Supporting information

DIBI, a 3-hydroxypyridin-4-one chelator iron-binding polymer with enhanced antimicrobial activity

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Materials and Methods

All chemicals were purchased from Sigma-Aldrich and VWR were used as received. The MOPS buffer (0.1 M MOPS, 0.8% NaCl) was prepared by dissolving the corresponding amount of MOPS acid, and NaCl in distilled water and titrating the solution with 2 M NaOH to a pH of 7.42. UV-vis spectra were collected using a Cary 100 Bio UV-vis spectrophotometer in 10 mm quartz cuvettes and a TECAN Infinite M1000 Pro microplate reader in 96-well Falcon plates. GPC characterization was carried out using either a Polymer Laboratories PLGPC 50 instrument or a Viscotek TDA302 and GPCmax system at 35 °C using equipped with refractive index, UV-vis (280 nm), light scattering and viscometer detectors. The synthesis of **5**, co-polymers and DIBI were adapted from the published procedures.[1,2]

Synthesis of 5 (*N*-[2-(3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)ethyl] methacrylamide)

To a solution of 3-hydroxy-2-methyl-4*H*-pyran-4-one (**1**) (1 g, 7.9 mmol, 1.0 equiv) in methanol (9 mL) sodium hydroxide (0.33 g, 8.3 mmol, 1.05 equiv) dissolved in 5 mL of water was added. To this solution, benzyl chloride (1.1 mL, 8.7 mmol, 1.1 equiv) was added dropwise to give a pale yellow clear solution. The mixture was then refluxed for 2 h at 85 °C. The reaction progress was monitored by TLC ($CHCl_3$:10% MeOH: 1% NEt_3). After the reaction was complete the methanol was removed under reduced pressure. The yellow orange oil obtained was mixed with 6 mL water and extracted with ethyl acetate (3 x 7 mL). The ethyl acetate extracts were combined and washed with 5% NaOH solution (3 x 3 mL) and water (3 x 3 mL) respectively. The organic layer was collected and dried over sodium sulfate and then removed under reduced pressure to give 1.5 g of **2** (87% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.05 (d, 1H), 7.39-7.36 (m, 5H), 6.38 (d, 1H), 5.02 (s, 2H), 2.12 (s, 3H). ^{13}C{^{1}H} NMR (400 MHz, DMSO-d$_6$): 174.4, 159.7, 155.5, 143.6, 137.4, 129.1, 128.8, 128.7, 116.9, 73.1, 14.9. Compound **2** (1.5 g, 6.9 mmol, 1.0 equiv) was dissolved in 22 mL methanol/water (1.1:1) solution and then placed into a round-bottom flask. To the above solution, *N*-(2-aminoethyl) methacrylamide hydrochloride (**3**) (synthesized according to the literature procedure,[3] 1.4 g, 8.3 mmol, 1.2 equiv) dissolved in 22 mL methanol/water (1:1) was added along with 5 mL of 2 N sodium hydroxide. The round-bottom flask was then fitted with a condenser and the resultant solution was heated to 95 °C for 2 h. The reaction progress was monitored by TLC ($CHCl_3$: 10% MeOH: 1% NEt_3). After the reaction was complete the solvent was removed, and an additional 10 mL of water was added to the residue whereupon the solution pH was adjusted to 7 with 1 N HCl. The aqueous layer was then extracted with DCM (3 x 10 mL) and the organic layer was dried with sodium sulfate and concentrated under reduced pressure to yield a brown viscous mass. Ethyl acetate (20 mL) was used to triturate the solid product with stirring. The solid was isolated and dried by filtration to give 1.3 g (56% yield) of **4**. Compound **4** (1.3 g) was suspended with 12 M HCl (10 mL). The resultant mixture was stirred overnight at room temperature. HCl was distilled off from the reaction mass under reduced pressure and the viscous mass obtained was dissolved in a minimal amount of water and the pH of the solution was adjusted to 7 by the slow addition of a 10% sodium bicarbonate solution (10 mL). Precipitates were filtered away from the solution and then the solution was concentrated under vacuum. The solution was cooled to 5 °C to precipitate **5**. The solid obtained was vacuum filtered and washed with cold water to give 0.6 g of **5** (62% yield) of the light brown product. The chemical shifts corresponded to that was reported in literature.[1]

General RAFT procedure for the synthesis of (poly[(N-vinylpyrrolidone)-co-(3-hydroxy-1-[N-(methacrylamido)ethyl]-2-methyl pyridin-4(1H)-one)]) co-polymers

Synthesis of polymer c is a representative example for the RAFT synthesis of the co-polymers. Into a two-neck 50 mL round bottom flask, equipped with a magnetic stirrer and a reflux condenser (3.3 g, 0.03 mol) *N*-vinyl-2-pyrrolidone and (0.77 g, 0.003 mol) **5** were dissolved in 4 mL of deionized water and the mixture was stirred for 20 min under N_2. To this mixture (0.136 g, 0.0007 mol) RAFT Agent, 2-[(Ethoxymethanethioyl)-sulfanyl]-2-methylpropanoic acid and (0.227 g, 0.0.002 mol) TMEDA were added and the total mixture was degassed by purging N_2 for 20 min. Post degasification, *tert*-butyl hydroperoxide (0.35 g, 0.004 mol) was added to the mixture. Thereafter, the mixture was heated to 40 ˚C and the reaction was continued at the same temperature for 18 h under N_2. After 18 h, the reaction solution was placed on a rotary evaporator to remove water under reduced pressure. The resulting solid was dissolved in methanol and filtered to remove any insoluble impurities and the filtrate was concentrated to approximately a 50 w/w % polymer solution. This solution was then slowly precipitated with 50 volumes excess MTBE under constant stirring. The precipitate was filtered and dried on a rotary evaporator at 50 ˚C under 35-50 mmHg for 4-6 h, until constant weight of co-polymer was observed. The mass yield of the co-polymer was 80% with respect to the mass of the monomers initially supplied to the polymerization reaction and the co-polymer was found to contain a 15.3 mol% of **5** as determined by ^{1}H NMR spectroscopy. The metal chelating co-polymer was found to have a molecular weight (M_w) of 3.4 kDa with a PDI (M_w/M_n) of 1.6.

Single crystal structure of 4 (CCDC 1812776)

Single crystal diffraction data were collected at 173 K using a Bruker D8 diffractometer equipped with an APEX II CCD detector and using Cu Kα radiation (l = 1.54178 Å). The structure was solved using direct methods (SHELXD) and the refinement on F2 was completed using the full-matrix least-squares program SHELXL-2014. The amido hydrogen atom was located from a difference Fourier map and allowed to freely refine, while the carbon-bound hydrogens were generated in idealized positions based on the sp^2 or sp^3 hybridization geometries of their parent atoms. See Table S1 for a full listing of crystallographic experimental parameters.

