Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

UiO-66-NH_2 as an effective solid support of quinazoline derivatives for antibacterial agents against gram-negative bacteria

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Section S1: Materials and General Methods

Chemicals used in this work. Sigma Aldrich (St. Louis, MO, USA) provided all of the reagents and chemicals, which were utilized without additional purification. The sorption studies were conducted using ultrahigh-purity grade N_2 from Air products (purity of 99.999%).

Analytical techniques. Thin-layer chromatography was performed on silica gel glass plates (Silica gel, 60 F254, Fluka, Merck, Darmstadt, Germany). Column chromatography was performed on Kieselgel S (silica gel S, 0.063–0.1 mm, Merck, Darmstadt, Germany). Melting points were recorded on a Gallenkamp apparatus (Toledo, OH, USA), and corrected. Elemental analysis was performed on a Leco Model CHN-600 elemental analyzer (Ontario, Canada). Fourier-transform infrared (FT-IR) spectra were collected using KBr pellets on a Thermo Nicolet model 470 FT-IR spectrophotometer (Thermo Scientific, Waltham, MA, USA). Nuclear magnetic resonance (NMR) spectra were recorded using a Varian-400 MHz spectrometer (^{1}H-NMR at 400 MHz and ^{13}C-NMR at 100 MHz; Agilent Technologies, Santa Clara, CA, USA) using deuterium dimethyl sulfoxide (DMSO-d_6). Tetramethylsilane was used as an internal reference and chemical shifts were stated as part per million; (δ values, ppm). Microwave synthesis was performed using the CEM microwave system (Matthews, USA) used to synthesize quinazoline derivatives **6a**–**c**. Absorption measurements were carried out using an Agilent 8453 spectrophotometer (Santa Clara, USA) supported with 1.0 cm quartz cells (Varian, Austria). Scanning electron microscopy (SEM) images were taken using an FEI SEM Quanta Inspect S50 scanning electron microscope (ThermoFisher PN1113094) operated at an accelerating voltage of 15–30 kV. Powder X-ray diffraction (PXRD) analysis was measured using a Shimadzu-6100 PXRD diffractometer (Shizmadu-series, Kyoto, Japan) using CuKα radiation with λ = 1.542 Å. Diffraction data were collected within the 2θ range of 20–80° at a rate of 1°/min. The measurement was performed at room temperature and atmospheric pressure. N_2 sorption measurements were performed using a PMI's BET Sorptometer (BET-201-AEL, PMI, USA). A liquid N_2 bath was used for measurements at 77 K. For thermogravimetric analysis (SHEMADZU (TGA–50) curve, a 5 mg sample was heated to 600 °C at a rate of 5 °C/min. The weight was monitored as a function of temperature. Detailed description of the morphology was examined by Transmission electron microscopy (TEM; CM10-Phillips Amsterdam, Netherland).

Section S2: Synthesis of Quinazoline Derivatives

5-Bromoanthranilic acid **2**.[1] 10.0 g of anthranilic acid **1** was dissolved in glacial acetic acid and cooled to below 15 °C. Then bromine in acetic acid was added until the color of the bromine became reddish-brown. Before this stage, the combination had been transformed into a dense mass of white crystals comprised of mono and dibromo anthranilic acid hydrobromides. The sample was heated in water containing concentrated hydrochloric acid and filtered while hot under suction after being washed with benzene and dried. Boiling water was used twice to remove the insoluble residue. When the filtrate was cooled, the monobromo anthranilic acid precipitated in large quantities.

6-Bromoquinazolin-4(3H)-one **3**.[2] Acetic acid (5 mmol, 0.3 ml) was added to a combination of 5-bromoanthranilic acid **2** (5.0 mmol, 1.08g) and formamide (50 mmol, 1.99 ml), and the mixture was heated under reflux for 4-6 hours. The resultant liquid was put into ice-cold water and stirred for 30 minutes after the reaction was completed. Compound **3** was obtained by filtering the precipitation and washing the filter cake with water.

6-Bromo-4-chloroquinazoline **4**.[3] In a water bath, a suspension of 6-bromoquinazolin-4(3*H*)-one **3** (0.01 mole, 2.25 g) in phosphorus oxychloride (0.05 mole, 7.5 ml) was heated for 2 hours with a few drops of pyridine. After cooling, the reaction mixture was gently poured over crushed ice. Compound **4** was obtained by filtering the solid produced, washing it with water, drying it, and purifying it using ethanol *via* crystallization.

General procedure for the synthesis of ***5a***,***b***. An amine (1.23 mmol) and Hunig's base (1.23 mmol, 0.21 ml) were added to a DMF (8 ml) solution of 6-bromo-4-chloroquinazoline **4** (1.23 mmol, 0.23g). For two hours, the reaction mixture was refluxed. The reaction mixture was diluted with EtOAc (100 ml) after it was finished. The organic layer was dried over anhydrous $MgSO_4$, then filtered before the solvent was extracted under reduced pressure. The compounds **5a**,**b** were obtained by purifying the residue directly on a silica column and eluting it in hexanes with a gradient of ethyl acetate (15-75%).

General Procedure of the Suzuki-Miyaura Reaction: A combination of 6-bromo-4-quinazoline **5a**,**b** (0.54 mmol) and tetrakis(triphenyl phosphine) palladium(0) (2.5 mol percent) was stirred for 1 hour at room temperature in DMF (30 ml) under nitrogen. Arylboronic acid (1.08 mmol) in water (2.0 ml) and sodium carbonate (1.62 mmol) were added to the above mixture. For 24 hours, the reaction mixture was refluxed. The solution was extracted into dichloromethane (3×50 ml) after 50 ml of water

was added. The organic layer was washed with water (3×100 ml) before being dried over anhydrous sodium sulfate. The crude product was purified by column chromatography [hexane:ethyl acetate (7:3)] before being recrystallized with ethanol.

Section S3: Characterization of Quinazoline Derivatives

5-Bromoanthranilic acid **2**. White powder; yield 83%; mp 213-215°C. ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 5.47 (brs, 2H, NH_2, exchangeable with D_2O); 6.66 (d, 1H, aromatic, *J = 8.0 Hz*); 7.01 (s, 1H, aromatic); 7.63 (d, 1H, aromatic, *J = 8.0 Hz*); 9.44 (brs, 1H, OH, exchangeable with D_2O). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 109.3 (aromatic); 117.8 (C-Br); 118.6, 127.9, 133.5 (aromatic); 152.9 (aromatic); 169.4 (C=O).

6-Bromoquinazolin-4(3H)-one **3**. White powder, yield 64%; mp 268°C. ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 7.69-7.71 (m, 1H, aromatic); 7.92 (s, 1H, aromatic); 7.97-8.02 (m, 1H, aromatic); 8.20 (d, 1H, aromatic, *J = 8.0 Hz)*; 10.26 (br, 1H, NH exchangeable with D_2O). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 121.8, 122.5, 127.0, 128.9, 136.1 (aromatic); 141.5 (C_2-quinazoline); 148.6 (aromatic); 159.9 (C=O).

6-Bromo-4-chloroquinazoline **4**. White powder, yield 59%. ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 7.91 (d, 1H, aromatic, *J = 8 Hz*); 8.00 (m, 1H, aromatic); 8.19 (d, 1H, aromatic, *J = 8 Hz*); 9.05 (s, 1H, aromatic). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 121.7, 122.4,127.0, 128.8, 141.5, 148.6 (aromatic Cs); 157.7 (C_2-quinazoline); 159.9 (C_4-quinazoline).

