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N^1,N^{10}-Ethylene-bridged flavinium salts derived from L-valinol: synthesis and catalytic activity in H_2O_2 oxidations

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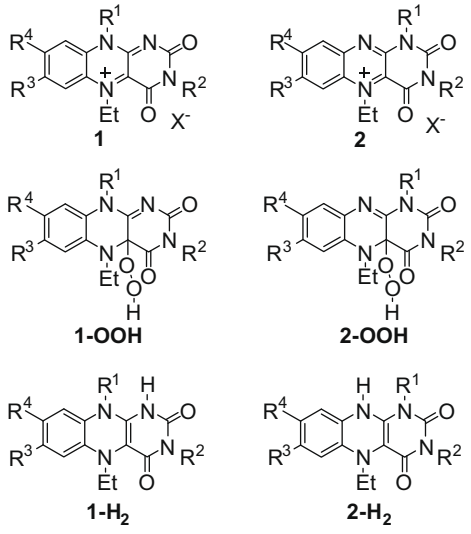
ABSTRACT

Three chiral N^1,N^{10}-ethylene-bridged flavinium salts with a stereogenic centre derived from L-valinol are prepared and investigated as oxidation catalysts. These salts efficiently catalyse chemoselective H_2O_2 oxidation of sulfides to sulfoxides and the oxidation of 3-phenylcyclobutanone to the corresponding lactone at room temperature. The flavinium salts react with hydrogen peroxide to form flavin-10*a*-hydroperoxide, which is the agent responsible for oxidation of the substrate.

Oxidation with hydrogen peroxide or oxygen catalysed by flavinium salts **1** or **2** seems to be a promising organocatalytic method that fulfils all the criteria for environmentally benign processes.[1–3] Flavinium salts are usually considered as flavoenzyme mimics that can transform, for example, sulfides into sulfoxides,[4–12] tertiary amines into *N*-oxides,[4,13] cyclic ketones into lactones[14] and hydrazine into diimide.[15,16] In several instances, chiral flavinium salts affording sulfoxides[17,18] or esters[19] with moderate enantioselectivity have also been described. The mechanism of flavinium salt catalysis in oxidations involves in situ formation of flavin hydroperoxide, which is the agent that oxidises the substrate.[1–3]

Although oxidations catalysed by flavinium salts have been studied in detail, the flavinium catalysts already investigated are limited to 5-alkylisoalloxazinium salts **1** (derivatives of natural flavins)[4,9–12,14–20] and 5-alkylalloxazinium salts **2** (non-natural derivatives that are also considered as flavinium salts in the literature).[5–9,12,13] Both 5-alkylflavinium salts **1** and **2** form flavin-4*a*-hydroperoxides **1-OOH** and **2-OOH** by reaction with hydrogen peroxide or by the reaction sequence including reduction to dihydro derivative **1-H$_2$** or **2-H$_2$** (with hydrazine or sodium dithionate) followed by reaction with molecular oxygen (Scheme 1).[1–3] The dihydro derivatives **1-H$_2$** and **2-H$_2$** have also been isolated and used as efficient catalysts in H_2O_2 oxidations.[5–8,13] In such cases, the dihydro derivatives are in fact precursors of the corresponding salts **1** and **2** which are formed in situ from **1-H$_2$** and **2-H$_2$** by the action of oxygen. Surprisingly, there have been no reports on reactions of N^1,N^{10}-ethylene-bridged flavinium salts **3** with a quaternary nitrogen at position 10. The only exception was a study of amine oxidation to aldehydes in the presence of substituted 1,10-ethyleneisoalloxazinium chlorides **3a–c** (Scheme 2).[21]



Scheme 1. Structures of 5-alkylflavinium salts **1** and **2**, and the corresponding flavin-4*a*-hydroperoxides, and dihydro derivatives.

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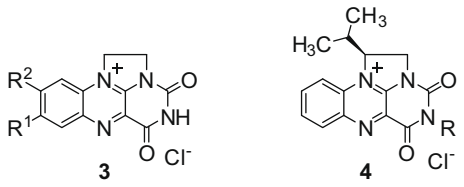


Scheme 2. N^1,N^{10}-Ethylene-bridged flavinium salts.