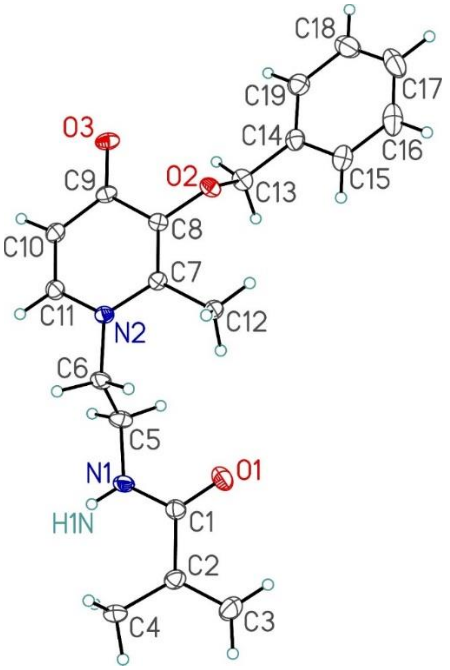


Figure S1. Molecular structure of **4**. Displacement ellipsoids for non-H atoms are shown at 30% probability level and H-atoms are represented by circles of arbitrary size.

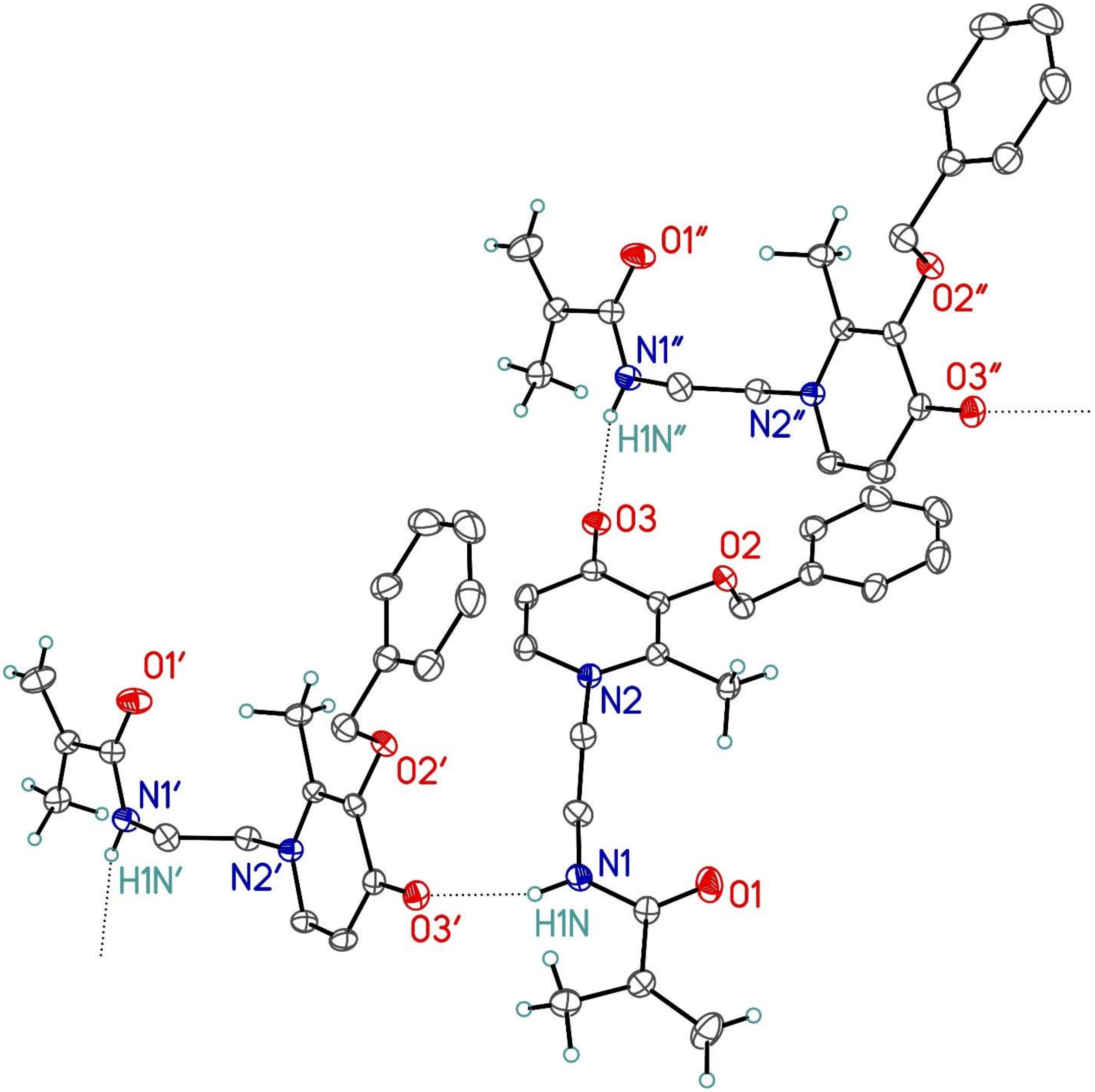


Figure S2. Illustration of hydrogen-bonded interactions between adjacent molecules in the crystal lattice. Primed atoms are related to unprimed ones via the crystallographic symmetry operation ($\bar{x}$, y–1/2, 1/2–z). Double-primed atoms are related to unprimed ones via the crystallographic symmetry operation ($\bar{x}$, 1/2+y, 1/2–z). The chain propagates in a direction parallel to the crystal unit cell's b axis.

Table S1. Crystallographic Experimental Details for **4**

A. Crystal Data

formula	$C_{19}H_{22}N_2O_3$
formula weight	326.38
crystal dimensions (mm)	0.55 × 0.20 × 0.14
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	7.24927 (18)
b (Å)	12.5565 (3)
c (Å)	19.2992 (5)
V (Å^3)	1756.72 (8)
Z	4
ρ_{calcd} (g cm^{-3})	1.234
μ (mm^{-1})	0.679

B. Data Collection and Refinement Conditions

diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	148.14
total data collected	12699 ($-8 \leq h \leq 8$, $-15 \leq k \leq 15$, $-24 \leq l \leq 24$)
independent reflections	3548 ($R_{\text{int}} = 0.0373$)
number of observed reflections (*NO*)	3497 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods/dual space (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–2014*[d])
absorption correction method	Gaussian integration (face-indexed)

Table S1. Crystallographic Experimental Details (continued) for **4**

range of transmission factors	1.0000–0.7087
data/restraints/parameters	3548 / 0 / 223
Flack absolute structure parameter[e]	0.01(4)
goodness-of-fit (S)[f] [all data]	1.062
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0318
wR_2 [all data]	0.0841
largest difference peak and hole	0.119 and –0.200 e Å^{-3}

[a] Obtained from least-squares refinement of 9847 reflections with $8.40° < 2\theta < 147.42°$.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c] Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779.

[d] Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8.

[e] Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. The low anomalous scattering power of the atoms in this structure (none heavier than oxygen) implies that the data cannot be used for absolute structure assignment, thus the Flack parameter is provided for informational purposes only. The molecule contains no stereogenic centers thus no claims about the absolute structure of the molecule are made.

