Synthesis of New 2-Ferrocenyl-5-fluoro-6-(4-substituted-1-piperazinyl)-1*H*-benzimidazoles of Potential Biological Interest

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New substituted 2-ferrocenylbenzimidazole derivatives are prepared by the oxidation of corresponding Schiff's bases *in situ*, generated from corresponding 1,2-diamino-4-fluoro-5-(1-piperazinyl)benzenes and 2-ferrocenecarboxaldehyde using nitrobenzene.

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Introduction.

Benzimidazoles are a well-known class of truly low-dose broad-spectrum anthelmintics with a high therapeutic index [1]. Several derivatives of this family of compounds are also anti-tumor agents [2], while others show activity against fungi [3].

A limited number of benzimidazoles carrying fluorine or 1-piperazinyl moieties as ring appendages are known from the literature. Recently, 4-fluoro-5-(4-piperazinyl)-1,2-diaminobenzene [4] has proven to be a valuable intermediate for the synthesis of various benzimidazole derivatives of biological interest, *e.g.*, as anticancer agents [5], tyrosine and serine/threonine kinase inhibitors [6], nociceptin receptor antagonists [7] or bactericides [8].

Moreover, introducing various metallocenes as substituents into the structure of some anti-tumor agents has led to a breakthrough in the treatment of testicular cancer [9]. Tamoxifen and its metabolite hydroxytamoxifen most widely used in cancer hormonetherapy are well known to be selective estrogen receptor modulators (SERMs) [10]. Thus, modification of this anti-cancer drug by replacing the aromatic phenyl residue in the β-position of tamoxifen by an aromatic ferrocenyl unit lead to a new and more effective treatment for breast cancer [11].

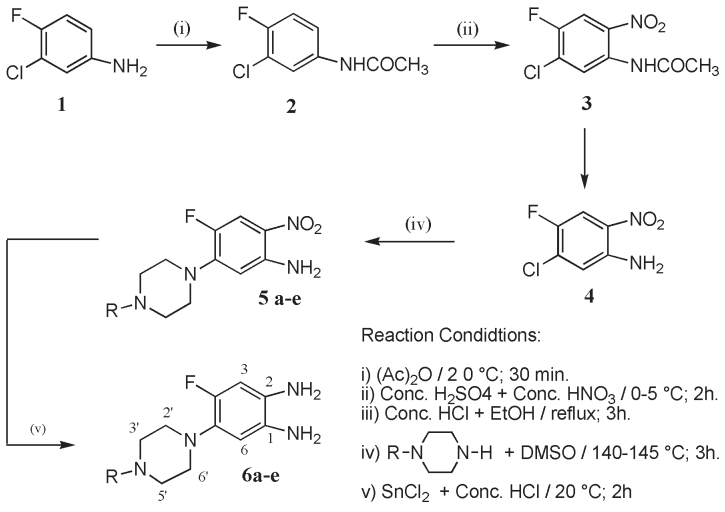
Recently, the synthesis and the biological properties of some 2-aryl-5-fluoro-6-(4-methyl-1-piperazinyl)benzimidazoles were reported [4a]. To further illustrate the biological activity of the substituted benzimidazole derivatives, the synthesis of some new 2-ferrocenyl-5-fluoro-6-(4-substituted-1-piperazinyl)benzimidazoles (**7a-e**, Scheme 2) is presented in this paper.

Results and Discussion.

