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Synthesis and structure of biologically active ferrocenylalkyl polyfluoro benzimidazoles

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Abstract

The title compounds were synthesized in quantitative yields by interacting α-hydroxyalkyl ferrocenes with polyfluoroalkyl benzimidazoles in an aqueous-organic medium in the presence of HBF_4. The resulting diastereomers and enantiomers were resolved using HPLC on silica bonded chiral stationary phases based on chiral cyclodextrins and cyclic antibiotics. The X-ray determination of molecular and crystal structure of 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)benzimidazole (**1**) was carried out.

Keywords: Ferrocene derivatives; α-Ferrocenylalkylation; Benzimidazole; Polyfluoro-benzimidazoles; X-ray crystal structure; Separation of enantiomers; HPLC; Chiral cyclodextrin sorbents

1. Introduction

A series of ferrocenylalkyl azoles has been synthesized earlier using the reaction of α-ferrocenylalkylation with corresponding azoles in aqueous-organic media [1]. Some of the compounds obtained were found to display high antitumour activity combined with low toxicity [2]. Fluorine containing benzimidazoles, being inhibitors of some metallo enzymes and showing antitoxic, antidiarrhea, antiviral, and immuno stimulating effects [3], are of utmost interest as components in the development of new ferrocene-containing drugs. The veterinary preparation 'ftorazol', which is used for the prophylaxis of young stock diseases, was developed on the basis of one compound of this series [4].

In the present work the synthesis of a number of ferrocenylalkyl polyfluoro benzimidazoles **1**–**5** was performed, and the X-ray structural study 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)benzimidazole (**1**) was carried out. The separation of synthesized diastereomers and enantiomers was achieved by HPLC on chiral columns with silica gel bonded cyclodextrins and cyclic antibiotics.

2. Results and discussion

2.1. Synthesis

The α-ferrocenylalkylation of nucleophilic substrates by hydroxyalkyl ferrocenes FcCH(R)OH in an aqueous-organic medium (in the presence of fluoroboric acid) constitutes a convenient way of introducing a ferrocenyl group into different azoles [1]. The synthesis occurs under aerobic conditions at room temperature within several minutes and often gives the target product in quantitative yields [5].

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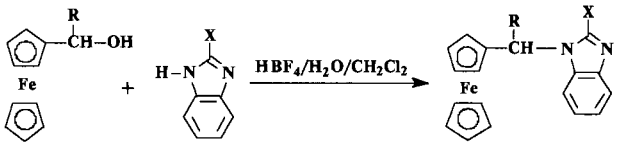
However, this method is only effective with respect to nucleophilic substrates with basic pK_a lower than 5.50 [6]. Stronger bases, for instance, imidazole (basic pK_a 7.00) and benzimidazole (basic pK_a 5.53) do not undergo α-ferrocenylalkylation under the above conditions, but, instead, readily form salts ImH·HBF_4 and BzImH·HBF_4 [7].

To reduce the azole basicity one can introduce different substituents exhibiting strong electron-acceptor properties, for example, fluorine-containing groups. In going from imidazole to 2-fluoroimidazole the basic pK_a value drops from 7.00 to 2.40 [8]. Thus, benzimidazole derivatives containing polyfluoroalkyl substituents in C-2 position, 2-(CF_3–O–CHF)BzImH (**6**), 2-(CF_3–CHF)BzImH (**7**), 2-(CHF_2–CF_2)BzImH (**8**) and 2-CF_3BzImH (**9**), readily enter ferrocenylalkylation reaction with equimolar amounts of ferrocenylmethanol (**10**) or 1-ferrocenylethanol (**11**) in the two-phase system methylene dichloride/45% solution of fluoboric acid in water. As a result, ferrocenylalkyl polyfluoroalkyl benzimidazoles **1**–**5** were synthesized in quantitative yields according to the following scheme:



R=H, X=CHF-O-CF_3 (1),
R=H, X=CHF-CF_3 (2),
R=H, X=CF_2-CHF_2 (3),
R=H, X=CF_3 (4),
R=CH_3, X=CHF-CF_3 (5).

Compounds **1**–**5** are yellow powder-like substances. They are stable in air, soluble in organic solvents and acidic aqueous solutions. Their composition and structure have been proved by elemental analyses as well as IR and NMR spectroscopy and mass spectrometry.

2.2. Separation of diastereomers and enantiomers

Each of the compounds **1** and **2** contains one asymmetric carbon atom in the polyfluoroalkyl substituents of the benzimidazole fragment and gives racemic mixtures of two enantiomers. Compound **5** was prepared from racemic 1-ferrocenylethanol (**11**) and thus contains two chiral centres. Therefore, two diastereomers of this complex, each in two enantiomeric forms, may be formed.

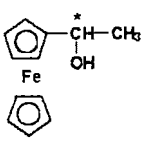
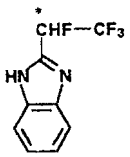
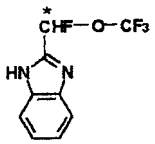
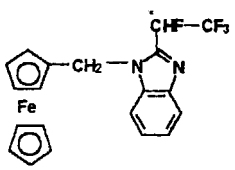
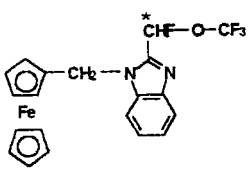
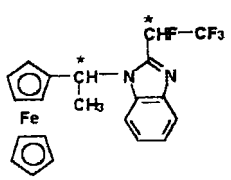
To separate mixtures of enantiomeric ferrocene derivatives, and, particularly, ferrocenylethanol **11**, Armstrong et al. [9] used high-performance liquid chromatography (HPLC) on columns with bonded chiral β-cyclodextrin groups. The size of the ferrocenyl fragment obviously permits formation of the inclusion complex with β-cyclodextrin which offers the 'guest' a relatively hydrophobic conical cavity with the approximate diameter of 7.8 Å. The chiral recognition of 'guest' enantiomers results from an enantioselective steric or polar interaction of the ferrocene substituent with hydroxyl groups sticking out on the surface of the cone of the cyclodextrin molecule.