[f] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0499P)^2 + 0.1872P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table S2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters for **4**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.5394(2)	-0.09809(11)	0.08569(8)	0.0507(4)*
O2	-0.15076(15)	0.18658(8)	0.16739(6)	0.0299(2)*
O3	-0.41697(15)	0.09418(10)	0.25142(6)	0.0352(3)*
N1	0.44857(19)	-0.22656(12)	0.15938(8)	0.0341(3)*
N2	0.09181(17)	-0.04338(10)	0.23403(6)	0.0273(3)*
C1	0.5713(2)	-0.18202(13)	0.11592(8)	0.0326(3)*
C2	0.7481(2)	-0.24263(13)	0.10520(9)	0.0333(3)*
C3	0.8512(3)	-0.2158(2)	0.04955(11)	0.0552(5)*
C4	0.8006(2)	-0.32767(15)	0.15371(10)	0.0388(4)*
C5	0.2686(2)	-0.17904(13)	0.17028(9)	0.0353(4)*
C6	0.2721(2)	-0.09765(13)	0.22890(8)	0.0304(3)*
C7	0.0532(2)	0.04687(12)	0.19629(7)	0.0257(3)*
C8	-0.1185(2)	0.09180(11)	0.20143(8)	0.0258(3)*
C9	-0.2631(2)	0.04930(12)	0.24493(8)	0.0280(3)*
C10	-0.2131(2)	-0.04696(13)	0.27990(8)	0.0331(3)*
C11	-0.0416(2)	-0.08891(13)	0.27382(8)	0.0317(3)*
C12	0.2030(2)	0.09518(13)	0.15309(9)	0.0329(3)*
C13	-0.2687(2)	0.17571(13)	0.10734(9)	0.0352(4)*
C14	-0.2962(3)	0.28519(13)	0.07807(8)	0.0339(3)*
C15	-0.1461(3)	0.34226(16)	0.05217(9)	0.0434(4)*
C16	-0.1694(4)	0.44391(19)	0.02675(10)	0.0563(6)*
C17	-0.3424(4)	0.49024(16)	0.02672(11)	0.0601(7)*
C18	-0.4917(4)	0.43521(18)	0.05188(11)	0.0553(6)*
C19	-0.4687(3)	0.33233(16)	0.07782(10)	0.0430(4)*
H1N	0.469(3)	-0.284(2)	0.1810(12)	0.045(6)

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table S3. Selected Interatomic Distances (Å) for **4**

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.226(2)	C7	C8	1.370(2)
O2	C8	1.3794(18)	C7	C12	1.498(2)
O2	C13	1.4468(19)	C8	C9	1.445(2)
O3	C9	1.2558(19)	C9	C10	1.431(2)
N1	C1	1.345(2)	C10	C11	1.355(2)
N1	C5	1.450(2)	C13	C14	1.499(2)
N2	C6	1.4772(19)	C14	C15	1.396(3)
N2	C7	1.376(2)	C14	C19	1.383(3)
N2	C11	1.3606(19)	C15	C16	1.378(3)
C1	C2	1.505(2)	C16	C17	1.383(4)
C2	C3	1.351(3)	C17	C18	1.373(4)
C2	C4	1.470(2)	C18	C19	1.395(3)
C5	C6	1.525(2)			

Table S4. Selected Interatomic Angles (deg) for **4**

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C8	O2	C13	113.61(11)	O2	C8	C9	118.16(13)
C1	N1	C5	120.98(14)	C7	C8	C9	123.30(13)
C6	N2	C7	121.64(12)	O3	C9	C8	122.45(14)
C6	N2	C11	118.22(13)	O3	C9	C10	123.86(14)
C7	N2	C11	120.00(13)	C8	C9	C10	113.69(13)
O1	C1	N1	121.96(16)	C9	C10	C11	121.33(14)
O1	C1	C2	121.98(16)	N2	C11	C10	122.51(15)
N1	C1	C2	116.04(14)	O2	C13	C14	107.09(12)
C1	C2	C3	117.03(17)	C13	C14	C15	120.12(17)
C1	C2	C4	120.00(14)	C13	C14	C19	120.92(16)
C3	C2	C4	122.97(17)	C15	C14	C19	118.94(17)
N1	C5	C6	111.61(13)	C14	C15	C16	120.5(2)
N2	C6	C5	110.13(12)	C15	C16	C17	120.1(2)
N2	C7	C8	119.07(13)	C16	C17	C18	120.23(18)
N2	C7	C12	118.72(13)	C17	C18	C19	119.9(2)
C8	C7	C12	122.16(13)	C14	C19	C18	120.4(2)
O2	C8	C7	118.36(13)				

Table S5. Hydrogen-Bonded Interactions for **4**

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	∠D–H···A (deg)
N1–H1N···O3[a]	0.85(2)	2.04(2)	2.8429(19)	157(2)

[a] At $\bar{x}$, $y-{}^{1}/2$, ${}^{1}/2-z$.

Table S6. Torsional Angles (deg) for **4**

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C13	O2	C8	C7	108.05(15)	N2	C7	C8	C9	0.1(2)
C13	O2	C8	C9	-76.58(17)	C12	C7	C8	O2	-2.3(2)
C8	O2	C13	C14	177.83(13)	C12	C7	C8	C9	-177.38(14)
C5	N1	C1	O1	2.6(3)	O2	C8	C9	O3	1.6(2)
C5	N1	C1	C2	-175.96(14)	O2	C8	C9	C10	-177.72(12)
C1	N1	C5	C6	-88.8(2)	C7	C8	C9	O3	176.73(13)
C7	N2	C6	C5	-88.23(17)	C7	C8	C9	C10	-2.6(2)
C11	N2	C6	C5	87.40(17)	O3	C9	C10	C11	-176.46(15)
C6	N2	C7	C8	177.88(13)	C8	C9	C10	C11	2.9(2)
C6	N2	C7	C12	-4.5(2)	C9	C10	C11	N2	-0.7(3)
C11	N2	C7	C8	2.3(2)	O2	C13	C14	C15	63.41(19)
C11	N2	C7	C12	179.90(14)	O2	C13	C14	C19	-114.93(16)
C6	N2	C11	C10	-177.79(15)	C13	C14	C15	C16	-178.40(16)
C7	N2	C11	C10	-2.1(2)	C19	C14	C15	C16	0.0(3)
O1	C1	C2	C3	-15.4(3)	C13	C14	C19	C18	178.53(16)
O1	C1	C2	C4	165.41(17)	C15	C14	C19	C18	0.2(3)
N1	C1	C2	C3	163.17(18)	C14	C15	C16	C17	0.0(3)
N1	C1	C2	C4	-16.1(2)	C15	C16	C17	C18	-0.1(3)
N1	C5	C6	N2	174.47(13)	C16	C17	C18	C19	0.3(3)
N2	C7	C8	O2	175.22(12)	C17	C18	C19	C14	-0.3(3)