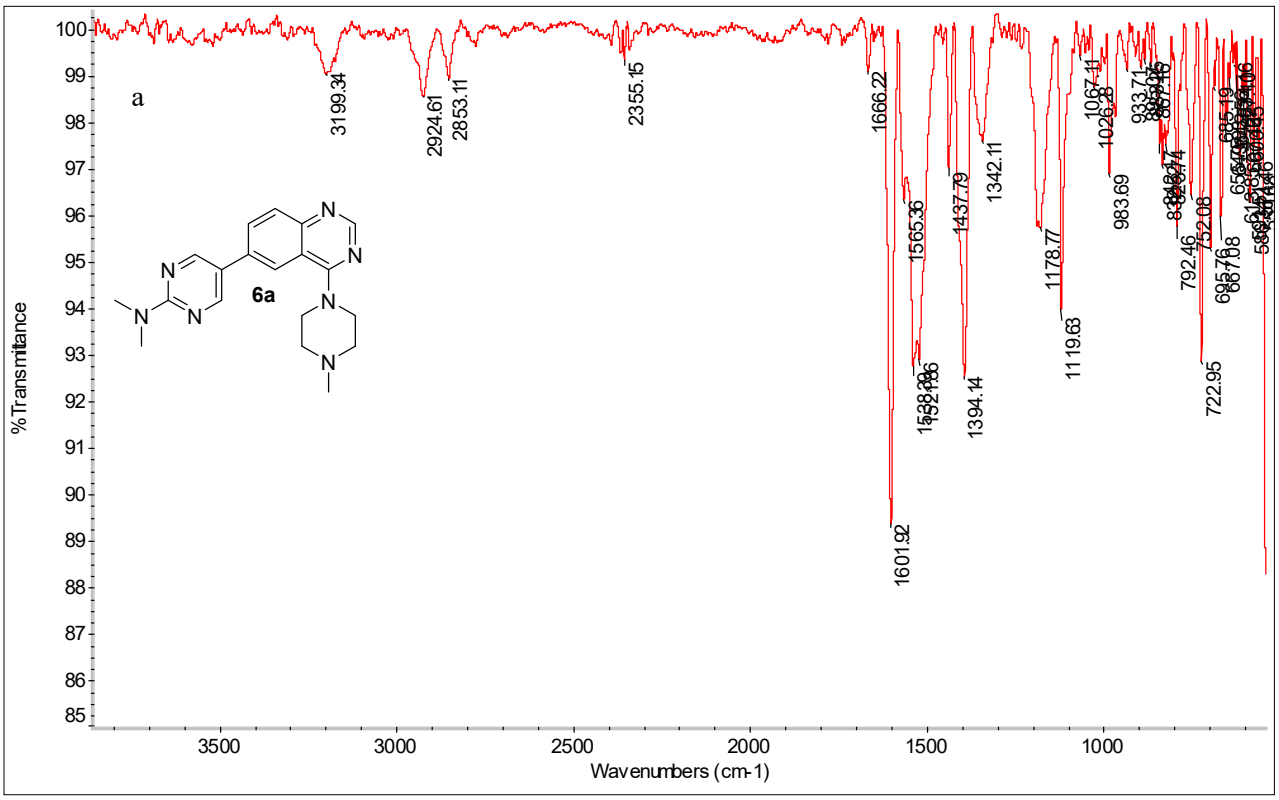
6-Bromo-4-(4′-N-methylpiperazin-1′-yl)quinazoline **5a**. Brown powder, yield 73%; mp 196°C. ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 2.24 (CH_3); 2.47 (m, 4H, piprazine); 3.75 (m, 4H, piprazine); 7.74 (d, 1H, aromatic, *J = 8 Hz*); 7.93-7.96 (dd, 1H, aromatic); 8.08 (d, 1H, aromatic); 8.63 (brs, 1H, aromatic). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 46.1, 49.4, 54.8 (methyl piprazine); 117.4, 118.3, 127.7, 130.7, 136.2, 150.6 (aromatic); 154.3 (C_2-quinazoline); 162.9 (C_4-quinazoline).

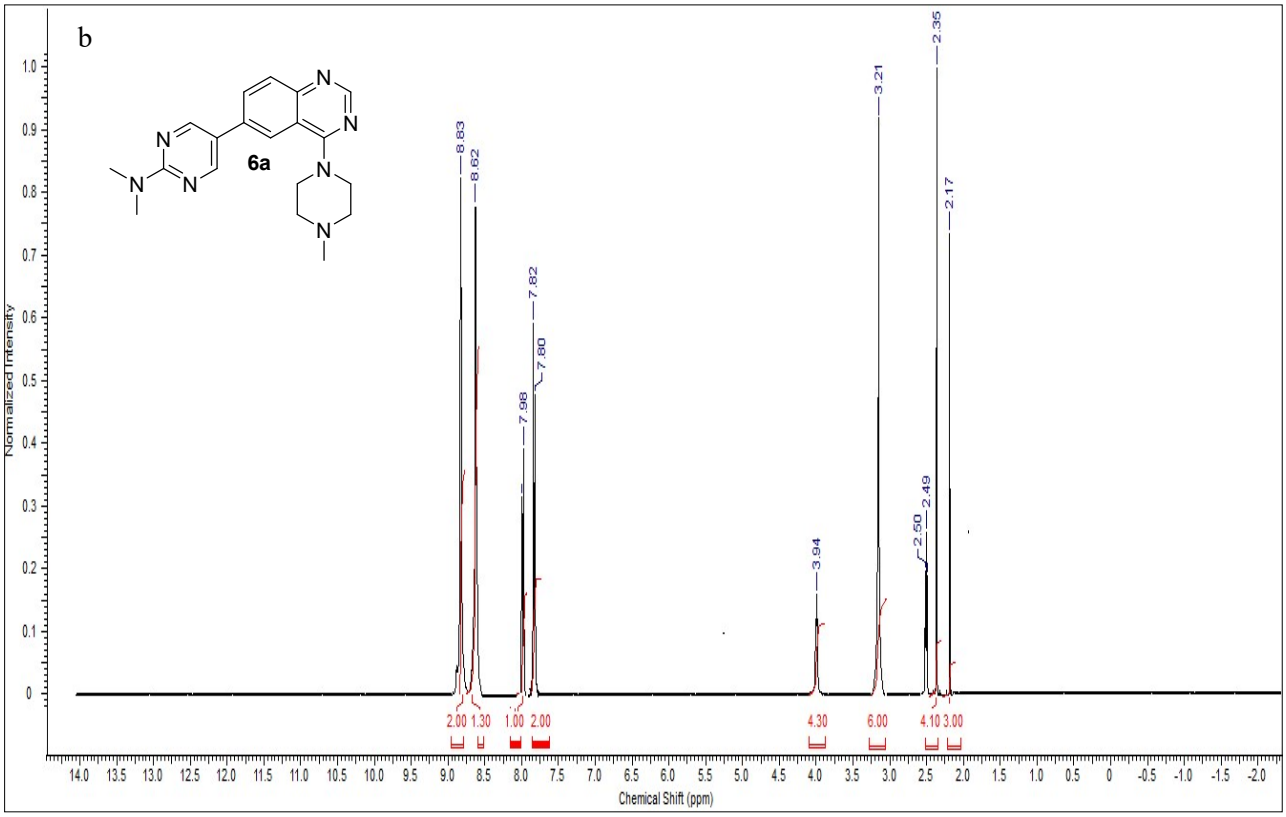
4-(6′-Bromoquinazolin-4′-yl)morpholine **5b**. Light brown powder, yield 77%; mp 179°C. ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 3.64-3.65 (m, 4H, morpholine); 3.79-3.81 (m, 4H, morpholine); 7.76 (d, 1H, aromatic, *J = 8.0 Hz*), 7.93 (m, 1H, aromatic); 8.07 (d, 1H, aromatic, *J = 8.0 Hz*); 8.91 (brs, 1H, aromatic). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 44.4, 66.4 (morpholine C's); 117.1, 118.1, 127.6, 130.7, 135.7,150.6 (aromatic C's); 152.1 (C_2-quinazoline); 161.7 (C_4-quinazoline).

N,N-Dimethyl-5-[4′-(4″-N-methylpiperazin-1″-yl)quinazolin-6′-yl]pyrimidin-2-amine **6a**. Brown powder, yield 74%; mp 292°C. IR (KBr, cm^{-1}): 3199 (aromatic C-H- *str.*); 2924 (C-H aliphatic); 1601 (C=N). ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 2.17 (s, 3H, CH_3, piprazine); 2.35 (m, 4H, piprazine); 3.21 (s, 3H, CH_3, dimethyl pyrimidine); 3.94 (m, 4H, piprazine); 7.80-7.82 (d, 1H, aromatic, *J = 8.0 Hz*); 7.98 (m, 2H, aromatic); 8.62 (s, 1H, aromatic), 8.83 (s, 2H, $H_{4,6}$-pyrimidine). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 37.2 (CH_3, dimethylpyrimidine), 45.3, 48.8, 54.3 (*N*-methylpiprazine); 117.1 (C_5-pyrimidine); 121.1, 129.3, 131.9, 132.5, 133.5 (aromatic); 144.2 ($C_{4,6}$-pyrimidine); 153.8 (aromatic); 155.1 (C_2-quinazoline); 156.5 (C_2-pyrimidine); 161.6 (C_4-quinazoline). Anal. Calcd for $C_{19}H_{23}N_7$: C, 65.31; H, 6.63; N, 28.06; Found: C, 65.76; H, 6.71; N, 28.34.

5-[4′-(4″-N-Methylpiperazin-1″-yl)quinazolin-6′-yl]pyrimidin-2-amine **6b**. Light brown powder, yield 70%; mp 288°C. IR (KBr, cm^{-1}): 3476, 3434 (NH_2); 3194 (aromatic C-H-*str.*); 2925 (C-H aliphatic); 1593 (C=N). ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 2.24 (s, 3H, CH_3); 2.31 (m, 4H, piprazine); 3.75 (m, 4H, piprazine); 6.91 (brs, 2H, NH_2 exchangeable with D_2O); 7.81 (d, 1H, aromatic, *J = 8 Hz*); 7.98-8.01 (m, 2H, aromatic); 8.16 (s, 1H, aromatic); 8.72 (s, 2H, $H_{4,6}$-pyrimidine). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 47.6, 53.2, 56.5 (methyl piprazine); 117.6 (C_5-pyrimidine); 118.8, 127.6, 129.3, 130.8, 131.9 (aromatic); 136.6 ($C_{4,6}$-pyrimidine); 150.5 (aromatic); 154.3 (C_2-quinazoline); 157.0 (C_2-pyrimidine); 163.1 (C_4-quinazoline). Anal. Calcd for $C_{17}H_{19}N_7$: C, 63.53; H, 5.96; N, 30.51; Found: C, 63.97; H, 6.04; N, 30.79.

