Supplementary Material for CrystEngComm

Supporting Information

Attempted construction of minoxidil:carboxylic acid cocrystals; 8 salts and 1 cocrystal resulted

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2 was a nonmerohedral twin and data were processed with TWINABS for the two domains. The compound crystallizes in the noncentrosymmetric space group *C2*. The asymmetric unit contained two closely spaced waters of solvation which were assigned the same thermal parameters and whose occupancies were constrained to sum to 100%. The placement of non-oxidized pyrimidine nitrogens on the two minoxidils is unambiguous.

Figure 1. Thermal-ellipsoids plot (50% probability level) of **2**.

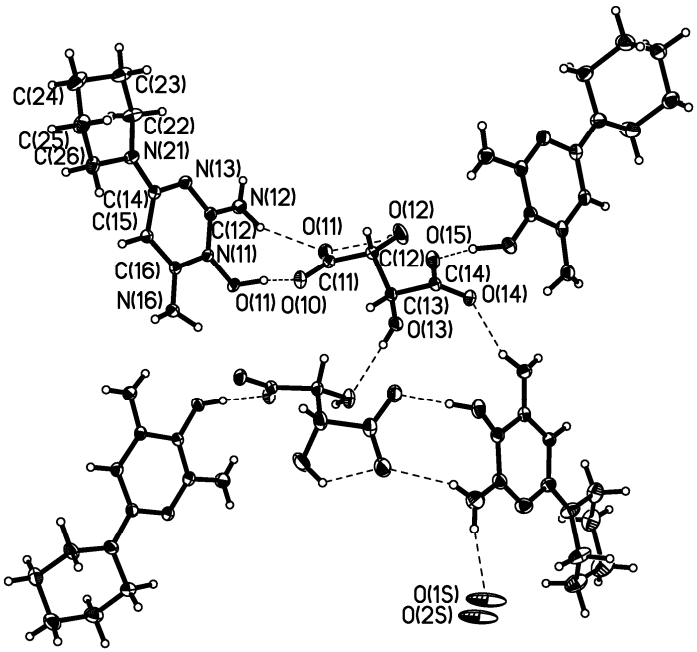

Table 1. Hydrogen bonds for **2** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O111-H111...O105	1.08(2)	1.40(2)	2.4665(16)	168.1(19)
O112-H112...O155	1.13(2)	1.34(2)	2.4539(17)	170(2)
O113-H113...O106	0.95(3)	1.59(2)	2.5337(16)	172(2)
O114-H114...O156	0.88(3)	1.66(3)	2.5310(17)	169(2)
O125-H125...O115	0.80(4)	2.14(3)	2.6300(19)	120(3)
O126-H126...O112#1	0.90(3)	2.18(3)	2.9512(17)	145(2)
O135-H135...O126	0.77(3)	1.99(3)	2.7591(18)	172(3)
O136-H136...O146	0.92(3)	1.97(4)	2.608(2)	125(3)
N121-H12A1...N131#2	0.90(2)	2.15(2)	3.0375(17)	167(2)
N122-H12A2...O115#3	0.92(3)	2.10(3)	2.991(2)	165(2)
N123-H12A3...O156#1	0.91(3)	2.05(3)	2.930(2)	160(2)
N124-H12A4...O(1S)	0.84(3)	2.11(3)	2.935(3)	168(2)
N121-H12B1...O115	0.94(2)	2.25(2)	3.1056(18)	151(2)
N122-H12B2...O106#3	0.86(2)	2.29(2)	3.1271(18)	167(2)
N123-H12B3...O155#1	0.78(3)	2.22(2)	2.9275(18)	152(2)
N124-H12B4...O146	0.84(3)	2.18(3)	2.892(2)	143(3)
N161-H16A1...O116	0.96(2)	2.10(2)	2.9118(16)	141.4(17)
N162-H16A2...O116#4	0.92(2)	2.21(2)	3.0796(19)	157(2)
N163-H16A3...O135#5	0.86(2)	1.97(2)	2.8279(18)	179(3)
N164-H16A4...O114	0.92(2)	2.37(2)	2.6311(17)	96.3(16)
N161-H16B1...O145#5	0.80(2)	2.07(2)	2.8501(16)	166(2)
N164-H16B4...O116#4	0.83(2)	2.07(2)	2.8844(17)	169(2)

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z #2 -x+1,y,-z #3 x,y-1,z #4 x-1/2,y-1/2,z #5 x+1/2,y+1/2,z

Complex **3** crystallized in the centrosymmetric space group *C2/c*, and the asymmetric unit contained one minoxidil, one-half diacid, and one water of hydration. The diacid sits on a crystallographic 2-fold axis. Geometry of the diacid was restrained by use of a "DFIX" command.