Table S7. Anisotropic Displacement Parameters (U_{ij}, Å^2) for **4**

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0463(8)	0.0483(7)	0.0577(8)	0.0229(6)	0.0010(6)	0.0081(6)
O2	0.0253(5)	0.0259(5)	0.0383(6)	0.0013(4)	-0.0057(4)	-0.0006(4)
O3	0.0197(5)	0.0387(6)	0.0472(6)	-0.0069(5)	0.0040(5)	0.0025(4)
N1	0.0229(6)	0.0330(7)	0.0464(7)	0.0059(6)	0.0032(6)	0.0059(5)
N2	0.0185(6)	0.0312(6)	0.0320(6)	0.0025(5)	0.0005(5)	0.0017(5)
C1	0.0277(8)	0.0354(8)	0.0347(7)	0.0032(6)	-0.0024(6)	-0.0001(6)
C2	0.0236(8)	0.0406(8)	0.0357(8)	-0.0003(6)	0.0001(6)	-0.0012(6)
C3	0.0358(10)	0.0791(15)	0.0508(11)	0.0152(11)	0.0103(9)	0.0036(10)
C4	0.0240(8)	0.0452(9)	0.0471(9)	0.0010(7)	0.0017(7)	0.0071(7)
C5	0.0202(7)	0.0361(8)	0.0496(9)	-0.0021(7)	-0.0028(7)	0.0032(6)
C6	0.0182(7)	0.0342(7)	0.0387(7)	0.0043(6)	-0.0029(6)	0.0034(6)
C7	0.0210(7)	0.0283(6)	0.0278(6)	-0.0006(6)	-0.0011(5)	-0.0027(6)
C8	0.0216(7)	0.0251(6)	0.0308(7)	-0.0021(6)	-0.0025(5)	-0.0018(5)
C9	0.0195(7)	0.0320(7)	0.0325(7)	-0.0067(6)	0.0007(5)	-0.0015(6)
C10	0.0242(7)	0.0380(8)	0.0372(8)	0.0046(6)	0.0065(6)	-0.0036(7)
C11	0.0273(8)	0.0329(7)	0.0349(7)	0.0055(6)	0.0014(6)	-0.0014(6)
C12	0.0227(7)	0.0375(7)	0.0386(8)	0.0064(6)	0.0047(6)	-0.0006(6)
C13	0.0370(9)	0.0342(7)	0.0345(8)	-0.0014(6)	-0.0068(7)	-0.0026(7)
C14	0.0396(9)	0.0367(8)	0.0254(7)	-0.0017(6)	-0.0031(6)	-0.0021(7)
C15	0.0474(11)	0.0495(10)	0.0334(8)	0.0035(7)	0.0014(8)	-0.0071(8)
C16	0.0805(16)	0.0527(11)	0.0357(9)	0.0089(8)	-0.0028(9)	-0.0196(12)
C17	0.104(2)	0.0365(9)	0.0400(10)	0.0059(8)	-0.0131(12)	0.0039(12)
C18	0.0744(15)	0.0479(11)	0.0436(10)	-0.0029(8)	-0.0075(10)	0.0195(11)
C19	0.0450(10)	0.0466(10)	0.0375(8)	-0.0001(7)	0.0008(8)	0.0055(8)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table S8. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms for **4**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H3A	0.963188	-0.252527	0.040366	0.066
H3B	0.811789	-0.160256	0.019605	0.066
H4A	0.918548	-0.358667	0.139298	0.047
H4B	0.705299	-0.383049	0.153726	0.047
H4C	0.812794	-0.297991	0.200450	0.047
H5A	0.178354	-0.235674	0.181480	0.042
H5B	0.227795	-0.143759	0.127036	0.042
H6A	0.300151	-0.133922	0.273207	0.036
H6B	0.370179	-0.044500	0.220053	0.036
H10	-0.301883	-0.082172	0.307933	0.040
H11	-0.013410	-0.152521	0.298274	0.038
H12A	0.150790	0.151091	0.123592	0.039
H12B	0.259016	0.040009	0.123979	0.039
H12C	0.297293	0.126044	0.183443	0.039
H13A	-0.388771	0.144323	0.120795	0.042
H13B	-0.210170	0.128767	0.072482	0.042
H15	-0.026895	0.310781	0.052065	0.052
H16	-0.066417	0.482211	0.009229	0.068
H17	-0.358044	0.560385	0.009237	0.072
H18	-0.610569	0.467120	0.051625	0.066
H19	-0.572014	0.294460	0.095409	0.052

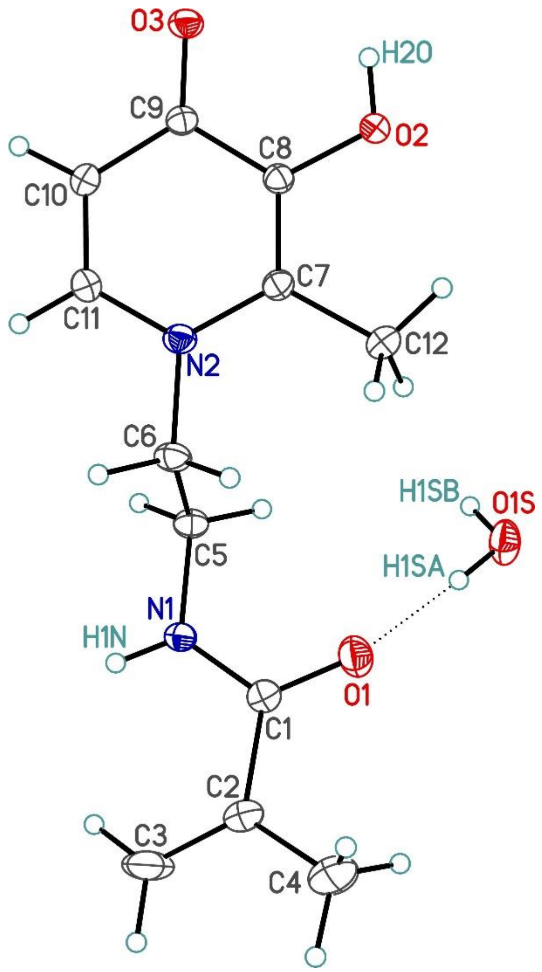


Figure S3. Perspective view of the *N*-[2-(3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)ethyl]-2-methylprop-2-enamide (**5**), monohydrate compound showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters, and only the major orientations of the rotationally disordered methyl groups (C4 and C12) are shown.

Table S9. Crystallographic Experimental Details for structure **5**.