5-(4′-Morpholinoquinazolin-6′-yl)pyrimidin-2-amine **6c**. Light brown powder, yield 83%; mp 293°C. IR (KBr, cm^{-1}): 3428, 3330 (NH_2); 3170 (aromatic C-H-*str.*); 2958 (C-H aliphatic); 1597 (C=N). ^{1}H-NMR [DMSO-d_6, 400 MHz]: (*δ, ppm*) 3.67-3.68 (m, 4H, morpholine); 3.81-3.84 (m, 4H, morpholine); 6.87 (brs, 2H, NH_2 exchangeable with D_2O); 7.81 (d, 1H, aromatic, *J = 8.0 Hz*); 8.01-8.06 (m, 2H, aromatic); 8.59 (s, 1H, aromatic); 8.66 (s, 2H, $H_{4,6}$-pyrimidine). ^{13}C-NMR [DMSO-d_6, 100 MHz]: (*δ, ppm*) 50.1, 66.4 (morpholine); 116.5 (C_5-pyrimidine); 121.1, 121.7, 129.2, 131.2, 133.1 (aromatic Cs); 150.7 ($C_{4,6}$-pyrimidine); 153.7 (aromatic); 156.9 (C_2-quinazoline); 162.8 (C_2-pyrimidine); 163.9 (C_4-quinazoline). Anal. Calcd for $C_{16}H_{16}N_6O$: C, 62.32; H, 5.23;N, 27.26; Found: C, 62.77; H, 5.30; N, 27.54.


a
6a
%Transmittance
Wavenumbers (cm-1)
3199.34
2924.61
2853.11
2355.15
1666.22
1601.92
1565.36
1437.79
1394.14
1342.11
1178.77
1119.63
1067.41
1026.28
983.69
792.46
722.95


b
6a
Normalized Intensity
Chemical Shift (ppm)
8.83
8.62
7.98
7.82
7.80
3.94
3.21
2.50
2.49
2.35
2.17
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1.00
2.00
4.30
6.00
4.10
3.00

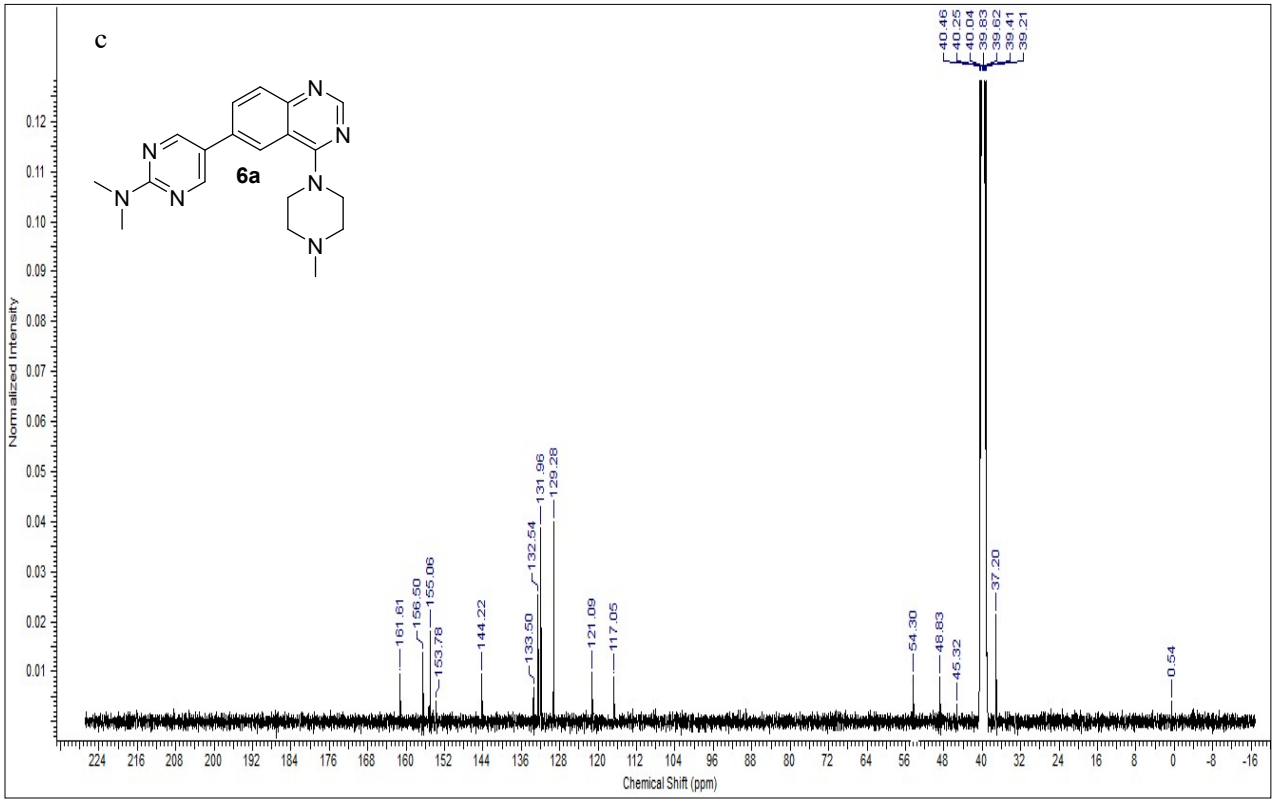
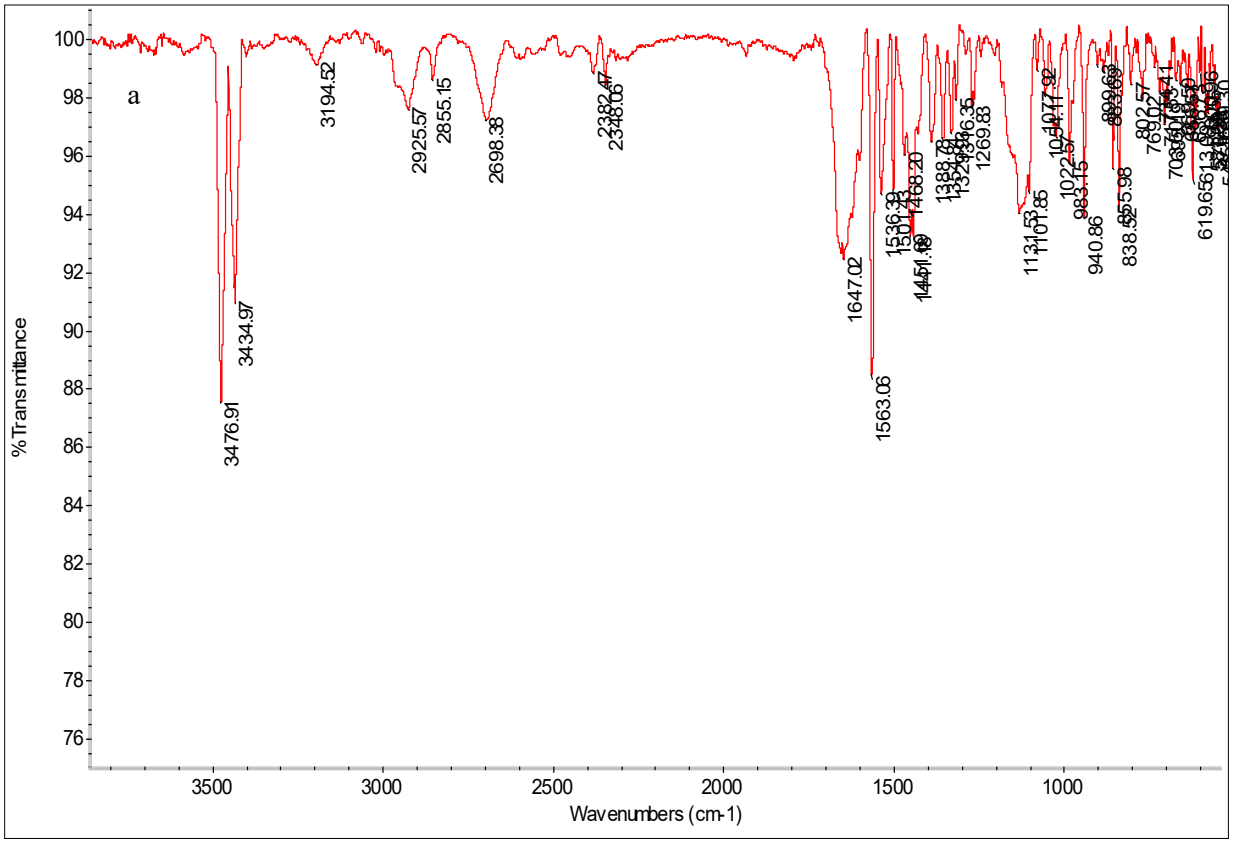
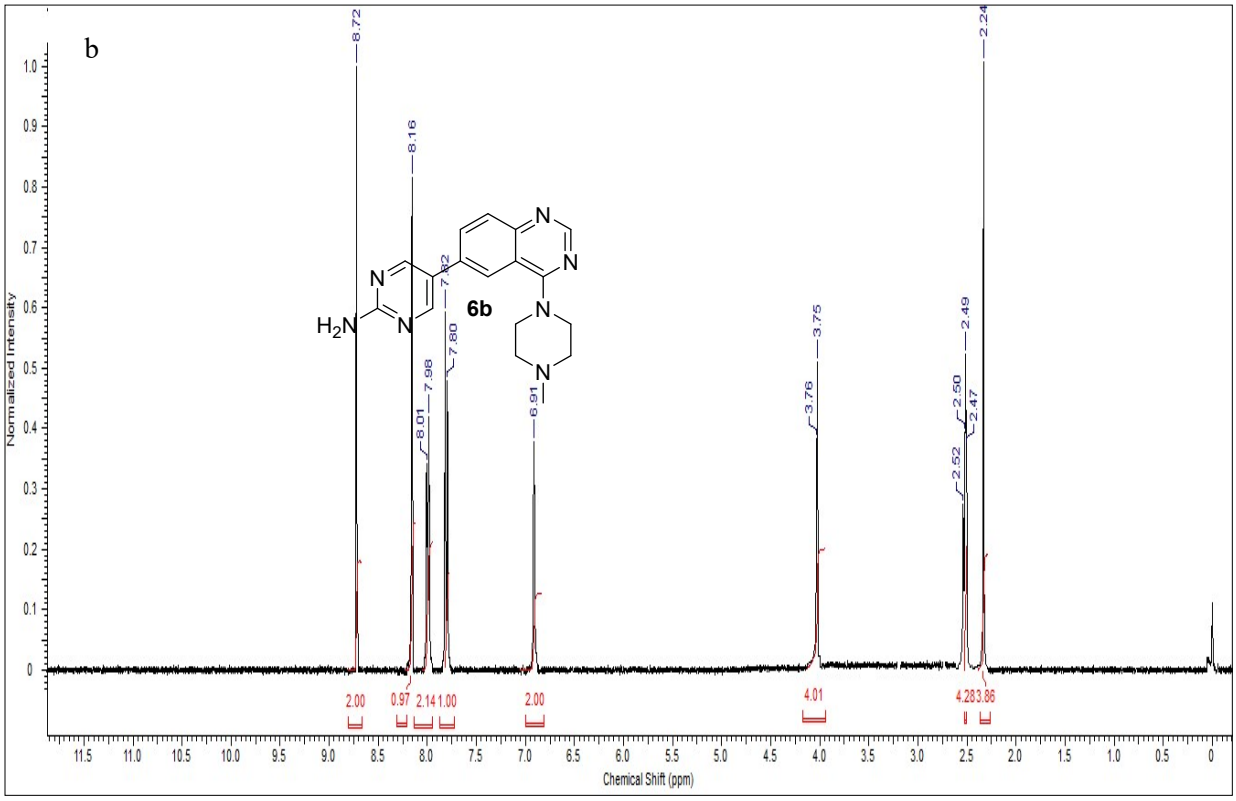


