MEHANOKEMIJSKA SINTEZA I ANTITUMORSKA ISPITIVANJA NOVIH OKSIM-ETERSKIH I ESTERSKIH HETEROCIKLIČKIH DERIVATA FEROCENA

ESTER AND OXIME-ETHER LINKED HETEROCYCLIC DERIVATIVES OF FERROCENE: MECHANOCHEMICAL SYNTHESIS AND ANTIPROLIFERATIVE EVALUATION

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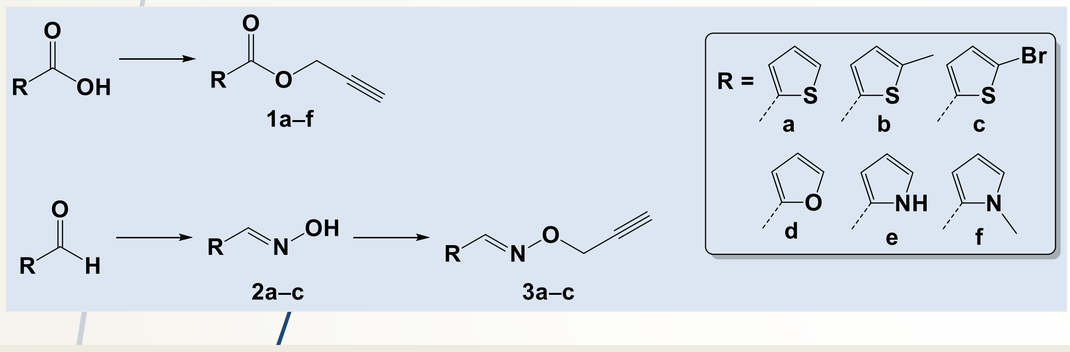
INTRODUCTION

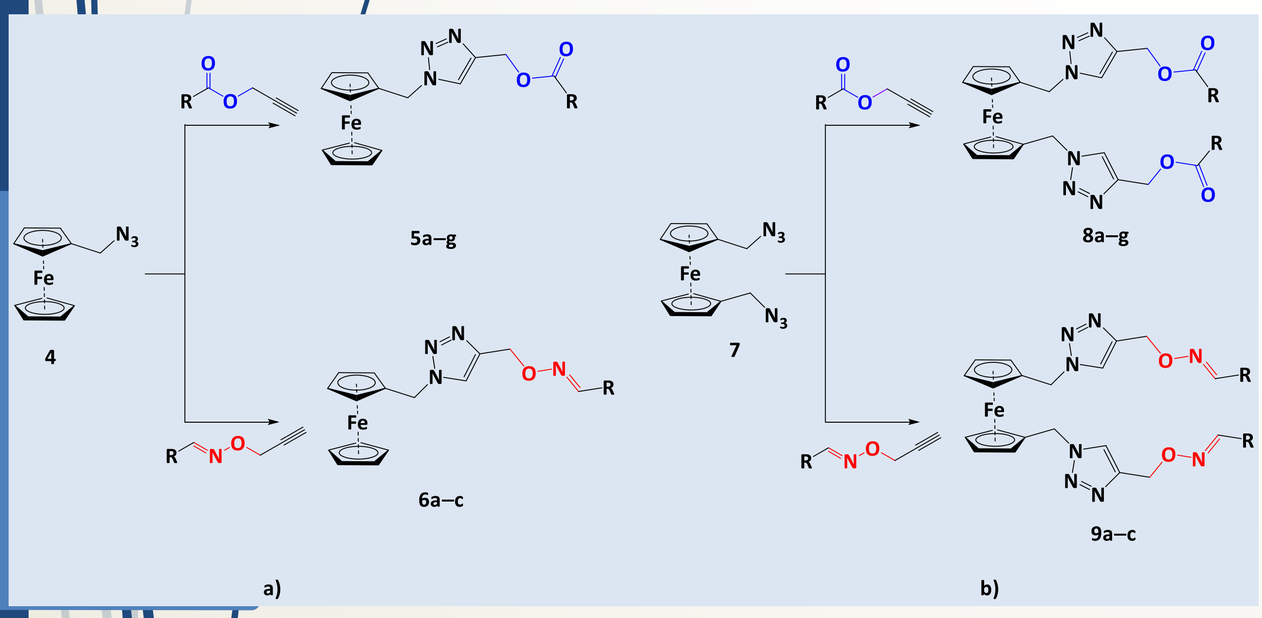
Cancer is one of the deadliest threats to human health worldwide. To overcome the current clinical problems associated with drug resistance, there is an urgent need to identify and test new promising molecular structures that represent potential drug candidates [1]. One of the most promising metal-containing scaffold explored in medicinal bioorganic chemistry is iron-containing sandwich-like ferrocene, due to its favourable physicochemical properties and reversible redox properties that enable ferrocene derivatives to be used as excellent candidates for drug development [2]. Ferrocenes are known to exert anticancer activity through formation of toxic quinone methide which alkylates glutathione (GSH), thus inhibiting the antioxidative system of cells or through a redox mechanism by its oxidation to ferrocenium form which generates reactive oxigen species (ROS) to toxic level [3, 4].

