Peroxide Chemistry of Triaryl-Substituted Imidazoles. Fenflumizole, a Non-steroidal, Anti-inflammatory Agent

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Fenflumizole, [2-(2,4-difluorophenyl)4,5-bis(4-methoxyphenyl)imidazole] is a non-steroidal, anti-inflammatory analgesic. It reacts quantitatively with $^1O_2$ forming 2-(2,4-difluorophenyl)-4-hydroperoxy-4,5-bis(4-methoxyphenyl)imidazole in a reversible reaction. In ethanol solution at ambient temperatures, the peroxide regenerates parent fenflumizole and $^1O_2$ together with minor quantities of other products. The structures of those products point to the intermediacy of a 1,3-endoperoxide and a dioxetane. These observations may be relevant to the biological activity of fenflumizole.

Fenflumizole [2-(2,4-difluorophenyl)-4,5-bis(4-methoxy-phenyl)imidazole (1, Scheme 2)] has been described as a non-steroidal, anti-inflammatory agent.[1] From clinical observations it also seems to be phototoxic, oedema being produced on mice tails after administration and light exposure.[2] Fenflumizole is a potent cyclooxygenase inhibitor,[3] a characteristic it shares with many other analgesics such as indomethacin and aspirin.[4] The other pathway of the arachidonic acid cascade involving lipoxygenase is not inhibited. In these biological processes arachidonic acid is converted into prostaglandins and leukotrienes in a series of steps involving formation and reaction of endoperoxides and hydroperoxides.[5,6] Furthermore, imidazoles as a group exhibit interesting peroxide chemistry. The stabilities of hydroperoxide-, endoperoxide- and/or dioxetane-functions on the imidazole ring are all influenced by the presence and nature of additional substituents.[7–14] This situation motivated an investigation of the peroxide chemistry of fenflumizole, thus seeking an explanation for its pharmaceutical mode of action.

Scheme 1 summarises the products and intermediates most commonly considered in the chemical reactions following oxidation of imidazoles with molecular singlet oxygen.

Whatever the initial step, the first detectable product is a 2,5-endoperoxide (3).[8] A priori, two isomeric pairs of diastereomers may arise by attack at the 2,4- or 2,5-positions of the imidazole ring, $^1O_2$ approaching from either side. Only one of them (3) is shown in Scheme 1. Thus, Ryang and Foote[8] have characterized the endoperoxides of various
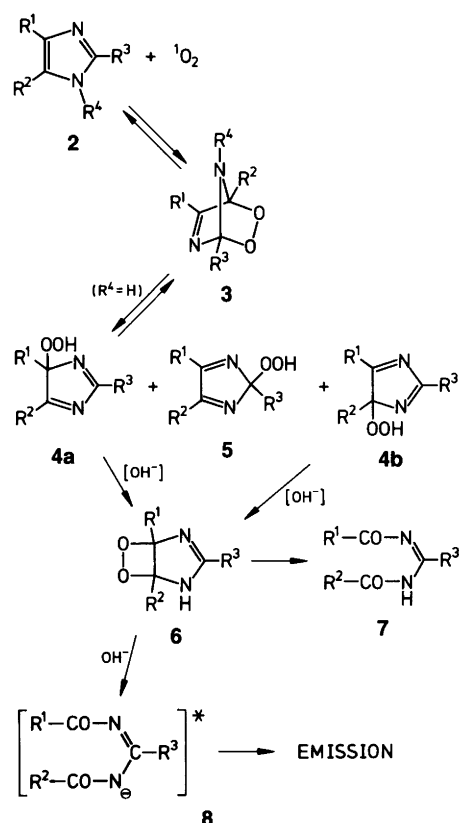
Scheme 1.

methyl-substituted imidazoles related to histidine by ^{1}H NMR spectroscopy at $-70\,^\circ$C and below.