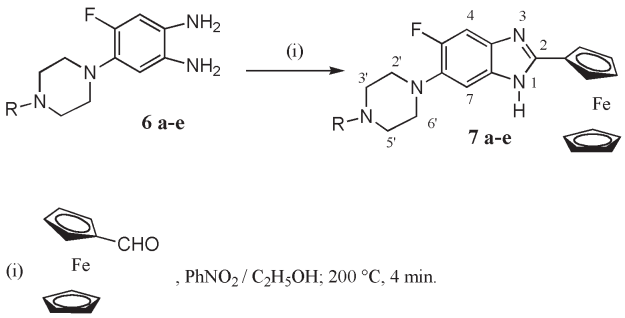
The key intermediates 1,2-diamino-4-fluoro-5-(1-pepirazinyl)benzene (**6a-e)** were synthesized from the commercially available 3-chloro-4-fluoroaniline by a sequence of steps involving acetylation, nitration, deacetylation, piperazinylation and stannous chloride reduction (Scheme 1). Physical and analytical data for the 2-nitroaniline derivatives **5a-e** and *o*-phenylenediamine derivatives **6a-e** are collected in Tables 1 and 2, respectively.

The crude 1,2-diaminobenzenes **6a-e**, were used immediately without further purification for the next condensation step, as these free diamines darken upon exposure to light or air.

Scheme 1



Scheme 2



The target compounds were prepared *via* the reaction of ferrocenylcarboxaldehyde with the corresponding 1,2-diamino-4-fluoro-5-(1-pepirazinyl)benzenes **6a-e** using nitrobenzene as a solvent and oxidant [4] to yield the corresponding 2-ferrocenyl benzimidoles **7a-e** in 81-91 % yield (Table 3).

According to reference [6] the intermediates are supposed to be Schiff's base derivatives which cyclize to yield the target compounds by the action of the oxidizing agent. However, the Schiff's bases were not isolated and were used immediately for the next oxidation step.

A general characterization of the target compounds **7a-e** was accomplished using ^{1}H NMR spectroscopy. A salient feature in the spectra of these compounds is the appearance of a characteristic group of signals corresponding to the ferrocenyl residue: five proton singlets are assigned to the unsubstituted cyclopentadienyl ring (δ 4.2 ppm) and two broad singlets to the monosubstituted ring (δ 4.4, 4.8 ppm).

The mass spectra of these compounds showed the correct molecular ions with relative high abundance. Physical and analytical data for the 2-ferrocenylbenzimidazole derivatives **7a-e** are collected in Table 3.

Preliminary Biological Tests.

The hydrochloride salts of the new benzimidazole derivatives (**7a-e**) were tested against four different pathogenic *Candida* species. There is evidence that **7a** and **7c** have potency comparable to that of azole-based (Miconazole and Ketonazole) antifungal agents. The minimum

Table 1

Experimental and Analytical Data of Compounds **5a-e**

Compound	Yield (%)	Mp[°C]	Molecular Formula	[M]+	Analysis (calcd./found)		
					C%	H%	N%
5a	95	152-153*	$C_{11}H_{15}FN_4O_2$	254	51.96	5.95	22.04
					51.91	5.92	21.97
5b	88	180-181	$C_{16}H_{17}FN_4O_2$	316	60.75	5.42	17.71
					60.44	5.26	17.69
5c	86	175-176	$C_{16}H_{16}ClFN_4O_2$	350	54.78	4.60	15.97
					54.63	4.51	15.80
5d	91	187-188	$C_{17}H_{19}FN_4O_3$	346	58.95	5.53	16.18
					58.81	5.47	16.07
5e	81	217-218	$C_{16}H_{16}F_2N_4O_2$	334	57.48	4.82	16.76
					57.73	4.77	16.66

* Lit. [4] m.p. 152-153.

Table 2

Experimental and Analytical Data of Compounds **6a-e**

Compound	Yield (%)	Mp[°C]	Molecular Formula	[M]+	Analysis (calcd./found)		
					C%	H%	N%
6a	82	96-97*	$C_{11}H_{17}FN_4$	224	58.91	7.64	24.98
					58.83	7.61	24.92
6b	81	117-118	$C_{16}H_{19}FN_4$	286	67.11	6.69	19.57
					67.14	6.66	19.47
6c	73	128-130	$C_{16}H_{18}ClFN_4$	320	59.91	5.66	17.47
					59.81	5.64	17.33
6d	68	155-156	$C_{17}H_{21}FN_4O$	316	64.54	6.69	17.71
					64.41	6.61	17.63
6e	72	128-129	$C_{16}H_{18}F_2N_4$	304	63.14	5.96	18.41
					63.05	5.91	18.33

* Lit. [4] m.p. 95-96.

