Supplementary Material

Convenient Syntheses of Cyanuric Chloride-derived NHC ligands, their Ag(I) and Au(I) complexes and Antimicrobial Activity

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Experimental Details

General procedure for the synthesis of chlorotriazines 1 and 2.[1] A fine slurry of cyanuric chloride was prepared by running a thin stream of a hot acetone solution of cyanuric chloride into ice-water. As appropriate, one or two mole equivalents of the amine (dissolved in acetone) were added at 4 ^{o}C using a dropping funnel. Concurrently, an aqueous solution of sodium carbonate (mole equivalent to the amine) was added at such rate that the reaction mixture remained essentially neutral. The reaction mixture was allowed to warm slowly to room temperature, subsequently the temperature was raised to 40-45 ^{o}C and stirred overnight. During reaction the mixture initially becomes clear, but as the product concentration increases it precipitates from solution. The crude precipitated product was filtered and washed with water. The product was recrystallised from a hot methanol or ethanol solution forming colorless crystals.

2-chloro-4,6-di(piperidinyl)-1,3,5-triazine, 1a. 18.44 g (100 mmol) of cyanuric chloride were used. The product was recrystallised from hot ethanol. Yield: 25.25 g, 90%. ^{1}H NMR (400MHz, d_1-$CHCl_3$) δ 1.51 (m, 8H, H^4), 1.58 (m, 4H, H^8), 3.66 (m, 8H, H^3). ^{13}C NMR (75 MHz, d-$CHCl_3$): δ = 24.75 (C^8), 25.87 (C^4), 44.53 (C^3), 164.23 (C^1), 169.58 (C^2). ESI-MS for **1a**, $C_{13}H_{20}ClN_5$ (*m/z*): 282.15 (100%, MH^+).

4,4'-(6-chloro-1,3,5-triazinediyl)dimorpholine, 1b. Cyanuric chloride (9.22g, 50 mmol), acetone (200mL) and ice water (200 mL), solution of morpholine (100 mmol, 8.7 mL) in acetone (10 mL), aqueous Na_2CO_3 (10.60 g, 100 mmol). The product was recrystallised from hot ethanol. Yield: 7.50 g, 53%. ^{1}H NMR (400 MHz, d-$CHCl_3$) δ 3.74 (8H, m), 3.81 (8H, m). ^{13}C NMR (75 MHz, d_1-$CHCl_3$): δ = 43.93 (C^4), 66.67 (C^3), 66.80 ($C^{3'}$), 164.55 (C^1), 169.78 (C^2). ESI-MS for **1b**, $C_{11}H_{17}ClN_5O_2$ (*m/z*): 286.10 (100%, MH^+).

4,4'-(6-chloro-1,3,5-triazinediyl)morpholine-piperidine, 1c. A solution of **2** (3.18 g, 13.6 mmol) in acetone (15 mL) was added to ice water (50 mL) forming a slurry. Morpholine (1.19 ml, 13.6 mmol) dissolved in acetone (15 mL) was added dropwise to the slurry. Na_2CO_3 (1.15 g, 13.7 mmol) was added portionwise so as the pH remained neutral, and the mixture stirred over night at room temperature. The mixture was filtered, and the solid recrystallised from hot EtOH yielding the title compound as a white solid (2.2 g, 57 %) ^{1}H NMR (250 MHz, d-$CHCl_3$) δ = 3.85 – 3.63 (m, 12 H), 1.76 – 1.47 (m, 6 H).

2,4-dichloro-6-(piperidinyl)-1,3,5-triazine, 2. 50 mmol cyanuric chloride in 80mL acetone / 100 mL H_2O, 50 mmol piperidine in 20mL acetone, 50 mmol Na_2CO_3. The product was recrystallised from hot methanol. Yield: 7.50 g, 53%. ^{1}H NMR (400MHz, d-$CHCl_3$) δ = 1.57 (m, 8H, H^4), 1.64 (m, 4H, H^8), 3.75 (m, 8H, H^3). ^{13}C NMR (75 MHz, d-$CHCl_3$): δ = 24.27 (C^8), 25.72 (C^4), 45.39 (C^3), 163.53 (C^1), 170.13 (C^2). ESI-MS for **2**, $C_8H_{11}Cl_2N_4$ (*m/z*): 233.08 (100%, MH^+).