Salts **3** are known to form 10*a*-adducts with primary and secondary amines, hydrazine or methanol.[22] Therefore, we expected that compounds **3** could also add hydrogen peroxide and thus could be used as catalysts for oxidations in a similar manner as flavinium derivatives **1** and **2**. In the present study, we modified the structure of ethylene-bridged salts **3** by incorporation of a stereogenic centre into the ethylene bridge. We assumed that the proposed chiral flavinium salts **4** (Scheme 2) could be easily prepared using natural amino acids as the source of chirality. The aim of this study was to verify the synthetic availability of chiral ethylene-bridged flavins **4** starting from an amino acid derivative (L-valinol was used in this study) and to investigate the ability of the prepared salts to catalyse oxidations with hydrogen peroxide.

The synthesis of flavinium compounds **4** was performed analogously to the procedure described for derivatives **3** starting from 1-fluoro-2-nitrobenzene (Scheme 3).[21] Catalytic hydrogenation of **5** gave N-substituted diamine **6**, which was condensed with alloxane hydrate (**7a**) to form flavin **8a**. The 3-methyl **8b** and 3-benzyl **8c** derivatives were obtained by alkylation of flavin **8a** with methyl iodide and benzyl bromide, respectively. Alternatively, **8b** was prepared by condensation of **6** with *N*-methylalloxane hydrate (**7b**)[23] (for details on the synthesis of **8** see the Supplementary data). The synthesis of salts **4** was completed by heating 10-(2-hydroxyethyl)flavins **8** in thionyl chloride under an argon atmosphere.[24]

Flavins **8a** and **8b** have already been reported but the authors did not provide any details on their synthesis.[25] They predicted possible steric crowding between the isoalloxazine plane and the substituents on the stereogenic carbon attached to N^{10} in **8**. Indeed, we observed two sets of signals in a ratio of approximately 2:1 in the ^{1}H NMR spectra of **8a–c** corresponding to the presence of two diastereomers of **8** differing in configuration at the N^{10}–C bond (for characterisation of **8**, see the Supplementary data).

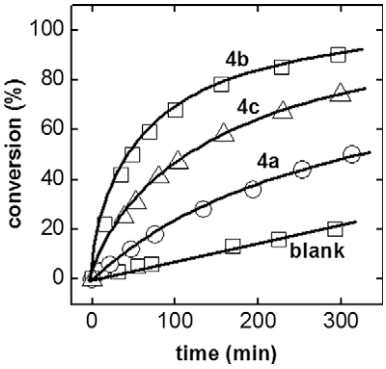
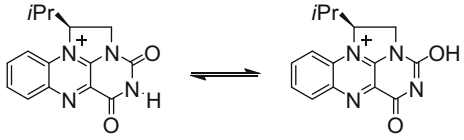


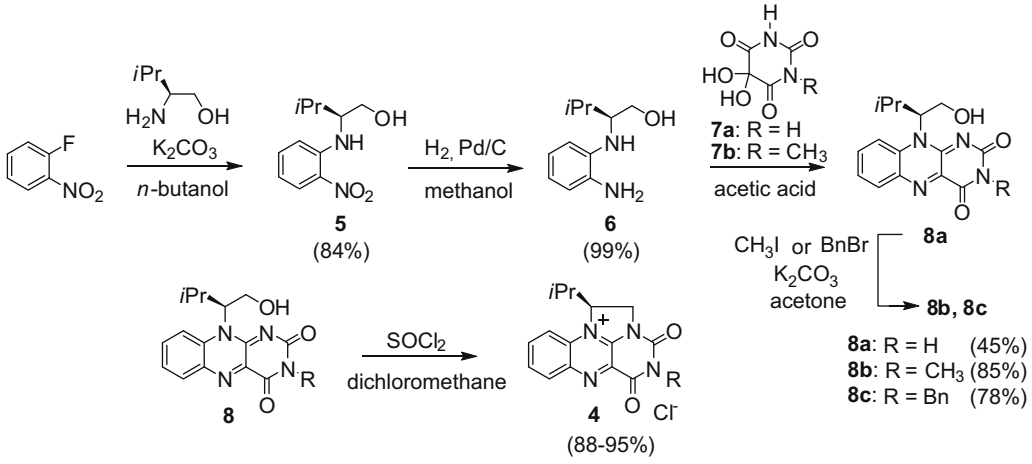
Figure 1. Oxidation of thioanisole with H_2O_2 catalysed by flavinium salts **4a–c** compared to the non-catalysed control reaction (blank). Conditions: *n*(thioanisole) = 0.255 mmol, *n*(H_2O_2) = 0.392 mmol, *n*(**4**) = 5.1 μmol, *T* = 25 °C, solvent = CD_3OD/H_2O.