Figure 2. Thermal-ellipsoids plot (50% probability level) of **3**.

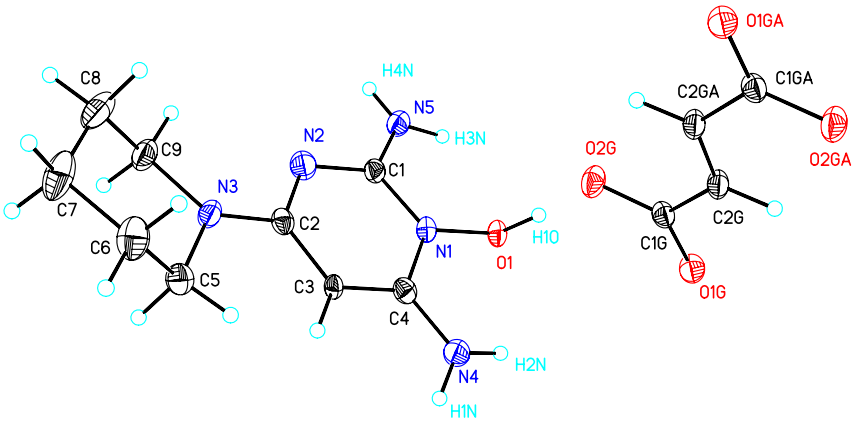

Table 2. Hydrogen bonds for **3** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1W)-H(1W)...O(1G)#2	0.89(4)	2.00(4)	2.818(2)	152(3)
O(1W)-H(2W)...O(1G)#3	0.90(4)	1.87(4)	2.768(2)	179(3)
N(5)-H(3N)...O(1)#4	0.91(3)	2.28(3)	3.124(3)	154(2)
N(5)-H(4N)...O(1G)#5	0.84(3)	2.22(3)	3.054(3)	177(3)
N(4)-H(1N)...O(1W)	0.89(3)	2.01(4)	2.895(3)	179(3)
N(4)-H(2N)...O(1W)#6	0.94(3)	2.12(3)	3.013(3)	159(3)
O(1)-H(1O)...O(2G)#7	1.06(3)	1.41(3)	2.475(2)	174(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2,-y+3/2,-z+2 #2 x,-y+1,z-1/2 #3 -x,-y+1,-z+1 #4 -x,-y+2,-z #5 x,-y+2,z-1/2 #6 -x,-y+1,-z #7 x,y,z-1

Complex **4** crystallized in the centrosymmetric space group *P2/c*, and the asymmetric unit contained one minoxidil, one-half diacid, and one water of hydration. The diacid sits on a crystallographic 2-fold axis. As with other members of this series, there were two alternate locations of the non-oxidized pyrimidine nitrogen. This disorder, as well as disorder in the unique methylene group of the diacid, were handled with free variables. Geometry of the diacid was restrained by use of a "DFIX" command.

Figure 3. Thermal-ellipsoids plot (50% probability level) of **4**.

