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# Synthesis and antimicrobial activity of some new pyrazole derivatives containing a ferrocene unit

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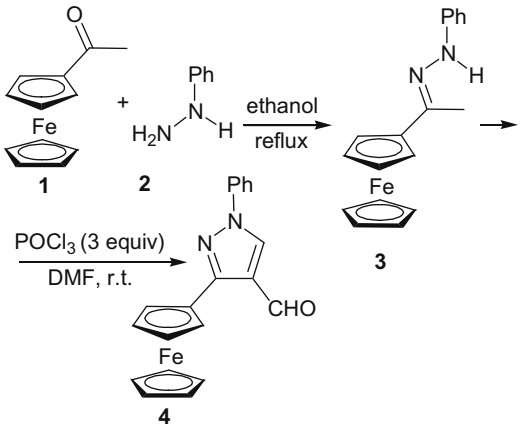
ABSTRACT

A series of new imines and amines have been synthesized by condensation of 1*H*-3-ferrocenyl-1-phenylpyrazole-4-carboxaldehyde with the corresponding amines, followed by reduction with sodium borohydride. The synthesized compounds have been screened for their in vitro antimicrobial activity against 11 bacteria and three fungal/yeast strains, using disc diffusion and broth microdilution susceptibility assays. They have shown a wide range of activities, from completely inactive to the highly active compounds.



There are only a few groups of compounds that have captured the attention of chemists so intensively as ferrocenes. Since the discovery of this sandwich complex in 1951,[1,2] a plethora of its derivatives has been synthesized and characterized following classical methods of organic chemistry. They are very appreciated for their outstanding stability, and have been applied in many fields of chemistry.[3] Thus, bioconjugates containing this metallocene represent new class of biomaterials, with the organometallic unit serving as a molecular scaffold, a sensitive probe, a chromophore, a biological marker, a redox-active site, a catalytic site, etc.[4] Substitution of the aromatic nucleus of a certain organic compound with a ferrocene unit can lead to the products possessing an unexpected biological activity which is absent or less manifest in the parent molecule.[5] Despite the fact that early attempts to apply ferrocene derivatives in medicine were not promising,[6,7] many ferrocenes have been synthesized until present and studied in that regard.[8–12] Since many heterocyclic compounds exhibit different biological activities—ferrocene containing heterocycles are of a particular interest, and a plenty of such compounds have been synthesized so far. The pyrazole motif makes up the core structure of numerous biologically active compounds.[13] Thus, some representatives of this heterocycle have affinity for the human CRF-1 receptor,[14] exhibit anti-viral/anti-tumor,[15–18] antibacterial,[19–23] anti-parasitic,[24,25] antipyretic,[26] anti-inflamatory,[23,26–28] analgesic,[28] fungistatic,[29] fungicidal,[30] and anti-hyperglycemic activity.[31,32] Nevertheless, it did not motivate chemists to invest too much labor into the synthesis of pyrazole containing ferrocenes, and only a limited number of publications devoted to this problem have appeared until present.[33,34]

Recently, we reported on the condensation of acetylferrocene (**1**) with phenylhydrazine (**2**) followed by intramolecular cyclization of the intermediate hydrazone **3** under Vilsmeier–Haack conditions leading to 1*H*-3-ferrocenyl-1-phenylpyrazole-4-carboxaldehyde (**4**, Scheme 1).[35]




**Scheme 1.** Synthesis of aldehyde **4**.

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In continuation of our interest in this chemistry, herein we wish to describe the synthesis, full spectral characterization and antimicrobial activity of several imines and amines obtained by condensation of this aldehyde with some primary amines, followed by reduction of the obtained imines into the corresponding secondary amines.

