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A New Cluster-Based MOF for Selective Gas Sorption and Treatment Effect on Acute Glomerulonephritis by Reducing NF-κβ Pathway Activation and Cytokines Release

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Abstract

A novel Co(II)-containing metal-organic framework $[Co_3(OH)_2(H_2TCPP)_2](DMF)_3$ (1) based on a linear trinuclear Co(II) cluster-based unit has been successfully prepared by using a nanosized tetracarboxylate ligand 2,3,5,6-tetrakis(4-carboxyphenyl)pyrazine (H_4TCPP) as the organic building block under the solvothermal reaction. Gas adsorption studies reveal that the mixtures of C_2H_2/CH_4 and C_2H_2/CO_2 could be selectively separated by the obtained resulting solvent free 1 (denoted as 1a hereafter). To deep evaluate the protective function of complex for AGN disease *in vitro,* the following experiments were conducted. Firstly, real time RT-PCR was carried out to determine the relative expression of Nf-κβ and tNf-α in the glomerulus cells after bacterial infection along with complex 1 treatment. Then, the ELISA was conducted to determine the IL-1β and IL-6 released by glomerular cells after complex 1 treatment. Finally, the results obtained through molecular docking exhibited possible regulation mechanism on the binding affinity between compound 1 and target protein.

Keywords: Metal–Organic Framework (MOF); Co(II)-Complex; Porous framework; Glomerular cells; Inflammatory response; Molecular docking

Introduction

Acute glomerulonephritis (AGN) is a common cause of renal injury, which is defined as a serious of glomerular diseases, presenting combined with an acute nephritic syndrome [1,2]. AGN has the serious of characters, ranging from asymptomatic, microscopic hematuria to the nephritic syndrome, nephrotic proteinuria, edema, hypertension, and acute renal injury [3,4]. AGN can be induced by various factors; the best well understood factor is the immunologically mediated injury to the glomerulus tissues. For example, the bacterial infection, virus infection, protozoa organisms and Henoch–Schonlein purpura (HSP) [5,6]. According to these infectious causes, post-streptococcal glomerulonephritis (PSGN) is the most common cause leading to the AGN procession. Thus, in this research, we aimed to explore the protective effect of the compound against the PSGN.

Separating the hydrocarbons is an indispensable process of industry, particularly acetylene of small molecule, due to acetylene is a significant start material for production of value-added chemicals, there is a great demand for acetylene with high purity [7-9]. It is difficult to separate C_2H_2 from CH_4 along with CO_2 via traditional cryogenic distillation separation technology, due to (a) their molecular weight, critical temperature as well as sublimation point are very similar, (b) energy consumption cannot be ignored [10]. Metal–organic framework (MOF) are a novel kind of materials with porous, which have broad application prospects in separation of C_2H_2/CH_4 along with C_2H_2/CO_2 [11-13]. This novel skeleton materials with porous can be finely tuned via selection of suitable building blocks to achieve high selectivity via the creation of suitable pore size and surrounds. On the other hand, Cobalt, as an important element within vitamin B_{12} active site, regulates DNA synthesis indirectly. Owing to its important biological activity, cobalt has attracted a lot of organometallic chemists along with biologists, with a view to its application in medicine. It has been reported that cobalt complexes have antiviral, antifungal, antimicrobial, activities of antioxidant along with parasitic, as well as activities of antiproliferative and antitumor [14-16]. Within this study, a novel metal-organic framework (MOF) material based on Co(II) with highly porosity $[Co_3(OH)_2(H_2TCPP)_2](DMF)_3$ (1) has been prepared under the solvothermal reaction. Gas adsorption studies reveal that the mixtures of C_2H_2/CH_4 and C_2H_2/CO_2 could be selectively separated by the obtained resulting solvent free 1 (denoted as 1a hereafter). In the biological research, we firstly performed the RT-PCR assay to detect the Nf-κβ, tNf-α relative expression level after bacterial infection and indicted compound treatment. The results showed that only the complex 1 could remarkably decreased the expression of Nf-κβ and tNf-α, but not compound and buffer solution. Then the IL-1β and IL-6 content in glomerular cells was also measured by ELSA detection kit, results showed that the compound inhibited the inflammatory level of glomerular cells. The possible binding modes of the compound with NF-κβ were acquired via pose scoring software along with molecular docking, which offered a possibility regulatory mechanism between the compound and target protein NF-κβ.