Scheme 4. Possible oxo-enol tautomerism in the case of salt **4a**.

The newly prepared compounds **4** were investigated as catalysts in various H_2O_2 oxidations known to be catalysed by flavinium salts: sulfoxidation, oxidation of tertiary amines and Baeyer–Villiger (BV) oxidation.[1,2] To be able to rank the efficiency of salts **4** compared to the reactivity of the previously reported flavinium catalysts, we typically applied reaction conditions analogous to those used in previous studies.[5,14]

The catalytic activity of salts **4** in the oxidation of sulfides with hydrogen peroxide was investigated under the conditions used by Minidis and Bäckvall with deuterated methanol as the solvent, a small excess of hydrogen peroxide, 2 mol % of the catalyst (relative to the substrate) at room temperature (for details see the Supplementary data).[5] Reactions were performed in NMR tubes and the conversion was monitored by ^{1}H NMR spectroscopy. Thioanisole was used first as a model substrate. Time course results for thioanisole oxidation in the presence of **4a**, **4b**, and **4c** (Fig. 1) clearly show that all the tested salts accelerated thioanisole oxidation compared to the control non-catalysed reaction. In contrast to the substantial



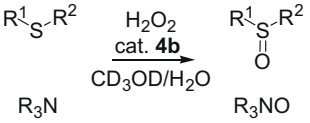
Scheme 3. Synthesis of flavinium salts **4**.

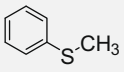
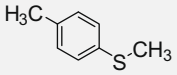
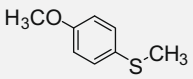
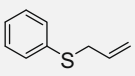
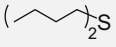
rate enhancement observed for the 3-alkylated salts **4b** and **4c**, the catalytic efficiency of non-substituted salt **4a** was relatively low, probably because of oxo–enol tautomerism (Scheme 4).[21,22] This equilibrium is in competition with the formation of the oxidising species, flavin hydroperoxide, which is the product of hydrogen peroxide addition to the flavinium salt.

To gain an insight into the reactivity of **4b** in H_2O_2 sulfoxidations, it was used for the oxidation of several other substrates (Table 1). As expected, oxidation of an electron-rich aliphatic sulfide (entry 5) was faster than that of aromatic sulfides (entries 1–4). In all cases, no over-oxidation was observed and sulfoxides were detected as the only products; no side oxidation of the double bond in allyl phenyl sulfide occurred (entry 4). Thus, from the point of view of selectivity, the oxidising system with **4b** is comparable to that with 5-alkyl derivative **2a-H$_2$** (**2a-H$_2$** was used as a precursor of **2a**; for the structure see Scheme 1, $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$).[5,6] Nevertheless the efficiency of **4b** is slightly lower than that of **2a-H$_2$** (Table 1). Although we observed rate enhancement from 11:1 to 19:1 in the presence of **4b**, the addition of **2a-H$_2$** accelerated sulfoxidation by a factor ranging from 12.5 to 74 compared to the non-catalysed reaction.