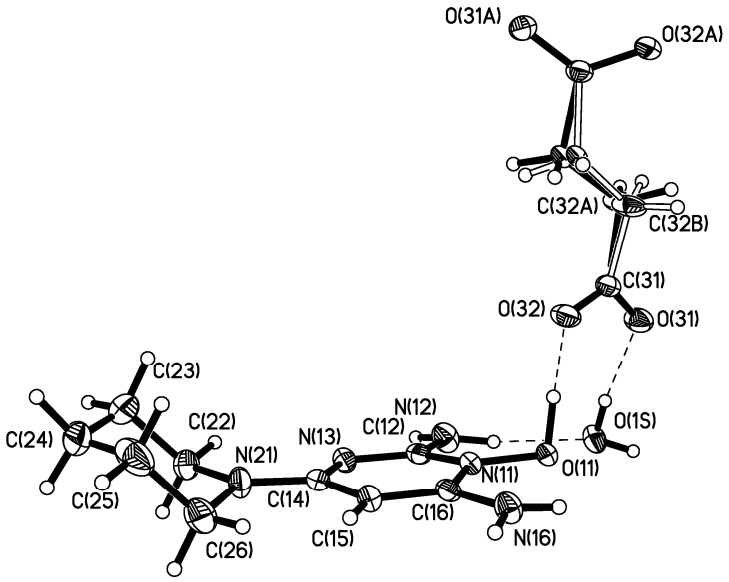

Table 3. Hydrogen bonds for **4** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(11)-H(11)...O(32)	1.010(15)	1.451(15)	2.4599(10)	176.7(14)
N(12)-H(12A)...O(1S)	0.905(17)	2.207(17)	3.0683(13)	158.8(15)
N(12)-H(12B)...O(1S)#2	0.859(18)	2.030(18)	2.8881(13)	176.5(17)
N(16)-H(16A)...O(11)#3	0.877(16)	2.219(16)	3.0326(11)	154.0(14)
N(16)-H(16B)...O(31)#4	0.886(17)	2.209(17)	3.0873(13)	170.9(14)
O(1S)-H(1A)...O(31)	0.900(18)	1.853(18)	2.7483(11)	172.8(15)
O(1S)-H(1B)...O(31)#5	0.846(17)	2.068(17)	2.8362(11)	150.6(15)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,-z+3/2 #2 -x,-y,-z+1 #3 -x,-y+1,-z+1 #4 x,-y+1,z-1/2 #5 -x,y,-z+3/2

The asymmetric unit of **5** contains one diacid and two minoxidils. One of the two unique minoxidil molecules exhibited disorder. Two orientations were identified for the piperidine fragment. This ratio was initially allowed to refine, then fixed at 70 : 30 for the last cycles of refinement. Two alternate placements of the reduced non-oxidized pyrimidine nitrogen were identified for the major (70%) species, and a free variable was used to adjust the ratio of these two sub-species. Only a single non-oxidized pyrimidine nitrogen was utilized for the minor species. The SHELXL "SAME" command was used to restrain the geometry of the three piperidine rings identified for the disordered minoxidil. Amino protons were constrained to idealized position by using the SHELXL "AFIX 93" command.

Figure 4. Thermal-ellipsoids plot (50% probability level) of **5**.