Table 3

Experimental and Analytical Data of Compounds **7a-e**

Compound	Yield (%)	Mp[°C]	Molecular Formula	[M]+	Analysis (calcd./found) C%	H%	N%
7a	91	>300	$C_{22}H_{23}FFeN_4$	418	63.17	5.54	13.39
					63.21	5.42	13.37
7b	84	188-189	$C_{27}H_{25}FFeN_4$	480	67.51	5.25	11.66
					67.44	5.16	11.71
7c	82	>300	$C_{27}H_{24}ClFFeN_4$	514	62.99	4.70	10.88
					62.93	4.59	10.80
7d	87	>300	$C_{28}H_{27}FFeN_4O$	510	65.89	5.33	10.98
					65.73	5.20	10.88
7e	82	>300	$C_{27}H_{24}F_2FeN_4$	498	65.07	4.85	11.24
					64.94	4.79	11.13

Table 4

Experimental and Analytical Data of Compounds **7a-e** Hydrochloride Salts

Compound	Yield (%)	Mp[°C]	Molecular Formula	[M]+	Analysis (calcd./found) C%	H%	N%
7a•HCl	91	220-222	$C_{22}H_{24}FFeN_4Cl$	455	58.11	5.32	12.32
					58.02	5.25	12.30
7b•HCl	84	>300	$C_{27}H_{26}FFeN_4Cl$	517	62.75	5.07	10.84
					62.69	5.00	10.76
7c•HCl	82	212-214	$C_{27}H_{25}Cl_2FFeN_4$	551	58.83	4.57	10.16
					58.77	4.50	10.08
7d•HCl	87	256-258	$C_{28}H_{28}FFeN_4OCl$	547	61.50	5.16	10.25
					65.44	5.09	10.18
7e•HCl	82	>300	$C_{27}H_{25}F_2FeN_4Cl$	535	60.64	4.71	10.48
					60.60	4.66	10.41

inhibitory concentration (MIC) of the hydrochloride salt of **7a** and **7c** to *C. glabrate* were (30 μg•ml^{-1}) using *miconazolenitrate* as a positive control (MIC 30 μg•ml^{-1})

Activity tests of the newly synthesized compounds against various tumor cell lines and pathogenic organisms are under way.

Conclusion.

The new 2-ferrocenyl benzimidazole derivatives **7a-e,** described herein, represent interesting targets for further biological evaluation and which may be used as electron reservoir systems and in fields such as electro catalysis.

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EXPERIMENTAL

IR spectra were acquired on Nicolet-MAGNA-IR-560 spectrophotometer. ^{1}H NMR spectra are reordered on a Bruker AM 250 FT spectrophotometer operating at 300 K in $CDCl_3$ using TMS as internal standard. Mass spectra (electron impact) were obtained on a Varian CH-7 spectrophotometer at 70 eV with an ion source temperature of 200 °C. Melting points were determined on an electrothermal melting temperature apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer elemental analyzer, model 240. Ferrocenecarbaldehyde and 3-chloro-4-fluoroaniline were purchased from Aldrich and used without further purification.

General Procedure for the Synthesis of Compounds **5a-e**.

A stirred solution of 5-chloro-4-fluoro-2-nitroaniline (**4**) (20 mmol) and N-substituted piperazine (60 mmol) in dimethylsulfoxide (10 ml) was refluxed for 2-3 hours at 140-145 °C, after which TLC analysis showed the starting material was no longer present. The reaction mixture was then cooled to room temperature and added to 50 ml water. The resulting solid was collected, washed exclusively with water, dried and crystallized from ethanol to give the title compounds.

4-Fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (**5a**).

This compound has mp 152-153 °C (Lit. [4] mp 152-153 °C).

4-Fluoro-5-(4-phenyl-1-piperazinyl)-2-nitroaniline (**5b**).

