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Synthesis and Antimicrobial/Cytotoxic Assessment of Ferrocenyl Oxazinanes, Oxazinan-2-ones, and Tetrahydropyrimidin-2-ones

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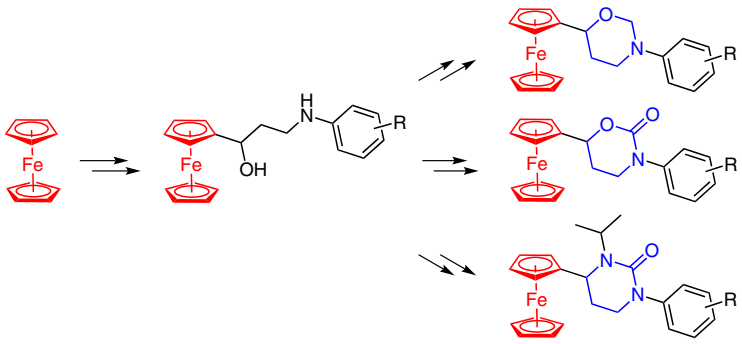

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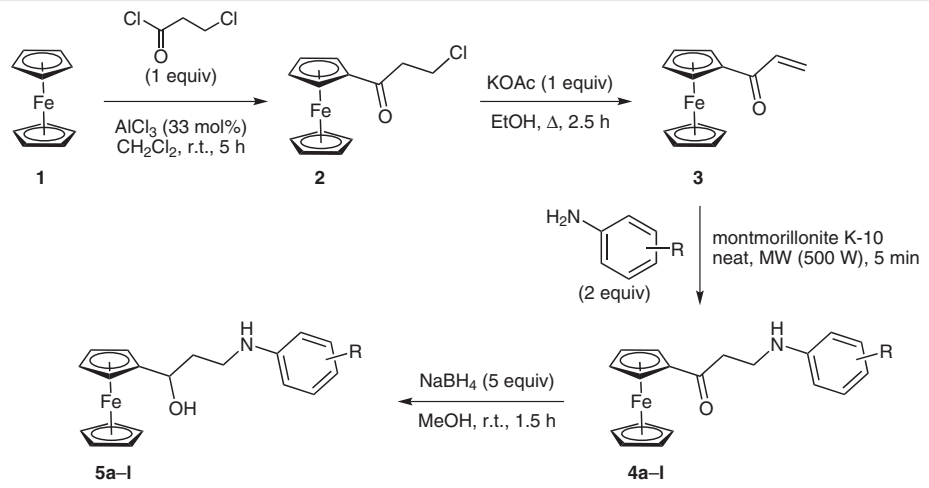
Abstract 3-Arylamino-1-ferrocenylpropan-1-ones, prepared through aza-Michael addition of aromatic amines to 1-ferrocenylpropenone, were transformed into the corresponding 1,3-amino alcohols upon $NaBH_4$-mediated carbonyl reduction. The latter amino alcohols were deployed as eligible substrates for the synthesis of a variety of ferrocene-containing heterocycles including 1,3-oxazinanes, 1,3-oxazinan-2-ones, and tetrahydropyrimidin-2-ones, which were subsequently evaluated for their antimicrobial and cytotoxic activities.

Key words ferrocenes, heterocycles, oxazinanes, oxazinan-2-ones, tetrahydropyrimidin-2-ones, cyclization, amino alcohols

Ferrocenes have attracted considerable interest over the years because of their versatility in many fields of research. Notable areas featuring important ferrocene derivatives include asymmetric catalysis[1] and bioactive compound development,[2] and, as a consequence, these fields have witnessed a steady growth of valuable scientific contributions. The combination of chemical stability, synthetic flexibility, and pronounced biological activities has turned ferrocenes into privileged scaffolds in medicinal chemistry, especially in relationship with the design of antimalarial,[3] antimicrobial,[4] and antitumor agents.[3,5] Consequently, the synthesis of new ferrocene derivatives continues to play an important role in current organic chemistry. On the other hand, the vast majority of pharmacophores in medicinal chemistry accommodates a heterocyclic core fragment in their structure, and this wide range of potential medicinal applications has catalyzed significant advances at the interface of heterocyclic chemistry and medicinal chemistry for many years. In light of the general biological importance of heterocyclic compounds and the medicinal interest in ferrocene derivatives, the design of ferrocene-containing heterocycles has emerged as an eligible approach toward the synthesis of new bioactive molecules,[6] and it is conceivable to expect important new contributions within this concept in the near future.

