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Review

Synthesis and activity of potential antitumor ferrocenes

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Abstract

Ferrocene and its derivatives shown interesting antitumor activities in both *in vivo* and *in vitro* studies. A variety of derivatives of ferrocene and ferricenfum salts have been synthesized and their structure-activity relationships have been explored in order to evaluate possible candidates as antitumor drugs.

1. Introduction

Recently, interest has increased research into the antitumor activity of ferrocenes in relation to their chemical properties. Ferrocene and the ferricenium salt were identified in 1951 [1] and 1952 [2,3] (Fig. 1). Later, the basic features of the bonding present in these compounds were

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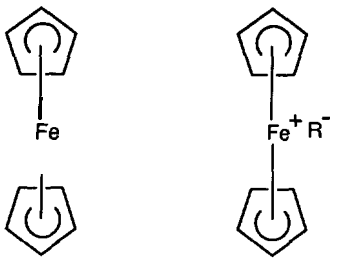


Fig. 1. Ferrocene (dicyclopentadienyliron) (Fc) and ferricenium salts (Fc^+).

enunciated by W. Moffitt [4] and J. D. Dunitz et al. [5]. More quantitative calculations were performed by E. M. Shustorovich et al. [6a-c] and C. J. Ballhausen et al. [7a-b]. These models have made use of the molecular orbital theory. The reason for this is clear in the case of ferrocene. The basic features in the bonding theory for sandwich compounds are obtained by the linear combinations of ring π orbitals transforming correctly in the point group symmetry D_{5d} and combining these with the appropriate metal orbitals.

The purpose of this paper is to review the synthesis and the antitumor activity of potential antitumor ferrocenes and ferricenium salts.

2. Alkylating agents of ferrocenes

Nitrogen mustards represented by Fig. 2 are well known as non-metabolically activated alkylating agents. The first nitrogen mustards were discovered to have anticancer activity and the first used clinically to treat a neoplastic disease which acts as alkylating agents [8]. These compounds were thought to be cytotoxic by their general inhibition of DNA synthesis [9]. These compounds undergo an internal nucleophilic substitution of chlorine as shown in Fig. 2.

Generally, alkylating agents for cancer treatment are known to depress hemopoiesis of leukemia. G. N. Yashchenko et al. [10] have introduced a nitrogen mustard type residue into ferrocenes and investigated the antitumor activity [11-13]. The nitrogen mustard type ferrocenes were synthesized from ferrocene carboxylic acid (I) or amino ferrocene (VI) as shown in Figs. 3 and 4 [10]. Some Schiff bases are known to have antitumor activity in their own right and instead of the electronic structure of iron, $[Ar](3d)^6(4s)2$, these complexes have the configuration $[Ar](3d)^7(4s)^1$ and are fairly labile to ligand substitution [14a-b].

Two types of nonpedigree mice and $C_{57}Bl_6$ mice were used for testing the antitumor activity of nitrogen mustard ferrocenes. The transplantable type tumors employed in the test were sarcoma 37 (S-