General procedure for the synthesis of PF_6 salts, 3d, 3e and 5d. To a water solution of the corresponding chloride salt, a 5- to 10-fold excess of NH_4PF_6 (dissolved in water) was added. The product precipitated immediately from the solution and collected by filtration after washing with small amounts of cold water. The solid was subsequently extracted into dichloromethane and dried over $MgSO_4$. Filtration and dryness under vacuum afforded the product as white crystalline solid.

2,4-dimethoxy-6-(piperidin-1-yl)-1,3,5-triazine, 9. 0.397 g (1.0 mmol) of the chloride salt **5a** were dissolved in 70 mL of methanol. Ag_2O (0.327 g, 1.4 mmol) was then added and the mixture was stirred for 2 days in the dark. The mixture obtained was evaporated to dryness, CH_2Cl_2 (20 mL) was added and the solution filtered over Celite. The clear solution was dried to afford the product as a white solid. Colourless crystals were grown by diffusion of ether into a CH_2Cl_2 solution of **9**. Yield: 0.180 g, 80%. ^{1}H NMR (400 MHz, d_1-$CHCl_3$): δ = 1.0 (br m, 6H, $H^{4/8}$), 3.72 (m, 4H, $H^{3/3'}$), 3.87 (s, 6H, Me). MS (ES^+, CH_3CN) 225.10 (100%).

Additional crystallographic data:

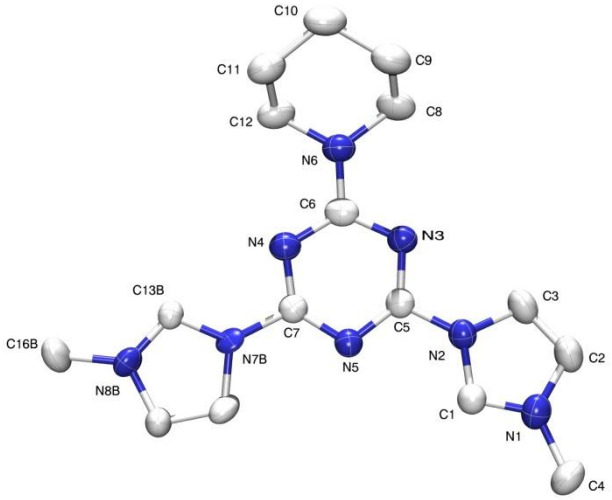

Figure S1. Thermal ellipsoid plots at 50% probability for the cation of **5d**. PF_6^- counterions were removed for clarity. Selected bond lengths (Å): C(1)-N(1) 1.326(6), C(1)-N(2) 1.345(6), C(13B)-N(7B) 1.32(3), C(13B)-N(8B) 1.30(2).