Further elaborating on our interest in ferrocene chemistry[7] and heterocyclic synthesis,[8] the present manuscript reports on the preparation of a set of novel, ferrocene-containing heterocyclic compounds and the preliminary evaluation of their biological activity. The particular objectives of this study comprised (i) assessment of the synthetic/chemical feasibility of γ-amino alcohol cyclizations employing 3-arylamino-1-ferrocenylpropan-1-ols as substrates to produce a small library of novel ferrocenyl heterocycles and (ii) determination of the biological profile of these new structures by means of antifungal/antibacterial activity tests and cytotoxicity analysis against cancer cell lines.

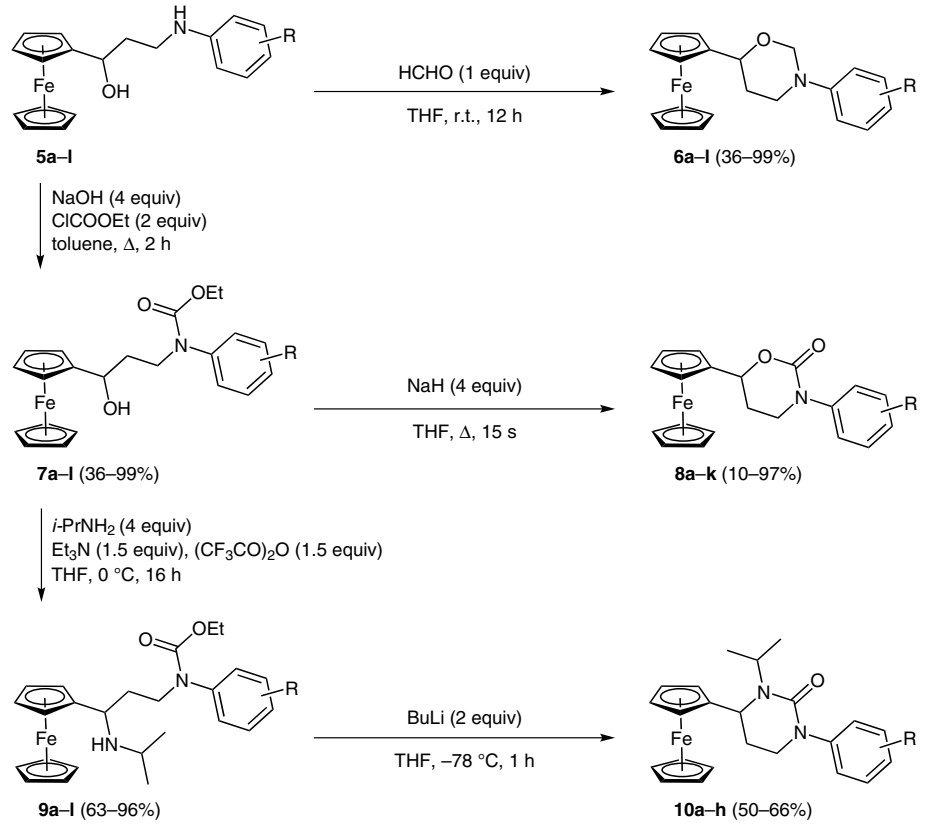
The synthesis of the premised 3-arylamino-1-ferrocenylpropan-1-ols **5** commenced with the Friedel–Crafts acylation of ferrocene **1** with 3-chloropropanoyl chloride in CH_2Cl_2 in the presence of $AlCl_3$ and the subsequent dehydrohalogenation of the obtained 3-chloro-1-ferrocenylpropan-1-one **2** utilizing KOAc in EtOH. Subsequently, microwave-promoted addition of a broad variety of aromatic amines across Michael acceptor **3** was realized under neat conditions in the presence of montmorillonite K-10, affording 3-arylamino-1-ferrocenylpropan-1-ones **4** in high yields.[7a] The latter ketones were then converted into the corresponding alcohols upon treatment with five equivalents of $NaBH_4$ in MeOH to produce a set of twelve 3-arylamino-1-ferrocenylpropan-1-ols **5** as useful new substrates for further derivatization (Scheme 1, Table 1). γ-Amino alcohols in general represent versatile synthons in organic chemistry,[9] and the corresponding 1,3-amino alcohol de-



Scheme 1 Synthesis of 3-arylamino-1-ferrocenylpropan-1-ols **5**

rived heterocycles are of broad interest from a biological point of view (antibacterial, antimalarial, anti-inflammatory, antitumor, etc.).