Figure S1. (a) IR spectrum; (b) ^{1}H-NMR spectrum; (c) ^{13}C-NMR spectrum for compound **6a**.


a
%Transmittance
Wavenumbers (cm-1)
3476.91
3434.97
3194.52
2925.57
2855.15
2698.38
2382.47
2348.06
1647.02
1563.06
1269.83
1131.53
1107.85
1022.54
983.15
940.86
838.52
795.98
619.65


b
6b
Normalized Intensity
Chemical Shift (ppm)
8.72
8.16
7.98
7.80
6.91
3.76
2.49
2.47
2.24
2.00
0.97
2.14
1.00
2.00
4.01
4.28
3.86

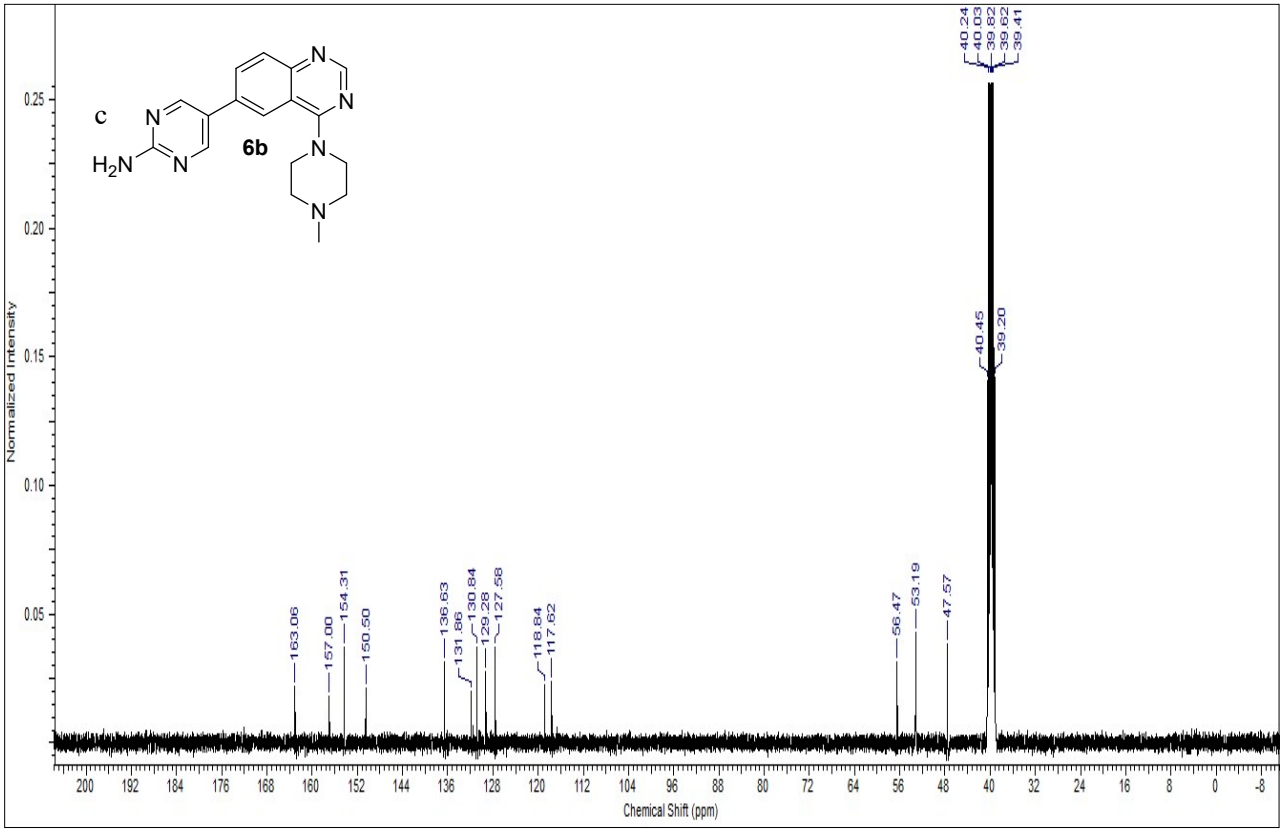
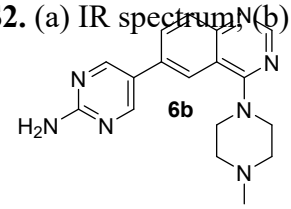
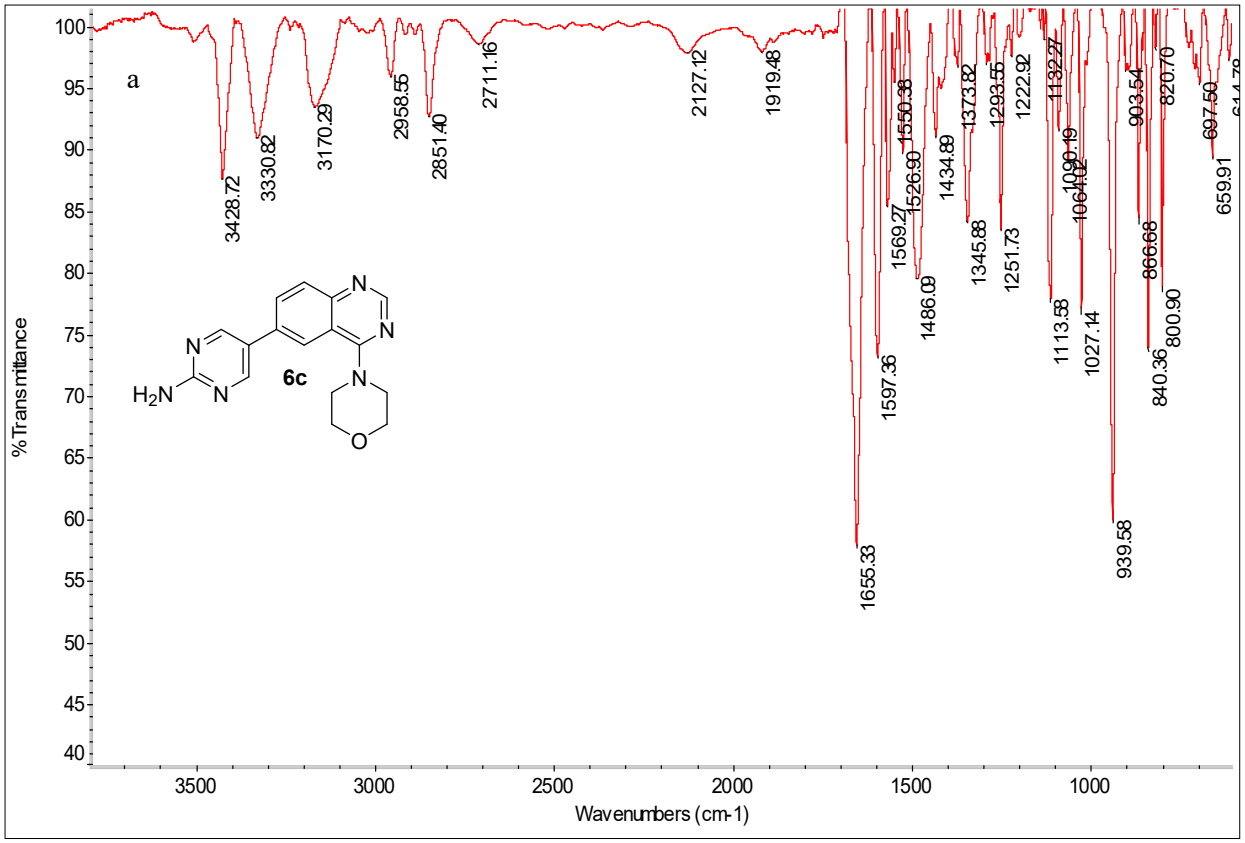
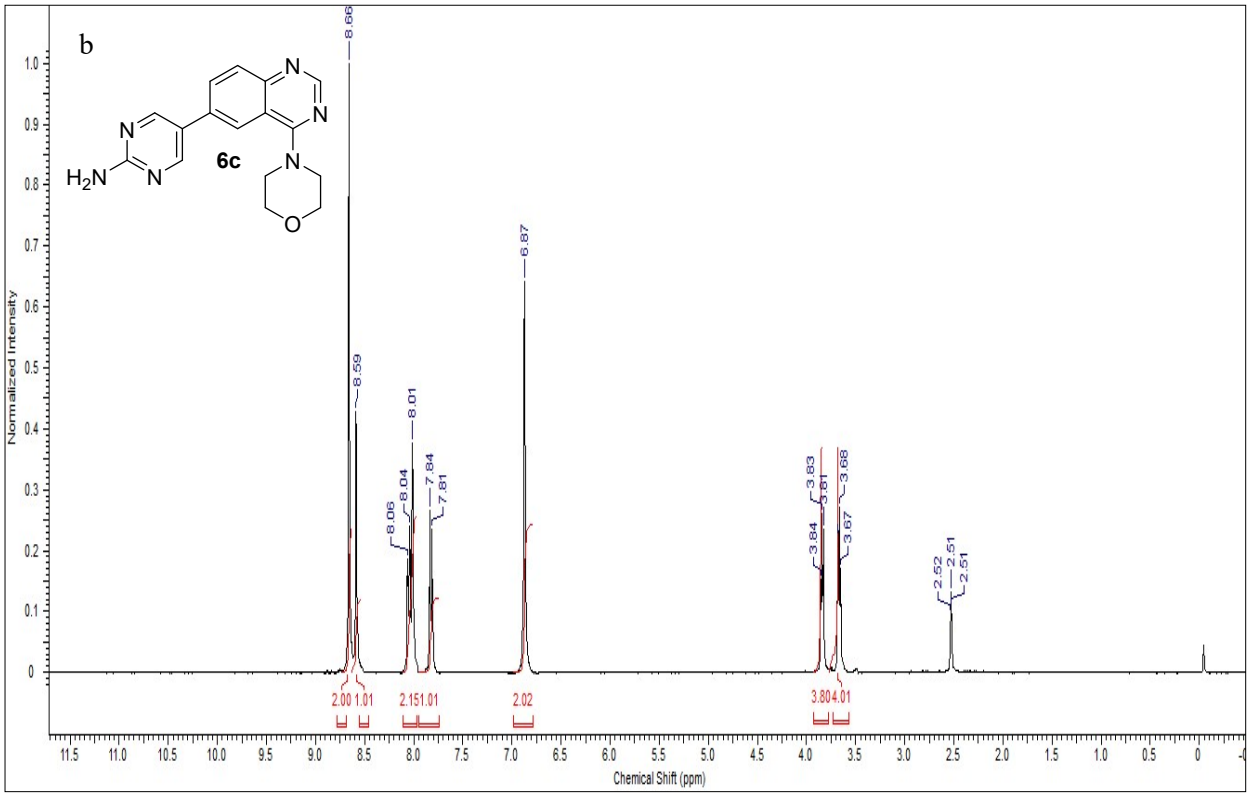


