Supporting Information

A multi-gram synthesis to pure HMF and BHMF

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Contents

Catalysts properties overview

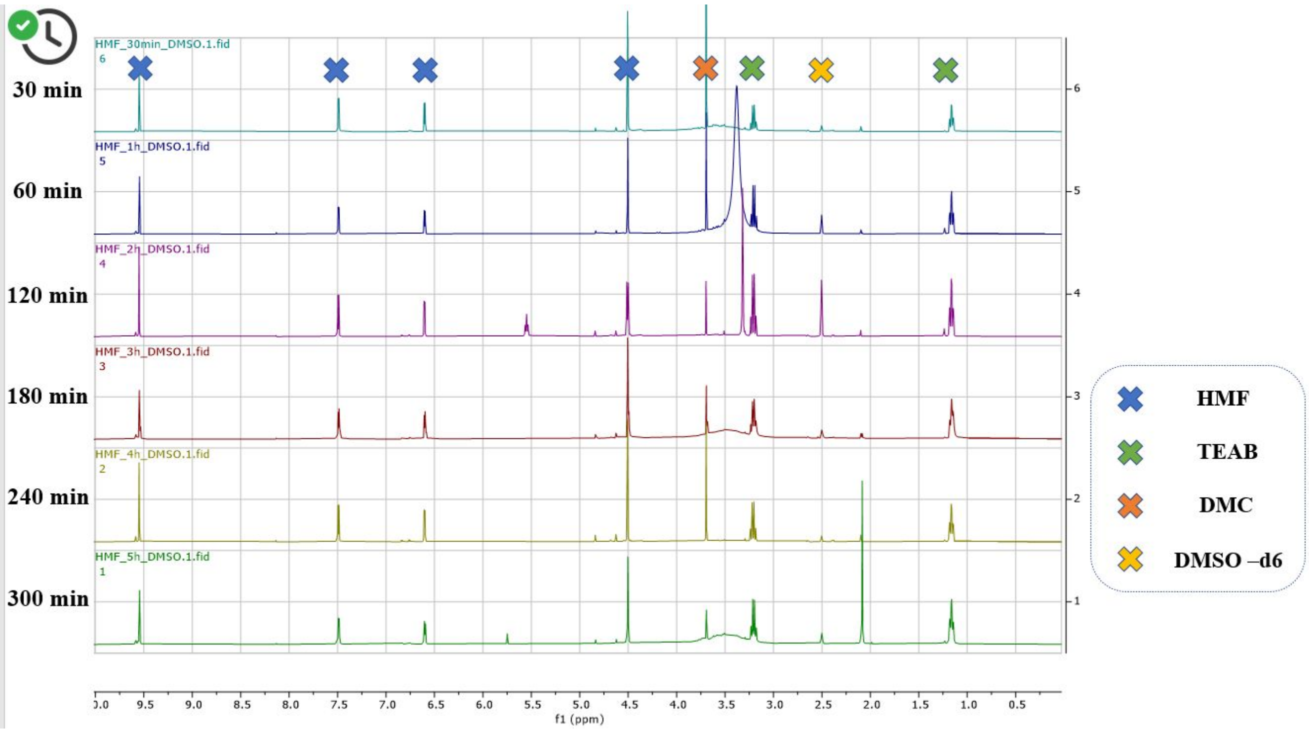
Table S1. Purolites and Amberlysts properties.