The studies have been started by synthesis of 1*H*-3-ferrocenyl-1-phenylpyrazole-4-carboxaldehyde (**4**), by previously described procedure.[35,36] This aldehyde was refluxed with amines **5a–i** in methanol in the presence of one drop of glacial acetic acid, giving imines **6a–i** in 70–97% isolated yields, the structures of which were confirmed by spectroscopic data.[36] The dried imines were, then, submitted to reduction with an excess of sodium borohydride, giving amines **7a–i** in 72–96% yields.[36]

The synthesized imines **6a-i** and amines **7a-i** were screened for their in vitro antimicrobial activity against 11 bacteria and three fungal/yeast strains using disc diffusion and broth microdilution susceptibility assays. In the disc diffusion assay,[37,38] the compounds were tested at the dose of 250 μg per disc (applied as a dimethyl sulfoxide solution), and the diameters of the growth inhibition zones were measured to the nearest mm. Measured susceptibility zones were the clear zones around the disc inhibiting the microbial growth. The obtained results are listed in Table 1. As it can be seen, the prepared compounds have shown a wide range of activities—from completely inactive compounds, through medium active to the highly active ones. The compounds **7g, 7h**, and **7i** were shown to be totally inactive towards all the tested microorganisms at the mentioned dose. The most active compounds were the amines **7a** and **7b**, showing reduction of bacterial and fungal growth comparable or higher than that exhibited by the standards used as positive controls (tetracycline, **8** and nistatine, **9**), especially against medically important pathogens. On the other hand, the most resistant strain was *K. pneumoniae* being completely unsusceptible to most of the tested compounds. It also seems that the Gram-positive and Gram-negative bacteria were equally resistant to all compounds, although it is recognized that the presence of certain cell-wall lipopolysaccharides is to be considered responsible for the greater resistance of Gram-negative strains,[39] corroborating the documented fact that ferrocene is capable to cross cell membranes.[40]

The imines have shown a more pronounced activity against the fungal organisms *A. niger*, and *C. albicans* compared to the bacteria tested and the yeast *S. cerevisiae*. Except in a few cases, this general moderate activity of imines, aside from **6c**, seems to be non-selective in respect to the bacteria tested. However, the situation is quite different in the case of amines, where a clear distinction between aliphatic, alicyclic and benzyl-type amines (**7a**, **7b**, and **7c–f**, respectively) from one, and aromatic amines (**7g–i**) from the other side does exist. The lower basicity and chelating ability of aromatic amines compared to the other ones might, perhaps, cause their lower antimicrobial properties. For example, the growth of *Candida* sp. is inhibited by iron deprivation,[40] thus, the chelating ability of the tested compounds could perhaps be acknowledged as the reason for the observed candidicidal activity. Furthermore, by coupling a pyrazole containing molecule (already known as the carriers of antimicrobial activity) to ferrocene (which interacts with the cytochrome P-450)[41] it might be possible to increase the pyrazoles incorporation and targeting toward cytochrome P-450 as proposed in the previous case of fluconazole.[40] It is known that the replacement of an aromatic group by the ferrocenyl moiety in penicillin and cephalosporines was improved their antibiotic activity.[42,43] However, a more recent publication by Biot et al.[40] reporting the synthesis and evaluation of a ferrocene-fluconazole analogue for antifungal activity against *Candida* sp. revealed a slight increase in fungal growth and a reversal of the effect of fluconazole at minimal inhibitory concentration.

It is interesting to note the almost complete lack of activity for amine **7f** possessing a thiophene moiety, while the imine analogue **6f** still showed significant activity. Generally, it seems that no correlation between the imine and amine activities can be drawn, supported by the fact that the most susceptible strains to the amines were the most resistant to the imines, and vice versa, and suggesting a probably different mode of activity for the two groups of compounds.

In order to make the discussion more easy to follow and the conclusions statistically supported, we performed agglomerative hierarchical clustering (AHC) on the mentioned samples (Table 1), using the Excel program plug-in XLSTAT version 2008.6.07. The method was applied utilizing the values of diameters of growth inhibition zones as original variables without any recalculation.

**Table 1**
The antimicrobial activity (diameters of growth inhibition zones[a] of ferrocene containing imines **6a–i** and amines **7a–i** in a disc diffusion assay at a **250** μg per disc dose

