INVESTIGATION IN LOADING 5-FLUOROURACIL ABILITY OF IRON-ORGANIC FRAMEWORKS

Hoai Phuong Nguyen Thi[*], Duc Ha Ninh

Institute of Chemistry and Materials, 17 Hoang Sam, Cau Giay, Ha Noi

[*]Email: *hoaiphuong1978@gmail.com*

ABSTRACT

Materials MIL-53(Fe), MIL-88(Fe) and MIL-100(Fe) have the ability to absorb many different compounds. In addition, the materials are small in size, highly bio-compatible, with no human toxicity. These materials were chosen to carry 5-fluorouracil (5-FU) for cancer treatment. Synthetic materials were characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD) and surface characteristics (BET). 5-FU loading and releasing ability of MIL-53(Fe), MIL-88(Fe) and MIL-100(Fe) have been investigated by UV-Vis spectrophotometer. The results showed that the MIL-53(Fe), MIL-88(Fe), and MIL-100(Fe) are capable of carrying 5-FU with capacity exceeding 0.131 g/g, 0.28 g/g, 0.66 g/g respectively and mostly released after 10 days. The cancer cell toxicity and slow drug release ability of MIL(Fe)@5-FU were also tested by *in-vitro* method. Iron-organic frameworks are promising materials for cancer treatment.

Keywords: MIL-53 (Fe), MIL-88 (Fe), MIL-100 (Fe), drug delivery, 5-FU, cancer treatment.

1. INTRODUCTION

The 5-fluorouracil molecule ($C_4H_3FN_2O_2$) of molar mass 130.1 g is relatively small. Because it contains both hydrogen bond donors and acceptors (N-H and C=O groups) it has the ability to shape co-crystals or salts after combination with other molecules, that could enhance the biological properties. 5-Fluorouracil (5-FU) is a chemotherapeutic agent employed in the treatment of several solid, such as breast, colorectal, and head and neck cancers. It has a broad spectrum of activity against various types of cancer and has a mode of action based on interfering with thymidylate synthesis. This leads to apoptosis in cancerous cells. The main challenge of using 5-FU is its short biological half-life, low selectivity and toxic side effects on the bone marrow and gastrointestinal tract [1]. In order to reduce these limitations, drug delivery systems have been considered for the controlled release of 5-FU drug to target site [2, 3]. Literature precedent shows that mesoporous silica nanoparticles [4], nano-gels [5], chitosan nanoparticles [6], cationic cyclo-dextrin/alginate chitosan nano-flowers [7], magnetic nanoparticles [8], metal-organic frameworks (MOFs) (transition metal except iron) [9, 10] have been used as potential systems for 5-FU drug delivery.

Recently, MOFs has become a hotspot in the field of material science and undergone a rapid development because of the multifunctional nature [11-19]. New ordered porous MOFs

exhibit a series of advantages like large surface area, tunable structure and composition, adequate biocompatibility and natural biodegradability. A family of biodegradable MOFs, based on Fe(III) clusters and polycarboxylate ligands, has been synthesized [20, 21] and recently transposed under the nanoscale regime following "green" technology [22−24]. Such materials proved to act as efficient "molecular sponges", rapidly soaking important amounts of hydrophilic and hydrophobic drugs directly from aqueous solutions [25]. Iron-organic frameworks - MIL(Fe) have been studied for its application in catalysis, environmental treatment, drug delivery, gas storage, etc. [26-29]

In its application as a drug carrier, MIL(Fe) have been studied for the application of ibuprofen, acetaminophen [30, 31]. We have synthesized MIL-100(Fe), MIL-101(Fe) for gas (NOx, CO) and volatile organic compound adsorption. In this study, we present results of MIL(Fe) synthesis and applicability in drug delivery for 5-FU by evaluation of loading-release and toxicity of the drug carrier system.