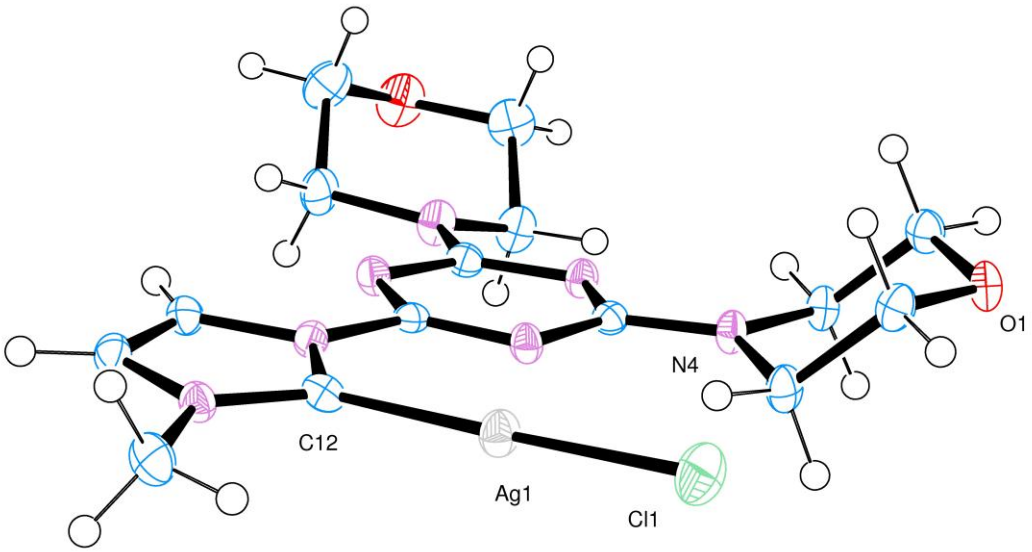

Figure S2. ORTEP ellipsoid plots at 50% probability of the Ag(NHC)Cl complexes. Selected bond lengths (Å) and angles (°) for **6b**: C(1)-Ag(1) 2.074(3), Ag(1)-Cl(1) 2.3321(8), C(1)-Ag(1)-Cl(1) 175.38(9).

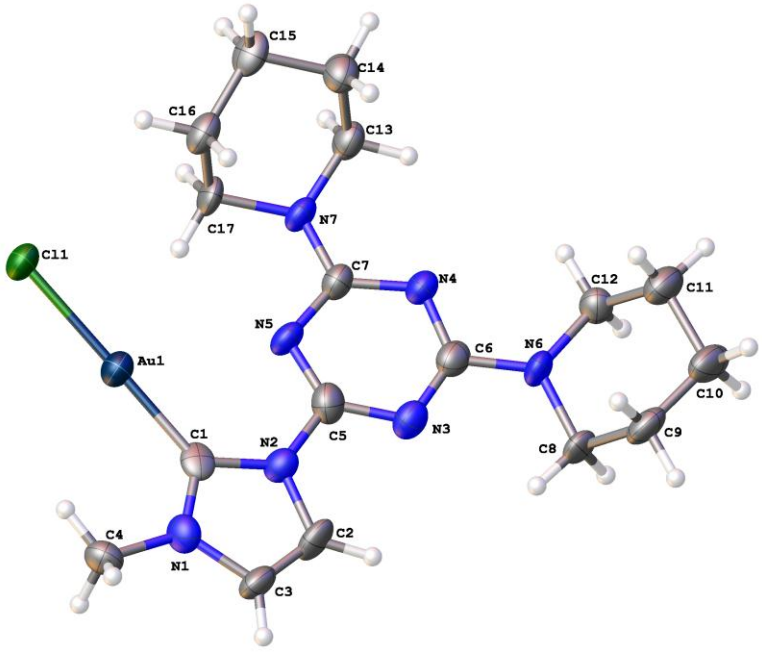

Figure S3. Thermal ellipsoid plots at 50% probability of the Au(NHC)Cl complexes. Selected bond lengths (Å) and angles (°) for **7a**: C(1)-Au(1) 1.962(14), Au(1)-Cl(1) 2.278(3), C(1)-Au(1)-Cl(1) 177.5(4).

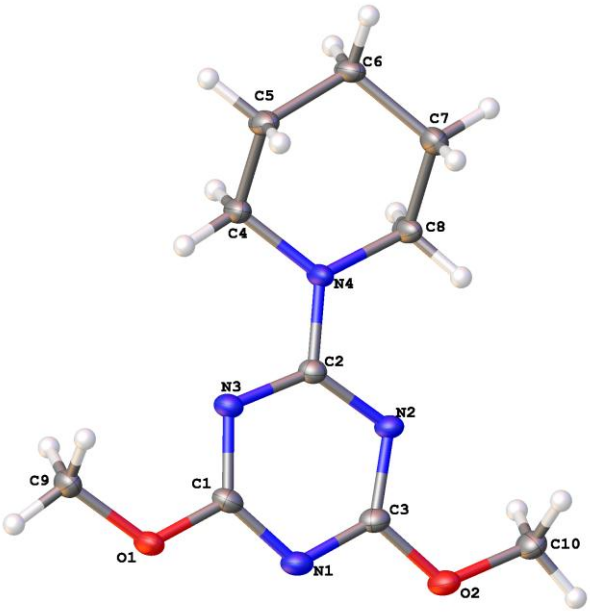

Figure S4. Thermal ellipsoid plots at 50% probability of **9**.