| Compound | Microorganism | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *B. subtilis* | *Cl. pyogenes* | *Enterococcus* sp. | *M. flavus* | *S. lutea* | *S. aureus* | *E. coli* | *K. pneumoniae* | *S. enteritidis* | *P. vulgaris* | *P. aeruginosa* | *A. niger* | *C. albicans* | *S. cerevisiae* |
| **6a** | 17 | 15 | 15 | n.a. | 16 | 16 | 17 | 15 | 18 | 17 | 16 | 17 | 20 | n.a. |
| **6b** | 15 | 17 | 16 | n.a. | 16 | n.a. | 17 | n.a. | 17 | 17 | 17 | n.a. | n.a. | n.a. |
| **6c** | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | 17 | n.a. | n.a. |
| **6d** | 17 | 16 | 16 | 15 | 18 | 14 | n.a. | n.a. | 16 | 15 | 17 | 16 | 17 | 18 |
| **6e** | 15 | 15 | 14 | n.a. | 16 | 15 | 16 | n.a. | 17 | 14 | 16 | 18 | 16 | n.a. |
| **6f** | 17 | 16 | 16 | 15 | 15 | 15 | 15 | n.a. | 15 | 18 | 16 | 18 | 20 | n.a. |
| **6g** | 19 | 17 | 16 | 17 | 18 | 16 | 18 | n.a. | 17 | 15 | 16 | 18 | 17 | n.a. |
| **6h** | 19 | 17 | 15 | 16 | 19 | 17 | 16 | n.a. | 16 | 17 | 18 | 17 | 16 | n.a. |
| **6i** | n.a. | 16 | 15 | n.a. | 14 | n.a. | 14 | n.a. | n.a. | n.a. | n.a. | 16 | 19 | n.a. |
| **7a** | 28 | 28 | 26 | 32 | 30 | 26 | 28 | 27 | 28 | 28 | 26 | 26 | 25 | 21 |
| **7b** | 23 | 23 | 25 | 24 | 23 | 23 | 21 | 24 | 24 | 23 | 24 | 22 | 21 | 25 |
| **7c** | 18 | 18 | 18 | 17 | 18 | 16 | 16 | n.a. | 17 | 16 | 17 | 17 | n.a. | 23 |
| **7d** | 16 | 16 | 15 | 16 | 17 | n.a. | n.a. | n.a. | 15 | 15 | 16 | 16 | 15 | 18 |
| **7e** | 20 | 18 | 22 | 20 | 17 | 17 | 17 | n.a. | 17 | 19 | 17 | 20 | 17 | 21 |
| **7f** | n.a. | n.a. | 15 | n.a. | n.a. | n.a. | n.a. | n.a. | 18 | n.a. | n.a. | n.a. | n.a. | 19 |
| **7g** | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| **7h** | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| **7i** | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Tetracycline | 27 | 27 | 28 | 31 | 27 | 25 | 27 | 23 | 26 | 26 | 26 | n.t. | n.t. | n.t. |
| Nistatine | n.t. | n.t. | n.t. | n.t. | n.t. | n.t. | n.t. | n.t. | n.t. | n.t. | n.t. | 18 | 19 | 17 |

n.a., not active; n.t., not tested.
[a] Mean values (in mm) of 5 experiments, including the disc diameter (12.7 nm).

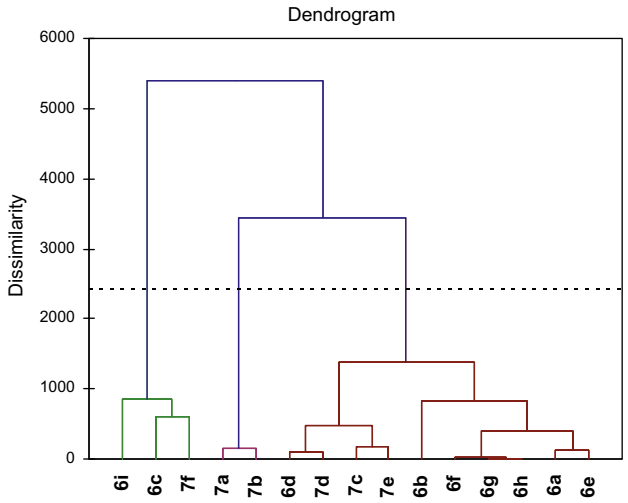
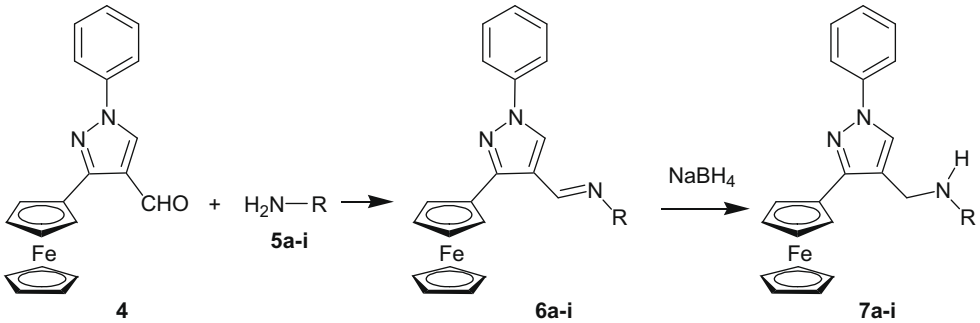