	Amberlyst-15	Amberlyst-36	CT151	CT269	CT275
Polymer structure	Macroporous polystyrene crosslinked with divinylbenzene				
Appearance	Spherical Beads				
Functional Group	Sulfonic Acid				
Ionic Form	H^+ form				
Particle Size Range	< 300 µm	600-850 µm	425 - 1200 µm		
Dry Weight Capacity	≥ 4.7 eq/kg (H^+ form)	≥ 5.4 eq/kg (H^+ form)	5.1 eq/kg (H^+ form)	5.2 eq/kg (H^+ form)	5.2 eq/kg (H^+ form)
Moisture Retention	≤ 1.6% (H^+ form)	51 - 57 % (H^+ form)	54 - 59 % (H^+ form)	51 - 57 % (H^+ form)	51 - 59 % (H^+ form)
Surface Area	53 m^2/g	33 m^2/g	15 - 25 m^2/g	35 - 50 m^2/g	20 - 40 m^2/g
Pore Volume	0.40 mL/g	0.20 mL/g	0.15 - 0.30 mL/g	0.30 - 0.50 mL/g	0.40 - 0.60 mL/g
Average Pore Diameter	300 Å	240 Å	250 - 400 Å	250 - 425 Å	400 - 700 Å
Temperature Limit	120 °C	150 °C	150 °C	130 °C	130 °C

a) All Purolite® information is available on https://www.purolite.com/index. All Amberlyst-15 information are available on the DuPont (https://www.dupont.com/content/dam/dupont/amer/us/en/watersolutions/public/documents/en/45-D00927-en.pdf).

[1]H-NMR spectra of a typical HMF synthesis at different times

(samples taken from #6 Table 1 reaction)