Experimental Procedure

Chemicals and measurements

The reagents along with solvents utilized in synthesis researches

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are all marketable and could be applied without further purification. The element content of H, C and N were analyzed by Perkin-Elmer 240C analyzer. Micromeritics ASAP 2020 surface area analyzer was used to determine CH_4, N_2, C_2H_2 and CO_2 adsorption isotherms. The central air conditioning system was installed at 23°C. The water bath adsorption isotherms at 296 K and liquid nitrogen and ice bath adsorption isotherms at 77 K and 273 K are adopted respectively.

Preparation and characterization for coordination polymer $[Co_3(OH)_2(H_2TCPP)_2](DMF)_3$ (1)

We put $Co(NO_3)_2{\cdot}6H_2O$ of 31 mg and 0.1 mmol, H_4TCPP which is 0.1 mmo and 56 mg, and added HBF_4 of 0.1 mL and 37%, mixed them into solid mixture, stored it in 4 mL DMF/ethanol/H_2O solution (v/v=6:1:1), we stirred it under the room temperature for half an hour. Then we transferred above reaction system to a 15 mL polytetrafluoroethylene high pressure hydrothermal reactor, heated rapidly to 120°C, and sealed for 72 hours at that temperature. Under the room temperature, the rate of reaction was reduced to 5°C /h. Compound 1 was precipitated as a pink bulk crystal with a yield of 47.2% (based on the $Co(NO_3)_2{\cdot}6H_2O$). The results of basic findings to $C_{73}H_{57}Co_3N_7O_{23}$: C, 55.60; H, 3.64; N, 6.22%. Found for C, 55.67; H, 3.49; N, 6.51%.

With Oxford X caliber E diffractometer we acquired the X-ray data of compound 1. Crysalispro software was used to analyze the strength data and convert it into HKL files. The SHELXS program based on direct method was used to establish the initial structure model of compound 1, and the SHELXL-2014 program based on least square method was modified. Mixing anisotropic parameters with non-H atoms of 1. Then the entire H atom by using AFIX command to geometrically fix on the C atom they are connected to. Table 1 details the crystallographic parameters along with refinement of compound 1.

Real time RT-PCR

During PSGN infection procession, the inflammatory response in the glomerular cells was reflected as the relative expression levels of Nf-κβ and tNf-α mRNA. Thus, in this experiment, the Nf-κβ genes and tNf-α expression level were detected by RT-PCR in accordance with the protocols with some modifications. Briefly, the glomerular cells in the phase of logarithmic growth were cultured in DMEM medium and planted in 6-well plates with final destiny of 5×10^5 cells per well. Then the cells were placed in an incubator of 37°C, 5% CO_2 condition for 12 hours incubation. Subsequently, the cells were randomly divided into five different groups, the control group (infected with PBS), the model group (infected with streptococcal strains + PBS treatment), H4TCPP group (infected with streptococcal strains + H_4TCPP treatment), buffer group (infected with streptococcal strains + buffer treatment) and the complex 1 group (infected with streptococcal strains, treated with complex 1). After infection and indication treatment, the total RNA in the glomerular cells was harvested with the TRIzol Reagent, and the concentration of the total RNA was quantified. Next, the RNA was reversely transcripted into cDNA with kit under the guidance of the manufacturer's proposal. Finally, the RT-PCR was carried out utilizing SYBR Green Master Mix (Roche) to determine tNf-α and Nf-κβ genes relative expression in the glomerular cells, gapdh wasn used as the internal control. The sequence of the primers was showed as follows: NF-κβ: CCACCCGGCTTCAGAATGG and AACCTTTGCTGGTCCCACAT,tnfα: CTGGGCAGGTCTACTTTGGG and CTGGAGGCCCCAGTTTGAAT, gapdh: AATGGGCAGCCGTTAGGAAA and GCGCCCAATACGACCAAATC. The results were calculated using 2−ΔΔCt method from triplicate preformation, and presented as mean ± SD.

ELISA detection

There is usually an increased level of inflammatory level in the local tissues on the occurrence of AGN, which is reflected as the high level of inflammatory cytokines IL-18 and IL-1β. Based on this, the ELISA assay was performed to detect the IL-18 and IL-1β content in glomerular cells after infected with streptococcal strains and compound treatment. This experiment was carried out under the guidance of the protocols. In brief, cells within the phase of logarithmic growth were collected and inoculated in 6-well plates among DMEM medium, 5×10^5 cells each well. After incubated at the condition of 37°C, 5% CO_2 for 12 hours, the cells were infected with bacteria and the compound was given for treatment. Next, the cell supernatant was collected from the wells and the content of the IL-18 and IL-1β was quantified with ELISA detection kit and microplate reader at 450 nm. The concentration of IL-18 and IL-1β in each group was calculated according the standard curve. This experiment was performed in triplicate