A. Crystal Data

formula	$C_{12}H_{18}N_2O_4$
formula weight	254.28
crystal dimensions (mm)	0.27 × 0.21 × 0.16
crystal system	monoclinic
space group	$P2_1/n$ (an alternate setting of $P2_1/c$ [No. 14])
unit cell parameters[a]	
a (Å)	7.13370(10)
b (Å)	25.5550(5)
c (Å)	7.17780(10)
β (deg)	101.3314(7)
V (Å^3)	1283.02(4)
Z	4
ρ_{calcd} (g cm^{-3})	1.316
μ (mm^{-1})	0.827

B. Data Collection and Refinement Conditions

diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	144.88
total data collected	8816 ($-8 \leq h \leq 8$, $-31 \leq k \leq 31$, $-8 \leq l \leq 8$)
independent reflections	2540 (R_{int} = 0.0144)
number of observed reflections (*NO*)	2441 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	intrinsic phasing (*SHELXT-2014*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–*

Table S9. Crystallographic Experimental Details for structure **5** (cont'd)

2016[d])	
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9495–0.8467
data/restraints/parameters	2540 / 0 / 183
goodness-of-fit (S)[e] [all data]	1.048
final R indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0379
wR_2 [all data]	0.1028
largest difference peak and hole	0.273 and –0.318 e Å^{-3}

[a] Obtained from least-squares refinement of 9868 reflections with 13.04° < 2θ < 144.52°.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c] Sheldrick, G. M. *Acta Crystallogr.* **2015**, *A71*, 3–8. (*SHELXT-2014*)

[d] Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8. (*SHELXL-2016*)

[e] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0531P)^2 + 0.4452P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table S10. Atomic Coordinates and Equivalent Isotropic Displacement Parameters for **5**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.48600(13)	0.67979(4)	0.00344(15)	0.0411(3)*
O2	0.37649(12)	0.53926(4)	0.73713(13)	0.0339(2)*
H2O	0.383(2)	0.5260(7)	0.850(3)	0.046(5)
O3	0.68100(12)	0.48017(3)	0.91591(12)	0.0305(2)*
N1	0.77134(15)	0.63969(4)	0.02933(14)	0.0264(2)*
H1N	0.887(2)	0.6389(6)	0.006(2)	0.035(4)
N2	0.75192(14)	0.58764(4)	0.51424(13)	0.0264(2)*
C1	0.64530(17)	0.67707(4)	-0.03971(16)	0.0273(3)*
C2	0.70605(19)	0.71698(5)	-0.17004(17)	0.0327(3)*
C3	0.8695(3)	0.71234(7)	-0.2394(2)	0.0568(5)*
C4	0.5824(3)	0.76142(8)	-0.2100(4)	0.0769(7)*
C5	0.73074(18)	0.60171(4)	0.16683(16)	0.0281(3)*
C6	0.78476(18)	0.62479(5)	0.36655(16)	0.0291(3)*
C7	0.57502(16)	0.58193(4)	0.56190(15)	0.0248(2)*
C8	0.55240(16)	0.54509(4)	0.69461(15)	0.0242(2)*
C9	0.70665(16)	0.51303(4)	0.79044(15)	0.0235(2)*
C10	0.88410(17)	0.52194(5)	0.73583(17)	0.0288(3)*
C11	0.90136(17)	0.55800(5)	0.60106(17)	0.0296(3)*
C12	0.41243(19)	0.61671(6)	0.47400(19)	0.0372(3)*
O1S	0.15536(14)	0.61932(4)	0.00528(17)	0.0427(3)*
H1SA	0.258(3)	0.6372(8)	-0.004(3)	0.058(5)
H1SB	0.191(3)	0.5883(9)	0.023(3)	0.065(6)

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table S11. Selected Interatomic Distances (Å) for **5**.

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.2372(15)	C2	C3	1.360(2)
O2	C8	1.3567(14)	C2	C4	1.432(2)
O3	C9	1.2708(14)	C5	C6	1.5279(16)
N1	C1	1.3384(16)	C7	C8	1.3712(16)
N1	C5	1.4534(14)	C7	C12	1.4985(17)
N2	C6	1.4757(14)	C8	C9	1.4345(16)
N2	C7	1.3785(15)	C9	C10	1.4152(16)
N2	C11	1.3555(16)	C10	C11	1.3591(17)
C1	C2	1.5041(17)			

Table S12. Selected Interatomic Angles (deg) for **5**.

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	N1	C5	121.27(10)	N2	C7	C8	118.91(10)
C6	N2	C7	121.91(10)	N2	C7	C12	120.23(10)
C6	N2	C11	117.92(10)	C8	C7	C12	120.84(11)
C7	N2	C11	120.16(10)	O2	C8	C7	118.17(10)
O1	C1	N1	122.05(11)	O2	C8	C9	119.05(10)
O1	C1	C2	120.57(11)	C7	C8	C9	122.78(11)
N1	C1	C2	117.36(11)	O3	C9	C8	120.90(10)
C1	C2	C3	122.75(12)	O3	C9	C10	124.32(11)
C1	C2	C4	114.89(13)	C8	C9	C10	114.77(10)
C3	C2	C4	122.31(14)	C9	C10	C11	121.15(11)
N1	C5	C6	109.40(9)	N2	C11	C10	122.21(11)
N2	C6	C5	112.29(9)				

Table S13**.** Hydrogen-Bonded Interactions for **5**.

D–H⋯A	D–H (Å)	H⋯A (Å)	D⋯A (Å)	∠D–H⋯A (deg)
O2–H2O⋯O3[a]	0.869(10)	1.834(19)	2.6492(12)	155.3(17)
N1–H1N⋯O1S[b]	0.874(17)	1.979(17)	2.8270(15)	163.2(15)
O1S–H1SA⋯O1	0.88(2)	1.95(2)	2.8221(14)	173.6(19)
O1S–H1SB⋯O3[c]	0.83(2)	1.98(2)	2.8083(13)	170(2)

[a] At 1–*x*, 1–*y*, 2–*z*.
[b] At 1+*x*, *y*, *z*.
[c] At 1–*x*, 1–*y*, 1–*z*.

Table S14**.** Torsional Angles (deg) for **5**.

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C5	N1	C1	O1	-3.13(18)	N1	C1	C2	C4	-168.42(16)
C5	N1	C1	C2	175.53(10)	N1	C5	C6	N2	-178.48(10)
C1	N1	C5	C6	-84.78(13)	N2	C7	C8	O2	-178.71(10)
C7	N2	C6	C5	-83.94(14)	N2	C7	C8	C9	1.77(17)
C11	N2	C6	C5	94.82(13)	C12	C7	C8	O2	3.19(17)
C6	N2	C7	C8	177.21(10)	C12	C7	C8	C9	-176.33(11)
C6	N2	C7	C12	-4.68(17)	O2	C8	C9	O3	-1.20(16)
C11	N2	C7	C8	-1.52(17)	O2	C8	C9	C10	179.80(10)
C11	N2	C7	C12	176.60(11)	C7	C8	C9	O3	178.32(10)
C6	N2	C11	C10	-178.58(11)	C7	C8	C9	C10	-0.68(16)
C7	N2	C11	C10	0.20(18)	O3	C9	C10	C11	-179.63(11)
O1	C1	C2	C3	-172.06(15)	C8	C9	C10	C11	-0.66(17)
O1	C1	C2	C4	10.3(2)	C9	C10	C11	N2	0.92(19)
N1	C1	C2	C3	9.3(2)					