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Formation of hydroperoxides (4 and 5) is conditioned by the existence of an N–H proton (R^4 = H) and their stability is greatly improved by perphenylation (R^1 = R^2 = R^3 = phenyl). Thus Dufraisse et al.[9] successfully isolated a so-called photooxide after photolysis of 2,4,5-triphenylimidazole (lophine) in the presence of air. They assigned to it the endoperoxide structure 3. Once in the crystalline state it could be stored at room temperature. Solid state pyrolysis at 170 °C led to the formation of 50 % molecular oxygen. They found the stability of the 'photooxide' to be much lower in solution, being highly dependent on the nature of the solvent. Later, the structure was correctly assigned to the C4-hydroperoxide,[11,12] which also is the key intermediate in the long recognized phenomenon of chemiluminescence from reactions between lophine and hydrogen peroxide in base.[10]

It seems that C2 is the thermodynamically favoured position for the hydroperoxy group (5) when the imidazole ring carries alkyl substituents[8] while C4(5) is preferred (4a, 4b) when the ring is perarylated.[11,12] The situation becomes more complicated in mixed systems. Two investigations have been reported dealing with imidazoles carrying alkyl in the 2-position and phenyls in the 4,5-positions. Wasserman et al.[7] reacted ethyl 3-(4,5-diphenyl-2-imidazolyl)propanoate with singlet oxygen at −78 °C and characterized the product by means of ^{13}C NMR spectroscopy (60 MHz). Only two singlets were observable from the ring-carbons and assigned C2 (167 ppm) and C4, C5 (124 ppm). Furthermore, only one set of phenyl carbons was observed. Provided that the resolution of a 60 MHz spectrometer is sufficient in this situation, the observation of symmetry is a valid argument indicating hydroperoxy substitution in the 2-position (structure 5); however, we question the assignments. Considering the fact that C2 is sp^3-hybridized while C4 and C5 are sp^2-hybridized, we would rather expect C2 at 124 ppm and C4, C5 at 167 ppm.

What we consider to be the same incorrect assignment is found in a communication by Graziano et al.[12] who performed similar experiments on 2-methyl-4,5-diphenylimidazole. They observed (^{1}H and ^{13}C NMR spectroscopy) the initial formation of its 2-hydroperoxide (5) at −15 °C in anhydrous chloroform. At room temperature, an equilibrium was established between the 2-hydroperoxide 5 and the 4-hydroperoxide 4. The relative structural assignments were based on a ^{13}C NMR spectrum of the reduced form of the 2-hydroperoxide 5 i.e. 2-hydroxy-2-methyl-4,5-diphenyl-2H-imidazole. The expected symmetry is not mentioned and the assignments of the ^{13}C absorptions of C2 and C5 in 5 are – in our opinion – reversed.

Results

Preparation and structural assignment. The reaction between fenflumizole (1) and singlet molecular oxygen proceeded smoothly to produce a crystalline compound, which decomposed without detonation at 160 °C. It reacted with triphenylphosphine to produce triphenylphosphine oxide

(TLC). Iodine was generated when it was reacted with iodide in acidic media. Titration of the iodine formed led to the equivalent weight 421.7 g equiv.$^{-1}$.

The structure of this product was established as 2-(2,4-difluorophenyl)-4-hydroperoxy-4,5-bis-(4-methoxyphenyl)-4H-imidazole (9, Scheme 2, M_w = 424.4) based on the following spectral observations (see the Experimental section for details) IR: 3070 (OH), 2820 (OH···N) and 1610 cm^{-1} (C=N); the absorption at 3420 cm^{-1} (NH) observed in the parent compound (1) was absent. MS: m/z = 424 (M^+) and 135 (100 %, 4-methoxyphenylcarbonyl); no peak was observed at m/z = 141 (difluorophenylcarbonyl). A molecular ion in the mass spectrum of a peroxide is unique. ^{1}H NMR δ: 13.7 (OOH), 8.64 (ortho-protons of 4-methoxyphenyl on C4). These protons appeared at 7.98 in the spectrum of fenflumizole (1). The large shift downfield is consistent with attachment of the very electronegative hydroperoxy group at C4. At the same time, the 4-(4-methoxyphenyl) group is twisted out of the plane of the imidazole ring. The protons on 5-(4-methoxyphenyl) showed another – clearly distinguishlable – AB-pattern. ^{13}C NMR δ: 190.9 (C5), 115.1 (C4) and 167.3 (C2, d, $^3J_{CF}$ = 5.9 Hz).