MTT assay

To evaluate the toxicity of complex 1 and H_4TCPP, the MTT assay was performed under the guidance of the instruction with some modification. In brief, the normal human cells HEK-293 were inoculated in 96 well plates, incubated with CO_2 of 5% at 37°C, for 12 hours. Then serious concentrations of H_4TCPP and complex 1 (0.25, 0.5, 1, 10, 100, 200 μM) was put to wells for one day cell treatment. Subsequently, the cell medium was discarded and the cells were washed using PBS for three times. MTT solution was added into the well for further treatment, followed by the DMSO addition so solve the formazan. Ultimately, every hole absorbance was determined at 490 nm. This experiment was carried at least three times in prediction of soil salinity indicators over the entire study area significant of the resulted prediction was made by RMSE

Molecular docking

Discovery studio 3.0 is widely utilized software of commerce. It was chosen as a platform for the simulation of molecular docking, which

Empirical formula	$C_{64}H_{36}Co_3N_4O_{20}$
Formula weight	1357.76
Temperature/K	293(2)
Crystal system	Orthorhombic
Space group	Pmna
a/Å	23.0236(3)
b/Å	15.6289(3)
c/Å	16.93200(18)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	6092.70(16)
Z	2
ρ_{calc}g/cm^3	0.740
μ/mm^{-1}	0.444
Data/restraints/parameters	6401/1/216
Goodness-of-fit on F^2	1.104
Final R indexes [I>=2σ (I)]	R_1=0.0899, ωR_2=0.2530
Final R indexes [all data]	R_1=0.0991, ωR_2=0.2581
Largest diff. peak/hole / e Å^{-3}	0.75/-1.42
CCDC	1953587

Table 1: Compound 1's crystallographic parameters along with refinement.

can realize molecular docking of proteins and small molecules. It is customized at the aim of better supporting the development of high-precision scoring function. The structure of ligand was derived from the structure of crystal acquired by measuring X-ray and downloaded from the protein date bank (PDB), using ligand preparation tools before the docking program was performed. The receptor protein, NF-κβ, was 1SVC (PDB ID) which has been widely utilized for the simulation of molecular docking along with the screening of drug since it has protein residues and double helix structure at the same time. The CDOCKER Tool has been utilized to generate the structures of receptor along with ligand for the simulation of molecular docking, grid box length is set at 40, it is enough large to cover all the docking bag and involve double helix chains as well as protein moieties.

Results and Discussion

Molecular structures

Title complex 1 could be afforded by making $Co(NO_3)_2 \cdot 6H_2O$ along with H_4TCPP to react in H_2O/EtOH/DMF mixed solvent under the evaluated temperature. It is noteworthy that the H_4TCPP ligand could not be dissolved in the solvents of water, EtOH as well as MeOH, but it could be dissolved into DMF along with DMA. Thus in the synthesis of complex 1, we choose DMF as the main solvent with the addition of EtOH and water as the assistant solvents. The results of refinement along with structural decomposition of crystal data under the room temperature show that complex 1 crystallizes within the orthogonal space group pmna, showing a three-dimensional skeleton structure along the b axis as well as c axis channels. Within this asymmetric unit, there are two Co(II) ions independent of crystals, a coordination water molecule, a half H_2TCPP_2- ligand, a μ2-OH group as well as a coordination water molecule, all of them are conducive to the formation of a neutral skeleton structure. Two kinds of Co(II) independent of crystal use the coordination modes of typical octahedron, in which the coordination environment of the center of Co(II) with four syn-syn bridged carboxylates along with two μ2-OH group is more complex than that of the terminal Co(II) with two undeportonated carboxyl groups, one μ2-OH group, a coordinated water molecule as well as two syn-syn bridged carboxylates. The distances of Co(II)–O bond are between 1.946(5) and 2.013(6) Å, which are similar to those of other coordination polymers based on Co(II) containing similar ligands of carboxylate. A remarkable feature of structure is the existence of $\{Co_3(OH)_2(COO)_4(HCOO)_4\}$ cluster, which is composed of two symmetrically related Co_2 ions along with a Co_1 ion passing through two μ2-OH groups as well as eight carboxylate groups of separate H_2TCPP connectors which have the separation of Co_1-Co_2 is 3.426 °A (Figure 1a). In addition, each H_2TCPP connector links six Co(II) ions of four independent $\{Co_3(OH)_2(COO)_4(HCOO)_4\}$ clusters to form a network of 3D porous (Figure 1b). There are two major molecular channels, the sizes of which are 7.82 ⊆ 9.95 and 9.07 ⊆ 13.06 °A 2 along c axis, respectively and a kind of channels, the size of which is 7.1 ⊆ 9.03 °A 2 along b axis (Figures 1c and 1d). In order to better understand the skeleton, 1' s network was simplified via TOPOS software. The cluster of $\{Co_3(OH)_2(COO)_4(HCOO)_4\}$ was regarded as 8-connected node while H_2TCPP connector was regarded as 4-connected node. Thus, the entire 1' s framework was simplified as (4,8)-connected network. The point symbol is {4^16.6^12}{4^4.6^2}2 belongs to the topology of scu-type.