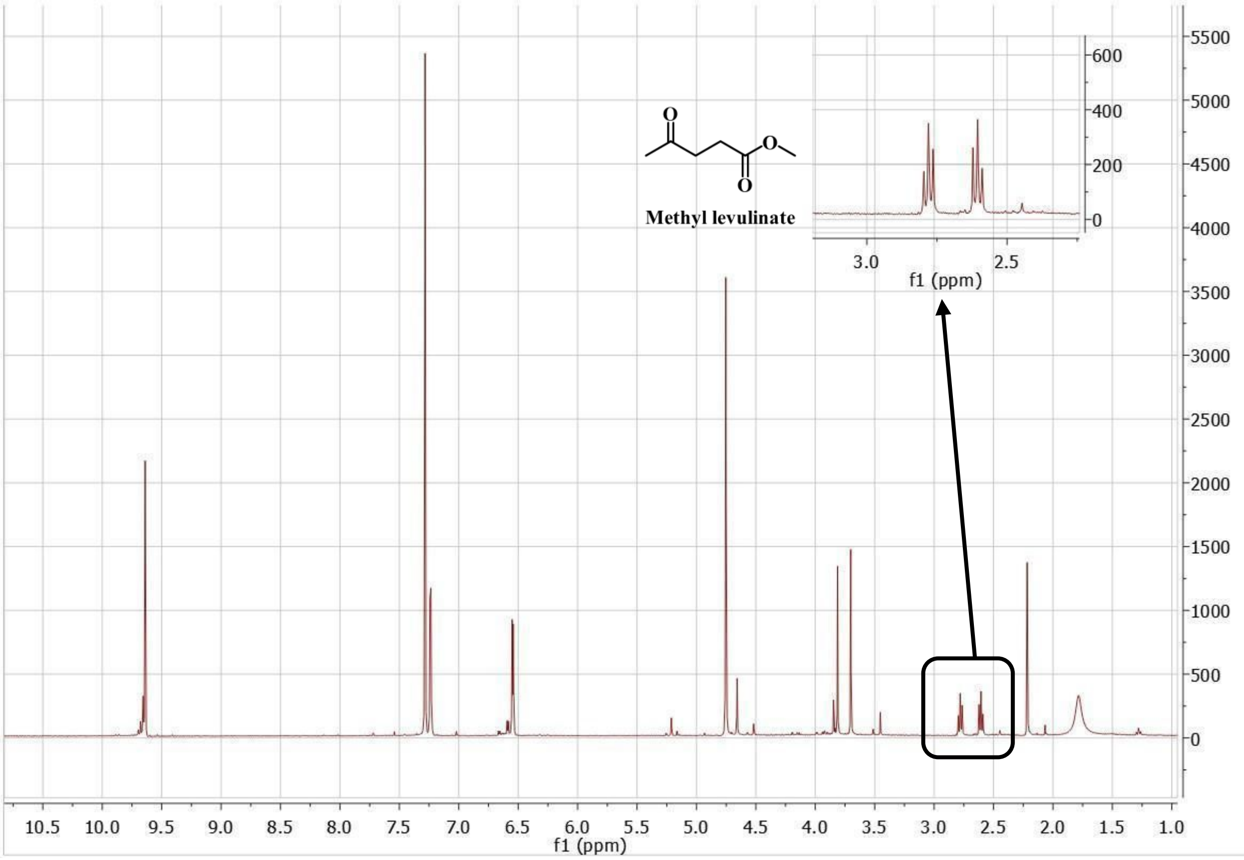


Additional reactions for the synthesis of HMF in autoclave

Table S2. *Synthesis of HMF in autoclave with temperatures higher than 110 °C.*

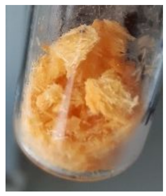
#	DMC [mL]	TEAB [%]	Purolite CT275DR [%]	T [C°]	Time [h]	^{1}H-NMR Selectivity [%]			HMF ^{1}H-NMR Yield [%]
						HMF	ML	Other	
1	40	10% wt.	5% wt.	120	2	**97**	3	0	68
2	40	10% wt.	5% wt.	130	2	**96**	4	0	70
3	40	10% wt.	5% wt.	150	2	**68**	18	16	46
4	40	10% wt.	5% wt.	150	4	**71**	4	25	60

^{1}H-NMR of #3, Table S2 in $CDCl_3$.



Crystallization/Purification of HMF

Table S3. Solvents used in the HMF crystallization trials.[a]

#	Solvent	HMF crystals	Crystal yield %	Crystals
1[b]	Et_2O	✓	ca. 50	Bubble-shape, yellow crystals 
2[b,d]	Et_2O + Hexane	✓	ca. 30	Needle-shape, yellow-orange crystals. 
3[c]	t-butyl methyl ether (TBME)	✗	/	/
4[c]	THF	✗	/	/
5[c]	2-MeTHF	✗	/	/
6[c]	Hexane	✗	/	/
7[b]	Acetone + Hexane	✗	/	/
8[b,e]	AcOEt + Hexane	✓	ca. 30	Needle-shape, yellow-orange. They melt faster. 
9[c]	AcOEt	✗	/	/

[a] After obtaining the dark brown reaction crude, solvent(s) was added, the organic phase was collected in a beaker and put in freezer for 48h; [b] Separation between organic phase and dark brown crude oil; [c] Solvent dissolves the dark brown crude oil; [d] 10 mL of Et_2O were poured in the reaction crude, than hexane was added until the formation of a white-yellow powder; this procedure repeated two more times, the recovered organic phase were then put in the freezer for 48h; [e] Dark brown oil dissolved in 5 mL of AcOEt, than hexane was added until the formation of a white-yellow powder; this procedure repeated two more times, the recovered organic phase were then put in the freezer for 48h.

Green metrics evaluation

Explanation of waste-related Green Metrics:

- E-kernel: Mass contribution to the total E-factor from reaction by-products, reaction side products, and unreacted starting materials;
- E-reaction solvent (E-rxn solv): Mass of reaction solvent necessary for the synthesis of the target product;
- E-catalyst (E-cat): Mass of the catalyst necessary for the synthesis of the target product;
- E-workup: Mass of the reagents used in the work-up procedures necessary to obtain the target product;
- E-purification (E-purif): Mass of the reagents used in purification procedures necessary to obtain the pure target product;

Comprehensive table for the evaluation of green metrics

Table S4. *Environmental assessment of different procedures with PMI lower than 100 (#1-17) and higher than 100 (#18-25).*