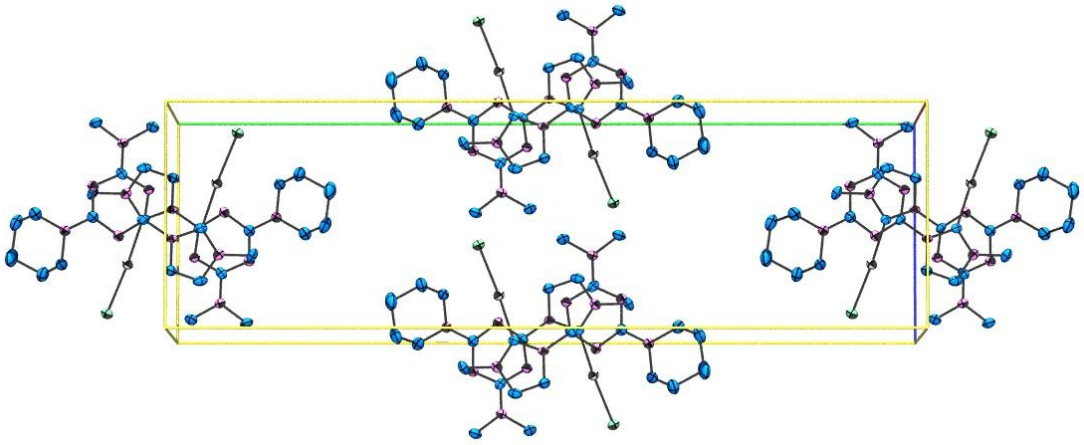

Figure S5. Crystal packing diagram of **10** illustrating the π-stacking between alternating triazine and imidazole rings. All hydrogens and solvent atoms are omitted for clarity.