According to the initial reaction rate, salt **4b** efficiently catalysed the oxidation of tertiary amines to N-oxides under identical conditions to those for sulfoxidation (for details see the Supplementary data). The rate enhancement for amine oxidation by **4b**, determined from the initial rate, is even comparable to that for **2a** (Table 1, entries 6 and 7).[13] However, oxidation catalysed by **4b** rapidly decelerates and at conversion rates of >15% the reaction course corresponds to the non-catalysed process (Fig. 2). This is probably caused by decomposition of the 1,10-ethylene-bridged flavinium catalyst under basic conditions. We confirmed the structure of the decomposition product, ester **9** (Scheme 5), in an independent experiment in which **9** was formed quantitatively by heating **4b** in methanol in the presence of triethylamine (see the Supplementary data for experimental details). An analogous product was previously observed on reaction of **3** with benzylamine.[21,22]

Table 1
Oxidation of sulfides and amines with H_2O_2 in the presence of 2 mol % **4b**[a]



Entry	Substrate	Conversion after 1 h (%)	Rate enhancement[b]	
			4b	**2a-H$_2$**[5,13]
1		56	19:1	—
2		53	16:1	74:1[c]
3		66	17:1	36:1[d]
4		37	11:1	—
5		93	13:1	12.5[d]
6	Et_3N	18	26:1	27:1[e]
7	$Ph–CH_2N(CH_3)_2$	14	43:1	67:1[e]

[a] Conditions: n(substrate) = 0.255 mmol, $n(H_2O_2)$ = 0.392 mmol, n(**4**) = 5.1 μmol, T = 25 °C.
[b] Rate enhancement for catalysed versus non-catalysed reactions calculated by dividing the rate of the catalysed reaction by that of the non-catalysed reaction at low conversion[5] (up to 10%).
[c] 1.83 mol % catalyst.
[d] 1.6 mol % catalyst.
[e] 2.5 mol % catalyst.

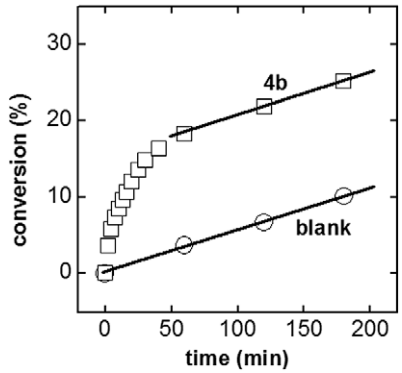
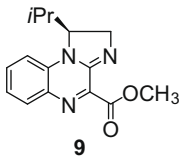


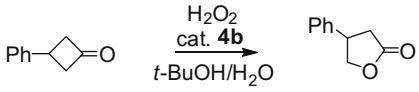
Figure 2. Oxidation of triethylamine with H_2O_2 catalysed by flavinium salt **4b**. Course of non-catalysed reaction (blank) is shown for comparison. Conditions: n(triethylamine) = 0.255 mmol, $n(H_2O_2)$ = 0.392 mmol, n(**4b**) = 5.1 μmol, T = 25 °C, solvent = CD_3OD/H_2O.



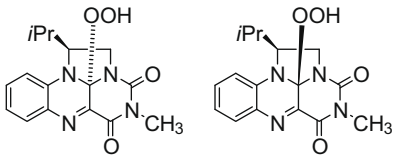
Scheme 5. The structure of the decomposition product of **4b**.

No alloxazinium salts have been investigated as catalysts for BV oxidation to date. Therefore, to test the catalytic activity of **4** in this reaction, we used the conditions described for BV oxidation in the presence of isoalloxazinium salts **1** (R^1 = Ph, $R^2 = CH_3$, $R^3 = R^4 = H$), with *t*-BuOH as the solvent, 5 mol % of the catalyst and two equivalents of H_2O_2 at room temperature.[14] In the presence of **4b**, oxidation of 3-phenylcyclobutanone (Scheme 6) was complete after 6 h. By contrast, only the starting material was isolated for the non-catalysed oxidation (for details see the Supplementary data).