One could expect that this mechanism of formation of inclusion compounds would also function in the case of benzimidazole derivatives of ferrocene. But the column with silica bonded β-cyclodextrin proved to be successful only in the case of ferrocenylethanol **11** which was resolved into two enantiomers with the selectivity $\alpha = 1.13$ (water/methanol of 50/50). Replacing the hydroxyl group of this compound by an imidazole fragment (compound **5**) results in a dramatic fall in the retention in the same eluent. A decrease of the methanol content in the eluent slightly enhances the sorbate retention time, but does not result in separation of the racemic mixture. These negative consequences are probably caused, first, by low solubility of compounds **1**, **2** and **5** in water-rich eluents and, second, by the large size of imidazole fragments, which hinders sterically the formation of 'host–guest' inclusion complexes.

The chiral sorbent based upon γ-cyclodextrin turned out to be more effective (Table 1). Using this chiral stationary phase, we managed to resolve all the examined ferrocenyl alkylimidazoles **1**, **2** and **5** in the same eluent, water/methanol mixture (50/50). The internal relatively hydrophobic cavity of the γ-cyclodextrin cycle is about 9.5 Å in diameter and may readily incorporate the bulky molecules of ferrocenyl alkylimidazoles. Moreover, the γ-cyclodextrin type selector succeeds in recognizing configuration of both the carbon atom directly attached to ferrocene and the stereogenic carbon atom in the fluoroalkyl substitutent of the benzimidazole fragment. This is evident from the successful resolution of compound **5** containing two asymmetric centres into four stereo isomers (Fig. 1). Vice versa, less bulky molecules of ferrocenylethanol **11** are weakly retained by γ-cyclodextrin and defy separation. This pair obviously violates the rule of 'guest–host' space complementarity.

Enantiomers of the initial polyfluoroalkyl substituted benzimidazoles **6** and **7**, without ferrocenyl moieties, are only weakly retained by the both sorbents based upon β- and γ-cyclodextrins, and can not be resolved in aqueous methanolic mixtures with the methanol content being varied in the range from 100 to 15%. No separation of enantiomers of these imidazoles could be achieved on columns with immobilized β-cyclodextrin derivatives, namely, acetyl-derivatized, hydroxypropyl-derivatized, and (*S*)- and (*R*)-naphthylethylcarbamate-derivatized β-cyclodextrins. The usage of water/acetonitrile, acetonitrile/triethylammonium acetate buffer (pH 5.0 and 7.0) and hexane/isopropanol mixtures proved unsuccessful as well.

Table 1
Enantiomeric resolution of racemic mixtures

No.	Compound	Chiral stationary phase	k'_1, k'_2	α	Eluent
11		β-Cyclodextrin	6.0, 6.8	1.13	MeOH/H_2O 50/50
7		Vancomycin	8.7, 9.0	1.038	Hexane/Propanol-2 90/3
6		Eight different CSPs	No resolution		
2		γ-Cyclodextrin	1.3, 1.8	1.38	MeOH/H_2O 50/50
1		γ-Cyclodextrin	1.3, 1.7	1.31	MeOH/H_2O 50/50
5		γ-Cyclodextrin	0.9, 1.1, 1.3, 1.6	**	MeOH/H_2O 50/50

** No assignment of four stereoisomers.

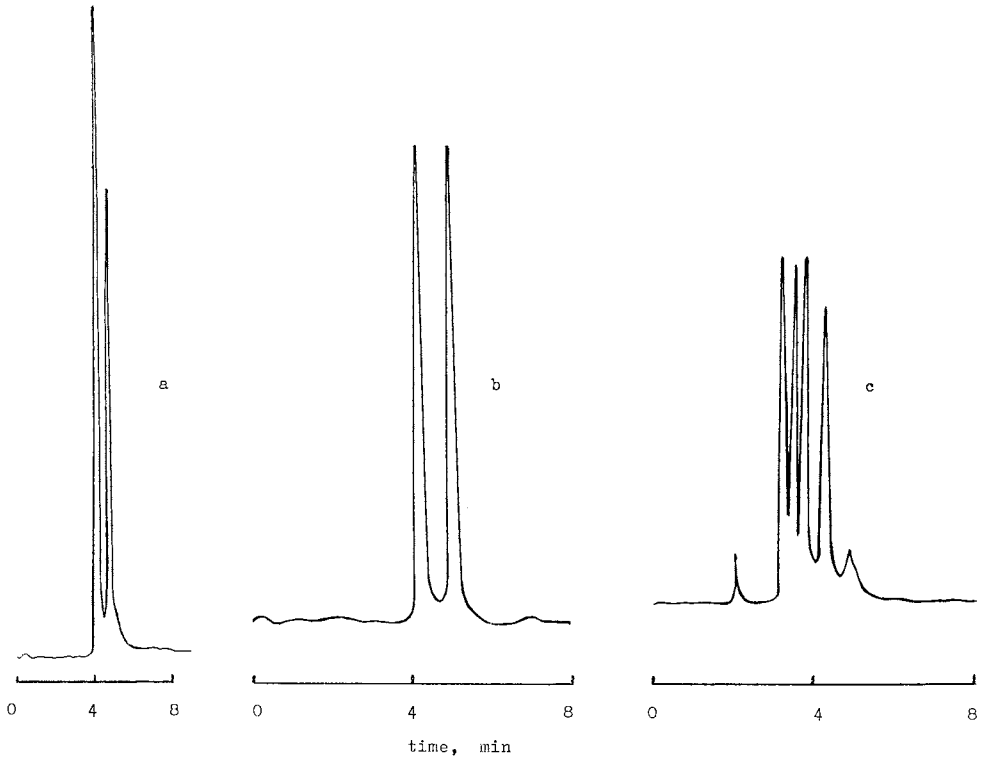


Fig. 1. Chiral resolution of ferrocenylalkyl benzimidazoles (CF_3–O–CHF)BzImCH_2Fc (compound **1**) (a), (CF_3–CHF)BzImCH_2Fc (compound **2**) (b), and (CF_3–CHF)CH(CH_3)Fc (compound **5**) (c). Column, silica bonded γ-cyclodextrin (Cyclobond II 2000), 250 × 4.6 mm, 5 μm. Eluent, water/methanol 50/50 (v/v), 1 ml min^{-1}. Detector, UV 254 nm.