Figure S2. (a) IR spectrum; (b) ^{1}H-NMR spectrum; (c) ^{13}C-NMR spectrum for compound **6b**.




a
%Transmittance
Wavenumbers (cm-1)
3428.72
3330.82
3170.29
2958.55
2851.40
2711.16
2127.12
1919.48
1655.33
1597.36
1569.27
1550.33
1526.90
1486.09
1434.89
1373.82
1345.88
1293.55
1251.73
1222.92
1132.27
1113.58
1090.19
1064.02
1027.14
939.58
903.54
866.68
840.36
820.70
800.90
697.50
659.91
6c


b
Normalized Intensity
Chemical Shift (ppm)
8.66
8.59
8.06
8.04
8.01
7.84
7.81
6.87
3.84
3.83
3.81
3.68
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2.15
1.01
2.02
3.80
4.01
6c

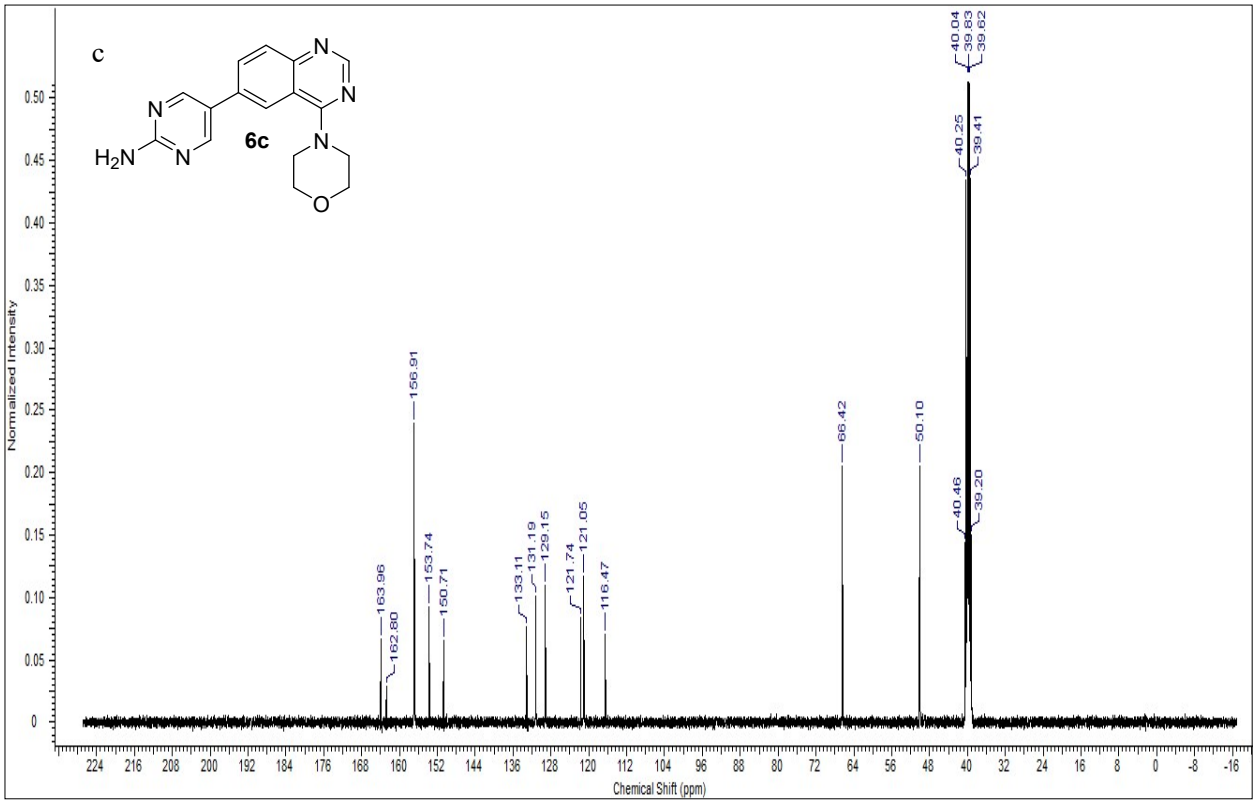

Figure S3. (a) IR spectrum; (b) ^{1}H-NMR spectrum; (c) ^{13}C-NMR spectrum for compound **6c**.