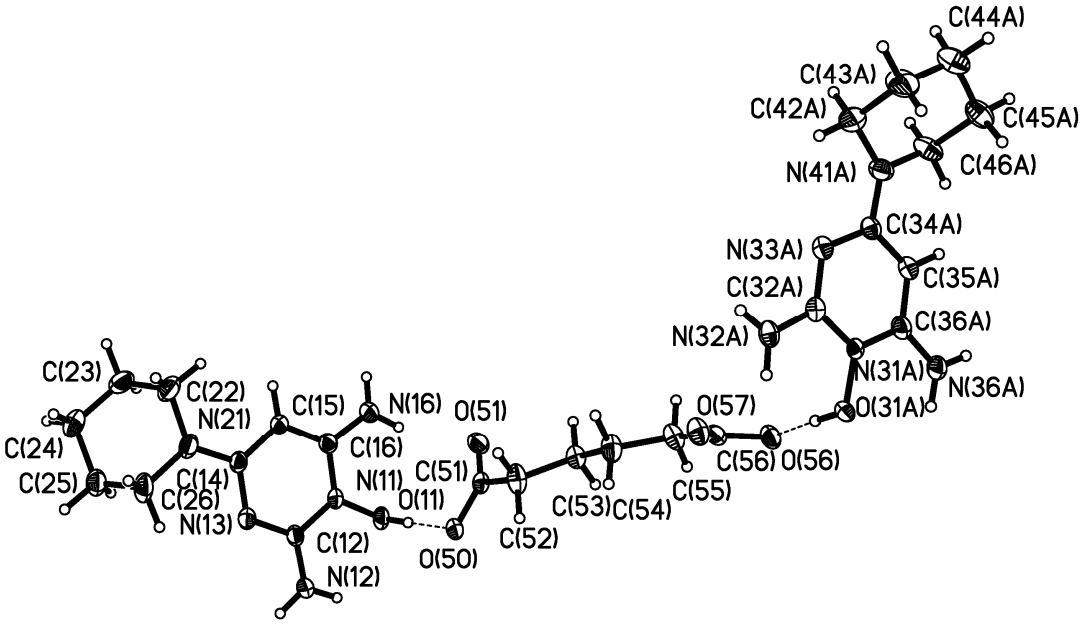

Table 4. Hydrogen bonds for **5** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(11)-H(11)...O(50)	0.977(17)	1.525(18)	2.5002(14)	175.3(16)
O(31A)-H(31A)...O(56)	0.92(2)	1.487(19)	2.408(9)	177.6(16)
N(16)-H(16B)...O(51)	0.88	2.31	2.9163(15)	126.5
N(16)-H(16A)...O(57)#1	0.88	2.01	2.8728(15)	165.2
N(12)-H(12A)...O(56)#2	0.88	2.07	2.8573(14)	148.7
N(12)-H(12B)...O(50)#3	0.88	2.14	2.9340(14)	150.5
N(32A)-H(32A)...O(51)#4	0.88	2.00	2.864(7)	166.8
N(32C)-H(32F)...O(57)	0.88	2.05	2.831(17)	147.8
N(36A)-H(36B)...O(50)#5	0.88	2.16	2.915(10)	144.2

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1/2,z-1/2 #2 x,y,z-1 #3 -x,-y+1,-z #4 x+1/2,-y+1/2,z+1/2 #5 x,y,z+1

The unit cell of **6** contains one molecule of hydroxy acid, one water of hydration, and 1 ½ molecules of minoxidil. The half-minoxidil is located on a crystallographic 2-fold axis. A complete molecule, populated to 50% and straddling the 2-fold axis, modelled this species. The placement of non-oxidized pyrimidine nitrogens on the two minoxidils is unambiguous.

Figure 5. Thermal-ellipsoids plot (50% probability level) of **6**.

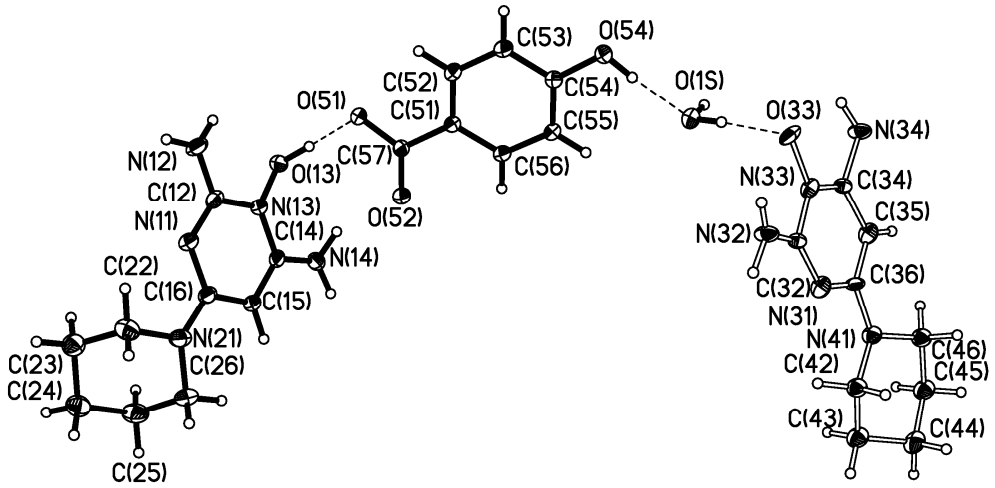

Table 5. Hydrogen bonds for **6** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(13)-H(13)...O(51)	0.994(12)	1.505(13)	2.4915(9)	171.0(11)
O(54)-H(54)...O(1S)	0.888(15)	1.760(15)	2.6477(10)	176.4(14)
O(1S)-H(1A)...O(33)	0.875(14)	1.83(2)	2.70(2)	174.3(13)
O(1S)-H(1B)...O(51)#1	0.890(14)	2.044(14)	2.9189(10)	167.3(12)
N(12)-H(12A)...O(54)#2	0.907(14)	2.046(14)	2.9485(12)	173.1(12)
N(12)-H(12B)...O(52)#3	0.817(14)	2.245(14)	2.8665(11)	133.3(12)
N(14)-H(14B)...O(51)#4	0.896(15)	2.067(16)	2.9520(11)	169.1(13)
N(32)-H(32A)...O(52)#5	1.03(3)	2.15(3)	2.989(4)	137(2)
N(34)-H(34B)...O(52)#6	0.83(3)	2.04(3)	2.850(4)	165(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,-y+1/2,-z+1 #2 x,-y,z+1/2 #3 -x+3/2,y-1/2,-z+3/2 #4 -x+3/2,y+1/2,-z+3/2 #5 -x+1,-y+1,-z+1 #6 x,-y+1,z-1/2

The crystal **7** contains a 1 : 2 ratio of minoxidil : acid. The one acid showed a nearly 60:40 ratio of two closely spaced disordered species. The other species was found to contain ~6% of a minor species that was very different in placement. Two closely spaced piperidine residues were located for the minoxidil, and as before, both alternate locations of the non-oxidized pyrimidine nitrogen were significantly populated. Both carboxylic acid and hydroxyl geometries were optimized using the SHELXL "AFIX 83" command.