In summary, the structural assignment of 9 is based on the following three key arguments. (i) Observation of two different 4-methoxyphenyl groups in the NMR spectra implies the absence of a plane of symmetry. (ii) Long-range coupling between the ortho-fluorine atom of the 2,4-difluorophenyl group and C2 permits unambiguous assignment of C2 in the ^{13}C NMR spectrum. Its chemical shift implies that it is not attached to an electronegative substituent such as hydroperoxy. (iii) The radical ion of 4-methoxycarbonyl is base peak in the mass spectrum while the fragment 2,4-difluorocarbonyl is absent.
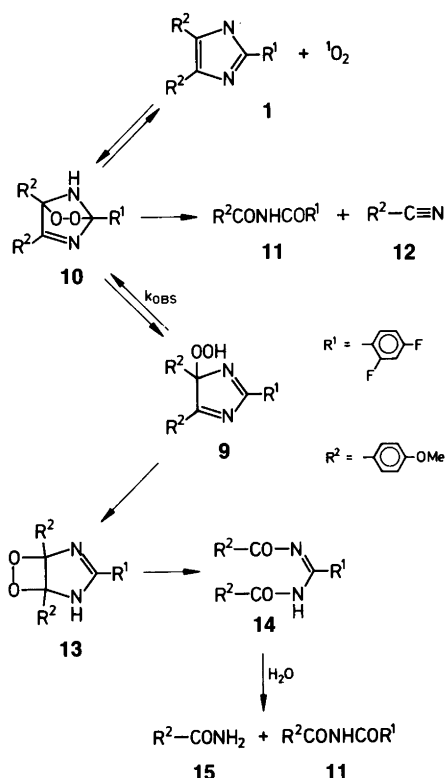
Thermal degradation of the hydroperoxide 9 in ethanol. Ethanol was the medium for the thermal degradation of 9 since the timescale for kinetic measurements at ambient temperatures was convenient. Hydroperoxide 9 is far more stable (weeks) in acetone and chloroform but less so (hours) in water.

Hydroperoxide 9 was boiled typically for 15 min in absolute ethanol and the reaction mixture worked up by column chromatography followed by isolation and identification. The accurate yields were determined in separate, analytical runs by means of high-pressure liquid chromatography.

The main product from the degradation is fenflumizole (1) in 91 % yield. In separate runs, the yield of molecular oxygen measured volumetrically at 25 °C after reaction at 78 °C was determined to be 87 %. As minor products were observed (Scheme 2) 2,4-difluoro-N,N'-bis(4-methoxybenzoyl)benzamidine (14, 3 %), 4-methoxybenzamide (15, 5 %), 2,4-difluoro-N-(4-methoxybenzoyl)benzamide (11, 2 %), and 4-methoxybenzonitrile (12, ca. 1 %).