New chiral columns with silica-gel-bonded macrocyclic antibiotics—vancomycin [10] and teicoplanin [11]—appeared to be more effective for the separation of racemic polyfluoroalkyl benzimidazoles. The molecules of the above antibiotics represent three and four mutually condensed macrocycles, respectively, and contain many different substituents. In such cases, enantioseparation may be possible via several different mechanisms, including π–π-complexation, hydrogen bonding, inclusion in a hydrophobic pocket, dipole stacking, steric interactions, or combinations thereof. The above bonded phases can be used under both normal-phase and reversed-phase elution conditions. The tetrafluoroethylbenzimidazole (compound **7**) in a hexane/isopropanol mixture (97/3) resolves partially on the teicoplanin column and almost completely on the vancomycin column (Fig. 2). On the other hand, of the ferrocene-substituted compounds **1**, **2** and **5** tested on the antibiotic columns, only compound **5** was separated into two (but not four!) fractions.

Hence, eight types of bonded chiral phases were tested, and by using one chiral phase or the other phase we managed eventually to find conditions for chiral resolution of four racemic mixtures, but not for compound **6.** Cyclodextrin columns appeared to be most effective. In this case the mechanism of chiral recognition is most easy to describe in terms of the formation of inclusion compounds, provided that the sizes of the interacting 'guest' and 'host' moieties correspond to each other.

The difficulties in separation of enantiomers of polyfluoroalkyl benzimidazoles **6** and **7** may result from a too small difference between the sizes of hydrogen and fluorine atoms attached to the asymmetric carbon atom. The presence of an additional flexible –O– unit in compound **6** as compared to **7** significantly decreases

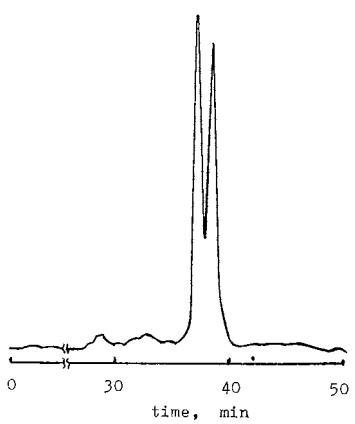


Fig. 2. Chiral resolution of benzimidazole 2-(CF_3–CHF)BzImH (compound **7**). Column, silica bonded vancomycin (Chirobiotic V), 250 × 4.6 mm, 5 μm. Eluent, hexane/isopropanol 97/3 (v/v), 1 ml min^{-1}. Detector, UV 254 nm.

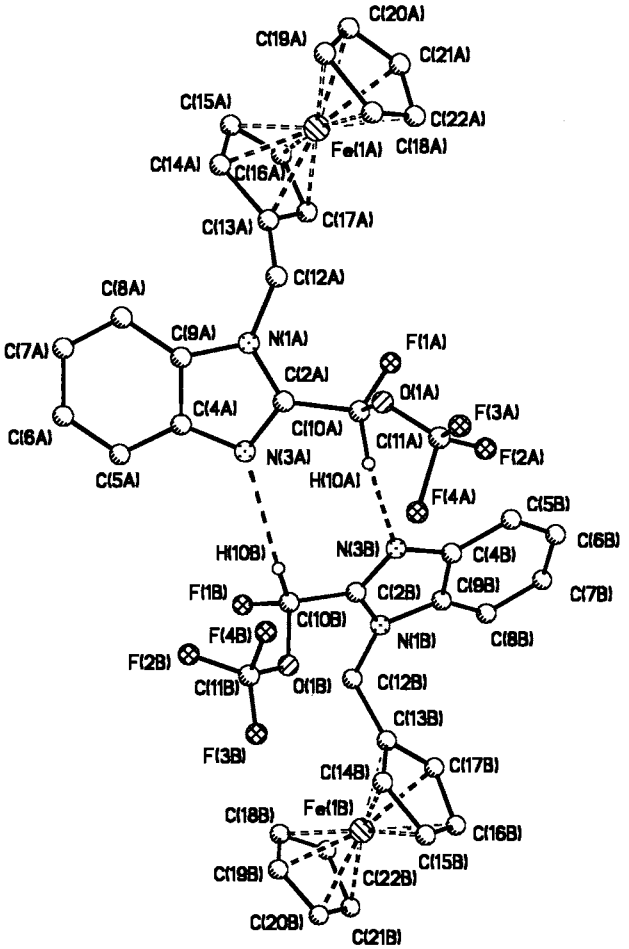


Fig. 3. Structure of molecules A and B linked by the C–H···N hydrogen bonds in crystal of 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)benzimidazole (**1**).

the conformational rigidity of the asymmetric centre environment, thus preventing chiral recognition of this centre's configuration. Only the introduction of the ferrocenylmethyl substituent into the imidazole cycle in the vicinity of the asymmetry centre of the fluorine containing substituent, makes the structure more rigid and facilitates the separation of enantiomers of both compounds **1** and **2**.

*2.3. X-ray study of 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)benz-imidazole (**1**)*

Molecule of **1** contains several H-bond acceptors and does not have any standard OH or NH donor groups. However, it does contain a CH group with increased acidity due to the fluorocontaining substituents. Therefore, one may have expected the formation of the CH···N hydrogen bonds in the crystal. Indeed, two independent molecules (A and B) in the crystal of **1** are linked into a dimer by hydrogen bonds of the C–H···N type formed by the N atoms of the benzimidazole system and the CH-groups of trifluoromethoxyfluoromethyl substituent (Fig. 3). The parameters of hydrogen bonds N(3A)···H(10B)–C(10B) and N(3B)···H(10A)–C(10A) are respectively: N···H 2.47(4) and 2.21(5) Å, C–H 0.92(4) and 1.12 (5) Å, N···C 3.322(5) and 3.293(5) Å; NHC angle 154(4) and 162(4)°.