A question arises regarding the structure of the flavin hydroperoxide responsible for H_2O_2 oxidations catalysed by salts **4**. To the best of our knowledge, all the described adducts of ethylene-bridged flavinium salts **3** have a nucleophile (amine, water or methanol) connected to position 10a.[22] Thus, it is reasonable to assume that hydrogen peroxide forms the corresponding flavin-10*a*-hydroperoxides with **3** and **4**. It is not possible to analyse hydroperoxides under oxidation conditions because solvent–flavinium salt adducts predominate in solution in protic solvents.[22] Therefore, we generated flavin hydroperoxide in an independent experiment by adding four equivalents of H_2O_2 (in the form of a urea–H_2O_2 complex) to an acetonitrile solution of **4b** in the presence of potassium carbonate as a base[26] (the formation of **4b-OOH** in this solution was confirmed initially by mass spectrometry). As expected, two sets of signals in the ^1H and ^{13}C NMR spec-



Scheme 6. BV oxidation of 3-phenylcyclobutanone catalysed by **4b**.



Scheme 7. Structure of flavin-10*a*-hydroperoxide **4b-OOH** (both diastereomers).

tra corresponding to the two diastereomers of **4b-OOH** (Scheme 7) were observed. The 3:1 ratio of signals in the ^{1}H NMR spectrum indicates a good diastereoselectivity for H_2O_2 addition to **4b**, which is the result of steric hindrance from the isopropyl group. From the ^{13}C NMR spectra it was evident that the signal for the C-10*a* atom was shifted from δ 142.9 in salt **4b** to δ 85.5 (major isomer) and δ 86.9 (minor isomer) in the adduct. Assignment of the C-10*a* signal for the salt and adducts was made on the basis of the HMBC spectrum, which contained signals corresponding to coupling between the hydrogen atoms of the CH_2 and CH groups in the bridge and the C-10*a* carbon atom.

The stereodifferentiation observed in the formation of **4b-OOH** prompted us to test salt **4b** as a catalyst in stereoselective oxidations. Unfortunately, preliminary experiments on the sulfoxidation of thioanisole in methanol at −20 °C showed only low stereoselectivity (<5% ee; for experimental details see the Supplementary data).

In conclusion, the N^1,N^{10}-ethylene-bridged alloxazinium salts **4** catalyse sulfide oxidations and BV oxidations with hydrogen peroxide. Salts **4** form 10*a*-hydroperoxide **4-OOH** in situ, which can oxidise various substrates in an analogous manner to its 4*a*-derivatives[1,2] **1-OOH** and **2-OOH**. The catalytic efficiency of **4b** is comparable to that of alloxazinium salts already reported. The relatively easy synthesis and the possibility of introducing a stereogenic centre into the side-chain make these ethylene-bridged alloxazinium salts promising catalysts. We found that only the isopropyl group does not result in enantioselectivity during sulfoxidation. On the other hand, the structures of catalysts **4** can be modified which could lead to efficient enantioselective catalysts. To the best of our knowledge, this study is the first example of the application of a flavinium salt with a quaternary nitrogen at position 10 for the catalysis of H_2O_2 oxidations.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.096.