These findings are rationalized in Scheme 2. In principle, 11 can be formed by two routes i.e. either via the endoperoxide 10, which can eliminate 4-methoxybenzonitrile, or by the route involving the dioxetane 13, which produces
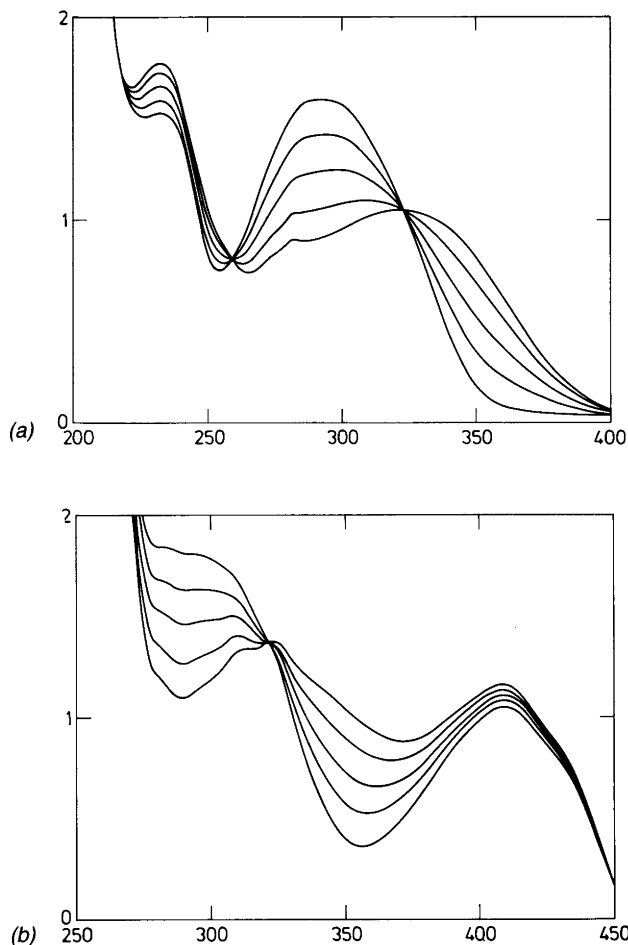
Scheme 2.

Fig. 1. Selected absorption spectra recorded during the degradation of 1 in ethanol in the absence (a) and in the presence (b) of DPBF. See the text.

the benzoylamidine 14. In turn, this can be hydrolysed by minor quantities of water present in the solvent to form 11 and 15.

Reacting 9 with a 0.3 M solution of 1,3-diphenylisobenzofuran (DPBF) in ethanol at room temperature under nitrogen led to identification of 1,2-dibenzoylbenzene and fenflumizole according to TLC and HPLC. Formation of 1,2-dibenzoylbenzene implies the intermediacy of singlet molecular oxygen.[15]

Kinetics of thermal degradation of 9. The rate of disappearance of 9 in the absence and presence of DPBF was monitored at different temperatures by means of absorption spectroscopy. Fig. 1 displays the spectral changes without (a) and with (b) DPBF. The first case features the absorption of the hydroperoxide (max. 332 nm) gradually changing into the spectrum of the products qualitatively identical with the absorption of fenflumizole (1) (max. 293 nm). Isosbestic points are observed at 324 and 259 nm. In Fig. (b) the absorption due to DPBF at 410 nm is diminished during the reaction.

The reaction was monitored at 350 nm and first-order kinetics were followed under all conditions and concentrations investigated. The observed rate constants are displayed in Table 1 along with the chemical yields of DPBF consumed relative to 9 reacted. From the temperature dependence, a linear Arrhenius plot was obtained from which an activation energy $E_a = 110$ kJ mol^{-1} was determined.

Table 1. Observed rate constants for thermolysis of 9 at various temperatures in the presence of DPBF.

T/°C	[9]/mM	[DPBF]/mM	k_{obs}/10^{-4} s^{-1}	Yield[a] (%)
21	0.0405	0	0.0331	
24	0.0405	0	0.0467	
32	0.0405	0	0.155	
39.5	0.250	0	0.498	
39.5	0.055	0	0.498	
39.5	0.055	0.029	0.480	4
39.5	0.11	0.070	0.478	9
39.5	0.055	0.078	0.503	14
39.5	0.055	0.15	0.483	38
39.5	0.11	0.15	0.486	38
39.5	0.25	0.28	0.498	52
42	0.0405	0	0.849	
48.5	0.0405	0	1.67	
51.5	0.0405	0	3.44	
56	0.0405	0	3.36	
65	0.0405	0	8.98	

[a]DPBF reacted relatively to the initial amount of 9.