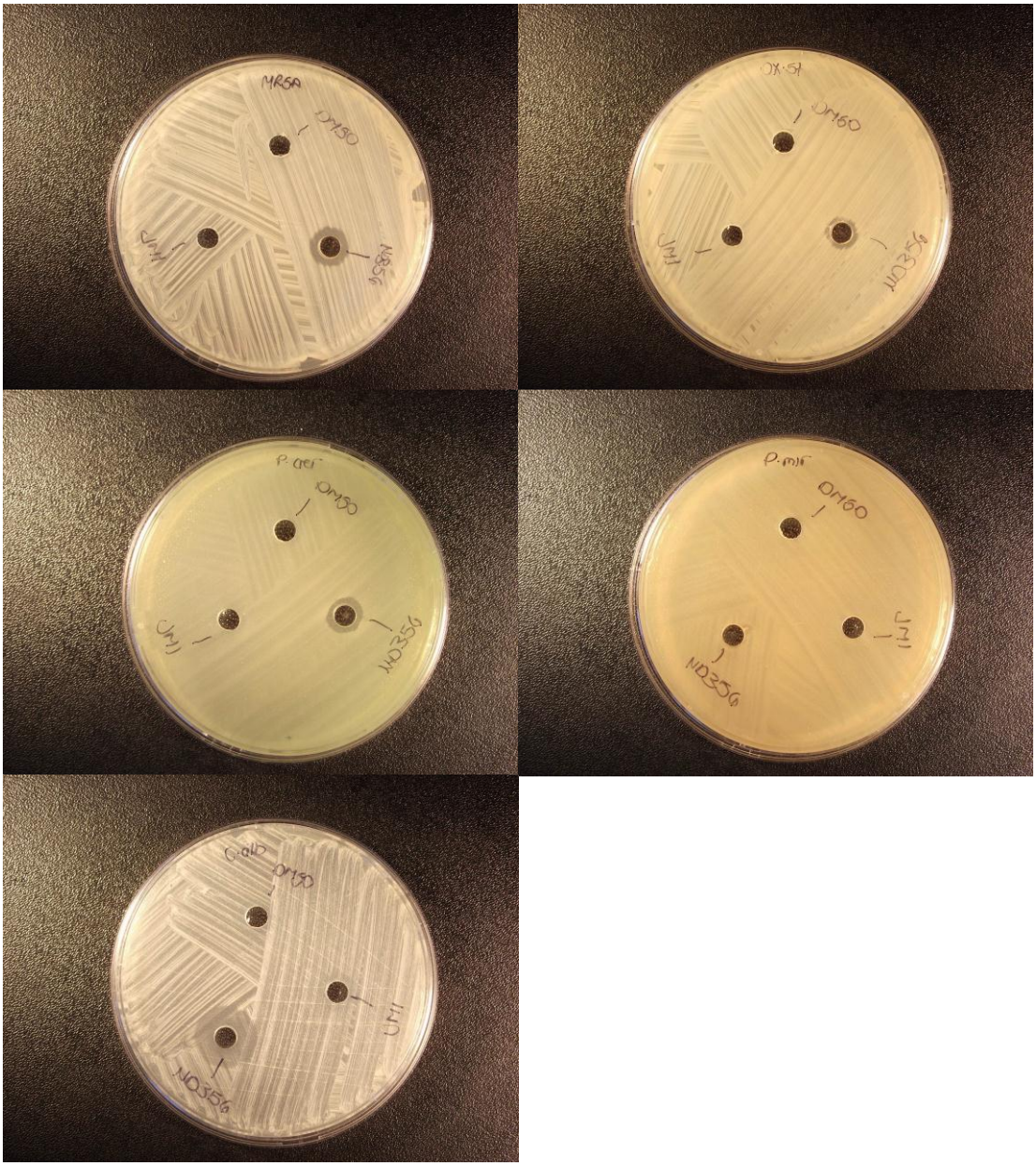

Figure S6. Culture cell plates testing the imidazolium salts **3a** (ND356 on disk) and **3b** (JM1 on disk). (a) MRSA; (b) Oxford Staphylococcus; (c) Pseudomonas Aeruginosa; (d) Proteus Mirabilis; and (e) Candida albicans.

References

1. (a) Thurston, J. T.; Dudley, J. R.; Kaiser, D. W.; Hechenbleikner, I.; Schaefer, F. C.; Holm-Hansen, D., *Journal of the American Chemical Society* **1951,** *73* (7), 2981-2983; (b) Matsuno, T.; Kato, M.; Tsuchida, Y.; Takahashi, M.; Yaguchi, S.; Terada, S., *Chem Pharm Bull* **1997,** *45* (2), 291-296.

Table S1 Crystallographic data for **5d**, **6a/b, 7a/b/c, 9**, **10** and **11**.