The following spectral data were recorded for compound **5b**: ^{1}H NMR: δ: 7.78 (d, *J* = 14.0 Hz, *H*-3), 6.77-7.22 (m, 5H, C_6H_5), 6.00 (d, *J* = 7.5 Hz, *H*-6), 3.30 (bt, *J* = 3.2 Hz, 4H, C2'-*H*, C6'-*H*), 3.21 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*), 5.4, 6.1 (bs, bs, 1H, 1H, NH_2).

4-Fluoro-5-[4-(4-chlorophenyl)-1-piperazinyl]-2-nitroaniline (**5c**).

The following spectral data were recorded for compound **5c**: ^{1}H NMR: δ: 7.80 (d, *J* = 15.0 Hz, *H*-3), 7.24 (d, *J* = 7.5 Hz, 2H, C_6H_4Cl), 6.87 (d, *J* = 7.5 Hz, 2H, C_6H_4Cl), 6.10 (d, *J* = 7.5 Hz, *H*-6), 3.38 (bt, *J* = 3.0 Hz, 4H, C2'-*H*, C6'-*H*), 3.10 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*), 5.10 (bs, 2H, NH_2).

4-Fluoro-5-[4-(4-methoxyphenyl)-1-piperazinyl]-2-nitroaniline (**5d**).

The following spectral data were recorded for compound **5d**: ^{1}H NMR: δ: 7.73 (d, *J* = 14.2 Hz, *H*-3), 6.87 (d, *J* = 7.5 Hz, 2H, $C_6H_4OCH_3$), 6.84 (d, *J* = 7.5 Hz, 2H, $C_6H_4OCH_3$), 6.06 (d, *J* = 7.5 Hz, *H*-6), 3.72 (s, 3H, $C_6H_4OCH_3$), 3.32 (bt, *J* = 3.2 Hz, 4H, C2'-*H*,C6'-*H*), 3.15 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*), 5.7, 4.5 (bs, bs, 1H, 1H, NH_2).

4-Fluoro-5-[4-(4-fluorophenyl)-1-piperazinyl]-2-nitroaniline (**5e**).

The following spectral data were recorded for compound **5e**: ^{1}H NMR: δ: 7.79 (d, *J* = 14.2 Hz, *H*-3), 6.88-6.99 (m, 4H, C_6H_4F), 6.12 (d, *J* = 7.5 Hz, *H*-6), 3.38 (bt, *J* = 3.2 Hz, 4H, C2'-*H*, C6'-*H*), 3.24 (bt, 4H, *J* = 3.0 Hz, 4H, C3'-*H* and C5'-*H*), 5.4, 4.9 (bs, bs, 1H, 1H, NH_2).

General Procedure for the Synthesis of Compounds **6a-e**.

To a solution of **5** (10 mmol) in conc. HCl (50 ml) was slowly added stannous chloride (11.22 g, 60 mmol) at room temperature during ten minutes. Stirring was continued for additional two hours. The reaction mixture was then cooled (ice-water bath) and treated gradually with a concentrated solution of sodium hydroxide (40 %) until the solution is strongly alkaline (pH 12-13). The resulting aqueous mixture was extracted with chloroform (3 X 50 ml). The organic layer was separated, filtered and concentrated *in vacuo*. The resulting solid was collected by suction filtration and crystallized from chloroform.

1,2-Diamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (**6a**).

This compound has mp 96-97 °C (Lit. [4] mp 95-96 °C).

1,2-Diamino-4-fluoro-5-(4-phenyl-1-piperazinyl)benzene (**6b**).

The following spectral data were recorded for compound **6b**: ^{1}H NMR: δ: 6.877.26 (m, 5*H*, C_6H_5), 6.52 (d, *J* = 14.0 Hz, 1H, *H*-3), 6.41 (d, *J* = 7.5 Hz, 1H, *H*-6), 3.28 (bt, *J* = 3.0 Hz, 4H, C2'-*H*, C6'-*H*), 3.14 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*), 4.7 (bs, 2H, NH_2).

