 137.4 (ArC), 149.2 (CO), 160.5 (CO) ppm. HR-MS (ESI): calculated for $C_{17}H_{21}N_4O_3^+$ ($M+H^+$): 329.16082, found: 329.16125.

4.8. Photochemical properties

UV–VIS spectra of flavinium salts **4** were measured on Varian Cary 50 spectrometer in acetonitrile (c(**4**) = 7.5·10^{-5} mol L^{-1}). The fluorescence spectra were measured on Varian Eclipse spectrometer (c(**4**) = 1·10^{-5} mol L^{-1}) using excitation wavelength λ = 364 nm.

Fluorescence quantum yields Φ_F (λ_{exc} = 364 nm) of flavinium salts **4** were determined by standard procedure in acetonitrile (c = 2.5.10^{-6} mol L^{-1}) using quinidinium sulfate[32] (c = 1·10^{-6} mol L^{-1} in sulfuric acid (0.5 mol L^{-1})) as a standard.

Quenching of fluorescence of flavinium salt **4a** (c = 1.7 · 10^{-5} mol L^{-1} in acetonitrile) was measured on Varian Eclipse spectrometer by adding anisole (0, 10, 100, 1000 and 10 000 molar equivalent relative to **4**) using excitation wavelength λ_{exc} = 364 nm.

4.9. DFT calculations

All the calculations were performed in the Gaussian 16 A.03 software package[33] without any constraints, except for the initial scan where one dihedral angle between flavin and pendant phenyl ring was frozen. The minima and transition states were confirmed by frequency calculations with no imaginary frequency or one imaginary frequency corresponding to the rotation of the phenyl ring, respectively. All the Gibbs energies were calculated at 298 K and include the ZPE correction and gas phase thermochemistry and were not scaled.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.029.

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