It is probably worth mentioning an interesting case of pseudo-diastereomerism, observed in the crystal of **1**. As a matter of fact molecule **1** contains one true chirality centre, namely that at the asymmetric C(10) atom. However, once we assume the conformation of the ferrocenyl-methylene-benzimidazole moiety observed in the crystal to be frozen, then this moiety on its own becomes the source of an additional non-central chirality, and the crystal of **1** may in these terms be regarded as the racemic mixture composed of both enantiomers of the two diastereomers. Indeed, the molecules A and B linked by the above mentioned C–H···N bond and shown in Fig. 3 have actually the same chirality (*R*) of the asymmetric centre at C(10). On the other hand the ferrocenyl-methylene-benzimidazole fragments arrangement in one of the depicted molecules (say, A) is in fact the mirror image of such arrangement in the other molecule (B). If, instead of molecule B, we plot its centrosymmetric counterpart (obviously, also present in the centrosymmetric crystal of **1**) we would see that its ferrocenyl-methylene-benzimidazole moiety conformation is very similar to that observed in molecule A, whereas the chiralities of the centres at C(10) will naturally be opposite. This description may be corroborated by the torsion angles C(2)–N(1)–C(12)–C(13) and N(1)–C(12)–C(13)–C(14) which have similar absolute values but opposite signs (114.6, −108.0° and −75.5, 75.4° for A and B, respectively) and the dihedral angles formed by the mean planes of the benzimidazole (N(1)–N(3)–C(2)–C(4–9) (BzP), C(13–17) Cp-ring (CpP), and methylene bridge N(1)–C(12)–C(13) (MtP) which do not depend on chirality and show the differences in the corresponding pairs between the A and B molecules of no more than 6° (BzP/CpP 75.7 and 81.6, BzP/MtP 104.8 and 100.7, CpP/MtP 64.4 and 68.9° in A and B, respectively). The conformations of trifluoromethoxyfluoromethyl chains in both molecules are essentially similar (Fig. 4), torsion angles F(1)–C(10)–C(2)–N(1), O(1)–C(10)–C(2)–N(1), H(10)–C(10)–C(2)–N(1) and C(2)–C(10)–O(1)–C(11), being equal to −57.3(5), 60.3(5), −179.4(8) and 150.0(6)° (molecule A), and −47.3(5), 70.0(5), −168.7(9) and 148.6(6)° (molecule B), respectively.

Benzimidazole fragments in both molecules are almost ideally planar (within 0.017 and 0.015 Å for A and B, respectively). The C(12) atom in molecule B shows significant displacement from the benzimidazole

plane (0.156(6) Å), which is probably due to the repulsion of the methylene group from the F(1) atom of the trifluoromethoxyfluoromethyl substituent. Indeed, the C(12) atom is displaced from the plane in the opposite direction as compared to the displacement of the F(1) atom, and the F(1B)···H(12B) distance (2.47(5) Å) is equal or even still slightly shorter than the sum of the corresponding van der Waals radii (2.54 Å [12]. The above-mentioned difference in the overall conformations of the independent molecules and in relative disposition of substituents in the imidazole ring results in somewhat more favourable steric environment in molecule A as compared to that of B (the F(1)···H(12B) distance in A is equal to 2.67(6) Å), so that the out-of-plane distortion at the imidazole C(2A) *ipso*-atom becomes no longer necessary (the displacement of the C(12A) atom from the plane is equal to 0.025(5) Å).

The geometry of ferrocenyl groups in both molecules is unexceptional: Cp-rings are almost parallel, dihedral angles C(13–17)/C(18–22) are equal to 3.1(4) and 4.1 (4)° in the A and B molecules, respectively, the relative conformation of the rings in both cases is close to eclipsed, the torsion angles C(13)–X(1)–X(2)–C(18) being equal to −10.4 and −6.3° (X(1) and X(2) represent the centroids of the of the Cp rings C(12–17) and C(18–22), respectively).