Selective gas sorption properties

Permanent porosity was determined via adsorption isotherm of N_2 at 77 K. Before measuring the gas adsorption, the synthesized 1 was exchanged with the dry acetone, and then activated in vacuum at 353 K at the aim of producing activated 1a. On the basis of (Figure 2a), the adsorption isotherm of N_2 reveals the adsorption behavior of type-I with the maximum N_2 uptake capacity of 173.3 cm^3g^{-1} with microporous materials characteristics. According to the adsorption isotherm of N_2 at 77 K, Brunauer-Emmett-Teller (BET) and the specific surface area of Langmuir were 713 m^2g^{-1} and 784 m^2g^{-1}, respectively. 1a's permanent micropore along with special structure impel us to study its latent applications as the adsorbents for important industrial gases for example, C_2H_4, C_2H_2, CO_2 as well as CH_4. C_2H_4, C_2H_2, CO_2 as well as CH_4 absorption isotherms were collected at 1 atm, 296 along with 273 K. According to Figures 2b and 2c, the isotherms are fully reversible without hysteresis. C_2H_2 uptake of complex 1a at 296 K and 273 K was 84.2 along with 103.8 cm^3g^{-1} at 1 atm, respectively. The adsorption capacity of C_2H_2 under the room temperature was much higher than UTSA-68 of 70.2 cm^3g^{-1}, ZJU-30 which is 51.5 cm^3g^{-1}, MIL-53 of 71.6 cm^3g^{-1}, MAF-2 which is 70.3 cm^3g^{-1}), as well as UTSA-35 of 64.8 cm^3g^{-1} adsorption capacity, but it lower than MOF-508 which is 89.4 cm^3g^{-1}. Compared with C_2H_2, complex 1a at 296 K can adsorb a small amount of CH_4 (13.4 cm^3g^{-1}) along with CO_2 (42.3 cm^3g^{-1}), revealing that complex 1a has the latent capacity to separate C_2H_2/CO_2 along with C_2H_2/CH_4 under environmental conditions. At 296 K, the absorption of C_2H_2/CO_2 in 1a was close to 2.2, lower than that of MAF-2 (3.7), but higher than other adsorbents (1.0-1.7) absorption. The higher absorption of C_2H_2 was because of mild pore size along organic ligands between π···π deposits as well as phenylacetylene molecules. At the same time, due to strong Lewis acidity of C_2H_2, the HC≡C≡H…N interactions also conducive to adsorption of C_2H_2. In order to study the feasibility of selective separation of C_2H_2 from binary mixture of C_2H_2/CH_4 along with C_2H_2/CO_2 in 1a, we calculated the adsorption selectivity using Ideal Adsorbed Solution Theory. Figure 2d shows the functional relationship between the adsorptive selectivity of the mixture of C_2H_2/CH_4 along with C_2H_2/CO_2 and the total volume gas pressure at 296 K in 1a. We can observe that selectivity of 1a in the condition of equal molar mixture of C_2H_2/CO_2 is 4.6-4.0 in the whole range of the room temperature and pressure, which is similar to UTSA-68a and UTSA-50a (5.0), indicating that 1a is a promising MOF for separation of C_2H_2/CO_2. The mixture of C_2H_2/CH_4 for C_2H_2 adsorption selectivity was deep assessed. Normally, the content of methane within natural gas in high-grade gas fields is more than 90%. Therefore, the adsorptive selectivity