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23. *N*-Methylalloxane monohydrate is not commercially available. It was prepared according to the procedure described in Ref. 12.
24. *General procedure for synthesis of* **4**: thionyl chloride (1 mL) was added to a slurry of flavin **8** (0.3 mmol) in dry CH_2Cl_2 (5 mL) and the reaction mixture was stirred under an argon atmosphere for 24 h. Hexane (5 mL) was added and the precipitate was collected by filtration, washed with hexane and dried under reduced pressure. *(S)-1-Isopropyl-1,2-dihydro-4,6(3H,5H)-dioxo-benzo[g]imidazo[1,2,3-i,j]pteridin-12-ium chloride* (**4a**): yield 95%. Yellow crystals, mp = 233–237 °C. $[\alpha]_D^{25}$ −196.2 (*c* 0.183, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.74 (d, 3 H, *J* = 6.6 Hz, CH_3), 1.14 (d, 3H, *J* = 6.9 Hz, CH_3), 2.75–2.93 (m, 1H, CH(CH$_3$)$_2$), 4.53 (dd, 1H, *J* = 10.8, 10.3 Hz, CH_2^A), 4.72 (dd, 1H, *J* = 10.7, 4.5 Hz, CH_2^B), 5.96–6.14 (m, 1H, CH–CH$_2$), 8.10 (dd, 1H, *J* = 7.5, 7.5 Hz, arom. H), 8.32 (dd, 1H, *J* = 8.4, 7.5 Hz, arom. H), 8.49 (d, 1H, *J* = 8.1 Hz, arom. H), 8.58 (d, 1H, *J* = 8.1 Hz, arom. H), 12.83 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.5, 18.7, 29.9, 45.9, 69.6, 118.5, 128.5, 131.7, 133.5, 136.1, 138.7, 140.1, 144.7, 147.1, 158.7. Anal. Calcd for $C_{15}H_{15}ClN_4O_2{\cdot}2H_2O$ (354.80): C, 50.78; H, 5.40; N, 15.79. Found: C, 50.51; H, 5.06; N, 15.86.
(S)-1-Isopropyl-1,2-dihydro-5-methyl-4,6(3H,5H)-dioxo-benzo[g]imidazo[1,2,3-i,j]pteridin-12-ium chloride (**4b**): yield 90%. Yellow crystals, mp 157.6–164.3 °C. $[\alpha]_D^{25}$ −195.0 (*c* .502, MeOH). ^{1}H NMR (600 MHz, CD$_3$CN): δ 0.75 (d, 3H, *J* = 6.86 Hz, CH_3), 1.19 (d, 3H, *J* = 6.8 Hz, CH_3), 2.92 (m, 1H, CH(CH$_3$)$_2$), 3.43 (s, 3H, N–CH_3), 4.65 (dd, 1H, *J* = 11.4, 4.9 Hz, CH_2^A), 4.69 (dd, 1 H, *J* = 11.4, 10.2 Hz, CH_2^B), 6.04 (m, 1H, CH–CH$_2$), 8.09 (dd, 1H, *J* = 6.7, 1.6 Hz, arom. H), 8.30–8.37 (m, 2H, arom. H), 8.54 (d, 1H, *J* = 8.5 Hz, arom. H). ^{13}C NMR (150.9 MHz, CD$_3$CN): δ 14.1 (CH_3), 18.2 (CH_3), 29.3 (N–CH_3), 30.4 (CH(CH$_3$)$_2$), 46.9 (CH_2), 70.5 (CH–CH$_2$), 118.4, 132.1, 134.3 and 140.0 (arom. CH), 129.7, 133.6, 142.0 and 142.9 (arom. quat. C), 147.4 and 158.2 (CO). Anal. Calcd for $C_{16}H_{17}ClN_4O_2{\cdot}2H_2O$ (368.83): C, 52.11; H, 5.74; N, 15.19. Found: C, 51.77; H, 5.97; N, 15.20.