Table S15**.** Anisotropic Displacement Parameters (U_{ij}, Å^2) for **5**.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0322(5)	0.0330(5)	0.0610(6)	0.0053(4)	0.0159(4)	0.0028(4)
O2	0.0240(4)	0.0483(5)	0.0304(5)	0.0135(4)	0.0079(3)	0.0045(4)
O3	0.0348(5)	0.0297(4)	0.0287(4)	0.0079(3)	0.0105(3)	0.0045(3)
N1	0.0280(5)	0.0263(5)	0.0258(5)	0.0039(4)	0.0076(4)	0.0004(4)
N2	0.0275(5)	0.0267(5)	0.0248(5)	0.0034(4)	0.0047(4)	-0.0042(4)
C1	0.0298(6)	0.0239(5)	0.0276(6)	-0.0018(4)	0.0042(5)	-0.0016(4)
C2	0.0406(7)	0.0271(6)	0.0288(6)	0.0039(5)	0.0029(5)	-0.0013(5)
C3	0.0782(12)	0.0465(9)	0.0557(10)	0.0259(7)	0.0378(9)	0.0141(8)
C4	0.0750(13)	0.0594(11)	0.1028(16)	0.0490(11)	0.0333(12)	0.0248(10)
C5	0.0334(6)	0.0229(5)	0.0285(6)	0.0032(4)	0.0071(5)	-0.0016(4)
C6	0.0330(6)	0.0270(6)	0.0275(6)	0.0045(4)	0.0063(5)	-0.0075(5)
C7	0.0250(6)	0.0258(5)	0.0227(5)	-0.0003(4)	0.0027(4)	-0.0002(4)
C8	0.0239(5)	0.0269(6)	0.0216(5)	-0.0011(4)	0.0043(4)	-0.0013(4)
C9	0.0269(6)	0.0227(5)	0.0210(5)	-0.0017(4)	0.0047(4)	0.0001(4)
C10	0.0252(6)	0.0321(6)	0.0286(6)	0.0044(5)	0.0042(4)	0.0047(5)
C11	0.0233(6)	0.0350(6)	0.0308(6)	0.0030(5)	0.0060(5)	-0.0019(5)
C12	0.0333(7)	0.0422(7)	0.0361(7)	0.0136(5)	0.0069(5)	0.0088(6)
O1S	0.0282(5)	0.0309(5)	0.0686(7)	-0.0004(5)	0.0084(5)	0.0036(4)

The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table S16**.** Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms for **5**.

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H3A	0.905060	0.739156	-0.317298	0.068
H3B	0.948075	0.682283	-0.209933	0.068
H4A[a]	0.626014	0.783750	-0.304000	0.092
H4B[a]	0.585017	0.781347	-0.092825	0.092
H4C[a]	0.451627	0.749583	-0.260379	0.092
H4D[b]	0.482425	0.759370	-0.134136	0.092
H4E[b]	0.523422	0.761773	-0.345311	0.092
H4F[b]	0.656811	0.793537	-0.177757	0.092
H5A	0.804838	0.569315	0.158743	0.034
H5B	0.593091	0.592695	0.138657	0.034
H6A	0.921376	0.634905	0.391437	0.035
H6B	0.708421	0.656818	0.373712	0.035
H10	0.993053	0.502372	0.794404	0.035
H11	1.022221	0.562597	0.566538	0.036
H12A[c]	0.459741	0.652398	0.464089	0.045
H12B[c]	0.315322	0.616781	0.553463	0.045
H12C[c]	0.355876	0.603677	0.346974	0.045
H12D[d]	0.294218	0.596173	0.445594	0.045
H12E[d]	0.438637	0.631789	0.356221	0.045
H12F[d]	0.398083	0.644894	0.562710	0.045

Derived with occupancies of 0.86[a], 0.14[b], 0.59[c] and 0.41[d].

Spectrophotometric characterization of 5 (3-hydroxy-1-(β-methacrylamidoethyl)-2-methyl-4(1H)-pyridinone)

Monomer **5** (0.1 g, 0.4 mmol) was dissolved in 100 mL of distilled water and diluted to a final concentration of 43.7 μM. The UV-vis spectrum of this solution showed two bands at 206 and 282 nm. To determine the extinction coefficient, an 86.2 μM stock solution of **5** was prepared by dissolving 101.8 mg of dry **5** in MOPS buffer. This solution was diluted accordingly to prepare 4 solutions with concentrations of 64.6, 43.1, 21.5 and 8.6 μM. The extinction coefficient was determined from the slope of the line of best fit for the absorbance readings at 282 nm of these solutions, ε = 13,102 $M^{-1}cm^{-1}$.

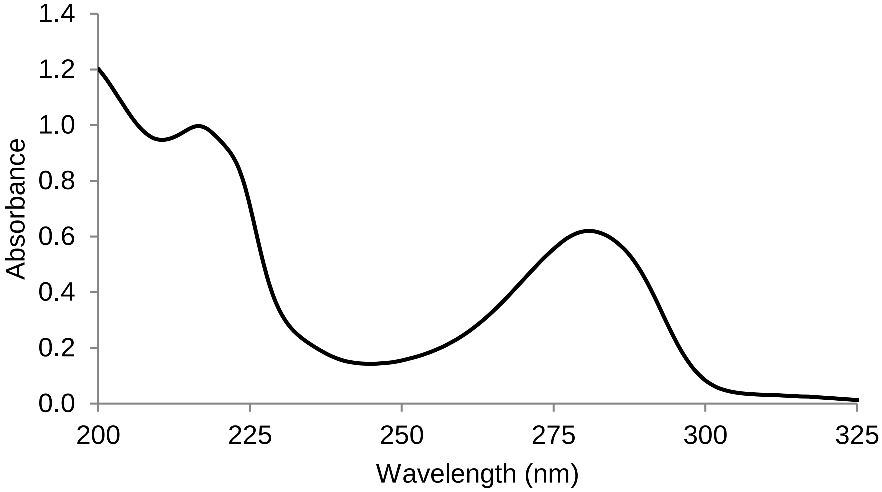


Figure S4. UV-vis spectrum of a 43.1 μM solution of **5** in distilled water pH 6.5.

Spectrophotometric characterization of DIBI (poly[(N-vinylpyrrolidone)-co-(3-hydroxy-1-[N-(methacrylamido)ethyl]-2-methyl pyridin-4(1H)-one)])

DIBI (6.7 mg, 0.7 μmol) was dissolved in distilled water to a final concentration of 6.2 μM. The UV-vis spectrum of this solution showed two bands at 198 and 282 nm. A 10.2 mM DIBI stock solution was prepared by dissolving 91.8 mg of dry DIBI in MOPS buffer. This solution was diluted accordingly to prepare 3 solutions of concentrations 10.2, 5.1 and 2.04 μM, and the absorbance of these solutions at 282 nm was determined by UV-vis spectrophotometry. The extinction coefficient was determined from the slope of the resulting line of best fit to the measured absorbances, ε = 124,845 $M^{-1}cm^{-1}$.