CHEMISTRY

The key intermediates *O*-propargylated esters and oxime-ethers were obtained by *O*-alkylation of the corresponding heterocyclic base with propargyl bromide in the presence of NaH, as a base (Scheme 1). Ester and oxime-ether linked heterocyclic derivatives of ferrocene were synthetized using regioselective copper(I)-catalyzed 1,3-dipolar cycloaddition under solvent-free mechanochemical conditions (Scheme 2).



Scheme 1. Synthesis of alkynyl derivatives **3a–c.** *Reagents and conditions: propargyl bromide, NaH, DMF,* overnight.

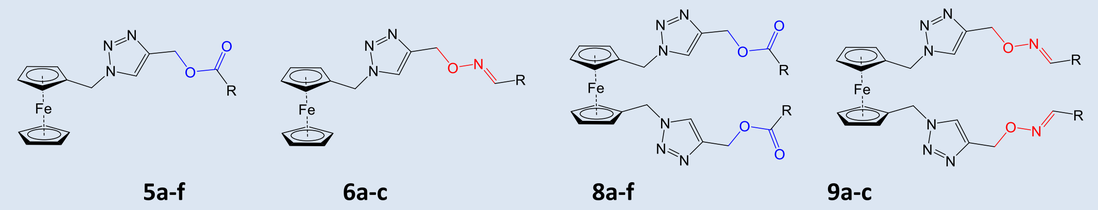


Scheme 2. Synthesis of *mono*- (a) and *bis*-substituted (b) ferrocene–heterocycle hybrids. *Reagents and conditions:* $Cu(OAc)_2$, 30 mL MeOH, two stainless-steel milling balls (7 mm), stainless-steel vessel, 90 min, rt, 25 Hz.

CONCLUSIONS

- ✓ Ester and oxime-ether linked *mono*- and *bis*-heterocyclic derivatives of ferrocene were successfully synthetized using green, mechanochemical synthesis.
- ✓ Ferrocene derivative **8f** with bis-*N*-methylpyrrole moiety was the most promising compound with strong and selective inhibitory activity against hepatocellular carcinoma (IC_{50}= **5±2** μM).

Table 1. The growth-inhibition effects (IC_{50}) *in vitro* of **5a–f**, **6a–6c**, **8a–f**, and **9a–c** on selected cancer cell lines.



Compd	IC_{50} (μM)				
	H460	MCF-7	SW620	HepG2	HEK293T
5a	>100	44±10	77±24	84±16	70±4
5b	>100	27±10	>100	40±9	57±41
5c	>100	59±40	>100	≥100	≥100
5d	>100	33±0.1	86±15	90±13	44±0.1
5e	40±1	18±2	36±4	24±4	20±8
5f	42±5	18±1	52±21	22±7	17±10
6a	>100	42±16	>100	67±34	84±15
6b	34±4	20±1	33±1	24±5	23±7
6c	41±5	16±4	35±10	25±16	22±7
8a	>100	51±23	>100	>100	>100
8b	>100	>100	84±12	44±7	25±14
8c	59±19	**6±3**	>100	**4±2**	13±0.4
8d	>100	>100	>100	>100	>100
8e	>100	12±2	>100	15±9	30±19
8f	≥100	>100	>100	**5±2**	**>100**
9a	62±3	**5±3**	≥100	**5±3**	7±2
9b	>100	12±2	≥100	**6±4**	33±23
9c	≥100	≥100	≥100	41±36	≥100

ANTIPROLIFERATIVE EVALUATION

Results of antiproliferative evaluations of compounds **5a–f**, **6a–6c**, **8a–f**, and **9a-c** on human tumour cell lines including lung carcinoma (H460), breast adenocarcinoma (MCF-7), colorectal carcinoma (SW-620), hepatocellular carcinoma (HepG2) as well as on normal embryonic kidney cell lines (HEK293T) are presented in **Table 1**. It can be noted that *bis*-substituted ferrocenes showed better inhibitory effect than their *mono*-substituted congeners. Among all tested compounds, *bis*-ferrocenes derivatives **8c**, **8f**, **9a**, and **9b** exhibited the best antiproliferative activity, particularly on hepatocellular carcinoma (HepG2) and breast adenocarcinoma (MCF-7) cells.

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