2. EXPERIMENTAL SECTION

2.1. Chemicals

Chemicals which were provided by Sigma-Aldrich: Terephtalic acid ($C_6H_4(COOH)_2$), ≥ 99 %; trimesic acid ($C_6H_3(COOH)_3$), ≥ 95 %; Iron (III) chloride hexahydrate ($FeCl_3.6H_2O$), ≥ 99 %; Dimethyl-formamide (DMF), $HCON(CH_3)_2$, ≥ 99.5 %; Ethanol (C_2H_5OH), 96 %; pure 5-fluorouracil (5-FU); phosphate buffered saline (PBS); Trichloroacetic acid (TCA); Sulforhodamine B (SRB).

2.2. Materials synthesis

The synthesis process is referred from our previous studies with the highest efficiency conditions:

- MIL-53(Fe) nanoparticles were synthesized at room temperature by ultrasonic method. 0.83 g of terephthalic acid (H_2BDC) and 1.35 g of $FeCl_3.6H_2O$ were dissolved in 25 ml of DMF in a glass beaker. It was sealed and placed in an ultrasonic tank with a frequency of 20 kHz and capacity of 100 W in 7 hours.

- MIL-88(Fe) nanoparticles were synthesized at room temperature by ultrasonic method. 0.270 g $FeCl_3.6H_2O$ is dissolved with distill water and add 0.166 g H_2BDC in 5 ml DMF for 15 mins in ultrasonic machine with a frequency of 20 kHz and capacity of 400 W.

- MIL-100(Fe) nanoparticles were synthesized at room temperature by sol-gel process. $FeCl_3.6H_2O$ is dissolved with distill water and added slowly trimesic acid (H_3BTC) 5.10^{-3} M for 1 hour under magnetic stirring.

- After the reaction, the product was repeatedly washed with double-distilled water and ethanol. The material was dried at 80 ^{o}C in 8 hours.

2.3. Characterization

XRD patterns of materials were determined by the PXRD instrument (X'Pert Pro) using Cu-K$_\alpha$ radiation in a range of 5 to 40° at the Institute of Chemistry and Materials, Academy of Military Science and Technology. Morphologies of the materials were investigated by scanning electron microscopy (SEM) with different magnification at Institute of Materials Science,

Vietnam Academy of Science and Technology. BET surface areas, pore size distribution, and pore volume were measured by nitrogen adsorption/desorption iso-therms, at 393 K on a Quantachrome instrument at Institute of Chemistry, Vietnam Academy of Science and Technology. The 5-FU concentrations were analyzed by UV-Vis spectroscopy from 200 nm to 400 nm at the Institute of Chemistry and Materials, Academy of Military Science and Technology.

2.4. Drug loading and release

- Drug loading experiment was carried out with 0.01 g material in 1 ml 5-FU 10 g/l for 72 hours. The product was filtered, dried at 80 ^{o}C in 3 hours.

- 0.01 g of loaded material was immersed in 20 ml DMF for 24 hours at room temperature. The drug-released MIL(Fe) was gotten out of mixture by centrifugation (15 min, 6000 round/min) and determined the drug concentration. The 5-FU concentration was determined by UV-Vis spectrometry at wavelength λ_{max} = 265 nm. The equation of 5-FU calibration curve is defined as y = 20. (0.042x - 0.013) where y is the optical absorption Abs. The amount of drug loaded inside the material is calculated by the formula:

$$Q = m_{5\text{-}FU}/m_{MIL(Fe)} \text{ (g/g)}.$$

- The drug-loaded MIL(Fe) was placed in a vial and dipped in 5 mL of a dissolution medium (phosphate buffer solution - PBS), pH 7.4 at 37°C. At predetermined time intervals, the dissolution medium was collected by centrifugation and determined the drug concentration. The 5-FU concentration was analyzed by UV-Vis spectroscopy. The efficiency of drug release from the material is calculated according to the following formula:

$$H_{time} = 100 \times Q/Q_{max} \text{ (\%)}$$

where: Q_{max} is the maximum load capacity of material.