The second part comprised the evaluation of ferrocenyl amino alcohols **5** as substrates for the synthesis of novel ferrocene-containing heterocyclic compounds (Scheme 2, Table 2). As stated in the introduction, ferrocenyl heterocycles represent valuable new targets in medicinal chemistry because of the combined properties of the ferrocene moiety and the heterocyclic core fragment.



Scheme 2 Synthesis of ferrocenyl oxazinanes **6**, oxazinanones **8**, and tetrahydropyrimidinones **10**

Table 1 Synthesis of 3-Arylamino-1-ferrocenylpropan-1-ols **5**: Substitution Patterns and Yields

Compound	R	Yield (%)[a]
5a	H	90
5b	2-Me	92
5c	3-Me	90
5d	4-Me	80
5e	Mes	91
5f	4-*n*-Bu	97
5g	2-F	93
5h	3-F	91
5i	4-F	95
5j	2-Cl	90
5k	3-Cl	98
5l	4-Cl	85

[a] After purification by means of column chromatography on Al_2O_3.

Table 2 Synthesis of Ferrocenyl Oxazinanes **6**, Oxazinanones **8**, and Tetrahydropyrimidinones **10**: Substitution Patterns and Yields

Compound	R	Yield (%)[a]
6a	H	78
6b	2-Me	99
6c	3-Me	98
6d	4-Me	99
6e	Mes	36
6f	4-*n*-Bu	81
6g	2-F	84
6h	3-F	99
6i	4-F	76
6j	2-Cl	77
6k	3-Cl	85
6l	4-Cl	77
8a	H	64
8b	2-Me	47
8c	3-Me	53
8d	4-Me	84
8e	4-*n*-Bu	80
8f	2-F	97
8g	3-F	84
8h	4-F	97
8i	2-Cl	10
8j	3-Cl	77
8k	4-Cl	89
10a	H	61
10b	3-Me	58
10c	4-Me	66
10d	4-*n*-Bu	60
10e	2-F	57
10f	4-F	63
10g	3-Cl	50
10h	4-Cl	53

[a] After purification by means of column chromatography (SiO_2) or preparative TLC chromatography (SiO_2).

A first route involved the direct cyclization of amino alcohols **5** to 6-ferrocenyl-1,3-oxazinanes **6** upon treatment with one equivalent of formaldehyde in THF, which were purified by means of column chromatography to afford oxazaheterocycles **6**[10] in moderate to excellent yields. 1,3-Oxazinanes have previously been reported to be interesting systems, both from a biological[11] and a synthetic[12] point of view. In a second route, ferrocenyl oxazinan-2-ones **8**[13] were premised. These systems were constructed via initial sodium hydroxide-assisted N-ethoxycarbonylation of amines **5** using two equivalents of ethyl chloroformate in toluene, followed by cyclization of the thus obtained intermediate carbamates **7** by reaction with four equivalents of NaH in THF. The desired heterocyclic scaffolds **8** were isolated after purification by means of column chromatography in low to excellent yields. Cyclic carbamates can be regarded as interesting compounds with a variety of applications, most notably as precursors for 1,3-amino alcohols,[14] as chiral auxiliaries,[15] and as the core substructure in a number of biologically active compounds.[16] Finally, diazaheterocyclic analogues of the above-mentioned oxazaheterocycles **8** were contemplated. To that end, the hydroxyl group in systems **7** was replaced with an isopropylamino substituent through reaction with four equivalents of *i*-$PrNH_2$ in THF at low temperature (0 °C) in the presence of 1.5 equivalents of Et_3N and 1.5 equivalents of $(CF_3CO)_2O$, affording diamino compounds **9**. The fact that the OH group in compounds **7** resides in α position with regard to the ferrocene moiety, comparable to a benzylic position because of the aromatic nature of the ferrocene unit, accounts for its increased chemical reactivity. Cyclization of diamino compounds **9** was then effected upon treatment with two equivalents of BuLi in THF, yielding 4-ferrocenyltetrahydropyrimidin-2-ones **10**[17] in good yields after purification. Pyrimidinones in general are known to have a long track record in bioactive compound development, for example as kinase inhibitors[18] or as anti-HIV agents.[19]

In summary, 3-arylamino-1-ferrocenylpropan-1-ols were deployed successfully for the synthesis of 31 new ferrocene-containing heterocyclic scaffolds. The combination of the ferrocene group and a heterocyclic unit in one molec-

ular framework might result in medicinally relevant new hybrid compounds because of the well-known biological properties of both entities. Variation of the substitution pattern across the aromatic ring at nitrogen results in additional molecular diversity within each class of heterocyclic motifs.