1,2-Diamino-4-fluoro-5-[4-(4-chlororphenyl)-1-piperazinyl]benzene (**6c**).

The following spectral data were recorded for compound **6c**: ^{1}H NMR: δ: 6.95 (d, *J* = 7.5 Hz, 2*H*, C_6H_4Cl), 6.86 (d, *J* = 7.5 Hz, 2*H*, C_6H_4Cl), 6.49 (d, *J* = 14.8 Hz, 1H, *H*-3), 6.42 (d, *J* = 7.4 Hz, 1H, *H*-6), 3.31 (bt, *J* = 3.2 Hz, 4H, C2'-*H*, C6'-*H*), 3.22 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*), 5.3 (bs, 2H, NH_2).

1,2-Diamino-4-fluoro-5-[4-(4-methoxyphenyl)-1-piperazinyl]-benzene (**6d**).

The following spectral data were recorded for compound **6d**: ^{1}H NMR: δ: 7.03 (d, *J* = 7.5 Hz, 2H, $C_6H_4OCH_3$), 6.89 (d, *J* = 7.5 Hz, 2*H*, $C_6H_4OCH_3$), 6.55 (d, *J* = 15.0 Hz, 1H, *H*-3), 6.46 (d, *J* = 7.5 Hz, 1H, *H*-6), 3.77 (s, 3H, $C_6H_4OCH_3$), 3.24 (bt, *J* = 3.0 Hz, 4H, C2'-*H*, C6'-*H*), 3.12 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*), 4.3 (bs, 2H, NH_2).

1,2-Diamino-4-fluoro-5-[4-(4-fluoroyphenyl)-1-piperazinyl]benzene (**6e**).

The following spectral data were recorded for compound **6e**: ^{1}H NMR: δ: 6.89-7.27 (m, 4H, C_6H_4F), 6.49 (d, *J* = 15.0 Hz, 1H, *H*-3), 6.42 (d, *J* = 7.5 Hz, 1H, *H*-6), 3.26 (bt, *J* = 3.0 Hz, 4H, C2'-*H*, C6'-*H*), 3.13 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*), 4.9 (bs, 2H, NH_2).

General Procedure for the Synthesis of Compounds **7a-e**.

A solution of the particular 1,2-diamino-4-fluoro-5-(4-substituted-1-piperazinyl)benzenes **6a-e** (1 mmol) and ferrocenylcarboxaldehyde (3 mmol) in (15) ml of ethanol/nitrobenzene (1/3) was refluxed for 1 h, then most of the ethanol was distilled off, the temperature elevated to about 200-205 °C and maintained for 5 min. The reaction mixture was cooled and allowed to stand over night at room temperature. Diethyl ether (20 ml) was then added and the reaction mixture was allowed to stand for 1 h. The resulting precipitate was collected and crystallized from diethyl ether to give the title compounds.

2-Ferrocenyl-5-fluoro-6-(4-methyl-1-piperazinyl) benzimidazole (**7a**).

The following spectral data were recorded for compound **7a**: ^{1}H NMR: δ: 12.23 (bs, 1H, N-*H*), 7.24 (2H*, *H*-4, *H*-7), 4.90 (bs, 2H, C_5H_4), 4.40 (bs, 2H, C_5H_4), 4.12 (bs, 5H, C_5H_5), 3.09 (bt, *J* = 3.2 Hz, 4H, C2'-*H*, C6'-*H*), 3.09 (bt, 4H, *J* = 3.0 Hz, 4H, C3'-*H*, C5'-*H*), 2.36 (s, 3H, N-C*H*3). FT-IR (KBr disk): 3078, 2924, 2791, 1639, 1567, 1480, 1409, 1373, 1322, 1183, 1148, 1009, 845, 722 cm^{-1}. EI-MS m/z : 418. *: These signals are masked by the signal of $CDCl_3$ peak.