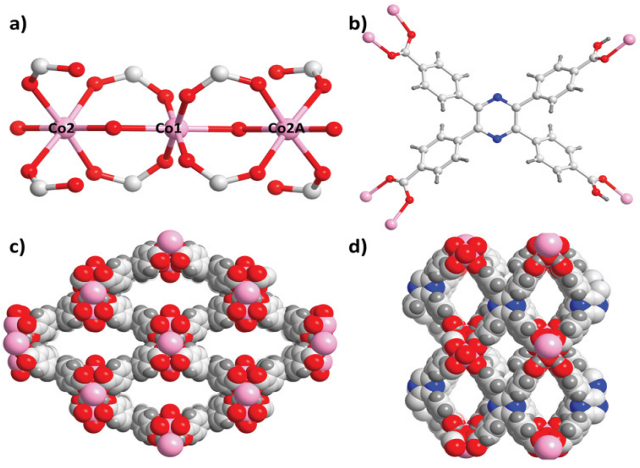

Figure 1: (a) A view of the cluster of $Co_3(OH)_2(COO)_4(HCOO)_4$ within 1. (b) H_2TCPP linker coordination pattern. The one-dimensional channels observed along the b axis (c) and the c axis (d).

of natural gas upgrading was calculated by using three representative molar consistences of C_2H_2 among the binary mixture of C_2H_2/CH_4, i.e., 0.1, 0.05 as well as 0.01. According to Figure 2d, in the range of 100 kPa, the selectivity of C_2H_2 to CH_4 exceeds 16, which means that the separating of natural gas and C_2H_2 will be very simple. Natural gas conversion is an efficient approach for the production of acetylene within modern chemical industry. In general, C_2H_2/CH_4 content ratio in pyrolysis gas is close to 1:1, so the adsorption selectivity of equimolar mixture of C_2H_2/CH_4 was calculated. The selectivity of 1a is between 16 and 19, which is similar to that of UTSA-34b, UTSA-34a as well as UTSA-33a.

Compound reduces activation of NF-κβ pathway in glomerular cells

As the central effector of the inflammatory signaling pathway, the NF-κβ protein plays a vital important role in the AGN disease. NF-κβ pathway activation could product many chemokines along with pro-inflammatory cytokines, for example IL-6 and IL-1β. These anti-inflammatory and regulatory cytokines were reported to take great role in the immune regulation. So, in this experiment, we want to detect the protective effect of compound on the AGN was mediated by the regulating of NF-κβ pathway, which was convinced via the RT-PCR assay. According to Figure 3, in model group, there is remarkably increased level of the Nf-κβ, tNf-α mRNA expression level in glomerular cells compared with the control group, reflecting a more serious state of the AGN. After complex 1 treatment, we can see Nf-κβ mRNA and tNf-α level expression was obviously reduced, which is significantly different from the model group. However, both H_4TCPP and the buffer solution have no effect on the decrease of activation of NF-κβ pathway.

Compound reduced IL-1β and IL-6 content in glomerular cells

As the down-stream production of the NF-κβ pathway, there was also a significantly increased level of IL-1β and IL-6 in glomerular cells, which is regarded as the important indicator of diagnostic criteria for acute glomerulonephritis. Thus, in this experiment, the level of IL-1β and IL-6 content in glomerular cells after infected with streptococcal strains and compound treatment was determined via ELISA. According to the results of Figure 4, there is a significant increased IL-6 and IL-1β level content in glomerular cells, which is significantly from control group ($p<0.001$). After compound 1 treated, IL-6 and IL-1 beta levels decreased significantly and almost returned to the normal level. However, both H_4TCPP and the buffer solution have no effect on the reduction of IL-1β and IL-6 content in glomerular cells. This result indicated the complex 1 could inhibit the inflammatory state in glomerular cells and exert a protective effect on AGN. Further studies need to be done on secondary variables that could be suitable for predicting salinity and sodicity variables and the choices of increasing accuracy regarding soil sampling distribution in the space.

Cell toxicity assay

Within previous research, we have authenticated that the synthetic complex showed excellent protective effect on AGN by reducing the NF-κβ pathway activation and the release of inflammatory cytokines. However, the prepared complex is based on the H_4TCPP ligand, which is notorious for its high toxicity. So, in this experiment, the MTT experiment was performed to detect the cell toxicity of both the complex 1 and H_4TCPP. As the results showed in Figure 5, after treated with the complex 1 and H_4TCPP, compared with control group, cell viability