Figure 6. Thermal-ellipsoids plot (50% probability level) of **7**.

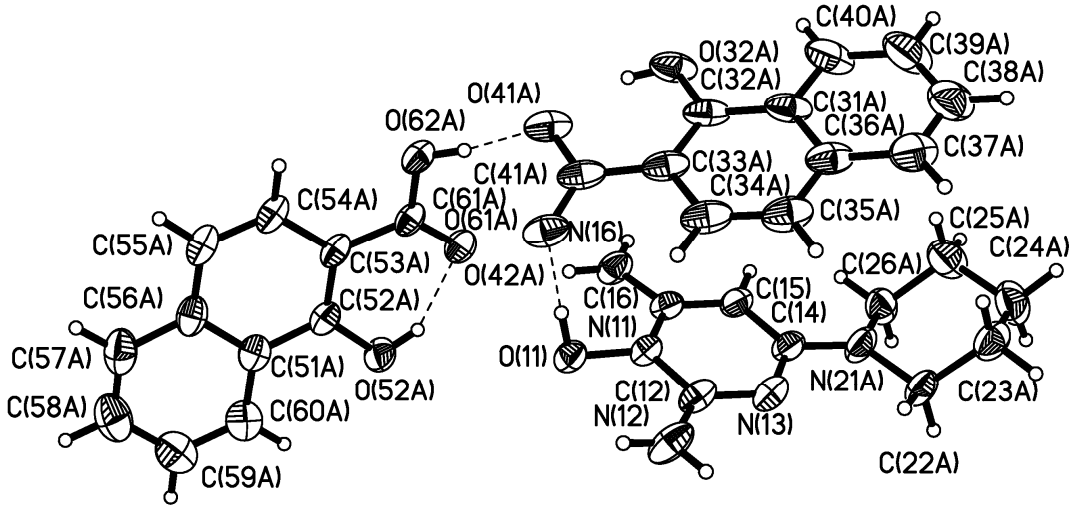

Table 6. Hydrogen bonds for **7** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(11)-H(11)...O(42A)	0.95(2)	1.64(2)	2.584(2)	175.1(19)
O(11)-H(11)...O(41B)	0.95(2)	1.90(5)	2.84(5)	173(2)
O(52A)-H(52A)...O(61A)	0.84	1.82	2.561(17)	146.6
O(52B)-H(52B)...O(61B)	0.84	1.92	2.61(3)	138.2
O(62A)-H(62A)...O(41A)	0.84	1.57	2.401(4)	172.5
O(62A)-H(62A)...O(42B)	0.84	1.08	1.91(3)	164.3
O(62B)-H(62B)...O(41A)	0.84	2.00	2.834(5)	172.1
O(62B)-H(62B)...O(42B)	0.84	1.51	2.34(3)	174.5
N(12)-H(12A)...O(62B)#1	0.84(3)	2.46(3)	2.977(9)	121(2)
N(12)-H(12B)...O(42A)#1	0.87(3)	2.00(3)	2.860(3)	170(2)
N(12)-H(12B)...O(41B)#1	0.87(3)	2.07(5)	2.92(5)	168(3)
N(16)-H(16A)...O(61A)#2	0.83(2)	2.24(3)	3.033(10)	160(2)
N(16)-H(16A)...O(61B)#2	0.83(2)	2.52(3)	3.311(15)	161(2)
N(16)-H(16B)...O(61A)	0.88(2)	2.07(3)	2.904(11)	158(2)
N(16)-H(16B)...O(61B)	0.88(2)	2.20(3)	3.064(15)	165(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+1,-z+1 #2 -x+1,-y+1,-z

The asymmetric unit of **8** contains a 2:1 ratio of minoxidil:acid and, in addition, contains a half-water of hydration, located on a crystallographic inversion center. The minoxidil molecules share a proton and are formally positively charged, and the acid has been deprotonated. Both minoxidils displayed significant populations of the two alternate non-oxidized pyrimidine nitrogens. The acid was present in two alternate configurations in the asymmetric unit, with nearly superimposable carboxylate groups but differing in orientation of the ring and hydroxyl group.