Section S4: Synthesis of UiO-66-NH_2 and UiO-66-NH_2 Loaded Drugs

Synthesis of UiO-66-NH_2. The methodology for producing UiO-66-NH_2 was previously reported.[4] In 90 mL of DMF, 750 mg $ZrCl_4$ (3.21 mmol) and 800 mg of 2-aminoterephthalic acid (4.4 mmol) were dissolved (Zr: ligand:DMF molar ratio of 1:1:220). The mixture was sonicated until all of the reactants had dissolved uniformly. The vial was heated for 24 hours at 120 °C. After that, the oven was turned off and the sample were collected out, allowed to cool, vacuum filtered, and completely washed with fresh DMF. After that, the solid was washed three times in acetone for three hours. Finally, the solid was recovered by filtering and dried for further 4 hours at 150 °C under vacuum. The crystalline structure of UiO-66-NH_2 was confirmed using PXRD.

Loading Quinazoline Derivatives on UiO-66-NH_2. In 5 ml of deionized water, 0.1 g of each quinazoline derivative (**6a**–**c**) was dissolved, followed by the addition of UiO-66-NH_2 (0.05g). This solution was stirred for 5 days at room temperature. To eliminate unloaded compounds, the finished product was washed three times with methanol and then dried at 60 °C.

Section S5: Characterizations of UiO-66-NH_2 and UiO-66-NH_2 Loaded Drugs

Powder X-Ray Diffraction (PXRD) analysis

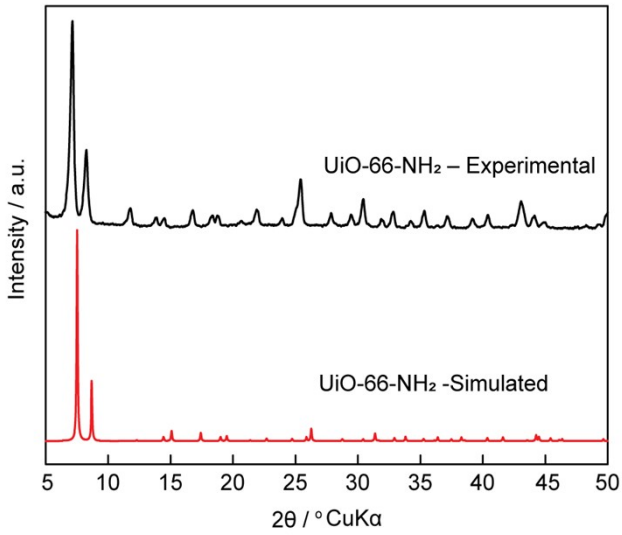

Figure S4. PXRD patterns of simulated and synthesized UiO-66-NH_2.

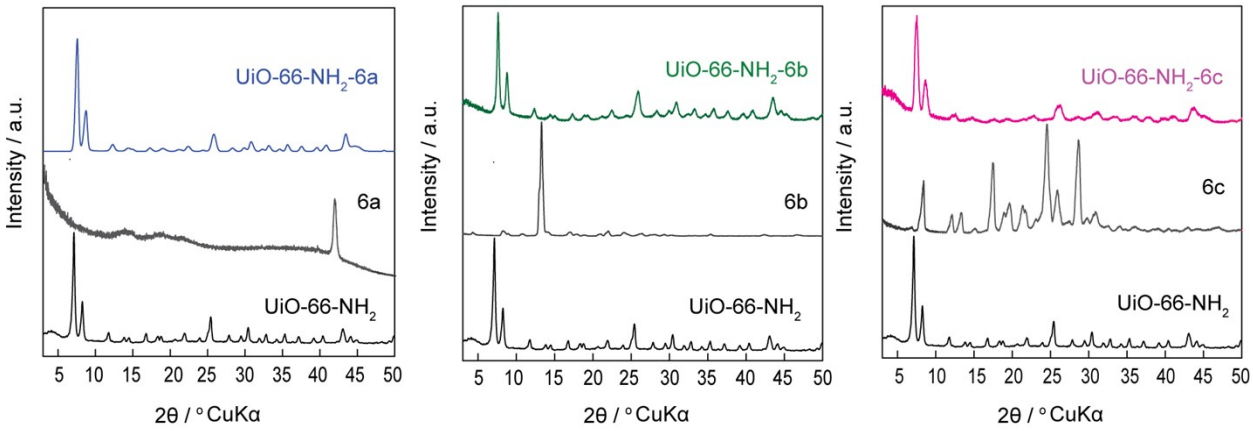

Figure S5. PXRD patterns of UiO-66-NH_2-**6a**, UiO-66-NH_2-**6b** and UiO-66-NH_2-**6c** in comparison with that of quinazoline compounds **6a**–**c** and UiO-66-NH_2.

PXRD patterns for UiO-66-NH_2 at pH 1–14

Test of Stability. Separately, 1000 mL of aqueous solutions with pH values of 1, 3, 7, 12, and 14 were produced. In the above aqueous solution, UiO-66-NH_2 (90 mg) was distributed individually. Then, the mixture was gently mixed and set aside for 24 hours. After that, the sample was centrifuged and dried in preparation for PXRD analysis.

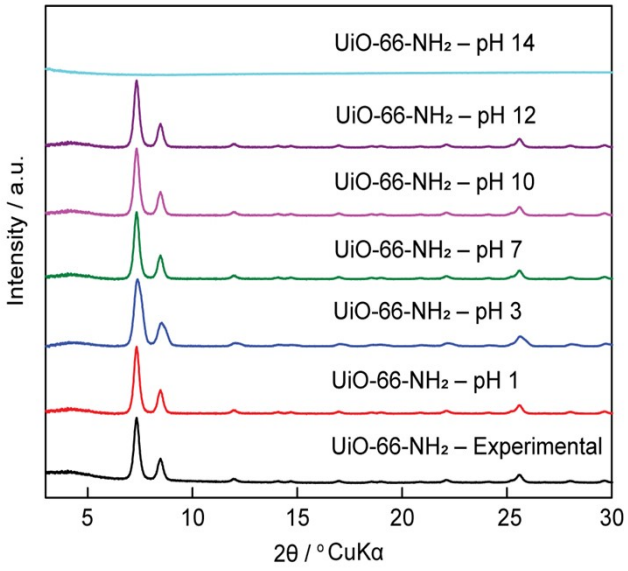

Figure S6. PXRD patterns for UiO-66-NH_2 immersed in solutions of pH 1; pH 3; pH 7; pH 10, pH 12; pH 14 for 24 h.

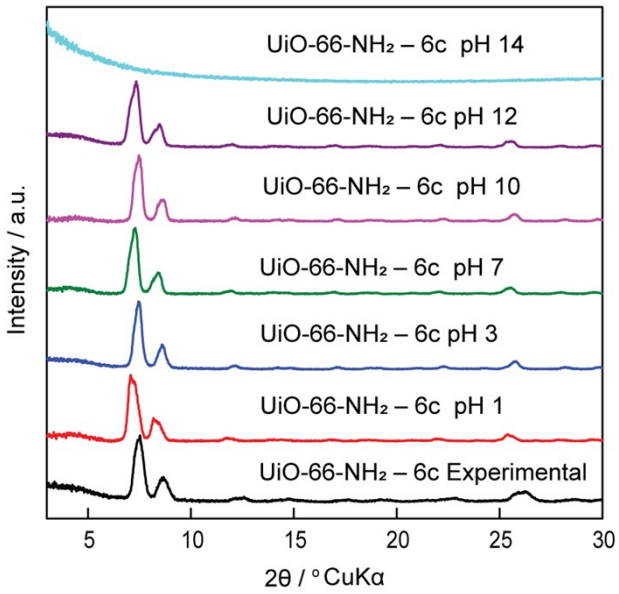

Figure S7. PXRD patterns for UiO-66-NH_2-**6c**: As-prepared sample and samples immersed in pH 1; pH 3; pH 7; pH 10, pH 12 and pH 14 solutions for 24 h.

Thermogravimetric Analysis (TGA) of UiO-66-NH_2

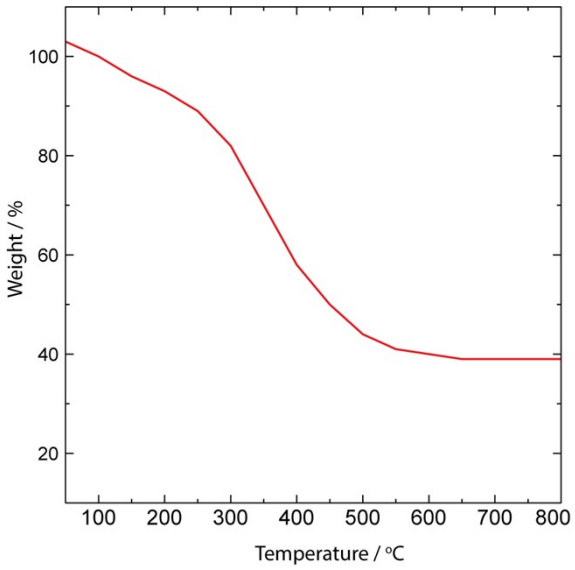

Figure S8. Thermogravimetric analysis of UiO-66-NH_2 measured under air flow.

