

Versatile Researches on Chiral Ferrocenes

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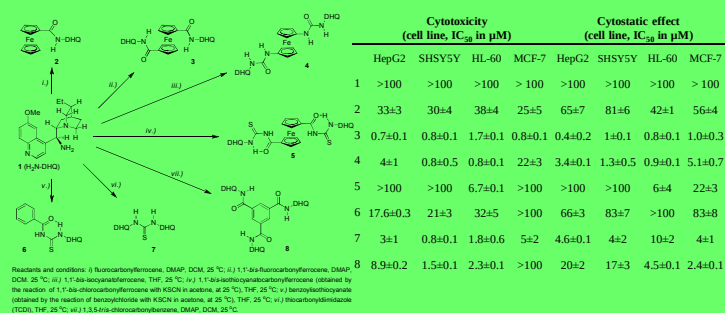


Introduction

Herein we briefly introduce four current researches in the field of ferrocene chemistry and biology. Since ferrocene-based molecules have a wide range of biological activities due to their specific structural and electronic nature we envisaged to build up some new classes of compounds and evaluate their potential in a few biological tests.

Cinchona derivatives of ferrocene

Chemotherapy is one of the most important methods in fighting cancer and several members of modified natural alkaloids serve as deserving drug against tumors. It is well-documented that the application of quinine derivatives in the field of cancer-detection and in chemotherapy [1] goes far back to the past. Since ferrocene-based molecules as anti-tumor agents are also promising materials with a wide range of biological activities [2] first we envisaged the synthesis of novel ferrocene-based quinines. The pronounced efficiency of several drugs with C2-symmetry and bis-quinolines [3] encouraged us to construct three ferrocene derivatives containing two quinine units with C2-symmetry and a reference benzene 1,3,5-tricarboxamide incorporating three quinine units with C3-symmetry. Two further purely organic models with one- and two quinine moieties, respectively, were also prepared as further references.



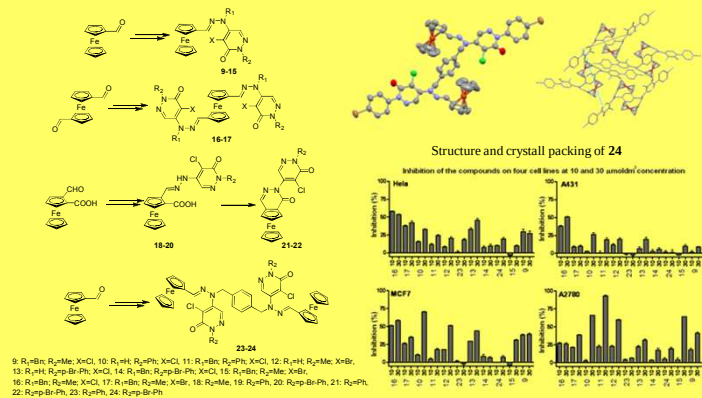
The bis- and tris-quinine derivatives exerted a dose-dependent in vitro antitumor activity at micromolar concentrations on the investigated tumor cell cultures. The ferrocene-based bis-amide 3 of pronounced activity can be considered as a promising lead structure for the development of a novel class of therapeutic agents. The highly promising results also obtained for a metallocene model containing two ureido functional groups (4) suggest that 1,1'-disubstituted ferrocene unit with easily rotating Cp-rings seems to be highly beneficial to the desired activity allowing the molecule to adopt a conformation in which the two cooperating groups are situated in optimal distance from each other.

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Ferrocene containing pyridazinones

For many years considerable attention has been paid to the chemistry and biological activity of pyridazines. The subfamily of pyridazinones sets forth various antitumor agents against colon-, lung-, breast-, renal- and CNS cancer [4]. Due to the ease of functionalization of the pyridazinone ring systems and their easy availability from hydrazine derivatives makes them a promising choice to be coupled to ferrocene core [5]. As the anti-tumor nature of ferrocene-based molecules has been referred earlier [2] first we envisaged the synthesis of three novel types of ferrocenyl-substituted hydrazinyl-pyridazinones using formyl-ferrocene, diformyl-ferrocene and (Sp)-2-formylferrocene-1-carboxylic acid [6].



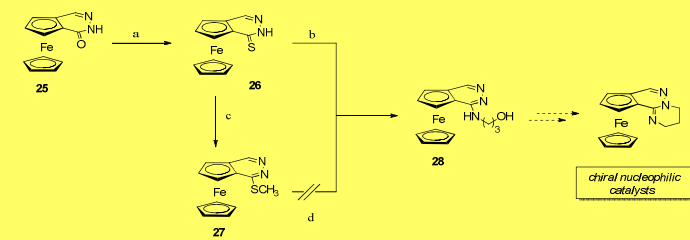
As showed above, a set of novel ferrocenyl-hydrazones, pyridazinones and planar chiral ferrocene-condensed pyridazinones were prepared. The ring closing procedure achieving compounds 21 and 22 was attempted by using carbonyldiimidazole instead of cyanuric fluoride [6]. In the case of compound 24 the efforts to grow suitable crystals for x-ray diffraction measurements were fruitful. Ongoing biological measurements show that the biological activities are far from the expected – only minor effects were observed against the appropriate cell lines.