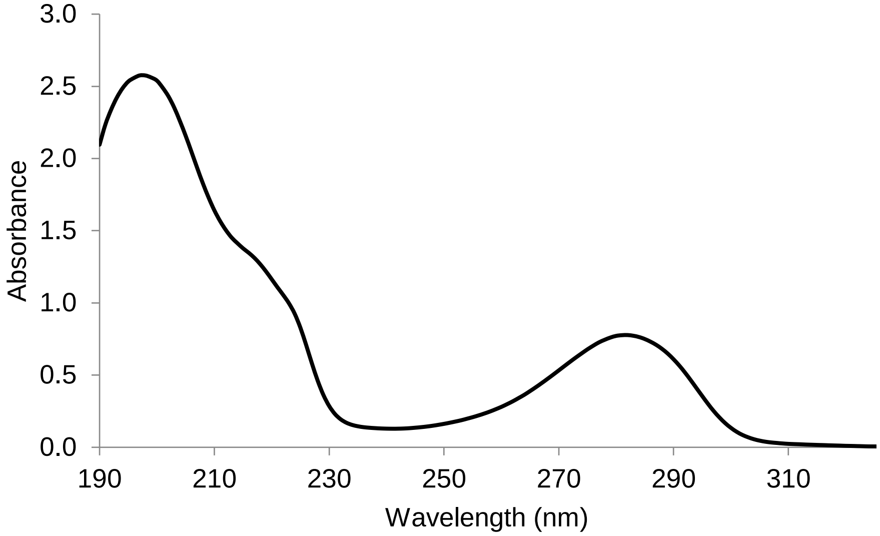


Figure S5. UV-vis spectrum of a 6.2 µM solution of DIBI in distilled water pH 6.5.

Gel permeation chromatography characterization of co-polymers

The polymers were analyzed by Gel Permeation Chromatography (GPC) using a Polymer Laboratories PLGPC 50 instrument by the following methods. Samples were dissolved at 2.5 mg/mL in dimethylformamide (DMF). The sample (50 µL) was applied to a Jordi DVB mixed bed and eluted with DMF at a flow rate of 0.8 mL/min at 50 ˚C. Narrow range polymethymethacrylate standards of known molecular weight were used to calibrate the system and samples were analyzed for relative molecular weight (M_n and M_w) and also polydispersion index PDI (M_w/M_n).

GPC characterization of DIBI

DIBI solutions of concentration 3 mg/mL were prepared in 0.2 M $NaNO_3$/0.01 M EDTA HPLC-grade water, the solutions were filtered through a 0.2 µm syringe filter and analyzed in triplicate with a calibrated tetra-detection GPC system. Calibration of the GPC detectors was carried-out with bovine serum albumin (BSA). For absolute molecular weight determination of the co-polymer dn/dc values were derived using Omnisec Malvern software.

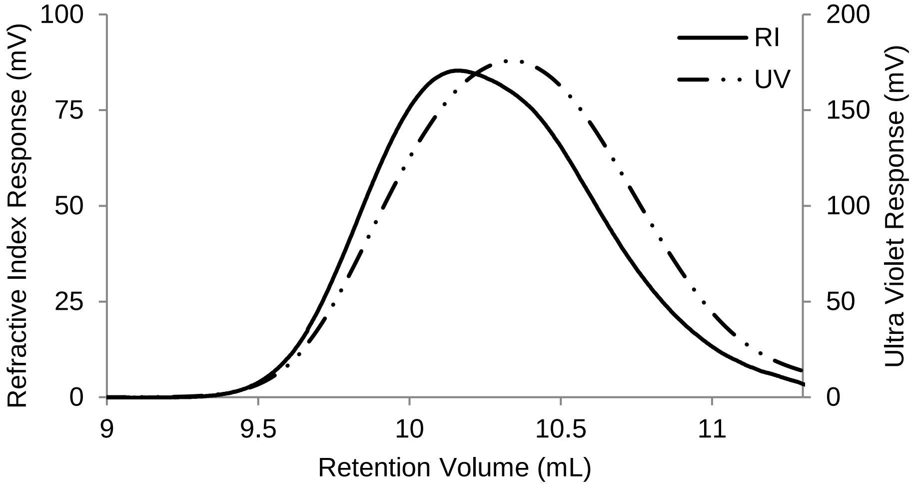
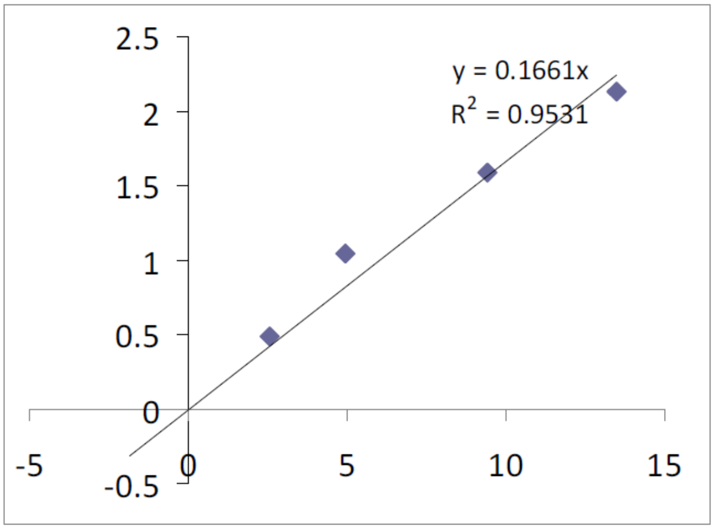


Figure S6. Size exclusion chromatogram showing the refraction index and the PDA trace of DIBI.

^{1}H NMR spectroscopy measurement of 5 in DIBI

Proton Nuclear Magnetic Resonance (^{1}H NMR) spectroscopy was used to estimate 3-hydroxy-1-(β-methacrylamidoethyl)-2-methyl-4(1*H*)-pyridinone (**5**) content of co-polymers as follows. Monomer **5** was added at various known concentrations to known quantities of polvinylpyrrolidone (PVP) homopolymer and the samples were analyzed in

d_6-DMSO for the characteristic **5** signal peak at 6.1 ppm relative to the PVP reference signals. This provided calibration curves for the content of **5** in the co-polymers. This calibration curve (r^2=0.95 to 0.98) then allowed direct measurement and determination of mol% **5** incorporation in the co-polymers.



Mol% **5**	Area
2.53	0.49
4.92	1.045
9.4	1.586
13.5	2.13

Figure S7. Calibration curve was drawn between mol% of **5** and its area under peak at 6.1 ppm keeping peak area constant for poly(NVP) at 0.8 to 2.4 ppm (^{1}H NMR spectrum shown below).