Figure 7. Thermal-ellipsoids plot (50% probability level) of **8**.

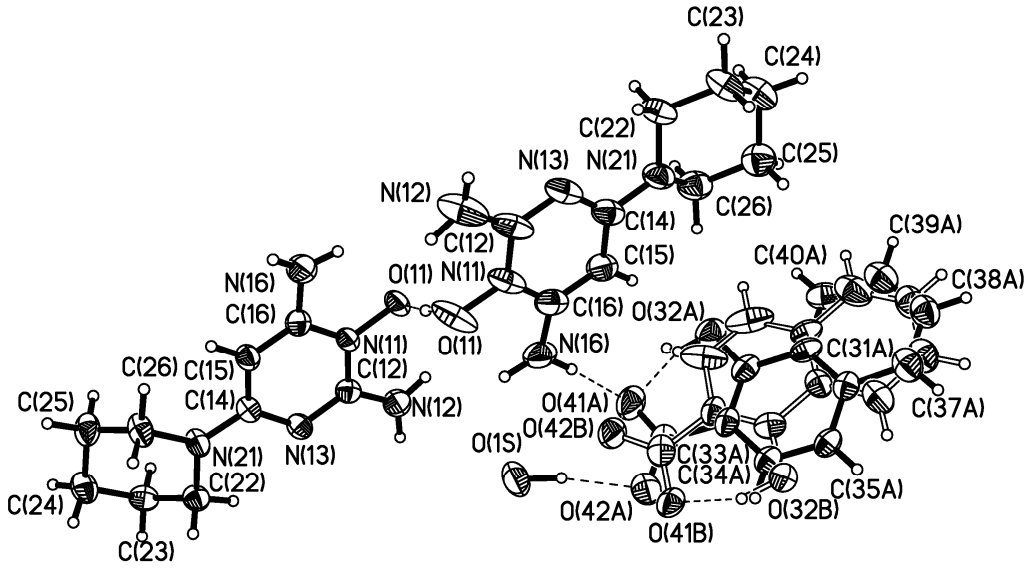

Table 7. Hydrogen bonds for **8** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1S)-H(1A)...O42A3	1.04(5)	2.01(5)	3.021(4)	163(4)
O(1S)-H(1A)...O42B3	1.04(5)	1.55(5)	2.440(5)	140(4)
O111-H111...O112	1.198(18)	1.219(19)	2.4166(18)	177.9(17)
N121-H12A1...O42A3#1	0.95(2)	2.00(2)	2.944(2)	171.2(16)
N121-H12A1...O41B3#1	0.95(2)	2.03(2)	2.963(4)	166.2(16)
N161-H16A1...O42A3#2	0.88(2)	2.12(2)	2.965(3)	161.0(19)
N161-H16A1...O41B3#2	0.88(2)	2.02(2)	2.900(4)	176(2)
N122-H12A2...O41A3#3	0.87(3)	1.92(3)	2.783(3)	168(2)
N122-H12A2...O42B3#3	0.87(3)	2.17(3)	2.907(5)	142(2)
N122-H12B2...O(1S)#2	0.92(3)	2.09(3)	2.840(3)	137(2)
N162-H16B2...O41A3	0.92(2)	2.01(3)	2.924(3)	173(2)
N162-H16B2...O42B3	0.92(2)	1.87(3)	2.708(4)	150(2)
O32A3-H32A3...O41A3	0.88(4)	1.64(4)	2.490(4)	161(4)
O32B3-H32B3...O41B3	1.03(6)	1.59(6)	2.556(6)	155(5)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y+1,-z+1 #2 -x+1,-y+1,-z+1 #3 x+1,y,z

The asymmetric unit of **9** contains two acids and two minoxidil molecules. One of the acids showed disorder over two sites. The sum of the occupancies for the two species were constrained to sum to 100%, and thermal parameters were pairwise constrained. The SHELXL "SAME" command was used to restrain the geometry of the three unique acids: the fully occupied molecule in residue 1, and the two partially occupied molecules in residue 2. Both minoxidils showed alternate placements of the non-oxidized pyrimidine nitrogen. Coordinates of the two acid hydrogens were idealized using the SHELXL "AFIX 83" command.