#	Method[b]	D-Fructose [g]	Catalyst	Rxn solvent	Yield [%]	E-kernel	E- rxn solv.	E-cat	E-workup	E-purif	E-total	PMI	Ref.
1*	B	0.64	CeP_3[c]	DMC-water	68	1.11	44.43	0.33	39.6	0	85.47	86.47	Dibenedetto *et al.*[28]
2[d]	C	1	HCl 0.25M	MIBK	74.3	0.92	23.02	21.54	0	0	45.48	46.48	Brasholz *et al.*[29]
3*	B	1	$FeCl_3/Et_4NBr$	NMP[e]	78	0.83	18.83	0.55	67.29	0	87.5	88.5	Tong *et al.*[30]
4*[f]	B	1.8	HBr/silica	THF	95	0.5	88.8	4.01	0.83	>>0	94.14	95.14	Rajmohan *et al.*[31]
5[d]	B	2.1	Ti/Si500	Dist water/TEAC	95.2	0.5	7.14	0.14	5.64	0	13.42	14.42	Novamont[32]
6[g]	B	5	[PPFPy][HSO_4]	DMSO	82.7	0.73	30.4	0.92	7.6	0	39.65	4.17[h]	Shi *et al.*[33]
7	B	5	[PPFPy][HSO_4]	DMSO	82.7	0.73	30.4	0.92	7.6	0	39.65	40.65	Shi *et al.*[33]
8[g]	B	5	[PPFPy][HSO_4]	DMSO	84.4	0.69	29.79	0.9	59.58	0	90.97	57.34[h]	Shi *et al.*[33]
9	B	5	[PPFPy][HSO_4]	MIBK/water	83	0.72	28.86	0.92	5.49	0	35.99	36.99	Shi *et al.*[33]
10[f],[i]	A	5	CO_2	H_2O	92	0.55	5.59	0	0	0	6.14	7.14	Motokucho *et al.*[34]
11[d],[f]	B	10	H_2SO_4/LiBr	DMAc	45.3	2.15	29.56	3.26	21.34	0	56.31	57.31	Kovash *et al.*[35]
12[g]	A	10	Pur CT275DR	DMC	50.3	2.03	12.96	0.45	27.3	6.49	49.24	14.25	This work
13	A	10	Pur CT275DR	DMC	72	0.98	8.45	0.3	17.8	0	27.53	5.13	This work
14*[f]	B	10	Amb-15	CH_3CN:TEAC	78	0.82	21.27	2.18	7.19	0	31.46	32.46	Brown *et al.*[36]
15*	B	20	Amb-15	DMC:TEAB	70	1.04	17.45	0.61	5.52	0	24.62	25.62	Musolino *et al.*[14]
16*	B	20	Amb-15	water	91	0.57	0.7	7.28	86.84	0	95.39	96.39	Simeonov *et al.*[9]
17*	B	20	BF_3 OEt_2	DMC	76	0.89	16.14	0.53	2.55	0	20.11	21.11	Musolino *et al.*[14]
18[m],[g]	B	1.5	H_2SO_4	[BMIM][Cl]	78	0.83	8.55	0.02	605.74	34.68	649.81	650.81	Galkin *et al.*[22]
19[m]	B	1.5	H_2SO_4	[BMIM][Cl]	78	0.83	8.55	0.02	605.74	0	615.13	616.13	Galkin *et al.*[22]
20*	B	9	Cationic resin/activate carbon	water	48	1.97	49.5	19.8	260.4	0	331.67	332.67	Vinke *et al.*[37]
21*	B	18	BF_3 OEt_2	DMSO-toluene	60	1.37	26.41	0.29	67.74	153.79	249.60	250.60	Musau *et al.*[38]
22[m],[g]	B	18	H_2SO_4	[BMIM][Cl]	72.9	0.96	7.83	0.02	647.79	37.03	693.69	694.69	Galkin *et al.*[22]
23[m]	B	18	H_2SO_4	[BMIM][Cl]	72.9	0.96	7.83	0.02	647.79	0	656.61	657,61	Galkin *et al.*[22]
24*[n]	C	70	WCl_6/HY	[BMIM]Cl/THF	55	1.62	170.04	0.27	0	0	171.93	172.93	Chan *et al.*[39]