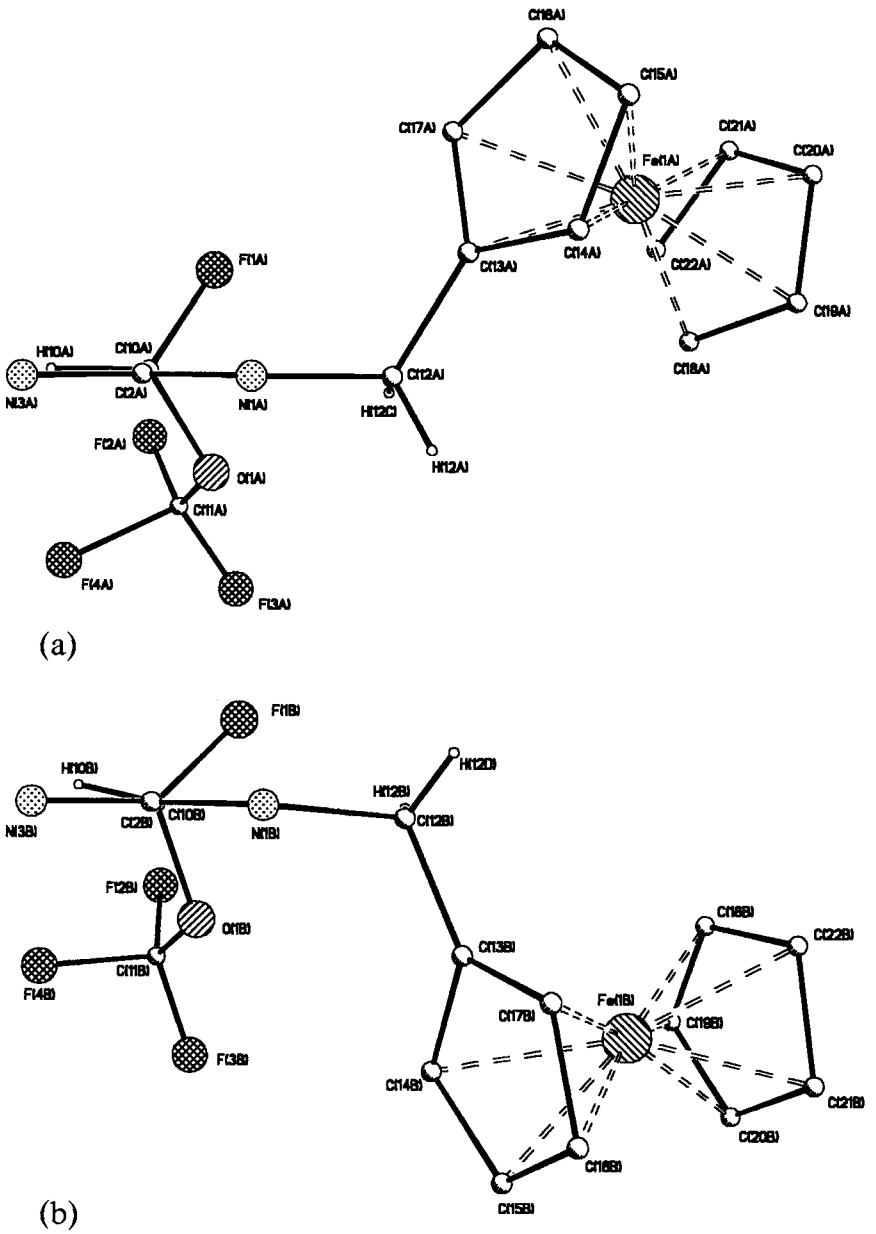


Fig. 4. View of the (benzimidazole)–CHF–CF_3 moieties in A (a) and B (b) molecules (projection along the C(2)–C(10) bond). The carbon atoms of the benzimidazole system and the hydrogen atoms of the ferrocenyl fragment have been omitted for clarity.

Table 2
The atomic coordinates (Å × 10^4, Å × 10^3 for H atoms) and equivalent isotropic (isotropic for H) displacement parameters (× 10^3 Å^2) for 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)benzimidazole (**1**)

Atom	*x*	*y*	*z*	U_{eq}/U_{iso}
Fe(1A)	1566(1)	2877(1)	2939(1)	56(1)
O(1A)	6250(3)	2369(3)	3638(2)	83(1)
N(1A)	5357(2)	468(3)	3593(2)	52(1)
N(3A)	7501(3)	−664(3)	3196(3)	66(1)
F(1A)	6023(3)	2030(3)	2238(2)	91(1)
F(2A)	7237(6)	3364(4)	2887(3)	160(2)
F(3A)	6335(6)	3818(5)	4285(4)	176(2)
F(4A)	8079(7)	2265(7)	3831(5)	209(3)
C(2A)	6513(3)	427(3)	3240(3)	59(1)
C(4A)	6962(3)	−1395(3)	3528(3)	57(1)
C(5A)	7560(4)	−2669(4)	3638(3)	72(1)
C(6A)	6795(4)	−3186(4)	3960(3)	75(1)
C(7A)	5452(4)	−2492(4)	4198(3)	69(1)
C(8A)	4851(4)	−1254(3)	4120(3)	57(1)
C(9A)	5631(3)	−718(3)	3779(2)	50(1)
C(10A)	6715(4)	1491(4)	2910(3)	68(1)
C(11A)	6822(11)	3048(9)	3621(5)	138(3)
C(12A)	4075(3)	1536(3)	3749(3)	53(1)
C(13A)	3225(3)	1476(3)	3169(3)	55(1)
C(14A)	2175(5)	1202(4)	3434(5)	83(2)
C(15A)	1611(6)	1267(4)	2706(6)	97(2)
C(16A)	2294(6)	1539(6)	1966(6)	117(3)
C(17A)	3294(4)	1685(6)	2225(3)	88(2)
C(18A)	1089(9)	4342(6)	3757(8)	129(3)
C(19A)	38(9)	4043(6)	3872(6)	137(3)
C(20A)	−271(6)	4186(5)	2993(7)	108(2)
C(21A)	468(9)	4521(7)	2449(7)	130(3)
C(22A)	1309(9)	4612(6)	2910(10)	134(3)
Fe(1B)	15790(1)	−3023(1)	809(1)	61(1)
O(1B)	11543(3)	−1683(3)	2942(2)	84(1)
N(1B)	11589(2)	−924(2)	957(2)	52(1)
N(3B)	9690(3)	449(3)	1763(2)	58(1)
F(1B)	10913(3)	−2634(3)	2077(2)	98(1)
F(2B)	10980(9)	−2664(7)	4017(4)	240(4)
F(3B)	12208(7)	−1923(8)	4185(4)	232(4)
F(4B)	10293(10)	−955(9)	4255(4)	265(4)
C(2B)	10632(3)	−660(3)	1702(3)	57(1)
C(4B)	10034(3)	982(3)	998(3)	52(1)
C(5B)	9411(4)	2162(4)	704(3)	65(1)
C(6B)	9972(4)	2451(4)	−89(3)	72(1)
C(7B)	11119(4)	1592(4)	−602(3)	71(1)
C(8B)	11767(4)	419(4)	−333(3)	60(1)
C(9B)	11210(3)	139(3)	481(2)	50(1)
C(10B)	10602(4)	−1508(4)	2434(3)	66(1)
C(11B)	11354(9)	−1882(9)	3806(5)	129(3)
C(12B)	12826(4)	−2031(3)	719(4)	61(1)
C(13B)	13921(3)	−1807(3)	822(3)	56(1)
C(14B)	14719 (5)	−1531 (6)	157 (4)	87 (2)
C(15B)	15590(5)	−1347(5)	549(7)	111(2)
C(16B)	15321(5)	−1438(5)	1447(6)	104(2)
C(17B)	14280 (4)	−1690 (5)	1639(4)	85 (2)
C(18B)	16159(17)	−4740(9)	710(18)	189(9)
C(19B)	16455(30)	−4548(17)	1411(22)	325(21)
C(20B)	17353(14)	−4254(13)	1225(15)	197(7)
C(21B)	17674(7)	−4185(8)	348(14)	155(4)
C(22B)	16827(21)	−4472(15)	−69(13)	237(12)
H(5A)	845(5)	−315(4)	348(3)	74(12)
H(6A)	729(4)	−420(4)	408(3)	85(14)
H(7A)	494(4)	−293(4)	443(3)	66(11)
H(8A)	406(4)	−83(4)	427(3)	65(12)
H(10A)	778(5)	111(4)	266(3)	87(14)
H(12A)	374(5)	165(4)	433(4)	85(15)
H(12C)	420(4)	225(4)	367(2)	52(9)
H(14A)	192(6)	127(6)	403(4)	115(24)
H(15A)	86(5)	110(4)	267(3)	81(13)
H(16A)	213(4)	151(4)	154(3)	59(12)
H(17A)	378(6)	208(5)	201(4)	105(20)
H(18A)	159(9)	453(8)	416(7)	195(35)
H(19A)	−45(9)	386(8)	441(7)	198(38)
H(20A)	−91(14)	391(12)	271(10)	342(62)
H(21A)	91(6)	414(6)	166(5)	127(22)
H(22A)	229(11)	436(9)	256(8)	219(47)
H(5B)	884(5)	264(4)	97(3)	74(15)
H(6B)	947(4)	323(4)	−28(3)	73(12)
H(7B)	1135(5)	175(5)	−112(4)	93(17)
H(8B)	1238(4)	−11(4)	−65(3)	69(13)
H(10B)	980(4)	−120(4)	281(3)	66(11)
H(12D)	1291(4)	−227(4)	16(3)	64(12)
H(12B)	1282(4)	−261(4)	110(3)	58(11)
H(14B)	1489(3)	−205(3)	−18(2)	27(9)
H(15B)	1644(6)	−106(5)	9(4)	131(20)
H(16B)	1605(7)	−149(6)	198(5)	139(23)
H(17B)	1384(6)	−159(5)	222(4)	108(19)
H(18B)	1513(15)	−461(12)	87(10)	295(71)
H(19B)	1600(4)	−424(4)	198(3)	49(11)
H(20B)	1830(11)	−413(9)	172(7)	207(39)
H(21B)	1826(12)	−374(10)	−11(8)	267(52)
H(22B)	1673(7)	−452(6)	−36(5)	88(23)