Compound	**5d**	**6a**	**6b**	**7a**	**7b**
Empirical formula	$C_{16}H_{22}F_{12}N_8P_2$	$C_{17}H_{25}AgClN_7$	$C_{15}H_{21}AgClN_7O_2$	$C_{17}H_{25}AuClN_7$	$C_{15}H_{21}AuClN_7O_2$
Formula weight	616.36	470.76	474.71	559.86	563.80
Temperature	120(2) K	120(2) K	120(2) K	100(2) K	120(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71075 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*P*21/*n*	*C*2/*c*	*P*21/*c*	*C*2/*c*	*P*21/*c*
Unit cell dimensions	a = 12.9534(6) Å	a = 32.5255(10) Å	a = 6.9514(2) Å	a = 33.142(6) Å	a = 7.0612(5) Å
	b = 12.4354(3) Å	b = 12.8841(3) Å	b = 20.5662(3) Å	b = 12.612(2) Å	b = 20.5399(16) Å
	c = 15.5327(7) Å	c = 9.4379(3) Å	c = 12.5800(3) Å	c = 9.2699(17) Å	c = 12.4713(8) Å
	α = 90°	α = 90°	α = 90°	α = 90°	α = 90°
	β = 99.439(2)°	β = 102.935(2)°	β = 94.3100(10)°	β = 103.990(7)°	β = 95.603(7)°
	γ = 90°	γ = 90°	γ = 90°	γ = 90°	γ = 90°
Volume	2468.14(17) Å^3	3854.70(19) Å^3	1793.40(7) Å^3	3759.8(11) Å^3	1800.1(2) Å^3
Z	4	8	4	8	4
Density (calculated)	1.659 Mg / m^3	1.622 Mg / m^3	1.758 Mg / m^3	1.978 Mg / m^3	2.080 Mg / m^3
Absorption coefficient	0.291 mm^{-1}	1.201 mm^{-1}	1.299 mm^{-1}	7.985 mm^{-1}	8.347 mm^{-1}
***F*(000)**	1248	1920	960	2176	1088
Crystal	Block; colourless	Lath; colourless	Fragment; colourless	Needle; Colourless	Plate; Colorless
Crystal size	0.36 × 0.20 × 0.16 mm^3	0.18 × 0.08 × 0.04 mm^3	0.08 × 0.06 × 0.04 mm^3	0.07 × 0.01 × 0.01 mm^3	0.20 × 0.20 × 0.02 mm^3
θ range for data collection	3.12 – 25.00°	3.03 – 27.48°	2.94 – 27.48°	3.04 – 25.03°	3.06 – 27.46°
Index ranges	$-15 \le h \le 15$, $-14 \le k \le 14$, $-18 \le l \le 18$	$-42 \le h \le 42$, $-16 \le k \le 16$, $-12 \le l \le 12$	$-9 \le h \le 9$, $-26 \le k \le 26$, $-16 \le l \le 16$	$-39 \le h \le 39$, $-15 \le k \le 15$, $-11 \le l \le 11$	$-9 \le h \le 9$, $-25 \le k \le 26$, $-16 \le l \le 16$
Reflections collected	26765	22599	21557	32275	19537
Independent reflections	4343 [R_{int} = 0.0810]	4416 [R_{int} = 0.0511]	4098 [R_{int} = 0.0624]	3305 [R_{int} = 0.2412]	4105 [R_{int} = 0.0450]
Completeness to θ = 27.48°	99.8 %	99.7 %	99.8 %	99.8 %	99.7 %
Absorption correction	Semi–empirical from equivalents	Semi–empirical from equivalents	Semi–empirical from equivalents	Semi–empirical from equivalents	Semi–empirical from equivalents
Max. and min. transmission	0.9550 and 0.9026	0.9535 and 0.8129	0.9499 and 0.9032	0.9244 and 0.6049	0.8508 and 0.2861
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	4343 / 55 / 410	4416 / 0 / 236	4098 / 0 / 236	3305 / 0 / 236	4105 / 0 / 236
Goodness-of-fit on F^2	1.042	1.125	1.061	0.902	1.097
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0744, *wR2* = 0.1850	*R1* = 0.0423, *wR2* = 0.0801	*R1* = 0.0369, *wR2* = 0.0749	*R1* = 0.0704, *wR2* = 0.1588	*R1* = 0.0283, *wR2* = 0.0629
***R* indices (all data)**	*R1* = 0.1132, *wR2* = 0.2144	*R1* = 0.0552, *wR2* = 0.0873	*R1* = 0.0510, *wR2* = 0.0810	*R1* = 0.0975, *wR2* = 0.1668	*R1* = 0.0333, *wR2* = 0.0651
Largest diff. peak and hole	0.800 and –0.468 e Å^{-3}	0.533 and –0.511 e Å^{-3}	0.483 and –0.810 e Å^{-3}	3.155 and –2.991 e Å^{-3}	1.261 and –1.174 e Å^{-3}
Extinction coeffcient	0.0037(11)				