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Discussion

As indicated by Ryang and Foote[8] and Wasserman *et al.*[7] the first observable product in the reaction between imidazoles and singlet oxygen is the 2,3-endoperoxide (**3**, Scheme 1). If one of the nitrogens carries a hydrogen atom, the primary endoperoxide can open up to either a 2- or a 4-hydroperoxide.[8] This choice of pathway is influenced by the electron distribution in the imidazole ring and possible stabilization by hydrogen bonding in the resulting, non-aromatic 2*H*- and 4*H*-imidazoles. In case of fenflumizole, the electronegative hydroperoxy group is more efficiently stabilized by the 4-methoxyphenyl group at C4 than by the 2,4-difluorophenyl at C2. Furthermore, the hydrogen bond established between the hydroperoxy group at C4 and N(1) creates a six-membered ring. This favourable arrangement is not available for a hydrogen bond involving a hydroperoxy group at C2.

Scheme 2 rationalizes the observations by suggesting two reaction routes both involving intramolecular nucleophilic attack by the hydroperoxy group on C2 and C5 leading to an endoperoxide and a dioxetane, respectively. In the base-triggered chemiluminescence experiments performed by White and Harding[12] on a series of lophine hydroperoxides with various substituents, the major products isolated were the dibenzoylbenzamidines **7** in yields of 70–80%. The lophines investigated, however, carried either phenyl or strongly electron-releasing substituents such as 4-methoxyphenyl and 4-(dimethylamino)phenyl on C2 of the imidazole ring. The 2,4-difluorophenyl group in fenflumizole clearly creates a relative drain of electrons on C2, thus attracting nucleophilic attack from the hydroperoxy group and favouring the reaction path via the endoperoxide.

The observation of first-order kinetics supports the suggested reaction mechanism (Scheme 2). The dibenzoylbenzene formed is not produced in a bimolecular reaction between **9** and DPBF.

Values have been reported[16] for the rate of physical decay of singlet oxygen in ethanol, $k_d = 8.1 \times 10^4$ s^{-1} and for the bimolecular rate constant for the reaction with DPBF, $k_r = 1.3 \times 10^9$ M^{-1} s^{-1}. The ratio $k_r/k_d = 1.6 \times 10^{-4}$ M expresses the concentration of DPBF at which 50% of the singlet oxygen molecules will be trapped by DPBF. As seen in Table 1 the amount of DPBF reacted relative to the initial amount of **9** reaches ca. 50% at a DPBF concentration of ca. 10^{-4} M. In qualitative terms this means that all the oxygen eliminated during thermal degradation of **9** is generated in the excited singlet state. Since the experimental procedures prevented investigations of higher concentrations of DPBF, it cannot be considered constant during the experiment. That is, conditions permitting a Stern–Volmer treatment of the data could not be met.

The energy of activation for the degradation of **9** is estimated as 110 kJ mol^{-1}, a little higher than the excitation energy of singlet oxygen (96 kJ mol^{-1}). Similar values have been determined for comparable systems. Thus, an activation energy of 116 kJ mol^{-1} was reported for the splitting of

9,10-endoperoxy-9,10-diphenylanthracene into the hydrocarbon and singlet molecular oxygen.[17]

Compound **9** is remarkably stable. The products isolated from the thermal degradation in ethanol show no incorporation of solvent molecules, neither is **9** easily hydrolysed. This illustrates its greater resistance towards bimolecular nucleophilic attack compared with hydroperoxides of other imidazoles such as the unsubstituted parent,[18] 2,4,5-triphenylimidazole,[9] 2-methyl-4,5-diphenylimidazole,[13] 4,5-diphenylimidazole, 4-phenylimidazole, 2,4-diphenylimidazole, and a series of fused-ring imidazoles.[7]

The stability of **9** towards hydrolysis is important when trying to evaluate its possible role in biological systems. The first step in the cyclooxygenase pathway of the arachidonic acid cascade is the uptake by arachidonic acid of two molecules of oxygen to form prostaglandin G$_2$, which contains an endoperoxide- as well as a hydroperoxide-group.[19–21] This transformation may involve singlet oxygen generated by an enzymatic process.[22] Fenflumizole could then interact by trapping the singlet oxygen. The hydroperoxide **9** could be formed directly in the enzymatic process in competition with the natural substrate. Once formed in this way, **9** has other possibilities for interference e.g. by 'mimicking' a higher concentration of peroxides and thus triggering a deceleration of the enzyme systems by a negative feed-back mechanism.