3. Experimental

IR spectra were recorded on a UR-20 spectrometer (Karl Zeiss), mass spectra were registered on a Kratos MS-890 mass spectrometer at the energy of ionizing electrons equal to 70 eV. ^{1}H-NMR spectra were obtained on a Bruker WP-200-SY spectrometer with operating frequency of 200.13 MHz at room temperature.

*3.1. Preparation of the initial ferrocenylmethanol (**10**) and 1-ferrocenylethanol (**11**)*

Ferrocenylmethanol (**10**) was synthesized according to the known procedure [13] and recrystallized from hexane. M.p. 81°C. Lit. [14] m.p. 81°C.

1-Ferrocenylethanol (**11**) was prepared according to the modified [6] procedure of Arimoto and Haven [13], described below. The synthesis was carried out under an argon atmosphere. The solution of 22.80 g (0.10 mol) of acetylferrocene in 400 ml of absolute diethyl ether freshly distilled over $LiAlH_4$ was added under stirring to 1.90 g (0.05 mol) of lithium aluminium hydride in 120 ml of absolute ether within 10 min at a temperature not higher than 15–20°C. The colour of the reaction mixture thus changed turning from orange to yellow. The contents of the reaction flask were

chilled to 0–5°C, and a saturated aqueous solution of 26.80 g of ammonium chloride was added. After 5 min stirring at 0–5°C the organic layer was siphoned off, washed with cold water (80 ml) to pH 7 and dried by sodium sulphate. After removal of ether 21.28 g of yellow needle-shaped crystals of ferrocenylethanol were obtained in 93% yield. M.p. 74–75°C. Lit. [13] m.p. 73–75°C (after recrystallization from hexane). ^{1}H-NMR (C_6D_6, δ): 1.31 (d, 3H, CH_3); 1.87 (s, 1H, OH); 3.97(t, 2H, C_5H_4); 4.00 (s, 5H, C_5H_5); 4.07 (q, 1H, C_5H_4), 4.13 (q, 1H, C_5H_4), 4.50 (m, 1H, CH). IR spectrum (KBr pellet, cm^{-1}): 3350–3015 (O–H), 1410, 1104, 1000, 810 (ferrocenyl moiety).

3.2. Synthesis of ferrocenylalkyl polifluoro benzimidazoles **1–5**

3.2.1. General procedure

To a mixture of 6.0 mmol of ferrocenylmethanol or 1-ferrocenylethanol and 6.00 mmol of the corresponding polyfluoroalkyl benzimidazoles (**6**–**9**) in 6.0 ml of methylene dichloride, 1.08 ml of 45% aqueous solution of fluoroboric acid was added with vigorous stirring. Agitation was continued for 5 min, then 15 ml of diethyl ether, the same amount of cold water, and 5–10 mg of ascorbic acid were added to the reaction flask. After vigorous shaking of the mixture the organic yellow-coloured solution was separated, washed with cold water (5×15 ml), the solvent was removed and the residue was dried over calcium chloride.

3.2.2. 1-Ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)benzimidazole (**1**)

Prepared from ferrocenylmethanol (**10**) and 2-(trifluoromethoxyfluoromethyl)benzimidazole (**6**) according to the general procedure. Yield 93%. R_f 0.29 (benzene). M.p. 125–127°C. Anal.: Found C, 56.03; H, 3.72; F, 16.95; N, 6.16%. Calc. for $C_{20}H_{16}F_4FeN_2O$: C, 56.03; H, 3.73; F, 17.58; N, 6.48%. ^{1}H-NMR (acetone-d_6, TMS): 4.15 (s, 2H, C_5H_4), 4.28 (s, 5H, Cp), 4.55(s, 2H, C_5H_4), 5.50 (s, 2H, CH_2), 7.35, 7.75 (m, 4H, Ph), 7.60 (s, 1H, CHF). MS, m/z: 432 [M^+]. IR spectrum (KBr pellet, cm^{-1}): 3108, 3007, 1540, 1479, 1438, 1240, 1191, 1110, 1018, 826.