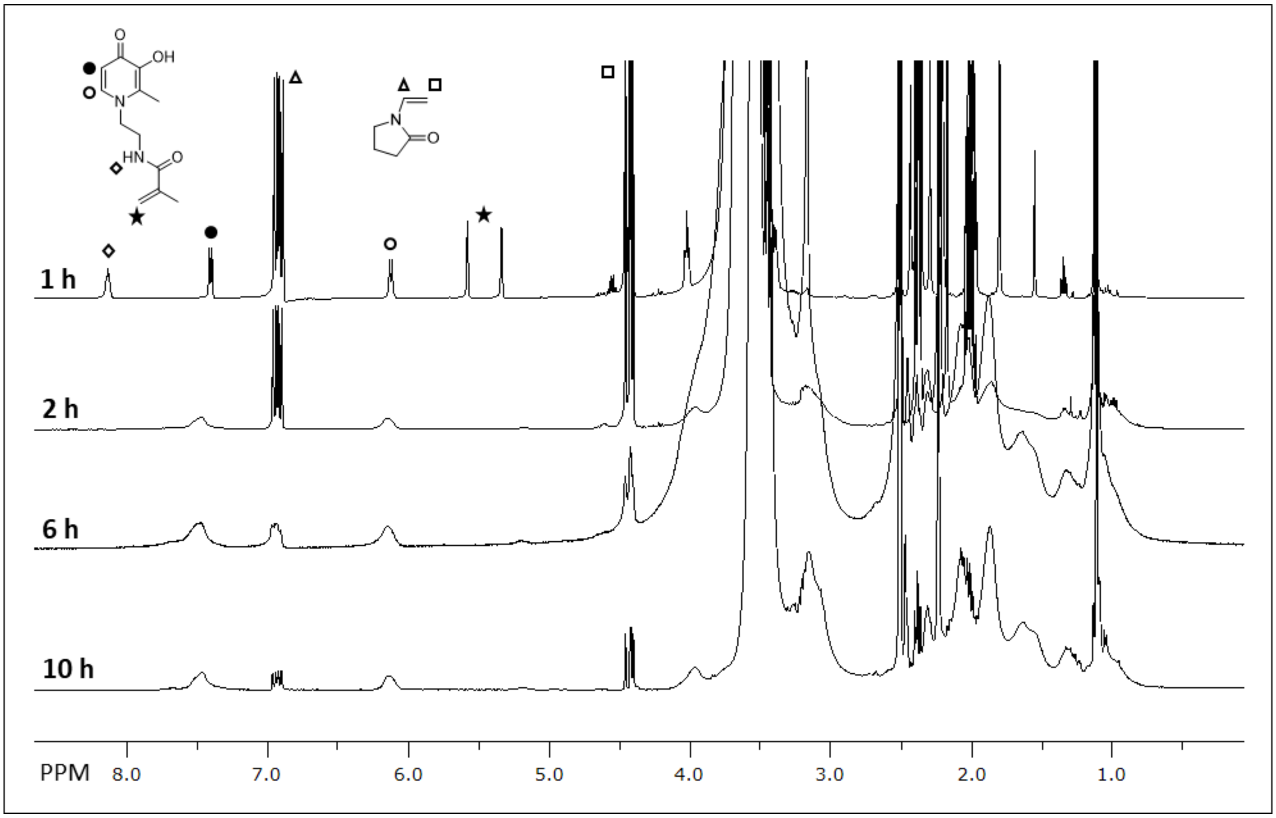


Figure S8. ^{1}H NMR stack-plot in DMSO-d_6 monitoring the DIBI reaction profile

Determination of monomer 5 content in DIBI

Dry DIBI (92.7 mg, 10.3 μmol) was dissolved in 100 mL of MOPS buffer. This solution was subsequently diluted to a final concentration of 52 μM and its absorbance was measured in triplicate. The absorbances were then interpolated in a calibration curve constructed with solutions of **5** with concentrations 86, 64, 43, 21 and 8.6 μM. The resulting concentration of **5** was then recalculated as equivalent **5** mass in the DIBI solution and w/w % in DIBI.

Spectrophotometric characterization of Fe chelation by DIBI

Dry DIBI (30.3 mg, 3.4 µmol) was dissolved in 25 mL of MOPS buffer. Aliquots of 1 mL of this solution were placed in vials, and increasing volumes of a 8.6 mM $Fe(NO_3)_3 \cdot 9H_2O$ solution in water were added in each vial. A corresponding amount of MOPS buffer was then added to each vial to reach a final reaction volume of 1.1 mL. The solutions were shaken gently in a shaker plate for 24 h, at which point the absorbance of 300 µL of each vial was recorded between 350 and 800 nm.

Microbial strains and culture conditions

Staphylococcus aureus ATCC 43300 (MRSA) and *Acinetobacter baumannii* ATCC 19606 were obtained from Dr. Ross Davidson, Nova Scotia Health Authority, Halifax, Canada, and *Candida albicans* SC 5314 was provided by Dr. Kelly Soanes, National Research Council, Halifax, Canada. The strains were routinely cultured from frozen stocks at -80°C, and the bacteria maintained on Trypticase Soy Agar (TSA, Sigma Aldrich) or Blood Agar (BA, Becton Dickinson), and *C. albicans* on Yeast peptone dextrose agar (YPDA, Difco BD). Liquid cultures were grown overnight at 35-37°C with shaking in Roswell Park Memorial Institute Medium 1640 (RPMI; Sigma-Aldrich) supplemented with 2% glucose, buffered with 0.165 M 3-(N-morpholino)-propanesulfonic acid (MOPS; Sigma-Aldrich).

Determination of minimum inhibitory concentration

The antimicrobial effects of DIBI, DFO, DFP, PVP, **5**, and co-polymers (a, b, c) were established by the minimum inhibitory concentration (MIC) determination by broth microdilution method as recommended by CLSI (CLSI, 2009), in 96-well round-bottomed microplates. Overnight RPMI cultures were diluted in fresh RPMI to an optical density (OD 600 nm) of 0.1 for bacteria and 0.12 for *C. albicans*, and MIC plates were inoculated at a final dilution of 1/200 for bacteria and 1/2000 for *C. albicans*. Iron-chelator stocks were diluted to the desired working concentration in RPMI and serial 1/2 dilutions of each compound were made. To confirm sterility of growth medium, some microplate wells were left un-inoculated as a negative growth control, while positive growth controls consisted of inoculated wells containing growth medium with no added antimicrobial treatment. The prepared microplates were incubated at 35°C for 48h in a static incubator. The MIC value for both *S. aureus* and *A. baumannii* was defined as the lowest concentration of chelator required to inhibit visible growth of the tested microbe at 48h post-inoculation (PI), whereas for *C. albicans* the MIC was the lowest concentration that achieved at least 80% growth inhibition (i.e. MIC_{80}) compared to untreated wells. At least two experiments with 2-4 replicates were performed.

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