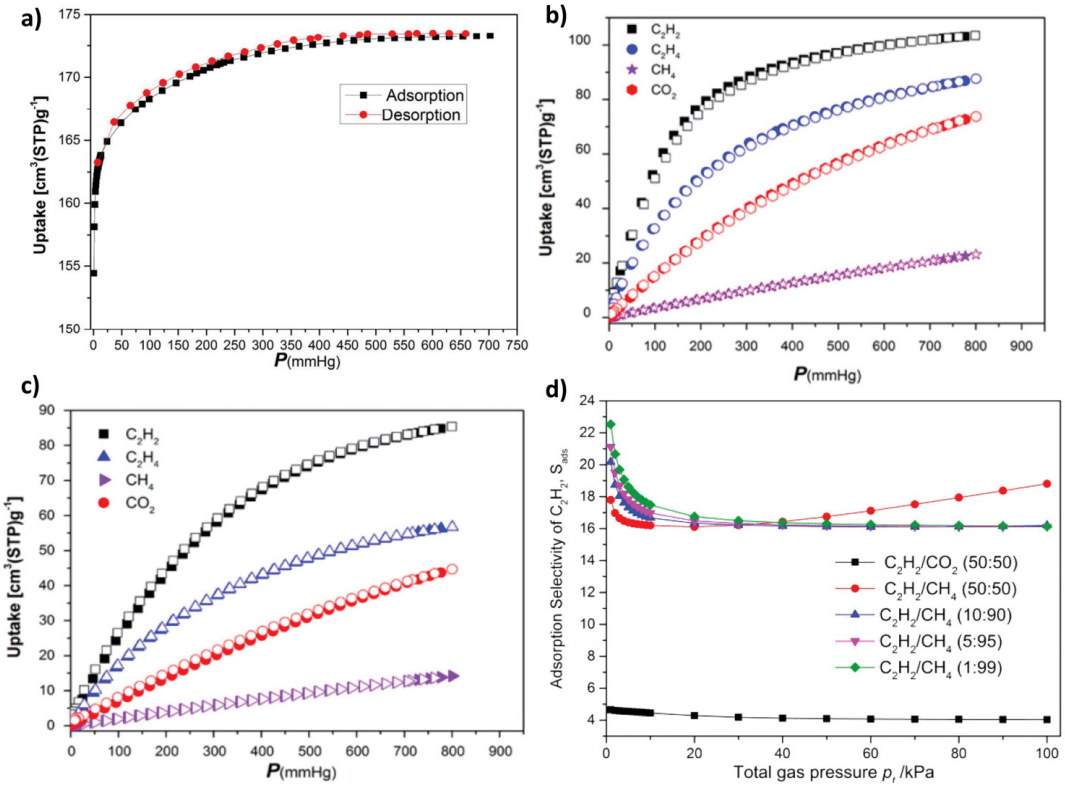

Figure 2 (a) At 77 K, 1a' s N_2 sorption isotherms; (b) At 273 K, 1a' s gas sorption isotherms; (c) At 296 K, 1a' s gas sorption isotherms; (d) The predicted IAST selectivity of 1a.

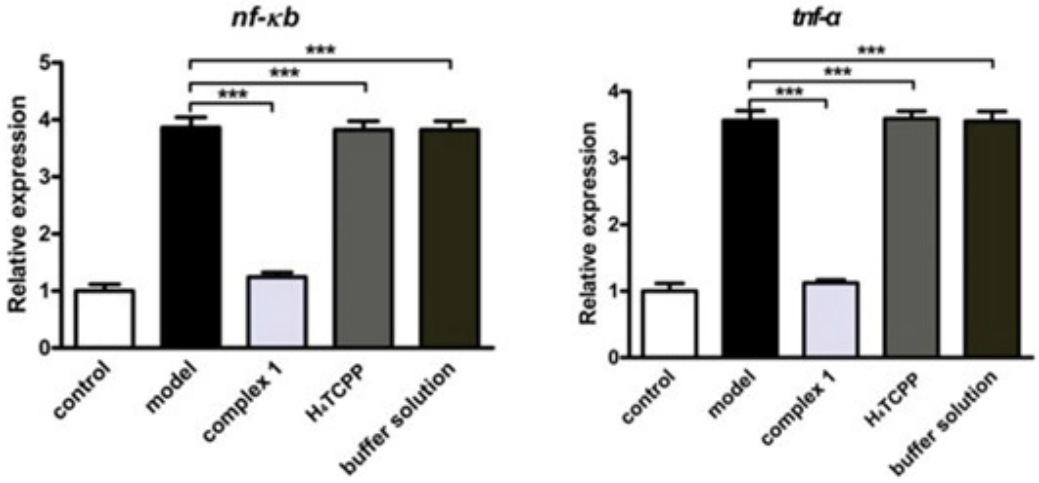

Figure 3: Decreased NF-kβ pathway activation in glomerular cells after complex 1 treatment. After streptococcal strains infection and indicated treatment, the relative expression of *nf-kβ*, *tnf-α* genes in glomerular cells were evaluated by RT-PCR. Data was presented as mean ± SD. *** means p<0.01.