3.2.3. 1-Ferrocenylmethyl-2-(α-hydrotetrafluoroethyl)benzimidazole (**2**)

The title compound was prepared from ferrocenylmethanol (**10**) and 2-(α-hydrotetrafluoroethyl) benzimidazole (**7**) according to the general procedure. Yield 100%. R_f 0.26 (hexane/diethylether 2:1). Anal.: Found C, 57.84; H, 4.12; Fe, 13.45; N, 6.37%. Calc. for $C_{20}H_{16}F_4FeN_2$: Ñ, 57.72; H, 3.87; Fe, 13.42; N, 6.73%. ^{1}H-NMR (acetone-d_6, TMS): 4.16 (s, 2H, C_5H_4), 4.23 (s, 5H, Cp), 4.51 (s, 2H, C_5H_4), 5.56 (m, 2H, CH_2), 6.69, 6.91 (m,1H, CHF), 7.38, 7.80 (m, 4H, Ph). MS, m/z: 416 [M^+]. IR spectrum (KBr pellet, cm^{-1}): 3110, 2935, 2880, 1478, 1440, 1320, 1282, 1218, 1193, 1130, 1056, 914, 876, 836.

3.2.4. 1-Ferrocenylmethyl-2-(β-hydrotetrafluoroethyl)benzimidazole (**3**)

Compound **3** was prepared from ferrocenylmethanol (**10**) and 2-(β-hydrofluoroethyl)benzimidazole (**8**) according to the general procedure. Yield 85%. R_f 0.47 (benzene). Anal.: Found C, 57.65; H, 3.92; F, 17.95; Fe, 13.00; N, 6.51%. Calc. for $C_{20}H_{16}F_4FeN_2$: C, 57.72; H, 3.87; F, 18.26; Fe, 13.42; N, 6.73%. ^{1}H-NMR (acetone-d_6): 4.16 (s, 2H, C_5H_4), 4.28 (s, 5H, Cp), 4.50 (s, 2H, C_5H_4), 5.54 (s, 2H, CH_2), 6.81, 7.08 (t, 1H, CHF_2), 7.42 (m, 2H, Ph), 7.80 (d, 1H, Ph), 7.87 (d, 1H, Ph). IR spectrum (KBr pellet, cm^{-1}): 3110, 2940, 2870, 1480, 1440, 1340, 1260, 1230, 1217, 1120, 1040, 944, 840, 820.

3.2.5. 1-Ferrocenylmethyl-2-trifluoromethylbenzimidazole (**4**)

Compound **4** was prepared from ferrocenylmethanol (**10**) and 2-trifluoromethyl-benzimidazole (**9**) according to the general procedure. Yield 96%. R_f 0.32 (hexane/diethylether 2:1). Anal.: Found C, 59.43; H, 3.87; Fe, 14.18; N, 7.19%. Calc. for $C_{19}H_{15}F_3FeN_2$: C, 59.40; H, 3.94; Fe, 14.54; N, 7.29%. ^{1}H-NMR (acetone-d_6, TMS):4.18 (t, 2H, C_5H_4), 4.27 (s, 5H, Cp), 4.50 (t, 2H, C_5H_4), 5.50 (s, 2H, CH_2), 7.41 (m, 2H, Ph), 7.82 (m, 2H, Ph). MS, m/z: 384 [M^+]. IR spectrum (KBr pellet, cm^{-1}): 3115, 2940, 2880, 1480, 1432, 1330, 1280, 1240, 1192, 1145, 1125, 1096, 1050,1038, 1010, 958, 930, 840.

3.2.6. 1-(α-Ethylferrocenyl)-2-(α′-hydrotetrafluoroethyl)benzimidazole (**5**)

The title compound was prepared as an orange oil from 1-ferrocenylethanol (**11**) and 2-(α-hydrotetrafluoroethyl)benzimidazole (**7**) according to the general procedure. The crystal product was obtained after recrystallyzation from hexane, yield 73%. M.p. 121–124°C. R_f 0.26 (hexane/diethylether 2:1). Anal.: Found C, 58.43; H, 4.23; Fe, 12.96; N, 6.40%. Calc. for $C_{21}H_{18}F_4FeN_2$: C, 58.63; H, 4.22; Fe, 12.98; N, 6.51%. ^{1}H-NMR (acetone-d_6, TMS): 1.92-2.06 (m, 3H, CH_3), 4.00–4.37 (m, 9H, 2Cp), 4,77 (s_{br}, 1H, CH), 6.42–6.94 (m, 1H, CHF), 7.07–7.75 (m, 4H, Ph). MS, m/z: 430 [M^+]. IR spectrum (KBr pellet, cm^{-1}): 3115, 3000, 2970, 1790, 1675, 1625, 1600, 1525, 1470, 1425, 1395, 1375, 1350, 1340, 1305, 1292, 1215, 1165, 1120, 1080, 1020, 942, 910.

Table 3
Bond lengths (Å) and selected angles (°) in 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)benzimidazole (**1**)