In the next part of this study, the novel ferrocenyl heterocycles **6**, **8**, and **10** were briefly assessed with regard to their antimicrobial and cytotoxic profile.

In a first screening, the antimicrobial activity of these ferrocenyl heterocycles was tested on one yeast strain (*Candida albicans* IHEM 374), one mold strain (*Aspergillus flavus* IHEM 5785), and four bacterial strains (*Bacillus cereus* LMG 6910, *Escherichia coli* LMG 8223, *Staphylococcus aureus* LMG 3195, and *Klebsiella pneumonia* ATCC 31488) by the disk diffusion method.[20] At a concentration of 500 µg per disk, only eight samples displayed weak antibacterial activity against *B. cereus*, and no other compound displayed antimicrobial activity toward any of the other microorganisms. The eight compounds showing minor activity against *B. cereus* comprised oxazinan-2-ones **8b**, **8f**, **8g**, and **8i** and tetrahydropyrimidin-2-ones **10a**, **10b**, **10c**, and **10e**. In a previous study we had demonstrated the antimicrobial effect of 3-arylamino-1-ferrocenylpropan-1-ones **4**,[7a] pointing to the potential of these ferrocene derivatives as antibacterial agents. From the present results, however, it can be concluded that carbonyl reduction and subsequent cyclization of ferrocenes **4** to ferrocenyl heterocycles **6**, **8**, and **10** is detrimental with regard to their overall antimicrobial potency.

In addition, the biological relevance of 28 ferrocenyl heterocycles with respect to their anticancer behavior was investigated in vitro against two human tumor cell lines (KB, Hep-G2). The results of these tests are depicted in Table 3. These data indicate that six compounds (**6f**, **6l**, **8i**, **8k**, **10b**, and **10d**) exert a low cytotoxic effect against both cell lines with IC_{50} values <100 µM, and one of them (**10d**) has a moderate activity with IC_{50} values <50 µM. These results point to the potential of ferrocenyl heterocycles **6**, **8**, and **10** as templates for the design of new cytotoxic agents upon further optimization.

Although a broader study is required to determine actual structure–activity relationships, it seems that the presence of a fluoro atom or a methyl group on the aromatic ring at nitrogen is beneficial for activity against *B. cereus*, and the presence of a chloro atom or a *n*-Bu group seems to enhance the cytotoxic activity of these ferrocenyl heterocycles.

In conclusion, 3-arylamino-1-ferrocenylpropan-1-ones were prepared through aza-Michael addition of aromatic amines to 1-ferrocenylpropenone and further transformed into the corresponding 1,3-amino alcohols upon $NaBH_4$-mediated carbonyl reduction. The latter amino alcohols were deployed as suitable substrates for the successful synthesis of a set of 31 new ferrocene-containing heterocycles bearing a 1,3-oxazinane, a 1,3-oxazinan-2-one, or a tetrahydropyrimidin-2-one scaffold. Preliminary antimicrobial and cytotoxic analyses revealed low to moderate bioactivity profiles for these new compounds.

Table 3 Cytotoxic Analyses of Ferrocenyl Heterocycles **6**, **8**, and **10**

Entry	Compd	IC_{50} (µM) KB	IC_{50} (µM) Hep-G2
1	**6a**	332.1	238.1
2	**6b**	211.5	218.9
3	**6c**	228.6	177.2
4	**6d**	213.3	207.7
5	**6e**	279.5	>328.8
6	**6f**	56.3	52.2
7	**6g**	170.6	194.1
8	**6h**	164.9	205.2
9	**6i**	>350.5	329.8
10	**6j**	195.1	125.8
11	**6k**	212.4	73.7
12	**6l**	60.8	50.8
13	**8a**	>354.4	>354.4
14	**8b**	>341.1	203.0
15	**8c**	194.9	185.8
16	**8d**	>341.1	>341.1
17	**8e**	301.4	242.3
18	**8f**	147.7	63.8
19	**8g**	171.0	182.0
20	**8h**	314.0	276.4
21	**8i**	77.0	69.7
22	**8j**	80.9	104.7
23	**8k**	52.7	61.6
24	**10a**	77.8	171.3
25	**10b**	59.6	61.8
26	**10c**	174.9	137.7
27	**10d**	44.4	42.2
28	**10f**	120.3	123.8
29	ellipticine	1.3	1.4