We wish to acknowledge the work of István Zupkó for the biological measurements, Mátyás Czugler and Tamás Holczbauer for the x-ray measurements and Pál Sohár for valuable consultations.

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Novel ferroceno[d]pyridazinones

In the last years, remarkable interest has been devoted to the ferrocene-based asymmetric nucleophilic acyl transfer catalysis. In the literature Fu's planar chiral ferrocene-DMAP seemed to be one excellent catalyst for this acylation process [7]. The planar chiral structure is intended to provide the asymmetric environment in the vicinity of nucleophilic atom. On the other hand, the first series of planar chiral ferroceno[d]pyridazinones was prepared by our group [6]. These facts encouraged us to continue our work in the field of planar chiral fused ferrocenes. We envisaged the synthesis of ferroceno[d]pyridazin-thione 26 in replacement reactions effected with by amino alcohols in the presence of mercuric chloride. Mercuric salts are known to facilitate related reactions [8].



Reagents and conditions: (a) Lawesson reagent, dry THF, reflux, 1 h (77%) (b) aminopropyl alcohol, dry THF, HgCl₂, 55 °C, 1 h (33%) (c) NaH suspension, dry THF, iodomethane, room temperature, 45 minutes (94%) (d) aminopropyl alcohol, tert-butanol or ethanol, reflux (decomposed)

Effective transformation of the carbonyl group using Lawesson reagent as thionation agent was successful for lactam 25. Our strategy was based on the activation of the thione-moiety by mercury salts [9]. Using aminoalcohol reagents as nucleophilic agent an ω-hydroxyalkylamino group can be introduced into the ferrocenopyridazine skeleton. In the first attempt, compound 26 was converted into the corresponding methylthio derivative 27 in good yield. Although several papers have reported details of analogous transformations, we have observed that 27 underwent complete decomposition on treatment with 3-aminopropanol. However, thiolactam readily reacted with the employed 3-aminopropanol in the presence of mercuric chloride. This transformation was not accompanied by uncontrolled oxidation process.

In the future, we plan to attempt the cyclisation of 28 to give the targeted catalyst. On the other hand, since thionamide 26 can be exploited as a versatile precursor we envisage to extend this particular replacement reaction to the use of further aminoalcohols containing central chirality.

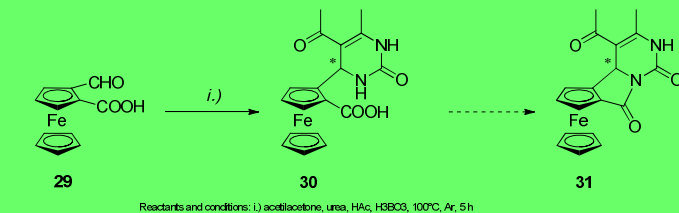
We hope that both types of chirality incorporated in the planned novel ferrocene- fused heterocycles representing a new class of nucleophilic catalysts will have sufficient control in variety asymmetric reactions capable of constructing products with excellent level of enantiomeric purity.

We wish to acknowledge the work of Gyömrői Ádám and Kovács Zoltán for chemical guidance.

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Biginelli-reaction on planar chiral ferrocene

By means of sequential annellations including Biginelli-reaction we initiated the preparation of a ferrocene-condensed pyrimido-pyrrolidine ring system of potential pharmaceutical interest as dihydropyrimidin derivatives have attracted great attention due to their pharmacological properties such as antibacterial-antihypertensive and calcium channel blocker activity as well as behaving as neuropeptide antagonists [10]. Biginelli-reaction is a simple one-pot method for the synthesis of dihydropyrimidines. The low-yielding condensations of β-dicarbonyl compounds with aldehydes and urea or thiourea can be improved using Lewis acids such as catalyst [11]. We started the preparation of pyrimido-pyrrolidine ring system with the Biginelli-reaction. We plan to evaluate the targeted compound in biological tests. In this context the production of the precursor ferrocenylpyrimidinone derivative necessary for the ring closing is also presented.



As showed above we have just started or preparative work achieving a novel planar chiral ferrocenyl-dihydropyrimidin 30. Actually the ring closing procedure is the subject of our ongoing synthetic study using the above mentioned protocol based on the use of cyanuric fluoride.

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