	A	B		A	B
Bond lengths					
Fe(1)–C(16)	2.004(5)	2.006(5)	F(4)–C(11)	1.451(12)	1.330(11)
Fe(1)–C(14)	2.013(5)	2.020(4)	C(2)–C(10)	1.494(6)	1.490(6)
Fe(1)–C(17)	2.012(4)	2.034(5)	C(4)–C(9)	1.393(5)	1.399(5)
Fe(1)–C(15)	2.017(5)	2.006(5)	C(4)–C(5)	1.416(6)	1.394(5)
Fe(1)–C(18)	2.022(6)	1.970(9)	C(5)–C(6)	1.351(7)	1.363(7)
Fe(1)–C(13)	2.022(3)	2.033(3)	C(6)–C(7)	1.405(6)	1.384(7)
Fe(1)–C(22)	2.025(6)	2.001(9)	C(7)–C(8)	1.370(6)	1.378(6)
Fe(1)–C(20)	2.027(5)	1.984(8)	C(8)–C(9)	1.390(5)	1.380(6)
Fe(1)–C(19)	2.029(6)	1.935(11)	C(12)–C(13)	1.490(5)	1.498(6)
Fe(1)–C(21)	2.041(6)	2.027(6)	C(13)–C(17)	1.417(7)	1.408(6)
O(1)–C(11)	1.306(7)	1.299(7)	C(13)–C(14)	1.430(6)	1.385(7)
O(1)–C(10)	1.410(5)	1.411(5)	C(14)–C(15)	1.371(8)	1.401(9)
N(1)–C(2)	1.360(4)	1.359(5)	C(15)–C(16)	1.369(10)	1.330(10)
N(1)–C(9)	1.377(5)	1.391(4)	C(16)–C(17)	1.418(8)	1.395(8)
N(1)–C(12)	1.472(4)	1.469(4)	C(18)–C(22)	1.303(12)	1.40(3)
N(3)–C(2)	1.314(5)	1.305(4)	C(18)–C(19)	1.448(13)	1.24(4)
N(3)–C(4)	1.363(5)	1.384(5)	C(19)–C(20)	1.416(12)	1.27(3)
F(1)–C(10)	1.377(5)	1.372(5)	C(20)–C(21)	1.283(11)	1.30(2)
F(2)–C(11)	1.239(7)	1.250(9)	C(21)–C(22)	1.374(13)	1.47(2)
F(3)–C(11)	1.258(8)	1.244(8)			
Bond angles					
C(11)–O(1)–C(10)	116.7(5)	119.5(5)	F(1)–C(10)–C(2)	109.8(3)	111.5(4)
C(2)–N(1)–C(9)	105.4(3)	105.2(3)	O(1)–C(10)–C(2)	109.2(3)	108.3(3)
C(2)–N(1)–C(12)	128.3(3)	129.2(3)	F(2)–C(11)–F(3)	116.8(7)	116.5(8)
C(9)–N(1)–C(12)	126.4(3)	125.4(3)	F(2)–C(11)–O(1)	120.6(7)	116.1(8)
C(2)–N(3)–C(4)	104.0(3)	104.3(3)	F(3)–C(11)–O(1)	112.5(6)	112.8(6)
N(3)–C(2)–N(1)	114.3(3)	115.0(3)	F(2)–C(11)–F(4)	95.2(8)	95.2(8)
N(3)–C(2)–C(10)	120.1(3)	119.4(3)	F(3)–C(11)–F(4)	100.6(7)	103.2(9)
N(3)–C(4)–C(9)	110.9(3)	110.0(3)	O(1)–C(11)–F(4)	106.4(7)	110.6(8)
N(3)–C(4)–C(5)	129.5(3)	130.5(3)	C(17)–C(13)–C(14)	105.3(4)	103.8(5)
N(1)–C(2)–C(10)	125.6(3)	125.7(3)	C(17)–C(13)–C(12)	126.6(4)	128.5(4)
N(1)–C(9)–C(4)	105.5(3)	105.6(3)	C(14)–C(13)–C(12)	128.1(4)	127.4(4)
N(1)–C(9)–C(8)	132.3(3)	132.1(3)	C(15)–C(14)–C(13)	110.5(6)	109.8(5)
N(1)–C(12)–C(13)	112.8(3)	111.4(3)	C(16)–C(15)–C(14)	107.2(5)	107.9(5)
C(9)–C(4)–C(5)	119.6(4)	119.5(4)	C(15)–C(16)–C(17)	110.1(6)	108.3(5)
C(6)–C(5)–C(4)	117.8(4)	116.4(4)	C(13)–C(17)–C(16)	106.8(6)	110.1(6)
C(5)–C(6)–C(7)	121.8(4)	121.1(4)	C(22)–C(18)–C(19)	107.6(8)	111(2)
C(8)–C(7)–C(6)	121.6(4)	122.3(4)	C(20)–C(19)–C(18)	103.2(7)	112(3)
C(7)–C(8)–C(9)	116.9(3)	118.4(4)	C(21)–C(20)–C(19)	109.8(8)	111(2)
C(8)–C(9)–C(4)	122.2(3)	122.3(3)	C(20)–C(21)–C(22)	109.4(9)	106(2)
F(1)–C(10)–O(1)	107.5(3)	106.8(3)	C(18)–C(22)–C(21)	109.9(9)	100(2)

3.3. Chromatographic separation of enantiomers

Following chiral columns (250 × 4.6 mm, 5 μm) were used: β-cyclodextrin (Cyclobond I 2000), γ-cyclodextrin (Cyclobond II 2000), hydroxypropyl-derivatized-β-cyclodextrin (Cyclobond I 2000 RSP), acetyl-derivatized β-cyclodextrin (Cyclobond I 2000 Ac), *R*-naphthylcarbamate-derivatized-β-cyclodextrin (Cyclobond I 2000 RN), (*S*)-naphthylcarbamate-derivatized-β-cyclodextrin (Cyclobond I 2000 SN), vancomycin (Chirobiotic V), teicoplanin (Chirobiotic T).

The HPLC system, Bruker LC 31, with a UV 254 detector was operated at a flow rate of 1.0 ml min^{-1} and ambient temperature.

3.4. X-ray study of 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)-benzimidazole (1)

Crystal data for 1-ferrocenylmethyl-2-(trifluoromethoxyfluoromethyl)-benzimidazole (**1**), $C_{20}H_{16}F_4FeN_2O$ ($M = 432.20$) light-yellow triclinic crystals, space group $P\bar{1}$, at 20°C $a = 11.981(4)$ Å, $b = 12.398(2)$ Å, $c = 14.962(4)$ Å, $\alpha = 87.32(2)°$, $\beta = 78.70(2)°$, $\gamma = 62.31(2)°$, $V = 1927.3(9)$ $Å^3$, $D_{calc.} = 1.490$ g cm^{-3} for $Z = 4$.

The unit cell parameters and the intensities of 8258 reflections were measured with the automatic CAD4 Enraf-Nonius diffractometer at 20°C using graphite-monochromated Mo–K_α radiation ($\lambda = 0.071073$ Å,

$\theta/2\theta$ scan technique, $\theta_{max} = 26°$, no absorption correction was applied, $\mu(Mo-K_\alpha) = 8.32\ cm^{-1}$). The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation. The H-atoms were located in the difference Fourier synthesis and included in the refinement with isotropic thermal parameters. Final discrepancy factors are $R_1 = 0.0555$ (on F for 5466 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1838$ (on F^2 for all 7425 independent reflections, which were used in the refinement of 633 parameters). All calculations were carried out on IBM PC with the SHELXTL PLUS 5 [15] program.

The atomic coordinates are given in Table 2, bond lengths and angles in Table 3.

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