2.5. *In-vitro* cytotoxic assay

The cancer cell inhibition ability was evaluated by *in-vitro* cytotoxic assay designed by the National Cancer Institute, on breast carcinoma human cancer cell line - MCF7. The experiments were performed at Institute of Biotechnology, Vietnam Academy of Science and Technology. The goal of cytotoxicity assay is to screen, detect substances that inhibit the growth or destruction of cancer cells in *in-vitro* conditions, through determining cellular protein content after dyeing with sulforhodamine B by measuring optical density OD at 515-540 nm. MCF7 breast cancer cells were precultured in 96-well microplates (7000 cells per well) for 24 h and then incubated with 5-FU (20.0-0.8 µg/ml) for different times.

3. RESULTS AND DISCUSSION

3.1. Material characterization

The chemical composition of the material was characterized by XRD technique showed in Figure 1. XRD pattern of the sample (Figure 1) can confirm that the crystal phase of the product is MIL(Fe) due to monoclinic symmetry [32].
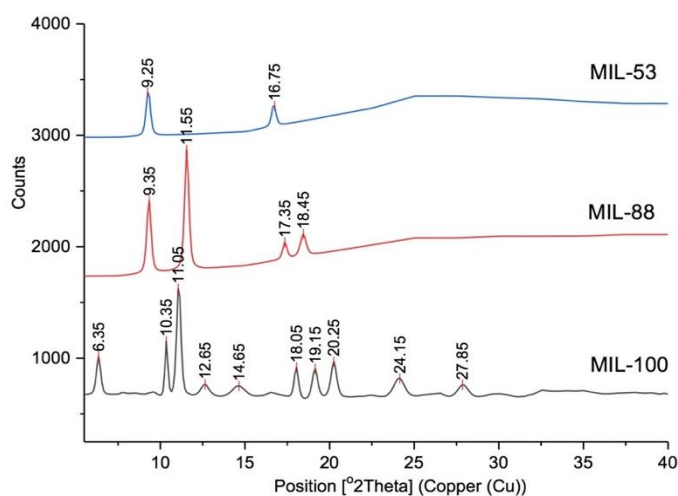
Figure 1. The XRD pattern of the MIL(Fe) materials.

Figure 2. The SEM images of the MIL-53(Fe), MIL-88(Fe), MIL-100(Fe) materials.

The morphology of the synthesized materials was observed by SEM method and shown in Figure 2. The SEM images show that the morphology of the materials is different. These differences relate to the conditions of synthesis and crystallization of the product including the ratio of reagents, solvents, synthetic techniques. The synthesized MIL(Fe) crystals are small, complete, homogeneous and have diameters of 200 nm to 500 nm. This size makes the material easy to move in the human body, especially in blood vessels.

The surface area and pore diameter are critical factors for drug adsorption and release in porous frameworks as drug delivery systems. The surface area of the materials measured by the N_2 adsorption isotherm was shown in Table 1 below. The surface characteristics of the materials are different. The MIL-88(Fe) has the smallest surface area and pore diameter compared to the other two materials. Meanwhile, the surface area of MIL-100(Fe) material is much larger than MIL-53(Fe) and MIL-88(Fe).

Table 1. Surface area, volume pore and diameter pore of the MIL(Fe) materials.

Materials	Surface area S_{BET} (m^2/g)	Volume pore (cm^3/g)	Diameter pore (nm)
MIL-53(Fe)	35.01	0.210 - 0.250	29.07 - 32.37
MIL-88(Fe)	17.42	0.032 - 0.034	8.05 - 9.00
MIL-100(Fe)	1,579.61	0.230 - 0.580	2.41 - 4.82

The surface area of the materials are related to its morphological state. As can be seen, MIL-53 exists in the "inhaled" state, so the value of surface area is quite low, but when it is saturated, it is maximally dilated [33]. For the MIL-88, the shape exists in long form just like grain and flexible structure [34]. Meanwhile, the MIL-100 has unchanged structure under different conditions. The results were found that, MIL-100(Fe) had the highest surface area (BET) and best storage capacity out of three MIL(Fe) samples equivalent to ZIF and MOF(Zn) [35, 17]. These surface parameters are related to the ability to carry and release drugs. The higher the surface area, the higher the carrying capacity. However, the higher the pore size, the faster the drug is released. The ability to bring and release drugs (5-FU) of these materials is presented in the next section.