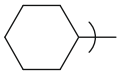
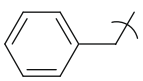
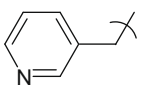
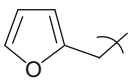

**Figure. 1.** Dendrogram (AHC analysis) representing antimicrobial activity (variables-diameters of growth inhibition zones) dissimilarity relationships of the synthesized compounds (observations) obtained by Euclidean distance dissimilarity (dissimilarity within the interval [0,5500]), using aggregation criterion-Ward's method. Three groups of the compounds were found C1–C3 (from left to right).

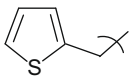
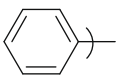
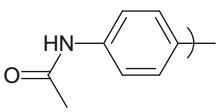
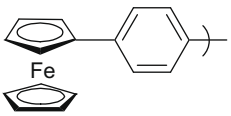
The results of AHC are presented in Figure 1. AHC was performed using Pearson dissimilarity (as aggregation criteria simple linkage, unweighted pair-group average and complete linkage were used) and Euclidean distance (aggregation criterion: weighted pair-group average, unweighted pair-group average and Ward's method). The definition of the groups was based on Pearson correlation, using complete linkage and unweighted pair-group average method. AHC analysis has clearly indicated the existence of three groups of compounds under study (designations of the compounds were given in Scheme 2).

Compounds from the first group C1, **6c**, **6i**, and **7f**, in addition to those that showed no activity at all (**7g**, **7h**, and **7i**), and that were not included in the AHC analysis, are distinguished from the rest of the samples by the very low susceptibility of all tested microorganisms towards them. At the same time, the two most active compounds **7a** and **7b** (the aliphatic amines) formed an independent clade C2 more related to each other then to the rest of the samples (class C3). Further subdivision of the tested compounds that fell into C3 is worthy of mentioning. The grouping of **6d** and **7d** suggests that the 3-picolyl moiety that is in common for the molecules might be responsible for the observed activity (especially against the fungi) of those compounds. Related to this subclade the group consisting of **7c** and **7e** further stresses the assumed importance of the amine type (benzyl and furyl) as the possible carrier of activity. On the other hand, the placement of 10 compounds into a single clade (C3) clearly points out to the non-selective antimicrobial nature of the synthesized compounds.

In order to make the antimicrobial data more reproducible we determined the minimal inhibitory concentrations (MIC) for the most active amines (**7a**, **7b**, and **7e**) and their respective imines (**6a**, **6b**, and **6e**). The results obtained in a microdilution broth susceptibility assay[44,45] (Table 2) confirmed the findings of the disk diffusion technique (Table 1). The MIC values of the selected compounds ranged from 46 to 225 μg/ml, suggesting a strong to medium antimicrobial activity, being, in some cases, of the same order of magnitude or greater compared to the positive controls used (Amikacin and Bifonazole). Again the compounds were almost completely non-selective in their antibacterial and antifungal effect. Specially worth noticing are the cases of some of the most resistant pathogenic bacteria *B. subtilis*, *Enterococcus* sp. and *P. aeruginosa*, where Amikacin was either less efficient then or comparable in action to compound **7a**. Compound **7a** is coming close to the 10 μg/ml MIC limit set for the efficient antimicrobial compounds.