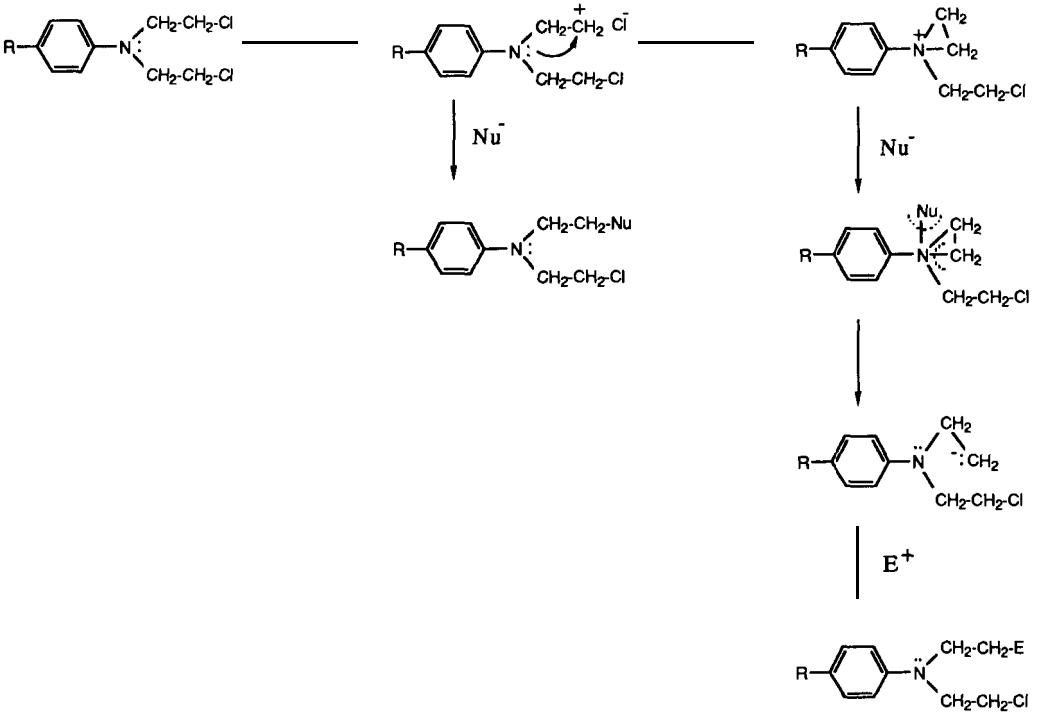


Fig. 2. Activation and reactions of nitrogen mustards. R: substituent; Nu^-: nucleophilic reagent; E^+: electrophilic reagent.

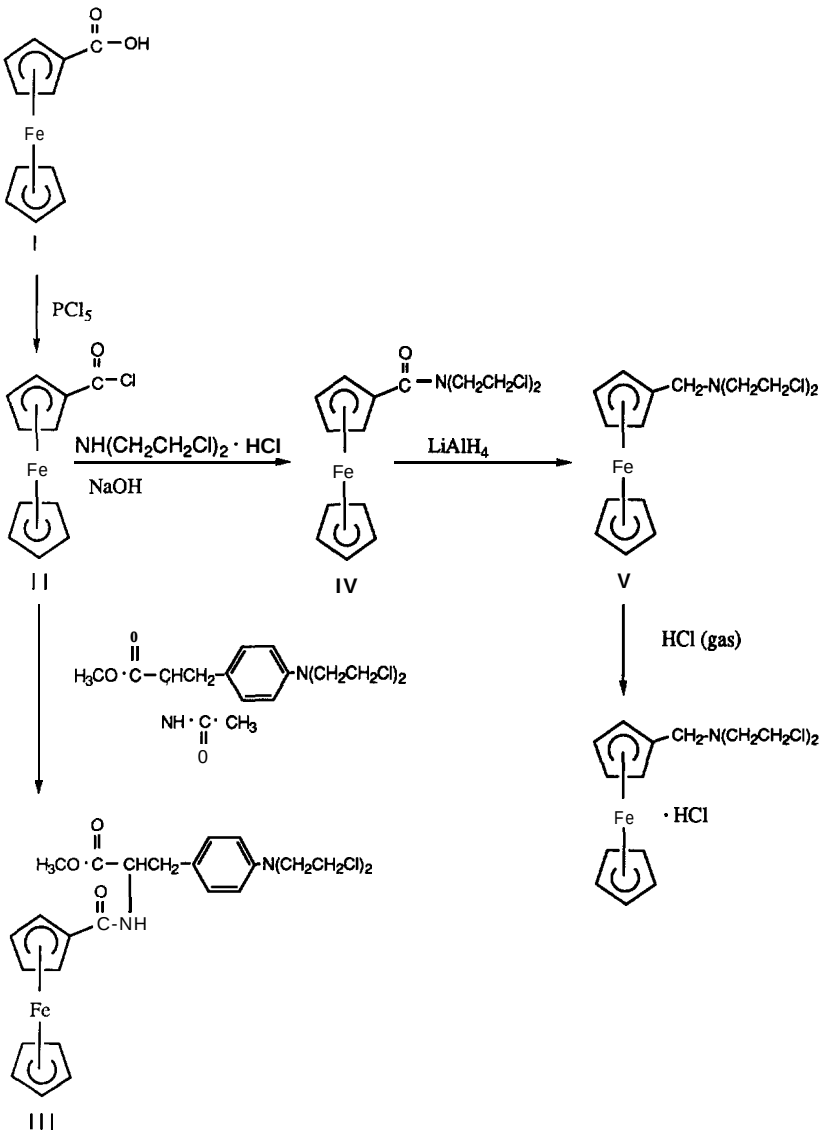


Fig. 3. Nitrogen mustard ferrocenes from ferrocene carboxylic acid (I).