3.2. Drug loading - release ability evaluation

By determining the 5-FU concentration in the DMF solution, the drug carrying capacity of MIL(Fe) materials was evaluated. The maximum load capacity of MIL-53(Fe), MIL-88(Fe) and MIL-100(Fe) corresponding to 0.131 g/g, 0.28 g/g and 0.66 g/g. This shows that the higher the surface area of the material, the higher the drug content in the material. However, this increase is not linear. Although the surface area of the MIL-100(Fe) is 90 times higher than the MIL-88(Fe), and 45 times higher than the MIL-53(Fe), the drug loading of MIL-100(Fe) is 2 to 5 times more than that of the MIL- 88(Fe) and MIL-53(Fe). Part of this may be due to the fact that the MIL-53(Fe) and MIL-88(Fe) are present in the "inhaled" state, so the surface area of these two materials is low. When they are absorbents, they are in the "hatching" state, so they can carry more drugs.

To determine the drug release ability, 0.01 g of the loaded material was soaked in 5 ml PBS solution at 37 $^{\circ}$C in different times and 5-FU concentration was measured. The results of drug release capacity are shown in Table 2 below:

Table 2. The results of 5-FU release of MIL(Fe) at different times.

No.	t, hours	MIL-53(Fe)		MIL-88(Fe)		MIL-100(Fe)	
		C_t, mg/l	H, %	C_t, mg/l	H, %	C_t, mg/l	H, %
1	0.25	60.286	23.01	115.749	20.67	261.037	19.78
2	2	92.762	35.41	174.392	31.14	483.290	36.61
3	16	163.952	62.58	290.196	51.82	882.064	66.82
4	24	177.571	67.78	307.199	54.86	875.427	66.32
5	48	190.286	72.63	310.166	55.39	865.800	65.59
6	72	209.762	80.06	358.693	64.05	983.783	74.53
7	120	243.190	92.82	430.447	76.87	1,160.019	87.88
8	168	256.952	98.07	408.554	72.96	1,192.259	90.32
9	240	258.619	98.71	444.825	79.43	1,210.337	91.69

Drug release efficiencies of all three materials in the first 15 minutes were quite similar and reached about 20 %. However, the 5-FU release rate of the materials is different. To achieve more than 80 % efficiency, MIL-53(Fe) material takes only 3 days. Meanwhile, after 3 days

MIL-100(Fe) only released 74.53 % drug content. And the drug release rate of MIL-88(Fe) only reached 79.43 % take up to 10 days. Other materials loading 5-FU had shorter release time, for example, $NH_2(CH_3)_2[Zn_3(L)_2 \cdot 3.5DMF]$ loading 5-FU 0.22 g/g had released 92 % of the drug for only 120 hours [17].

3.3. Activity of MIL-Fe@5-FU system on cancer cells

The cytotoxicity of 5-FU in MCF7 cells was evaluated based on its effect on cell growth by using the cytotoxic assay. The cytotoxicity of 5-FU was dose-dependent, the maximum cell death seen at concentration of 20 μg/ml. The evaluated results of the suppression of cancer cell over time are presented in Table 2 below, with IC_{50} is concentration of drug at which 50 % of the target is inhibited:

Table 3. IC_{50} of 5-FU and MIL(Fe)@5-FU system on MCF7 (μg/ml).