2-Ferrocenyl-5-fluoro-6-(4-phenyl-1-piperazinyl)benzimidazole (**7b**).

The following spectral data were recorded for compound **7b**: ^{1}H NMR: δ: 11.73 (bs, 1H, N-*H*), 6.91-7.33 (m, 7H, C_6H_5, *H*-4, *H*-7), 4.85 (bs, 2H, C_5H_4), 4.42 (bs, 2H, C_5H_4), 4.22 (bs, 5H, C_5H_5), 3.39 (bt, *J* = 3.0 Hz, 4H, C2'-*H*, C6'-*H*), 3.34 (bt, 4H, *J* = 3.2 Hz, 4H, C3'-*H*, C5'-*H*). FT-IR (KBr disk): 2925, 2817, 1597, 1567, 1474, 1409, 1264, 1230, 1144, 941, 845, 818 cm^{-1}. EI-MS m/z : 480.

2-Ferrocenyl-5-fluoro-6-[4-(4-chlorophenyl)-1-piperazinyl]benzimidazole (**7c**).

The following spectral data were recorded for compound **7c**: ^{1}H NMR: δ: 11.73 (bs, 1H, N-*H*), 6.91-7.39 (m, 6H, C_6H_4Cl, *H*-4, *H*-7), 4.92 (bs, 2H, C_5H_4), 4.40 (bs, 2H, C_5H_4), 4.11 (bs, 5H, C_5H_5), 3.31 (bt, *J* = 3.0 Hz, 4H, C2'-*H*, C6'-*H*), 3.20 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*). FT-IR (KBr disk): 3078, 2817, 2356, 1634, 1598, 1490, 1470, 1444, 1224, 1142, 1101, 942, 814 cm^{-1}. EI-MS m/z : 514/516.

2-Ferrocenyl-5-fluoro-6-[4-(4-methoxyphenyl)-1-piperazinyl]-benzimidazole (**7d**).

The following spectral data were recorded for compound **7d**: ^{1}H NMR: δ: 12.30 (bs, 1H, N-*H*), 6.86-7.33 (m, 6H, $C_6H_4OCH_3$, *H*-4, *H*-7), 4.90 (bs, 2H, C_5H_4), 4.44 (bs, 2H, C_5H_4), 4.12 (bs, 5H, C_5H_5), 3.76 (s, 3H, $C_6H_5OCH_3$), 3.25-3.29 (m, 8H, C2'-*H* , C2'-*H*, C3'-*H*, C5'-*H*). FT-IR (KBr disk): 3073, 2822, 2356, 1634, 1506, 1470, 1413, 1229, 1137, 937, 814, 712 cm^{-1}. EI-MS m/z: 510.

2-Ferrocenyl-5-fluoro-6-[4-(4-fluorophenyl)-1-piperazinyl]benzimidazole (**7e**).

The following spectral data were recorded for compound **7e**: ^{1}H NMR: δ: 11.53 (bs, 1H, N-*H*), 6.90-7.00 (m, 6H, C_6H_4F, *H*-4, *H*-7), 4.94 (bs, 2H, C_5H_4), 4.41 (bs, 2H, C_5H_4), 4.12 (bs, 5H, C_5H_5), 3.26 (bt, *J* = 3.0 Hz, 4H, C2'-*H*, C6'-*H*), 3.22 (bt, 4H, *J* = 3.1 Hz, 4H, C3'-*H*, C5'-*H*). FT-IR (KBr disk): 3071, 2810, 2346, 1644, 1578, 1490, 1470, 1447, 1224, 1142, 1101, 943, 815 cm^{-1}. EI-MS m/z: 498.

General Procedure for the Synthesis of the Hydrochloride Salts of Compounds **7a-e**.

Hydrogen chloride gas was bubbled into a cold solution containing the particular 2-ferrocenylbenzimidazole (**7a-e) (**1 mmol) in dry THF (10 ml) for 20 min. The resulting precipitate was collected, washed several times with cold THF and crystallized from ethanol to give the title compounds.

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