37), mammary cancer adenocarcinoma AK-755, Lewis light tumor, and sarcoma 180 (S-180). The antitumor activities were estimated by the percentage inhibition of the tumor growth (%), and calculated from the following equation.

$$T\,(\%) = (Pk\text{-}Po)/Pk \times 100\ (\%)$$

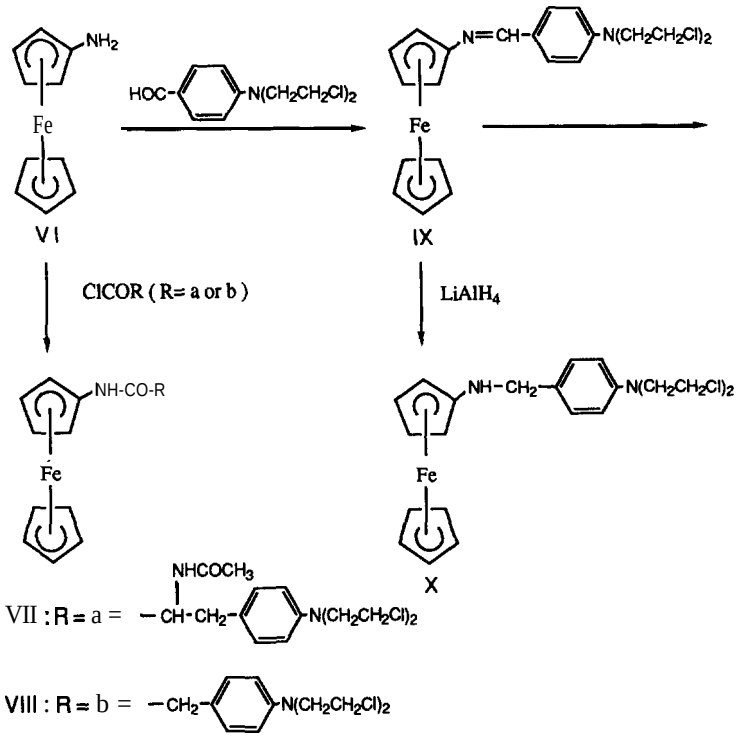
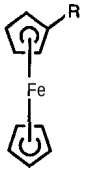


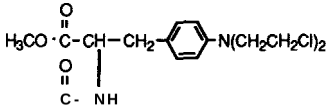
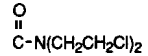
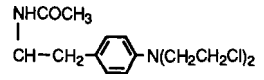
Fig. 4. Nitrogen mustard ferrocenes from amino ferrocene (VI).

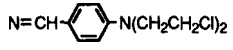
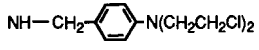
where T is the % inhibition of the tumor; Pk and Po are the mean weights of the tumors in the untreated control group and the treated group, respectively. From Table 1, it can be seen that the antitumor activity of the nitrogen mustard ferrocenes is very small and in some cases, they have stimulated the tumor growth. Furthermore, the antitumor activity of this combination was similar to the individual nitrogen mustards. This suggested that the introduction of the ferrocene residue into the nitrogen mustard group (dichloroethylamino group) with an antitumor efficiency is not effective in depressing the hemopoiesis of leukemia. However, some nitrogen mustard ferrocenes have shown low antitumor activity [10].