Material / Time, hours	5-FU	MIL-53(Fe)@5-FU	MIL-88(Fe)@5-FU	MIL-100(Fe)@5-FU
24	3.38 ± 0.32	8.97 ± 1.01	16.27 ± 2.41	13.72 ± 2.53
48	3.09 ± 0.48	6.72 ± 0.45	9.64 ± 1.52	9.41 ± 1.63
72	2.48 ± 0.17	5.25 ± 0.73	7.09 ± 0.68	6.09 ± 0.97
96	2.38 ± 0.19	3.77 ± 0.11	6.48 ± 0.57	5.87 ± 0.67
120	1.65 ± 0.18	3.75 ± 0.40	5.18 ± 0.61	4.68 ± 0.51

The results of the cytotoxicity test show that the MCF7 cells inhibitory capacity of different systems is different. As time increases, the inhibitory capacity on the cancer cells of all materials increases. However, this increase from the material is different. This result is related to the slow release of drugs from the carrier materials. The slower the release of drugs, the lower the inhibitory capacity. In Ref. 36, the IC50 values of 5-FU@DsAgNCs on MCF7 cells was 1.5 μg/mL. This shows that the slow release of these carriers is limited. From the results in Table 3, MIL-100(Fe) has the best storage capacity. Meanwhile, MIL-53(Fe) release drugs out of the material faster. However, the choice of material as carrier depends on other factors such as particle size, biological compatibility of the system, etc. Therefore, we are studying the biometric compatibility and the orientation to select the MIL(Fe) materials of cancer treatment applications.

4. CONCLUSION

The MIL(Fe) materials were successfully synthesized from $FeCl_3$ salt and poly-carboxylic acid. The morphology of the materials is different with the particle size ranges from 200 nm to 500 nm. The results were found that, MIL-100(Fe) had the highest surface area (BET) and best storage capacity out of three MIL(Fe) samples. With many advantages such as high carrying capacity, long lasting storage, small size, good bio-compatibility and high toxicity on cancer

cells, MIL(Fe) material is promising material for drug delivery on cancer treatment.

REFERENCES

1. Arias J. L. - Novel strategies to improve the anticancer action of 5-fluorouracil by using drug delivery systems, Molecules **13** (2008) 2340-2369.

2. Luo H., Ji D., Li C., Zhu Y., Xiong G., Wan Y. - Layered nanohydroxyapatite as a novel nanocarrier for controlled delivery of 5-fluorouracil, International Journal of Pharmaceutics **513** (2016) 17-25.

3. Pan G., Jia T. T., Huang Q. X., Qiu Y. Y., Xu J., Yin P. H., Liu T. - Mesoporous silica nanoparticles (MSNs)-based organic/inorganic hybrid nanocarriers loading 5-Fluorouracil for the treatment of colon cancer with improved anticancer efficacy, Colloids and Surfaces B **159** (2017) 375-385.

4. Egodawatte S., Dominguez S., Larsen S. C. - Solvent effects in the development of a drug delivery system for 5-fluorouracil using magnetic mesoporous silica nanoparticles, Microporous and Mesoporous Materials **237** (2017) 108-116.

5. Zhu K., Ye T., Liu J., Peng Z., Xu S., Lei J., Deng H., Li B. - Nanogels fabricated by lysozyme and sodium carboxymethyl cellulose for 5-fluorouracil controlled release, International Journal of Pharmaceutics **441** (2013) 721-727.

6. Yang H.C., Hon M.H. - The effect of the molecular weight of chitosan nanoparticles and its application on drug delivery, Microchem. Journal **92** (2009) 87-91.

7. Lakkakula J. R., Matshaya T., Krause R. W. M. - Cationic cyclodextrin/alginate chitosan nanoflowers as 5-fluorouracil drug delivery system, Materials Science and Engineering C **70** (2017) 169-177.

8. Ehi-Eromosele C. O., Ita B. I., Iweala E. E. J. - Silica coated LSMO magnetic nanoparticles for the pH-Responsive delivery of 5-Fluorouracil anticancer drug, Colloids and Surfaces A **530** (2017) 164-171.

9. Seda Keskin, Seda Kızılel - Biomedical Applications of Metal Organic Frameworks, Industrial & Engineering Chemistry Research **50** (4) (2011) 1799-1812.