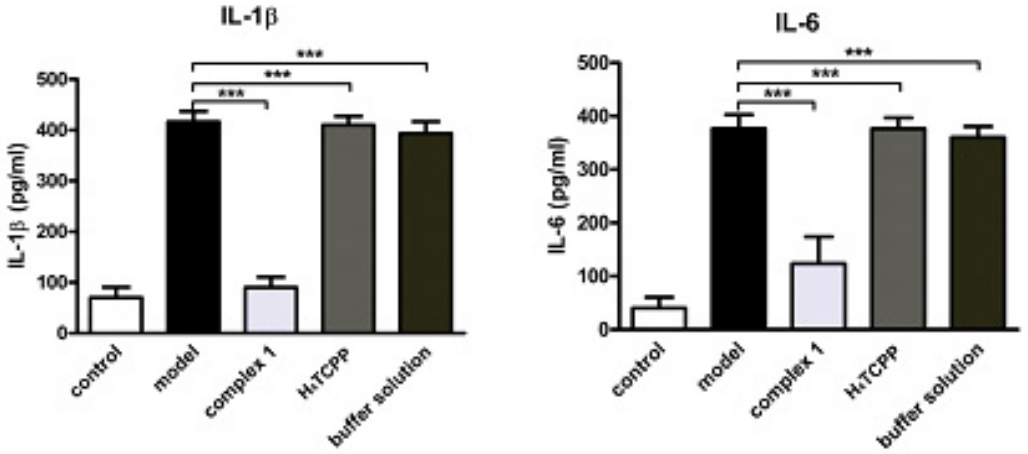

Figure 4: Reduced IL-1β and IL-6 content in glomerular cells after treated with complex 1. The glomerular cells were infected with streptococcal strains and treated with compound. The IL-1β and IL-18 content in glomerular cells was evaluated by ELISA. This experiment needed to repeat for three or more times. *** means p<0.01.

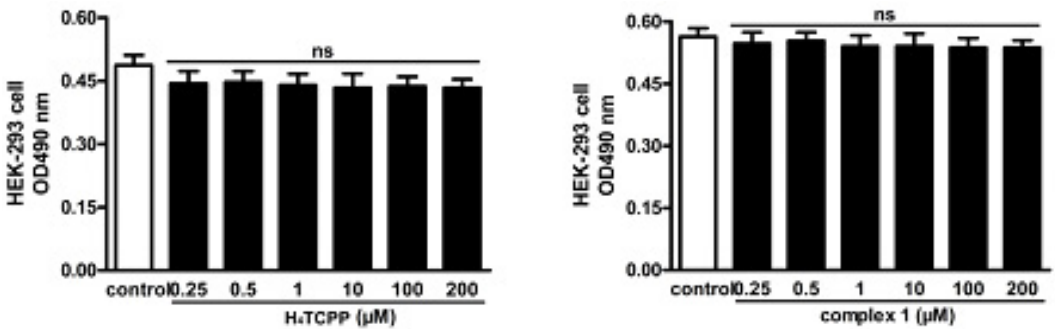

Figure 5: No toxicity of complex 1 and H_4TCPP on the normal human cells. With complex 1 and H_4TCPP we treated HEK-293 cells, and determined cell viability via MTT method. ns means no difference compared with the normal group.