M. Wenzel et al, [15] have synthesized **ferrocenealdehyde-N-methyl-N-β-chloroethylhydrazone** (XI) from ferrocenealdehyde and **N-methyl-N-β-**chloroethylhydrazine hydrochloride according to the method of H. Bohme et al. [16] and synthesized **1-ferrocenyl-3-phenylpropen-1-one-3** (XII) from ferrocenealdehyde and acetophenone according to the method of E. R. **Hauser** et al. [17] and M. Wenzel et al. [18]. These compounds were

Table 1
Antitumor activity of nitrogen mustard ferrocenes



Compd. No.	R	Strain and sex of mice	Type of tumor	Therapeutic dose [mg/kg]	Inhibition of tumor [%]
III		Nonpedigree			
		female	s-37	250	39
		male	S-I 80	250	13
		Type $C_{57}Bl_6$			
		male	Lewis tumor	300	20
		female	AK-755	250	19
		Nonpedigree			
		female	s-37	5	22
IV		Type $C_{57}Bl_6$			
		male	Lewis tumor	5	10
		female	AK-755	5	9
		Nonpedigree			
		female	s-37	200	66
		male	S-i 80	200	-26
VII		Type $C_{57}Bl_6$			

		male	Lewis tumor	200	-12
		female	AK-755	200	**18**
		Nonpedigree			
		female	s-37	300	**18**
		male	**S-180**	300	13
VIII		**Type $C_{57}Bl_6$**			
		male	Lewis tumor	300	**38**
		female	AK-755	300	52
		Hybrid			
		male	L-1210	a	**-18**
IX		**Type $C_{57}Bl_6$**			
		male	Lewis tumor	a	**0**
		female	AK-755	a	-44
		Nonpedigree			
		female	s-37	a	-20
		Hybrid			
		male	L-1210	a	**-18**
X		**Type $C_{57}Bl_6$**			
		male	Lewis tumor	a	0
		female	AK-755	a	-6
		Nonpedigree			
		female	s-37	a	12

Note; A minus sign denotes stimulation of tumor growth and in the case of leucosis L-1210, a decrease in lifespan.

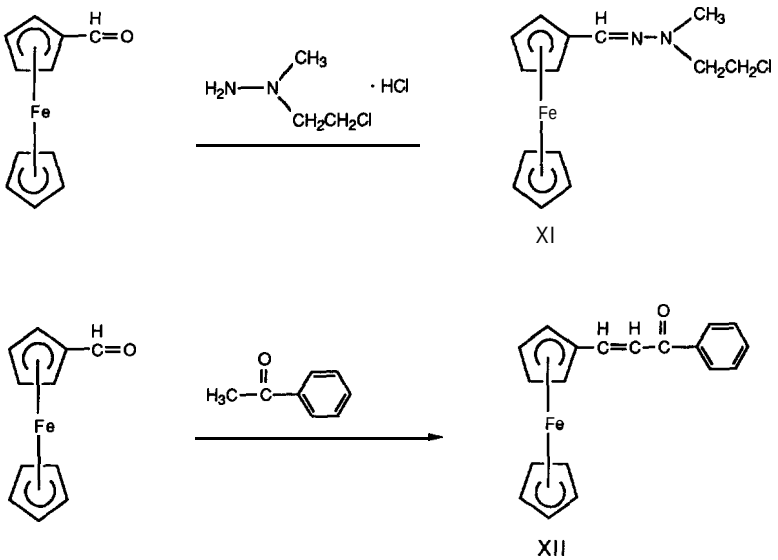
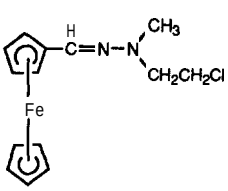
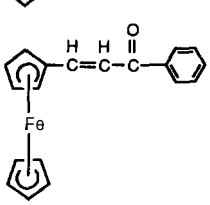


Fig. 5. Synthesis of antitumor potential fsrrocenes from ferrocenealdehyde.

Table 2
Antitumor activity of **ferrocenealdehyde-N-methyl-N-β-chloroethylhydrazone** (XI) and **1-ferrocenyl-3-phenylpropen-1-one-3** (XII) against Ehrlich **ascites** tumor

Compd. No	Compound	Concentration (mol/l)[a] $10X10^{-6}$	$5x10^{-6}$
		Increasing in % of untreated control group	
XI		35 ± 6	71 ± 4
XII		25 ± 9	34 ± 13

a: Incubation after 3 day administration in vitro.