10. Joseph Della Rocca, Demin Liu, Wenbin Lin - Nanoscale Metal-Organic Frameworks for Biomedical Imaging and Drug Delivery, Accounts of Chemical Research **44** (2011) 957-968.

11. Suh M. P., Park H. J., Prasad T. K., Lim D. - Hydrogen storage in metal-organic frameworks, Chemical Reviews **2** (2012) 782-835.

12. Czaja A. U., Trukhan N., Müller U. - Industrial applications of metal-organic frameworks, Chemical Society Reviews **5** (2009) 1284.

13. Kumar P., Deep A., Kim K. - Metal-organic frameworks for sensing applications, TrAC Trends in Analytical Chemistry **73** (2015) 39-53.

14. Murray L. J., Dincă M., Long J. R. - Hydrogen storage in metal-organic frameworks, Chemical Society Reviews **5** (2009) 1294.

15. Gu C., Li F., Li B., Xu J., Yang S., Luo M., Liu J., Liu G. - Rational synthesis of aporous polyhedral metal-organic framework carrier for controllable drug release, Inorganic Chemistry Communications **73** (2016) 26-29.

16. Kumar S., Kumar R., Ratnam A., Mishra N. C., Ghosh K. - Novel drug delivery system for photo induced nitric oxide (NO) delivery, Inorganic Chemistry Communications **53** (2015) 23-25.

17. Li Q., Wang J., Liu W., Zhuang X., Liu J., Fan G., Li B., Lin W., Man J. - A new (4,8)-connected topological MOF as potential drug delivery, Inorganic Chemistry Communications **55** (2015) 8-10.

18. Silva I. M. P., Carvalho M. A., Oliveira C. S., Profirio D. M., Ferreira R. B., Corbi P. P., Formiga A. L. B. - Enhanced performance of a metal-organic framework analogue to MIL-101(Cr) containing amine groups for ibuprofen and nimesulide controlled release, Inorganic Chemistry Communications **70** (2016) 47-50;

19. Wu J., Xu J., Liu W., Yang S., Luo M., Han Y., Liu J., Batten S. R. - Designed metal-organic framework based on metal-organic polyhedron: drug delivery, Inorganic Chemistry Communications **71** (2016) 32-34.

20. Horcajada P., Serre C., Vallet-Regi M., Sebban M., Taulelle F., Ferey G. - Metal-Organic Frameworks as Efficient Materials for Drug Delivery, Angewandte Chemie International Edition **45** (2006) 5974-5978.

21. Horcajada P., Surble S., Serre C., Hong D.Y., Seo Y. K., Chang J. S., Greneche J. M., Margiolaki I., Ferey G. - Synthesis and Catalytic Properties of MIL-100(Fe), an Iron(III) Carboxylate with Large Pores, Chemical Communications **27** (2007) 2820-2822.

22. Agostoni V., Anand R., Monti S., Hall S., Maurin G., Horcajada P., Serre C., Bouchemal K., Gref R. - Impact of Phosphorylation on the Encapsulation of Nucleoside Analogues within Porous Iron(III) Metal-Organic Framework MIL-100(Fe) Nanoparticles, Journal of Materials Chemistry B **1** (2013) 4231-4242.

23. Marquez A. G., Demessence A., Platero-Prats, A. E., Heurtaux D., Horcajada P., Serre, C., Chang J. S., Ferey G., Antonio de la Pena-O'Shea V., Boissiere C., et al. - Green Microwave Synthesis of MIL-100 (Al, Cr, Fe) Nanoparticles for Thin-Film Elaboration, European Journal of Inorganic Chemistry **32** (2012) 5165-5174.

24. Seo Y. K., Yoon J. W., Lee J. S., Lee U. H., Hwang Y. K., Jun C. H., Horcajada, P., Serre, C., Chang J. S. - Large Scale Fluorine-Free Synthesis of Hierarchically Porous Iron(III) Trimesate MIL-100(Fe) with a Zeolite Mtn Topology, Microporous and Mesoporous Materials **157** (2012) 137-145.