[a] E-excess is not reported in the table as its value was zero for all the synthetic procedure reported; the reported metrics do not consider the preparation of the catalyst; procedures signed by a star were already reported in our previous article [13] [b] A = Autoclave, B = Batch, C = Continuous flow; [c] CeP_3 is Cerium Phosphate catalyst with formula $[(Ce(PO_4)1.5(H_2O)(H_3O)0.5(H_2O)_{0.5})]$; [d] Amounts of work-up and/or purification materials are not reported in the original article; [e] NMP = N-Methyl-2-pyrrolidone; [f] Excluding column chromatography; [g] Including purification; [h] DMSO is partially recovered; [i] Reaction conducted for 148 h; [l] NHC is 1,3-bis(2,6-diisopropylbenzyl)imidazolylidene; [m] Aqueous solution of NaCl/NaHCO3 not included; [n] Reaction conducted in continuous biphasic system over a 42 h period where 7 cycles of 10 g each of D-fructose run at 6 h intervals were combined.

Ecoscale evaluation

Table S5. Ecoscale scores for the selected procedures for HMF synthesis and isolation.

Reference	Amount of D-fructose g	Ecoscale value	Comments
Brasholz *et al.*[29]	1.00	56	Continuous flow reaction
Galkin *et al.*[22]	1.5	76	Purification included
Novamont[32]	2.10	89	Ti/Si 500 (catalyst) not included
		67	Reagent for catalyst synthesis included
Shi *et al.*[33]	5.00	83	[PPFPy][HSO_4] not included, DMSO recovered by distillation from reaction crude
		36	Reagent for catalyst synthesis included
Shi *et al.*[33]	5.00	81	[PPFPy][HSO_4] not included, DMSO recovered by distillation from reaction crude; purification by AcOEt/H_2O extraction
		34	Reagent for catalyst synthesis included
Shi *et al.*[33]	5.00	82	MIBK/water extraction
		32	Reagent for catalyst synthesis included
Motokucho *et al.*[34]	5.00	80	Reaction performed for 168 h in autoclave; amount of CO_2 employed not specified
Kovash *et al.*[35]	10	43	HMF isolated as yellow liquid
This work with purif. (50 % yield)	10	60	Purolite not available in the database (Amb-15 used instead of Purolite)
This work, no purif. (72% yield)	10	71	Purolite not available in the database (Amb-15 used instead of purolite)
Galkin *et al.*[22]	18	71	Large-scale reaction in rotatory evaporator

Comparison of Yield, E-factor and PMI of reactions with PMI > 100.