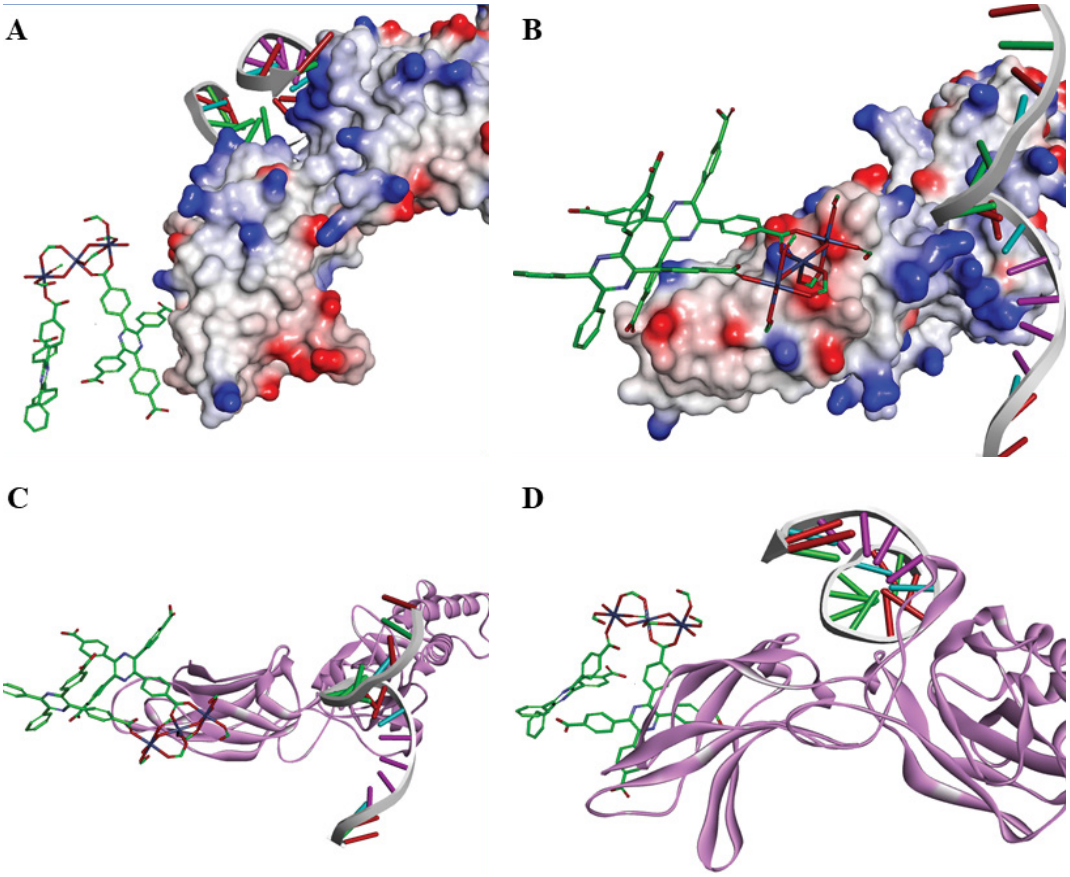

Figure 6: The whole view of the binding modes compound interacting with the receptor protein NF-κβ (PDB: 1SVC) (A, B). Local views indicate that functional groups of the compound are fully wrapped into the surface grooves of receptor interaction site, suggesting that the compound might influence the binding affinity between DNA and protein. Compounds are represented as green models with rod-shape, while proteins are represented as the surface models of ionizable (C, D). Binding pattern stick model of NF-κβ and the synthetized compound.

had no significant effect. This result indicated both the complex 1 and H_4TCPP have no toxicity on normal human cells.

Molecular docking

The results exhibited that the synthesized compounds have the latent ability to influence the binding affinity with protein. At the aim of understanding compound and targeting DNA-protein complex possible binding patterns, the molecular docking simulation was performed. Figures 6A and 6B shows both surface binding mode and possible binding patterns views. It can be observed that ligands spherical representation has been processed at the docking bags. From the surface, several functional groups of the compound showed the latent interactions with the target protein. The local views that revealed in Figures 6C and 6D show binding interaction between receptor and ligand. We can observe that the two functional groups of the compound have been wrapped into the binding surface of protein sites along with helix chains; such binding modes will further affect the binding affinity with the target protein

Conclusion

In summary, we have successfully generated a microporous Co-based metal-organic frame based on the trinuclear cluster of $Co_3(OH)_2(COO)_4(HCOO)_4$ under solvothermal reaction. The content of complex 1 was determined via elemental analysis along with single crystal X-ray diffraction. The research of gas adsorption revealed that C_2H_2/CH_4 and C_2H_2/CO_2 mixtures could be selectively separated by the obtained activation 1a. In biological research, the protective effect of the compound on AGN was evaluated. Firstly, the RT-PCR was carried out to determine Nf-κβ and tNf-α relative expression in glomerular cells after combined therapy, the results exhibited the complex 1 could significantly reduce Nf-κβ and tNf-α relative expression. The IL-1β and IL-6 content in glomerular cells also suggested the compound could reduce the inflammatory level of bacterial infected glomerular cells and paly a protective role in the AGN. The results of ligand posture scoring module along with molecular docking offered a latent binding pattern of targeted protein NF-κβ as well as synthetic compound, and offered a possible mechanism for the interaction between the compound and NF-κβ protein.

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