25. Horcajada P., Chalati T., Serre C., Gillet B., Sebrie C., Baati T., Eubank J. F., Heurtaux D., Clayette P., Kreuz C. - Porous Metal-Organic-Framework Nanoscale Carriers as a Potential Platform for Drug Delivery and Imaging, Nature Materials **9** (2010) 172-178.

26. Tuan A. Vu, Giang H. Le, Canh D. Dao, Lan Q. Dang, Kien T. Nguyen, Quang K. Nguyen, Phuong T. Dang, Hoa T. K. Tran, Quang T. Duong, Tuyen V. Nguyen and Gun D. Leed - Arsenic removal from aqueous solutions by adsorption using novel MIL-53(Fe) as a highly efficient adsorbent, RSC Adv. **5** (2015) 5261–5268.

27. Tuan A. Vu, Giang H. Le, Canh D. Dao, Lan Q. Dang, Kien T. Nguyen, Phuong T. Dang, Hoa T. K. Tran, Quang T. Duong, Tuyen V. Nguyen, and Gun D. Lee - Isomorphous substitution of Cr by Fe in MIL-101 framework and its application as a novel heterogeneous photo-Fenton catalyst for reactive dyes degradation", RSC Adv. **4** (2014) 41185-41194.

28. Nguyen Thi Hoai Phuong, Le Thanh Bac, Ninh Duc Ha, Doan Thi Ngai - Study on

synthesis metal-organic framework based on Fe-BDC, Journal of Chemistry **53** (4e1) (2015) 33-36 in Vietnamese.

29. Nguyen Thi Hoai Phuong, Doan Thi Ngai, Tran Dinh Tuan, Ninh Duc Ha - Synthesis and optical catalytic charactization of Fe-BDC and Cr-BDC materials, Journal of Chemistry **53** (4e1), (2015) 43-47 (in Vietnamese).

30. Patricia Horcajada, Christian Serre, Guillaume Maurin, Naseem A. Ramsahye, Francisco Balas, María Vallet-Regí, Muriel Sebban, Francis Taulelle and Gérard Férey - Flexible Porous Metal-Organic Frameworks for a Controlled Drug Delivery **130** (21) (2008) 6774-6780.

31. Jeff Gordon, Hossein Kazemian, Sohrab Rohani - MIL-53(Fe), MIL-101, and SBA-15 porous materials: Potential platforms for drug delivery, Materials Science and Engineering C **47** (2015) 172-179.

32. Xianghui Li, Weilin Guo, Zhonghua Liu, Ruiqin Wang, Hua Liu - Fe-based MOFs for efficient adsorption and degradation of acid orange 7 in aqueous solution via persulfate activation, Applied Surface Science **369** (2016) 130-136.

33. Esra Yilmaz, Emine Sert, Ferhan Sami Atalay - Comparison of solvothermal and ionothermal methods on catalytic activity of MIL-53(Fe), Anadolu University Journal of Science and Technology A- Applied Sciences and Engineering **18** (2017) 1107-1117.

34. Mingyan Ma, angelique Betard, Irene Weber, Roland A. Fischer, and Nils Metzler-Nolte - Iron-based Metal-Organic Frameworks MIL-88B and NH_2-MIL-88B: High Quality Microwave Synthesis and Solvent-induced Lattice "Breathing", Crystal Growth Design **13**(6) (2013) 2286-2291.

35. Maryam Gomar, Saeid Yeganegi - Adsorption of 5-fluorouracil, hydroxyurea and mercaptopurine drugs on zeolitic imidazolate frameworks (ZIF-7, ZIF-8 and ZIF-9), Microporous and Mesoporous Materials **252** (2017) 167-172.

36. Ishita Matai, Abhay Sachdev and Gopinath P. - Multicomponent 5-fluorouracil loaded PAMAM stabilized-silver nanocomposites synergistically induce apoptosis in human cancer cells, Biomaterials Science **3** (2015) 457-468.