| 5,6 and 7 | R | Yields (%) 6 | 7 |
|---|---|---|---|
| a | $(CH_3)_3C$— | 88 | 87 |
| b |  | 86 | 91 |
| c |  | 97 | 86 |
| d |  | 79 | 72 |
| e |  | 92 | 88 |

| 5,6 and 7 | R | Yields (%) 6 | 7 |
|---|---|---|---|
| f |  | 95 | 85 |
| g |  | 84 | 94 |
| h |  | 70 | 96 |
| i |  | 84 | 77 |

**Scheme 2.** Synthesis of imines **6a–i** and amines **7a–i**.

**Table 2**
Minimal inhibitory concentration (MIC, μg/ml) of selected imines (**6a**, **6b**, and **6e**) and amines (**7a**, **7b**, and **7e**)

| Microorganism | 6a | 6b | 6e | 7a | 7b | 7e | Amikacin | Bifonazole |
|---|---|---|---|---|---|---|---|---|
| Sample | | | | | | | | |
| *B. subtilis* | 225 | 167 | 92 | 52 | 78 | 113 | 42 | n.t. |
| *Cl. pyogenes* | 155 | 167 | 86 | 53 | 83 | 74 | 15 | n.t. |
| *Enterococcus* sp. | 191 | 161 | 124 | 50 | 65 | 73 | 65 | n.t. |
| *M. flavus* | 158 | 191 | 145 | 46 | 69 | 84 | 2 | n.t. |
| *S. lutea* | 149 | 101 | 92 | 49 | 61 | 85 | 2 | n.t. |
| *S. aureus* | 161 | 168 | 99 | 53 | 78 | 132 | 11 | n.t. |
| *E. coli* | 168 | 145 | 129 | 53 | 71 | 93 | 5 | n.t. |
| *K. pneumoniae* | 158 | 78 | 103 | 55 | 66 | 70 | 8 | n.t. |
| *S. enteritidis* | 179 | 161 | 96 | 51 | 61 | 83 | 8 | n.t. |
| *P. vulgaris* | 191 | 167 | 130 | 53 | 77 | 95 | 7 | n.t. |
| *P. aeruginosa* | 141 | 168 | 130 | 53 | 77 | 124 | 50 | n.t. |
| *A. niger* | 167 | 87 | 82 | 53 | 61 | 85 | n.t. | 9 |
| *C. albicans* | 168 | 101 | 73 | 66 | 64 | 92 | n.t. | 32 |
| *S. cerevisiae* | 118 | 158 | 194 | 97 | 98 | 86 | n.t. | 6 |

n.t., not tested.

The presented results on the antimicrobial properties of these ferrocene containing molecules urge further investigations in this direction with compounds **7a** and **7b** as the leads. Such a non-selective and strong activity promises a possible use in the combat against antibiotic-resistant strains of microorganisms as demonstrated for a ferrocene derivative against the chloroquine-resistant *Plasmodium berghei* N and *P. yoelii* NS in vivo.[5,46]

## Acknowledgments

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## Supplementary data

The detailed synthetic and biological procedures, as well as full spectral characterization of the new compounds are given. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.01.006.

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36. For the detailed experimental procedures and spectral characterization of the new compounds see Supplementary data. Here we give the complete analytical data for compound **7a**. Yield: 0.88 g (87%). Dark red oil. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.27, s (9H, $CH_3$); 3.89, s (2H, $CH_2$); 1.43, br s (1H, NH); 4.11, s (5H, Fc); 4.31, t (2H, *J* = 1.96 Hz, Fc) 4.83, t (2H, *J* = 1.96 Hz, Fc); 7.18–7.26, m (1H, *p*-phenyl); 7.40, t (2H, *J* = 8.40 Hz, *m*-phenyl); 7.70, dd (2H, *J* = 8.44 and 1.36 Hz, *o*-phenyl); 7.89, s (1H, Pz); $^{13}$C NMR (200 MHz, $CDCl_3$): 29.16, 37.37, 50.69, 67.28, 68.53, 69.28, 78.38, 118.46, 120.67, 125.62, 126.50, 129.28, 140.13, 149.51. 15 IR ($cm^{-1}$, KBr pellets): 509, 762, 1209, 1366, 1401, 1504, 1563, 1598, 2958, 3229. Anal. Calcd for $C_{24}H_{27}FeN_3$ (413.13): C, 69.74; H, 6.58; N, 10.12. Found: C, 69.63; H, 6.56; N, 10.10.
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