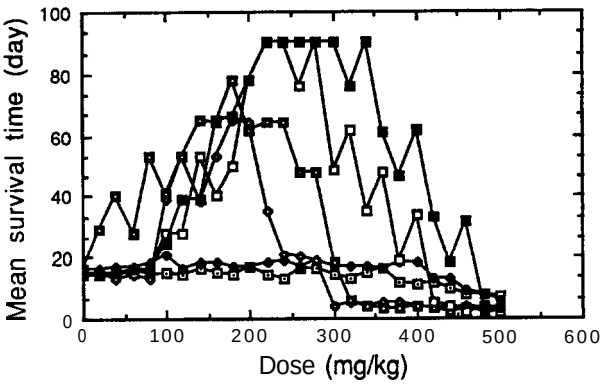


Fig. 6. Dosedependent influence of Fc and **(Fc⁺)s** on the mean survival time of mice bearing **Ehrlich ascites** tumor.

Fc (III); $Fc^+(FeCl_4)^-$ (XV); $Fc^+[C_6H_2(NO_2)_3O]^-$ (XVII); $Fc^+(H^5Mo_7O_{24})^-2H_2O$ (XIV); $Fc^+(1/2 \cdot Cl_3FeOFeCl_3)^{2-}$ (XVI); $Fc^+(Cl_3C{\cdot}COO \; j \; 2CCl_3COOH$ (XVIII)

tested for their antitumor activities against Ehrlich **ascites** tumors (Fig. 5) (Table 2).

3. Miscellaneous antitumor agents of ferricenium salts

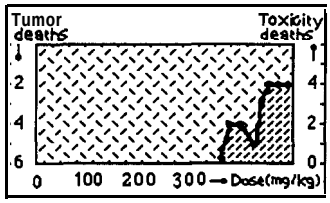
Some miscellaneous antitumor agents of ferricenium salts (XIV-XVIII) were prepared according to literatures **[3,** 19, 20, 21, 221.

The antitumor activity against Ehrlich **ascites** tumor was investigated in **CF1** mice for ferrocene (Fc) (XIII), and five types of ferricenium salts (XIV-XVIII) as a new type of water soluble antitumor agents **[23].** Fig. 8 shows the results of the tests by i.p. injection; the unsubstituted ferrocene (XIII) is inactive because of its water-insolubility (Fig. 6) **[23].**

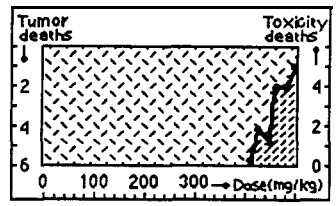
Ferricenium **picrate** (XVII) showed higher cure rates in the dose administrations of 220, 240 and 280 mg/kg. Ferricenium trichloroacetate (XVIII) also has good cure rates of 100% in the relatively broad dose range of 220-300 **mg/kg.** The ferricenium **picrate** (XVII) and ferricenium trichloroacetate (XVIII) can be expected to prolong and increase the lifespan of the mice by 490%. With both compounds (XVII and XVIII), the period between the optimum therapeutic range and the toxic ranges is very close together. The therapeutic indices (T.I.) are low compared with their T.I. of other antitumor metallocene as cis-platin. At higher dose rates, the antitumor activity of ferricenium salts has disappeared. The mechanism of antitumor activity of the ferricenium salts is to be investigated (Figs. 6, 7).

Table 3 shows the pharmacological and toxicological data ferrocene (Fc) and ferricenium salts **(Fc^+)[23].** The ferricenium salts (XV-XVIII) are very soluble in water, but ferricenium heptamolybdate (XIV) has no

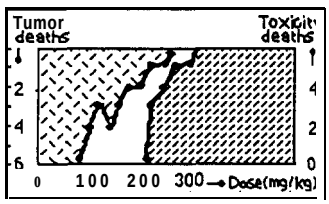
Fc (XIII)

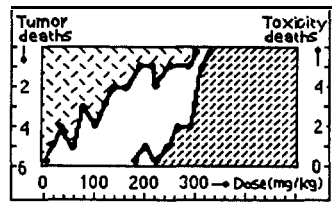


Ferricenium heptamolybdate (XIV)