Fourier-Transform Infrared (FT-IR) analysis

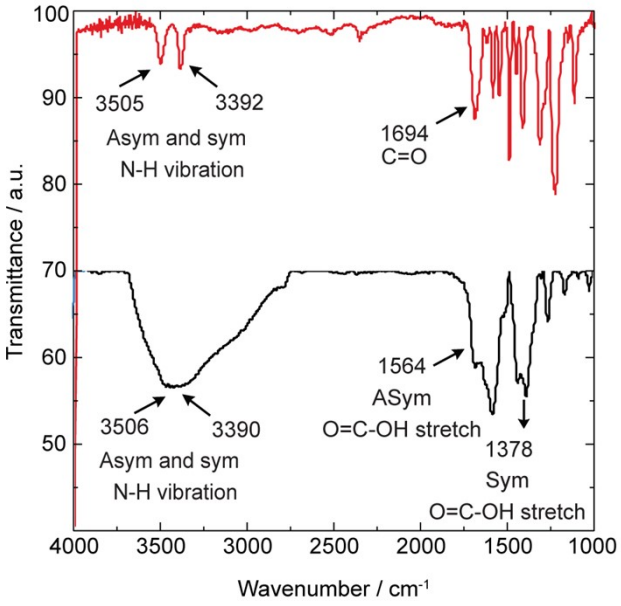

Figure S9. FT-IR spectra of 2-aminoterephthalic acid and UiO-66-NH_2 colored in red and black, respectively.

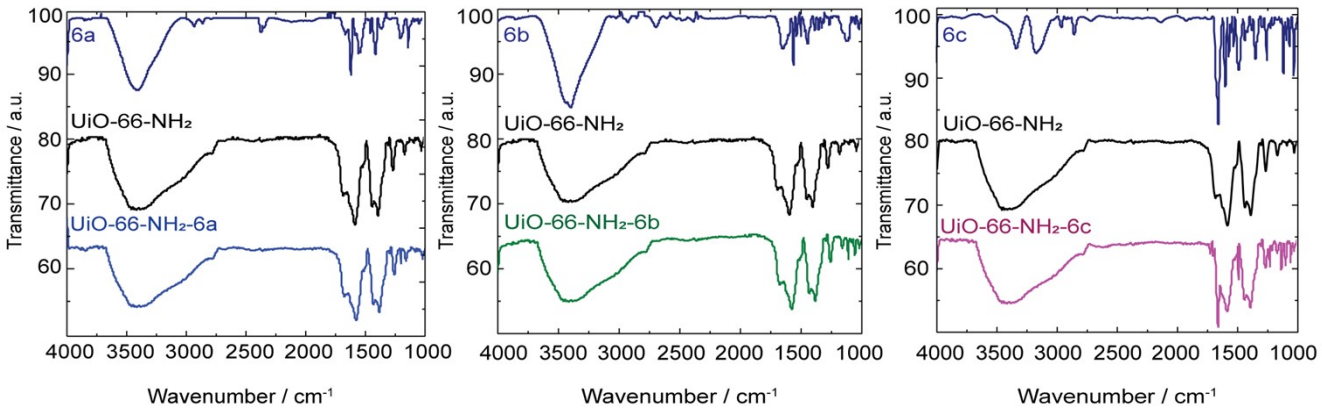

Figure S10. FT-IR spectra of UiO-66-NH_2-**6a**, UiO-66-NH_2-**6b** and UiO-66-NH_2-**6c** in comparison with that of free compounds and UiO-66-NH_2.

Section S6: Scanning Electron Microscopy (SEM)

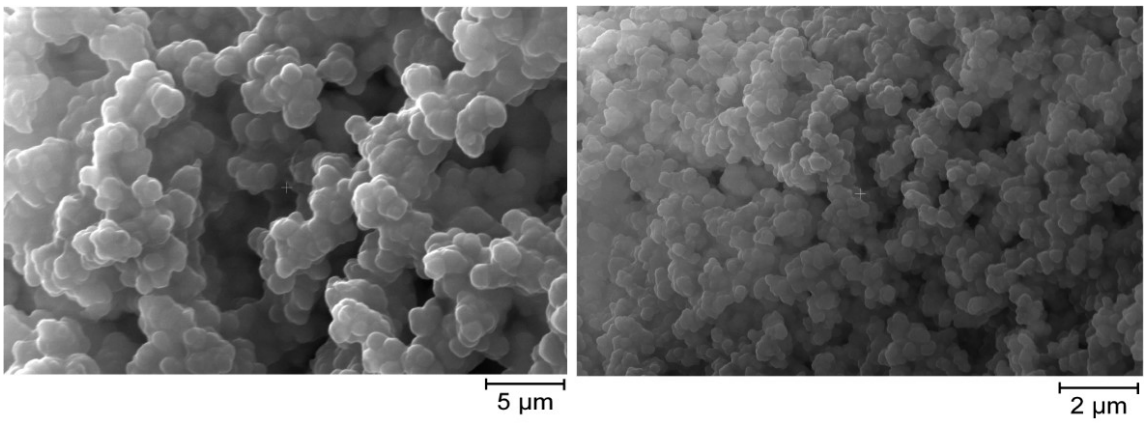

Figure S11. SEM images of UiO-66-NH_2 showing ball-shaped crystals.

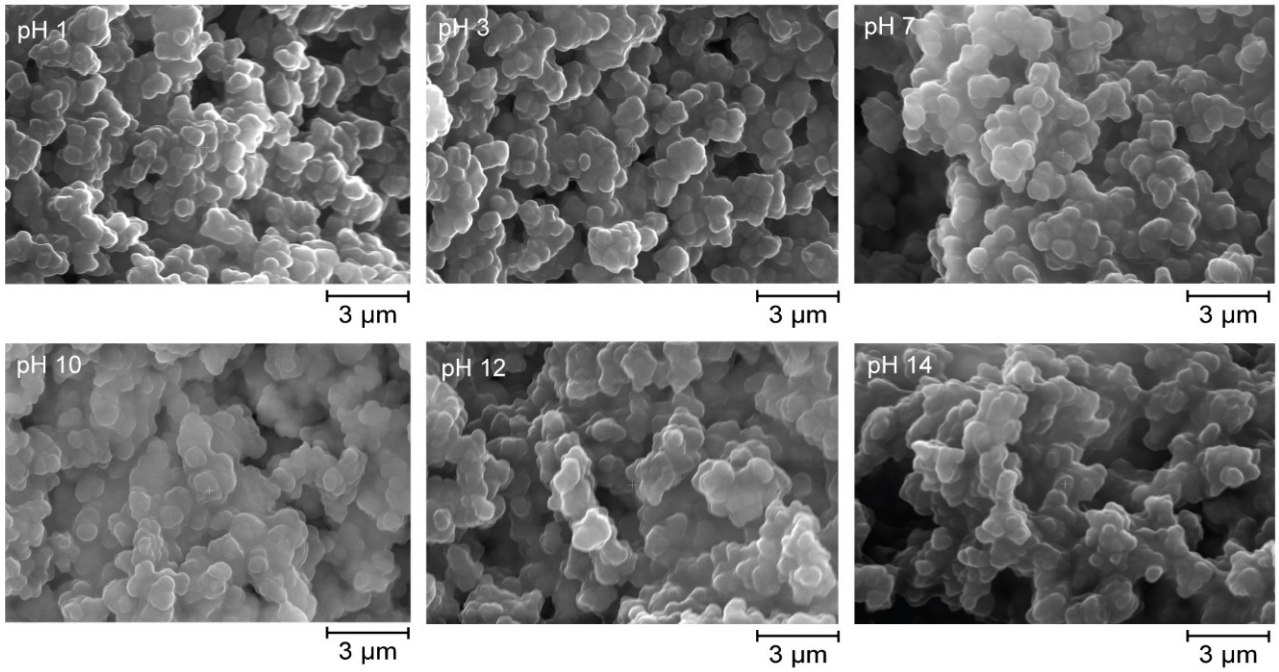

Figure S12. SEM images of UiO-66-NH_2 crystals. The images were taken after the treatment at indicated pH values for 24 h.