The phototoxicity of fenflumizole may likewise be related to the production of singlet molecular oxygen *in vivo* by exposure to sunlight.[23]

The recognition of singlet molecular oxygen as a very important and reactive species in biological systems has gained a lot of momentum in recent years. In fenflumizole we have detected a biologically acceptable molecule, which can react with and release singlet oxygen, i.e. can serve as a singlet oxygen carrier. This has the effect of extending the 'lifetime' and permitting singlet oxygen to react at locations remote from its site of production. Since **9** is lipophilic it is likely that the site of photodynamic action is the cell membrane.

Experimental

Fenflumizole, 2,4-difluoro-*N*,*N'*-bis(4-methoxybenzoyl)-benzamidine, 4-methoxybenzamide, 2,4-difluoro-*N*-(4-methoxybenzoyl)benzamide, and 4-methoxybenzonitrile were kindly supplied from Dumex Ltd. 1,3-diphenylisobenzofuran was from Sigma. All chemicals were analytical grade and used as received.

IR spectra were obtained on a Perkin–Elmer 157 spectrophotometer, UV spectra on a Unicam SP800A or a Shimadzu UV-260, NMR spectra on a JEOL FX 90 Q and mass spectra on an AEI MS-902 spectrometer. HPLC was performed on a Waters 600E instrument with a Waters 990 photodiode array detector. All experiments were followed by TLC on Merck Alufolie (0.2 mm) with CH$_2$Cl$_2$–heptane–ethyl acetate–ethanol (300:300:60:1) as the eluent.

Estimation of the equivalent weight of **9** was made according to Ref. 24.

Fenflumizole: Spectral data. MS [IP 70 eV; 100 °C; *m/z* (% rel. int.)]: 392 (100, M^+), 377 (22, M^+-CH_3), 196 (19, M^{2+}).

^1H NMR [90 MHz, $(CD_3)_2CO$, Me_4Si] δ 3.79 (6 H, s, $-OCH_3$), 6.89 (4 H, d, *J* 8.85 Hz, $4-MeOC_6H_4-$), 7.07 (1 H, dt, $^3J_{HH}$ 8.6 Hz, $^3J_{HF(4)}$ 8.6 Hz, $^4J_{HH}$ 2.5 Hz, H5 in $C_6H_3F_2-$), 7.18 (1 H, dt, $^3J_{HF(2,4)}$ 9.46 Hz, $^4J_{HH}$ 2.5 Hz, H3 in $C_6H_3F_2-$), 7.48 (4 H, d, *J* 8.85 Hz, $4-MeOC_6H_4-$), 8.23 (1 H, m, $^4J_{HF(2,4)}$ 6.72 Hz, $^3J_{HH}$ 8.47, $^5J_{HH}$ 0.61 Hz, H6 in $C_6H_3F_2-$), 12.31 (1 H, br s, NH).

^{13}C NMR $(CDCl_3$, 22.5 MHz): δ imidazole ring: 131.9 (C2), 125.2 (C4 and C5); δ 2-(2,4-difluorophenyl) group: 114.4 ($^2J_{CF}$ 14.7 Hz, $^4J_{CF}$ 3.4 Hz, C1), 159.2 ($^1J_{CF}$ 248.0 Hz, $^3J_{CF}$ 11.7 Hz, C2), 104.0 ($^2J_{CF}$ 26.3 Hz, C3), 162.4 ($^1J_{CF}$ 250.1 Hz, $^3J_{CF}$ 12.8 Hz, C4), 112.3 ($^2J_{CF}$ 21.4 Hz, $^4J_{CF}$ 1.3 Hz, C5), 130.0 ($^3J_{CF}$ 9.2 Hz, C6); δ 4- and 5-(4-methoxyphenyl) groups: 139.8 (C1), 129.0 (C2), 113.9 (C3), 158.0 (C4), 55.3 (CH_3O-).