Acknowledgment

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(10) **6-Ferrocenyl-3-phenyl-1,3-oxazinane (6a)**
Yield 78%, dark yellow solid; mp 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2 H), 7.13–7.09 (m, 2 H), 6.93–6.87 (m, 1 H), 5.30 (dd, *J* = 10.7, 2.3 Hz, 1 H), 4.74 (d, *J* = 10.7 Hz, 1 H), 4.48 (dd, *J* = 11.2, 2.4 Hz, 1 H), 4.22 (ca. dt, *J* = 2.5, 1.3 Hz, 1 H), 4.17 (ca. dt, *J* = 2.5, 1.3 Hz, 1 H), 4.15–4.07 (m, 2 H), 4.12 (s, 5 H), 3.91 (ddt, *J* = 13.5, 4.3, 2.3 Hz, 1 H), 3.49 (ddd, *J* = 13.5, 12.7, 2.9 Hz, 1 H), 2.02 (dddd, *J* = 13.1, 12.7, 11.2, 4.3 Hz, 1 H), 1.78 (ddt, *J* = 13.1, 2.9, 2.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 129.1, 120.5, 118.4, 88.9, 81.3, 76.0, 68.6, 68.0, 67.8, 67.3, 66.0, 49.9, 29.2. MS (ES$^+$): *m/z* = 348.1 [MH$^+$]. Column chromatography (SiO_2): hexane–EtOAc, 8:2 (v/v). ESI-HRMS: *m/z* calcd for $C_{20}H_{22}FeNO$ [M + H]$^+$: 348.1050; found: 348.1041.

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(17) **6-Ferrocenyl-3-phenyl-1,3-oxazinan-2-one (8a)**
Yield 64%, yellow solid; mp 148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 2 H), 7.37–7.33 (m, 2 H), 7.29–7.24 (m, 1 H), 5.31 (dd, *J* = 9.5, 3.0 Hz, 1 H), 4.36 (ca. dt, *J* = 2.5, 1.3 Hz, 1 H), 4.28 (ca. dt, *J* = 2.5, 1.3 Hz, 1 H), 4.23–4.19 (m, 2 H), 4.24 (s, 5 H), 3.81 (ddd, *J* = 11.7, 10.2, 4.9 Hz, 1 H), 3.70 (ddd, *J* = 11.7, 5.5, 4.1 Hz, 1 H), 2.45 (dddd, *J* = 13.8, 4.9, 4.1, 3.0 Hz, 1 H), 2.28 (dddd, *J* = 13.8, 10.2, 9.5, 5.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 143.1, 129.4, 126.9, 126.0, 86.3, 76.2, 69.1, 68.5, 68.4, 67.4, 66.1, 47.9, 28.9. IR (ATR): ν = 1685 (C=O) cm^{-1}. MS (ES$^+$): *m/z* = 362.1 [MH$^+$]. Column chromatography (SiO_2): hexane–EtOAc, 8:2 (v/v). ESI-HRMS: *m/z* calcd for $C_{20}H_{20}FeNO_2$ [M + H]$^+$: 362.0844; found: 362.0834.

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(21) **4-Ferrocenyl-3-isopropyl-1-phenyltetrahydropyrimidin-2-one (10a)**
Yield 61%, orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2 H), 7.25–7.20 (m, 2 H), 7.16–7.09 (m, 1 H), 4.46 (t, *J* = 3.9 Hz, 1 H), 4.24 (d × t, *J* = 2.4, 1.2 Hz, 1 H), 4.20–4.09 (m, 3 H), 4.16 (s, 5 H), 4.13–4.10 (m, 1 H), 3.62–3.46 (m, 2 H), 2.33–2.15

(m, 2 H), 1.37 (d, J = 6.8 Hz, 3 H), 1.28 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 144.3, 128.8, 126.0, 125.2, 91.2, 69.4, 68.9, 68.4, 66.7, 66.0, 53.0, 50.9, 45.2, 31.7, 21.3, 20.9. IR: ν = 1636 (C=O) cm^{-1}. MS (ES$^+$): m/z = 403.2 [M + H]$^+$. Preparative chromatography (SiO_2): hexane–EtOAc, 6:4 (v/v). ESI-HRMS: m/z calcd for $C_{23}H_{27}FeN_2O$ [M + H]$^+$: 403.1473; found: 403.1475.

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