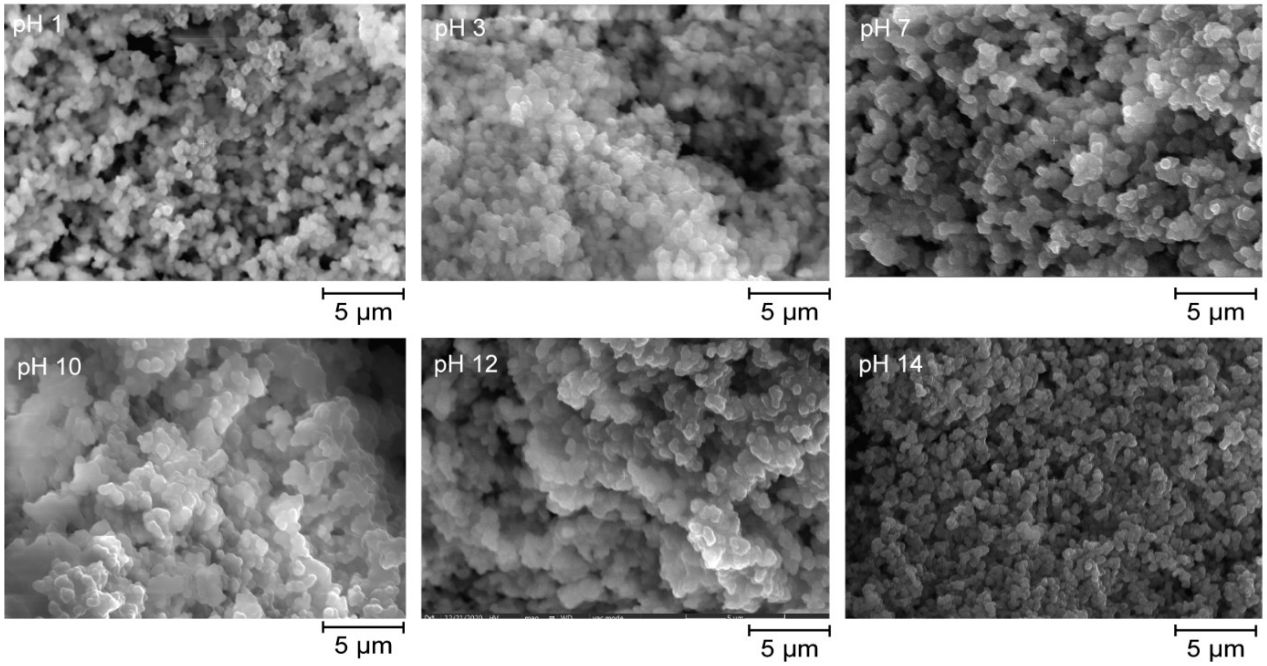

Figure S13. SEM images of UiO-66-NH_2-**6c** crystals, the images were taken after the treatment at indicated pH values for 24 h.

Section S7: Drug Release From UiO-66-NH_2

In 10 mL of a 400 mg/L quinazoline compounds **6a**–**c** aqueous solution, 50 mg of UiO-66-NH_2 were charged. The solution was stirred for 24 hours at 25 °C before being centrifuged for roughly 10 minutes. UV-Vis spectroscopy analysis was used to calculate the drug concentration, and the quinazoline load was computed using the equation below:

$$\text{Quinazoline wt \%} = \frac{quinazoline\ compound\ (mg)}{MOF\ (mg)}\%$$

The drug loading (wt%) is equal to the weight of quinazoline compounds in the MOF divided by the overall weight of the prepared MOF. The drug loading (wt percent) has been computed as 82, 86 and 87 % respectively, using the proposed formula UiO-66-NH_2-**6a**, UiO-66-NH_2-**6b**, and UiO-66-NH_2-**6c.** The quinazoline molecules **6a**–**c** from the UiO-66-NH_2 were released *in vitro* in two buffers: buffer acetate (pH 5) and phosphate buffer saline (pH 7.4). In this method, loaded UiO-66-NH_2 (0.02 g) was added to 50 ml of each buffer individually. The solution was then stirred for 3 days at 37 degrees Celsius. 5 mL of the solution was taken out each time and rapidly replaced with the same quantity of fresh buffer. A UV-Vis spectrophotometer set to 323 nm was used to determine the quantity of

medication released from MOF. The calibration curve was used to calculate the concentration of quinazoline compounds **6a**–**c** in each sample. Using the equation,[5] the adjusted concentration of released quinazoline compounds **6a**–**c** was calculated:

$$Ctcorr = Ct + \frac{v\sum_{0}^{t-1} Ct}{V}$$

where Ctcorr is the corrected concentration at time t, Ct is the estimated quinazoline compounds **6a**–**c** concentration at time t, v is the volume of the generated samples, and V is the total volume of release solution.

In Vitro Drug Release Kinetics

The *in vitro* drug release mechanism of ciprofloxacin and Quinazolines compounds **6a**–**c** from UiO-66-NH_2 in phosphate buffer pH 7.4 and acetate buffer pH 5.0 can be described by fitting the dissolution data in Korsmeyer Peppas model (Table S1). Drug transport constants (K) and transport exponents (n) of the different formulations were determined using Korsmeyer-Peppas equation (see Eq. (1))

Korsmeyer–Peppas kinetics:

$$\frac{Mt}{M\infty} = k.t^n \qquad (1)$$

In this equation, Mt/M∞ shows the fractional permeated drug, t is the time, K is the transport constant (dimension of time^{-1}), and n is the transport exponent. The release constant K provides mostly data on the drug formulation such as structural characteristics of the nanocarriers, whereas n is important since it is related to the drug release mechanism (i.e. Fickian diffusion or non-Fickian diffusion).

Table S1. The Korsmeyer Peppas model fitting of drug release parameters (k, n, R^2) at pH 7.4 and pH 5.0.

		Ciprofloxacin	**6a**	**6b**	**6c**
pH 7.4	K	29.56128	31.89508	30.68302	31.5652
	n	0.226188	0.228145	0.231275	0.22252
	R^2	0.993956	0.998023	0.994015	0.991814
pH 5.0	K	40.96269	47.20377	44.05073	50.12687
	n	0.17903	0.181586	0.182902	0.150544
	R^2	0.981576	0.955371	0.963257	0.965006

Section S8: Antibacterial Activity

Tested Microorganisms: Antibiotic pan-susceptible gram-positive (*Staphylococcus aureus* ATCC 25923 and *Enterococcus feacalis* ATCC 29212) and gram-negative (*Escherichia coli* ATCC-25922) standard strains were used to investigate the effects of different compounds.[6] Pseudomonas aeruginosa, a gram-negative clinical isolate resistant to the third generation cephalosporins and carbapenems , but sensitive to ciprofloxacin, gentamicin, amikacin, and colistin.

Determination of MIC: For the quantitative measurement, the broth microdilution assay was utilized. Pure compounds **6a**–**c** were serially diluted in 50 µL of Muller Hinton Broth (Oxoid) and inoculated with 50 µl of a 1:100 diluted 0.5 MacFarland bacterial suspension at a final concentration of 10^6 colony forming units (CFU)/mL in 96-well microplates (Nunc). The growth of the organism tested was visually evaluated after an 18-hour incubation period at 37 °C, and the drug's MIC was defined as the lowest dose that inhibited observable growth of the organism.

Determination of MBC: To calculate MBC for **6a**–**c,** 10 µL of suspension was drop-inoculated onto Mueller-Hinton agar (MAST) plates from the wells of the MIC plates where no apparent growth was detected. After an overnight incubation at 37 °C, colonies were counted. MBC was defined as the compound with the lowest concentration that inhibited colony formation.

Zone of inhibition determination for new formulations: A disk diffusion technique developed by Bauer et al. was used to investigate the antibacterial activity of novel formulations and free compounds.[7] Using a sterile swab, lawn Muller Hinton agar plates evenly with a bacterial culture set to 0.5 McFarland standard. After drying for 60 minutes at 140 °C, the plates were utilized for the sensitivity test. Staphylococcus aureus and Escherichia coli were utilized as bacteria. A specified

concentration of the materials (10 μg/mL) in HCl (0.1 mol/mL) was produced to test their antibacterial activity. The generated disks containing 5 μg/ml concentrations of the tested compounds were then put on the Mueller-Hinton agar surface to be inoculated. As a result, the plates were incubated at 35 °C for 24 hours and the inhibition zone was measured in millimeters.

Section S9: Transmission Electron Microscopy (TEM)

The morphological alterations in *E. coli* cells treated with UiO-66-NH_2-**6c** were investigated by TEM. The same technique was used on treated and control bacterial cells. After incubation, the pellets were fixed in Carnovsky's fixative at 25 °C for 3–4 hours with a combination of 2 percent paraformaldehyde and 2.5 percent glutaraldehyde. After that, the bacteria were rinsed three times for five minutes in 0.1 M phosphate buffer (pH 7.2). In an Eppendorf tube, bacteria were centrifuged for 15 minutes at 10,000 rpm. The bacterial pellet was resuspended in 1.0 mL phosphate buffer and adsorbed on formvar carbon-coated supports. Agar 200-mesh copper grids were generated by floating the grids above a drop of the bacterial isolate. Submerging grids in 12 percent (w/v) aqueous uranyl acetate for 5 minutes and then rinsing them three times with Milli-Q water stained the bacteria on the grids. A Philips CM10 transmission electron microscope was used to investigate and photograph the grids at an accelerating voltage of 80 kV. The images are taken at various magnifications.[8–10]

Section S10: References

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