IR (KBr): 3410 (NH), 2950–2900 (C–H), 1615, 1595, 1520, 1500, 1290, 1250, 1180, 840 cm^{-1}.

UV [abs. ethanol (log ϵ)]: 290 (4.39) nm.

Preparation of 2-(2,4-difluorophenyl)-4-hydroperoxy-4,5-bis(4-methoxyphenyl)imidazole. Fenflumizole (510 mg) was dissolved in 50 ml ethanol. Methylene blue was added (final conc. 1×10^{-5} M) and the flask was irradiated with a 750 W tungsten lamp for 2 h while oxygen was bubbled through. Methylene blue was removed on a silica column in the cold and the solvent was evaporated under reduced pressure. The faintly yellow solid was used without further purification. M.p. 155–160 °C (decomp. with emission of light). Anal. $C_{23}H_{18}N_2O_4$: C, H, N.

MS [IP 70 eV; 140 °C; *m/z* (% rel. int.)]: 424 (10, M^+), 212 (2, M^{++}), 135 (100, $CH_3-Ph-CO^+$).

^1H NMR (90 MHz, $CDCl_3$, Me_4Si): δ 4.0 (3 H, s, $-OCH_3$), 4.19 (3 H, s, $-OCH_3$), 7.11 [2 H, d, *J* 8.85 Hz, $5-(4-MeOC_6H_4-)$], 7.24 [2 H, d, *J* 8.85 Hz, $5-(4-MeOC_6H_4-)$], 7.81 [2 H, d, *J* 8.85 Hz, $4-(4-MeOC_6H_4-)$], 8.64 [2 H, d, *J* 8.85 Hz, $4-(4-MeOC_6H_4-)$], 6.77 (1 H, dt, $^3J_{HH}$ 8.98, $^3J_{HF}$ 8.98, $^4J_{HH}$ 2.1 Hz, H5 in $C_6H_3F_2-$), 6.9 (1 H, $^3J_{HF}$ 8.98, $^4J_{HH}$ 2.1 Hz, H3 in $C_6H_3F_2-$), 8.73 (1 H, m, $^3J_{HH}$ 8.98, $^4J_{HF}$ 6.64 Hz, H6 in $C_6H_3F_2-$).

^{13}C NMR $(CDCl_3$, 22.5 MHz): δ imidazole ring: 167.3 ($^3J_{CF}$ 5.9 Hz, C2), 190.0 (C4), 115.5 (C5); 2-(2,4-difluorophenyl) group: 134.3 ($^2J_{CF}$ 10.0 Hz, C1), 165.2 ($^1J_{CF}$ 271.0 Hz, $^3J_{CF}$ 17.0 Hz, C2), 104.7 ($^2J_{CF}$ 25 Hz, $^2J_{CF}$ 26.5 Hz, C3), 162.7 ($^1J_{CF}$ 271.0 Hz, $^3J_{CF}$ 19.0 Hz, C4), 110.5 ($^3J_{CF}$ 21.0 Hz, $^4J_{CF}$ 0.2 Hz, C5), 115.2 ($^3J_{CF}$ 2.0 Hz, C6); 4-(4-methoxyphenyl) group: 126.8 (C1), 132.4 (C2/C6), 113.9 (C3/C5), 163.6 (C4), 55.0 (CH_3O); 5-(4-methoxyphenyl) group: 123.4 (C1), 128.3 (C2/C6), 113.9 (C3/C5), 160.1 (C4), 55.3 (CH_3O).

IR (KBr): 3450 (br, OOH), 3200 (OCH_3), 2820, 1660, 1595, 1550, 1520, 1470, 1415, 1320, 1295, 1260 (br), 820 cm^{-1}.

UV [abs. ethanol (log ϵ)]: 228 (4.53), 350 (4.29) nm.

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