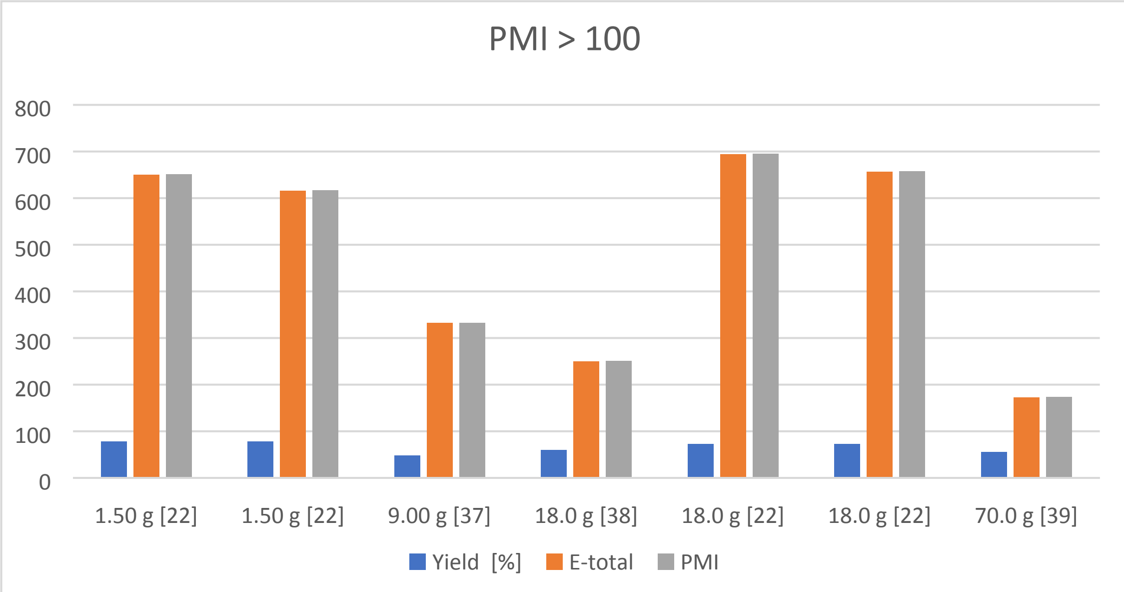
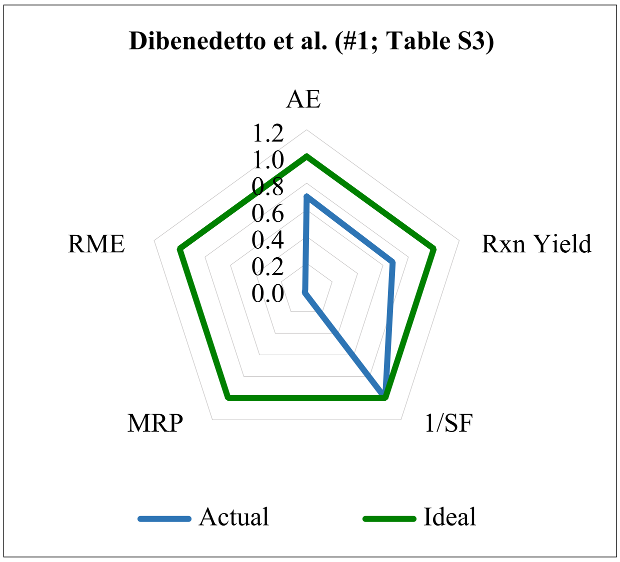
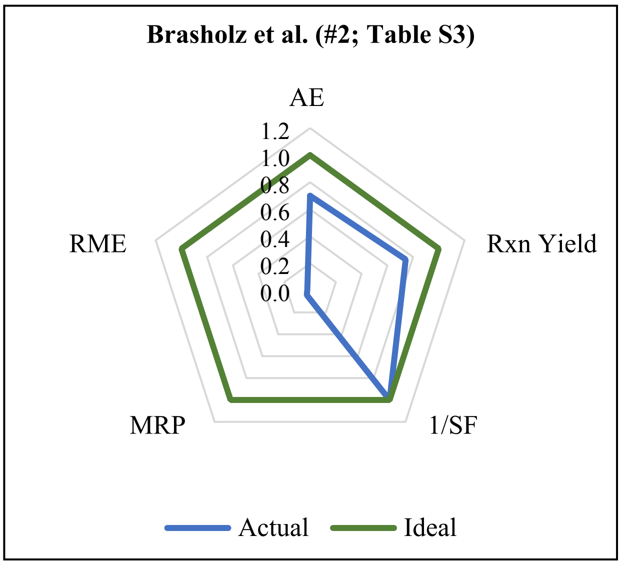
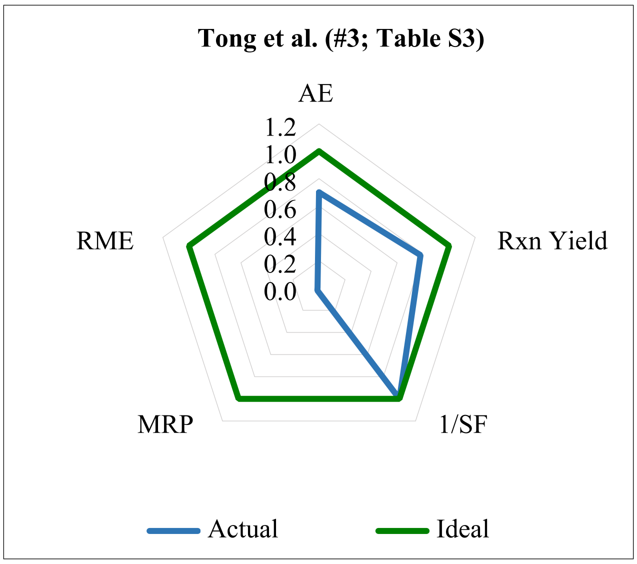