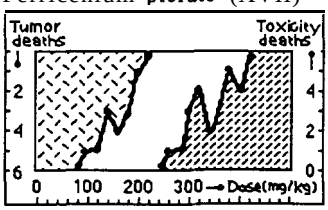


Ferricenium tetrachloroferrate (XV), Ferricenium-μ-oxo-bis(trichloroferrate)(XVI)





Ferricenium picrate (XVII)



Ferricenium trichloroacetate (XVIII)

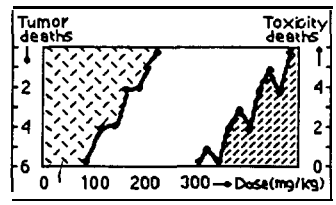


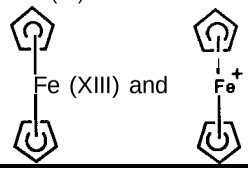
Fig. 7 Dose-dependent influence of ferrocene (Fc) and ferricenium salts Fc^+R^- observed within 90 days respectively. The number of tumor deaths: ▨ ; the number of toxic deaths: ▨ ; the number of cures: □ .

inhibiting effect because of its low water solubility. Both the tetrachloroferrate (XV) and μ-oxo-bis-trichloroferrate (XVI) have shown excellent efficiencies with the survival rate of 67% and 83% respectively of the CF_1 mice after administration with the optimum doses. Consequently, the corresponding mean survival period was extended to 65 and 78 days respectively, leading to increases in the lifespan of 350% and 380% compared with the untreated control groups (Fig. 6, Table 3).

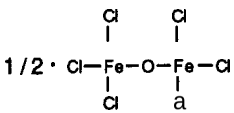
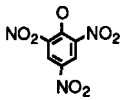
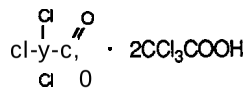
Table 3 shows the effect of a treatment with ferrocene (Fc) (XIII) and with ferricenium salts (Fc^+) (XIV-XVIII) on the occurrence of the tumor deaths, toxic deaths, and cures [23]. The toxic symptoms of the CF_1 mice treated with high doses of ferricenium salts (Fc^+) were diminished activity, shagginess of the fur, hyposthenia, and neuro-muscular disorder.

Table 3

Pharmacological and toxicological data of ferrocene (Fc) and ferricenium salts (Fc^+)



Fe (XIII) and $Fe^+ R^-$ (XIV – XVIII)

Compd. No.	R	Maximum cure rate (%)	Optimum dose range (mg/kg)	LD_{50} (mg/kg)	LD_{100} (mg/kg)	T.I.*
XIII	Fc	0		440	>500	
XIV	$H_5Mo_7O_{24} \cdot 2H_2O$	0		450	>500	
XV		67	180-200	240	300	1.3
XVI		83	180	290	320	1.3
XVII		100	220-240	340	420	1.7
XVIII		100	220-300	400	480	2.0

* Defined as LD_{50}/ED_{90}. T.I. values of cytostatic metal complexes for comparison purpose: cis-platinum, 8.1 ; titanocene dichloride, 3.3; titanocene dibromide, 4.5.

P. Kopf-Maier et al. [24] have studied the antitumor activity of ferricenium trichloroacetate (mono-trichloroacetate) (IXX), ferricenium trichloroacetate (di-trichloroacetate) (XVIII), ferricenium picrate (XVII), and ferricenium μ-oxo-bis-trichloroferrate (XVI). Mice inoculated with Ehrlich ascites tumors, followed by treatment with a single dose of ferricenium picrate (XVII) at 220 mg/kg i.p., showed 100% survival at 90 days after the treatment, whereas, the untreated mice had a mean survival of only 14.6 days. Ferricenium trichloroacetate (di-trichloroacetate) (XVIII) gave the similar results but the trichloracetate (mono-trichloracetate) (IXX) was less effective.

4. Conclusion

Little research has been devoted for synthesis and development of a screening test for the antitumor potential of ferrocenes. What research has been conducted to date has shed some light on the synthesis of potential uses of ferrocenes.

Still, the antitumor potential candidates of select ferrocenes with some predictable antitumor activities remains to be investigated. This will be one of the most fascinating tasks for cancer researchers in the near future.

5. References

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