Compound	**7c**	**9**	**10**	**11**
Empirical formula	$C_{16}H_{23}Ag_{0.25}Au_{0.75}ClN_7O$	$C_{10}H_{16}N_4O_2$	$C_{15}H_{22}AgCl_4N_7$	$C_{14}H_{21}AuClN_7$
Formula weight	539.56	224.27	550.07	519.79
Temperature	100(2) K	100(2) K	100(2) K	100(2) K
Wavelength	0.71075 Å	0.71073 Å	0.71075 Å	0.71075 Å
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	*P*21/*c*	*P*–1	*P*21/*c*	*P*21/*c*
Unit cell dimensions	*a* = 7.0421(7) Å	*a* = 7.3461(6) Å	*a* = 6.6913(3) Å	*a* = 6.627(6) Å
	b = 20.089(2) Å		*b* = 32.6023(17) Å	*b* = 9.6686(8) Å
	c = 13.0920(13) Å	*b* = 8.7159(8) Å	*c* = 9.7316(6) Å	*c* = 26.780(3) Å
	α = 90°		α = 90°	α = 90°
	β = 94.120(7)°	*c* = 8.8803(9) Å	β = 94.225(7)°	β = 96.24(4)°
	γ = 90°		γ = 90°	γ = 90°
Volume	1847.3(3) Å^3	543.28(9) Å^3	2117.2(2) Å^3	1705.8(15) Å^3
Z	4	2	4	4
Density (calculated)	1.940 Mg / m^3	1.371 Mg / m^3	1.726 Mg / m^3	2.024 Mg / m^3
Absorption coefficient	6.412 mm^{-1}	0.099 mm^{-1}	1.473 mm^{-1}	8.791 mm^{-1}
F(000)	1056	240	1104	1000
Crystal	Platelet; Colourless	Block; Colourless	Block; Colourless	Blade; Colourless
Crystal size	0.03 × 0.02 × 0.01 mm^3	0.11 × 0.06 × 0.06 mm^3	0.05 × 0.05 × 0.02 mm^3	0.15 × 0.03 × 0.01 mm^3
θ range for data collection	3.07 – 25.03°	3.23 – 27.47°	3.05 – 27.48°	3.06 – 27.47°
Index ranges	$-8 \le h \le 8$, $-23 \le k \le 23$, $-15 \le l \le 15$	$-6 \le h \le 9$, $-11 \le k \le 11$, $-11 \le l \le 11$	$-7 \le h \le 8$, $-41 \le k \le 42$, $-12 \le l \le 8$	$-8 \le h \le 7$, $-12 \le k \le 12$, $-30 \le l \le 34$
Reflections collected	19357	5038	14274	7571
Independent reflections	3267 [R_{int} = 0.1547]	2470 [R_{int} = 0.0544]	4842 [R_{int} = 0.0802]	3756 [R_{int} = 0.0240]
Completeness to θ = 27.48°	99.8 %	99.0 %	99.6 %	96.1 %
Absorption correction	Semi–empirical from equivalents	Semi–empirical from equivalents	Semi–empirical from equivalents	Semi–empirical from equivalents
Max. and min. transmission	0.9387 and 0.8309	0.9941 and 0.9892	0.9711 and 0.9300	0.9172 and 0.3522
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	3267 / 0 / 239	2470 / 0 / 148	4842 / 0 / 247	3756 / 0 / 211
Goodness-of-fit on F^2	0.965	1.102	1.082	1.185
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0574, *wR2* = 0.1238	*R1* = 0.0744, *wR2* = 0.2089	*R1* = 0.0742, *wR2* = 0.1601	*R1* = 0.0282, *wR2* = 0.0581
***R* indices (all data)**	*R1* = 0.0972, *wR2* = 0.1403	*R1* = 0.0854, *wR2* = 0.2163	*R1* = 0.1188, *wR2* = 0.1801	*R1* = 0.0377, *wR2* = 0.0596
Largest diff. peak and hole	1.958 and –1.287 e Å^{-3}	0.679 and –0.345 e Å^{-3}	2.203 and –0.905 e Å^{-3}	1.416 and –0.941 e Å^{-3}