Figure 8. Thermal-ellipsoids plot (50% probability level) of **9**.

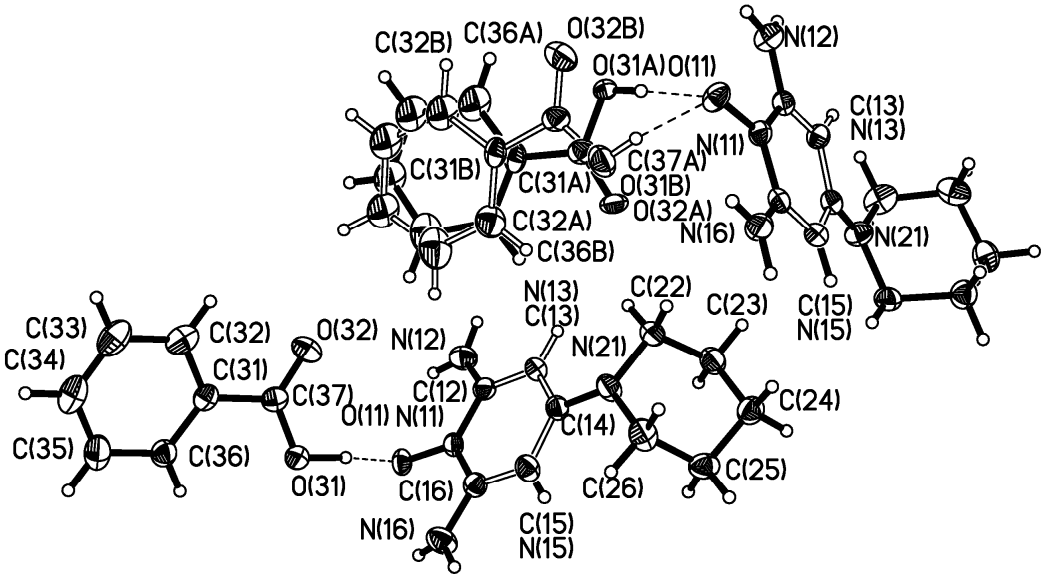

Table 8. Hydrogen bonds for **9** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N121-H12A1...O111#1	0.84(3)	2.26(3)	2.969(2)	143(2)
N121-H12B1...O31A2#2	0.86(3)	2.23(3)	3.068(3)	164(2)
N121-H12B1...O32B2#2	0.86(3)	1.85(3)	2.693(4)	164(2)
N161-H16A1...O112#3	0.91(3)	2.13(3)	2.988(3)	157(2)
N161-H16B1...O32A2#4	0.80(3)	2.13(3)	2.827(3)	145(2)
N122-H12A2...O111#5	0.89(2)	2.10(2)	2.923(2)	153(2)
N122-H12B2...O321#2	0.83(2)	2.09(3)	2.904(2)	167(2)
N162-H16A2...O112#6	0.85(2)	2.19(2)	2.936(2)	147(2)
N162-H16B2...O311#4	0.92(3)	2.19(3)	3.083(2)	163.5(18)
O311-H311...O111	1.12(2)	1.38(2)	2.4895(16)	175(2)
O31A2-H31A2...O112	0.84	1.61	2.442(3)	172.8
O31B2-H31B2...O112	0.84	1.86	2.693(4)	173.6

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z #2 -x+1,-y,-z+1 #3 x,y+1,z-1 #4 -x+1,-y+1,-z+1 #5 x,y-1,z+1 #6 -x+1,-y,-z+2

Table 10. pK_a's of minoxidil and the carboxylic acids incorporated within this study

compound	API or coformer	pK_a	ΔpK_a[b]	salt/cocrystal
---	minoxidil	6.32[a]	---	
2	L-tartaric acid	3.02	3.30	salt
3	fumaric acid	3.03	3.29	salt
4	succinic acid	4.21	2.11	salt
5	adipic acid	4.44	1.88	salt
6	4-hydroxybenzoic acid	4.58	1.74	salt
7 and 8	1-hydroxy-2-napthoic acid	2.70	3.62	salt
9	benzoic acid	4.19	2.13	cocrystal

a. pK_a value was obtained by using the ACD/p*K*a DB version 7.0 program.
b. ΔpK_a values were determined by equation, pK_a(base/API)-pK_a(acid).