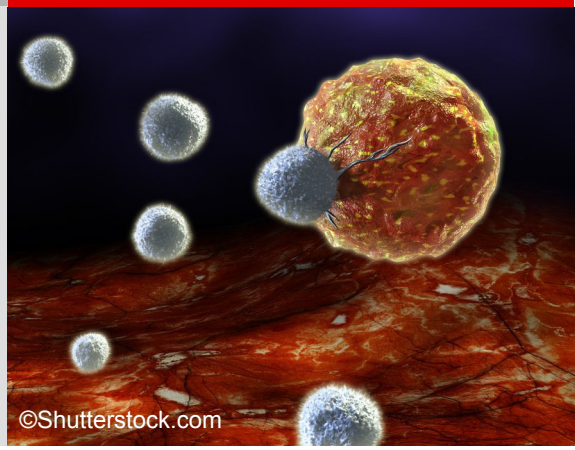
Fighting Cancer with Ruthenium Complexes

Ruthenium complexes are promising agents to induce apoptosis and inhibit growth of tumor cells which makes them a centerfold in investigations to cure cancer. Microwave synthesis can support the anticancer-drug research by efficient methods to generate various ruthenium complex derivatives.



1 Introduction

In recent years G-quadruplex DNA, has been a target for antitumor drugs as it is closely related to tumor cell growth. Especially ruthenium complexes of small polycyclic molecules bind strongly to G-quadruplex DNA stabilizing it and inducing apoptosis. Therefore the interest in quick and simple methods to prepare such promising agents is evident.

In the current work two coordinated ruthenium complexes have been prepared under microwave irradiation. In this approach the unique silicon carbide (SiC) reaction vessel was used to make heating of the applied non-polar, thus low microwave-absorbing, solvent even more efficient. The rapid heating within the SiC vessel helps to give access to the desired compounds in short time keeping reaction cycles to a minimum.

2 Equipment

Synthesis of the ruthenium complexes was performed in a Monowave 300 microwave synthesis reactor utilizing SiC reaction vessels C10 (see Fig. 1).

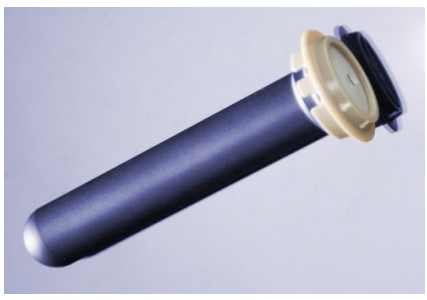
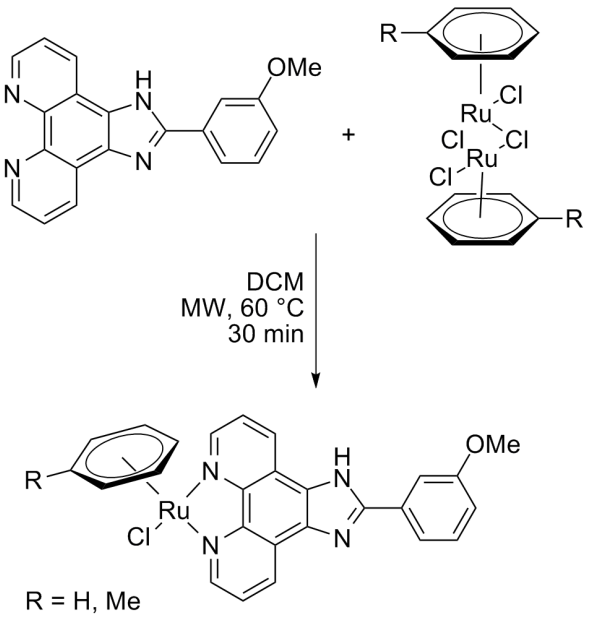


Fig. 1 10 mL silicon carbide vessel for Monowave 300

3 Experimental

In a typical setup dimeric $[ArRuCl_2]_2$ as the ruthenium source and the chelating phenanthroline derivative *m*-MOPIP were placed in a SiC vessel and dissolved in dichloromethane.[1] Before charging the vessel with the compounds it was already flushed with nitrogen. After sealing the vessel the septum was punched with a needle and the vessel was purged with nitrogen again for approximately 30 sec to create an inert atmosphere.[2] After subjecting the vessel to the microwave cavity the mixture was heated to 60 °C and kept at the target temperature for 30 minutes (see Fig. 2) to smoothly form the desired arene ruthenium complexes (Scheme 1).



Scheme 1:MW-assisted synthesis of arene Ru(II) complexes

After cooling to room temperature the solvent was removed in a rotavapor and the residue was resolved in methanol. After filtration slow evaporation of the solvent at room temperature furnished the yellow crude product.

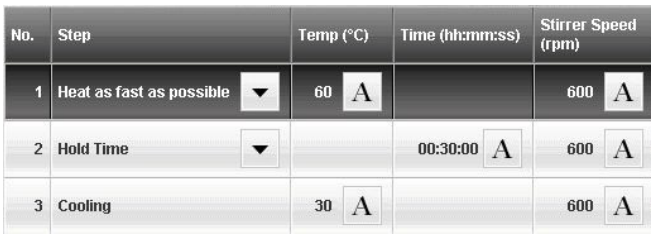


Fig. 2 Reaction parameters

4 Results

The established microwave process proved to be highly efficient since quantitative conversion and excellent isolated yield could be achieved in only 30 minutes at low temperatures. This is a clear improvement compared to the standard protocol under conventional heating which provides only moderate yields after 4 h reaction time.

As shown in Table 1 the enhancement in isolated yield was even more significant employing the methylated ruthenium source.[1]

Table 1: .Methods comparision

	Microwave T = 60 °C		**Conventional** T = 60 °C	
	Time	Yield	Time	Yield
R = H	30 min	88%	240 min	72%
R = Me	30 min	90%	240 min	68%

The resulting compounds have been characterized by X-ray single crystal diffraction. The effects of the complexes on cell viability and its antitumor activity were screened against human liver cancer HepG2 cells by MTT assay.

The evaluation of the prepared complexes revealed great selectivity between normal and cancer cells as well as excellent binding affinity to *c-myc* G4 DNA. Furthermore replication of the *c-myc* oncogene was effectively inhibited in vitro.[1] These findings make the newly prepared complexes highly potential compounds for ongoing anti-cancer drug research.

5 Conclusion

It was demonstrated that effective heating with the unique silicon carbide vessels in Monowave 300 can considerably reduce the time for preparing potential drug candidates in medicinal research. Coordinated, chelating ruthenium complexes reveal excellent application potential as small molecule inhibitors of *c-myc* G4 DNA.

Employing the automated version of Monowave 300 with its autosampler MAS24 can increase the throughput for preparing these compounds since up to 24 derivatives can be prepared efficiently within 12 h overnight.

6 References

[1]Q. Wu et al., *Dalton Trans.* **2014**, *43*, 9216-9225

[2]see application report XCAIA035EN for details

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