(S)-1-Isopropyl-1,2-dihydro-5-benzyl-4,6(3H,5H)-dioxo-benzo[g]imidazo[1,2,3-i,j]pteridin-12-ium chloride (**4c**): yield 88%. Yellow crystals, mp 133.7–141.1 °C. $[\alpha]_D^{25}$ −177.4 (*c* 0.438, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.75 (d, 3H, *J* = 6.7 Hz, CH_3), 1.15 (d, 3H, *J* = 7.0 Hz, CH_3), 2.80–2.93 (m, 1H, CH(CH$_3$)$_2$), 4.63 (dd, 1H, *J* = 11.4, 10.5 Hz, CH_2^A), 4.80 (dd, 1H, *J* = 11.4, 4.7 Hz, CH_2^B), 5.17 (d, 1H, *J* = 18.2 Hz, Ph–CH_2^A), 5.22 (d, 1H, *J* = 18.2 Hz, Ph–CH_2^B), 6.06–6.15 (m, 1H, CH–CH$_2$), 7.25–7.47 (m, 5H, arom. H – phenyl), 8.13 (dd, 1H, *J* = 7.9, 7.6 Hz, arom. H), 8.35 (dd, 1H, *J* = 8.5, 7.3 Hz, arom. H), 8.52 (d, 1H, *J* = 8.2 Hz, arom. H), 8.62 (d, 1H, *J* = 8.5 Hz, arom. H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.6, 18.7, 30.0, 45.8, 46.8, 69.5, 105.0, 118.5, 128.4, 128.5, 128.7, 129.1, 131.9, 133.6, 135.2, 136.2, 139.0, 140.4, 143.6, 147.6, 158.2. Anal. Calcd for $C_{22}H_{21}ClN_4O_2{\cdot}2H_2O$ (444.93): C, 59.39; H, 5.66; N, 12.59. Found: C, 59.47; H, 5.31; N, 12.58.
25. Shinkai, S.; Nakao, H.; Tsuno, T.; Manabe, O.; Ohno, A. *Chem. Commun.* **1984**, 849.
26. Hydroperoxide **4b-OOH** was prepared in an NMR tube by dissolving salt **4b** (10 mg; 0.029 mmol) in CD$_3$CN (600 μL) and adding urea–H_2O_2 complex (12 mg; 0.127 mmol) and anhydrous K_2CO_3 (20 mg; 0.145 mmol). The mixture was sonicated for 10 min before analysis. ^{1}H NMR (600 MHz, CD$_3$CN): major isomer δ 0.15 (d, 3H, *J* = 6.8 Hz, CH_3), 0.94 (d, 3H, *J* = 6.9 Hz, CH_3), 2.20 (overlapped m, 1H, CH(CH$_3$)$_2$), 3.23 (s, 3H, N–CH$_3$), 3.95 (dd, 1H, *J* = 11.5, 7.8 Hz, CH_2^A), 4.02 (dd, 1H, *J* = 11.5, 1.7 Hz, CH_2^B), 4.63 (overlapped m, 1H, CH–N), 7.06 (dd, 1H, *J* = 7.4, 7.3 Hz, arom. H), 7.14 (dd, 1H, *J* = 8.2, 8.2 Hz, arom. H), 7.43 (dd, 1H, *J* = 7.4, 7.3 Hz, arom. H), 7.71 (d, 1H, *J* = 7.9 Hz, arom. H); minor isomer: δ 0.90 (d, 3H, *J* = 6.9 Hz, CH_3), 1.12 (d, 3H, *J* = 7.0 Hz, CH_3), 2.41 (sept, 1H, *J* = 7.0 Hz, CH(CH$_3$)$_2$), 3.19 (s, 3H, N–CH$_3$), 3.64 (dd, 1H, *J* = 10.4, 2.0 Hz, CH_2^A), 3.71 (dd, 1H, *J* = 10.4, 3.5 Hz, CH_2^B), 4.17 (m, 1H, CH–N), 6.98 (dd, 1H, *J* = 8.1, 7.9 Hz, arom. H), 7.11 (d, 1H, *J* = 8.4 Hz, arom. H), 7.40 (dd, 1H, *J* = 8.6, 8.6 Hz, arom. H), 7.63 (dd, 1H, *J* = 7.9, 1.2 Hz, arom. H). ^{13}C NMR (150.9 MHz, CD$_3$CN): major isomer δ 13.5 (CH_3), 18.7 (CH_3), 27.7 (CH(CH$_3$)$_2$), 28.6 (N–CH_3), 42.7 (CH_2), 62.6 (CH–CH$_2$), 85.5 (C–OOH), 117.4, 121.2, 130.1 and 132.1 (arom. CH), 132.6 and 135.2 (arom. quat. C), 149.3 and 161.6 (CO); minor isomer δ CH_3 and (CH(CH$_3$)$_2$) signals are overlapped with signals of the major species, 28.3 (N–CH$_3$), 45.8 (CH$_2$), 66.1 (CH–CH$_2$), 86.9 (C–OOH), 114.2, 120.3, 130.1 and 132.1 (arom. CH), 131.8 and 135.3 (arom. quat. C), 150.2 and 162.8 (CO). HR-MS: (M+H$^+$) calcd: 331.14008; found: 331.14062.