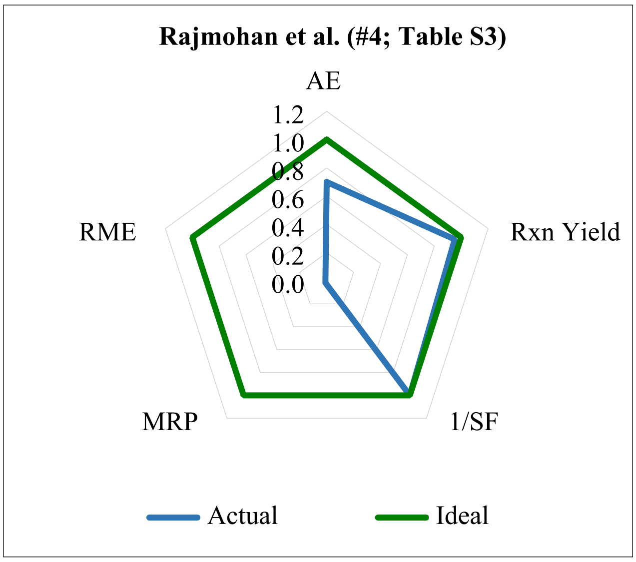
Figure S1. *Comparison of yield %, E-total and Process Max Intensity (PMI) of procedures with PMI higher than 100; with the amount of D-Fructose employed below each set of bars.*

Radical pentagon analysis






Tong et al. (#3; Table S3)
AE
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Rxn Yield
1/SF
MRP
RME
Actual
Ideal


Rajmohan et al. (#4; Table S3)
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0.6
0.4
0.2
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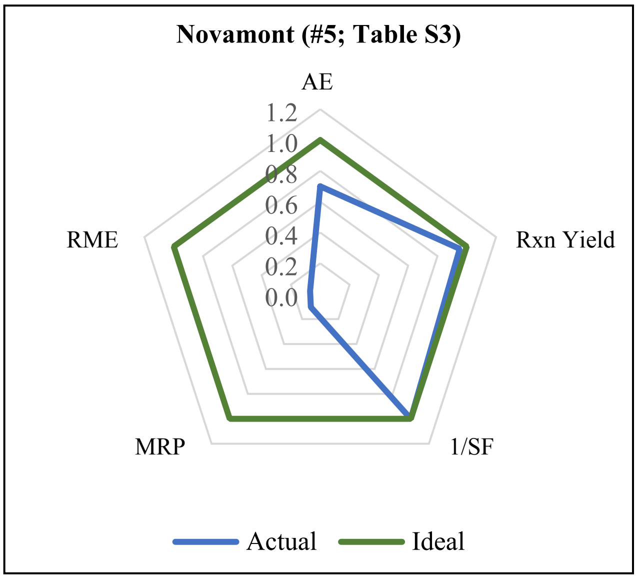
Rxn Yield
1/SF
MRP
RME
Actual
Ideal


Novamont (#5; Table S3)
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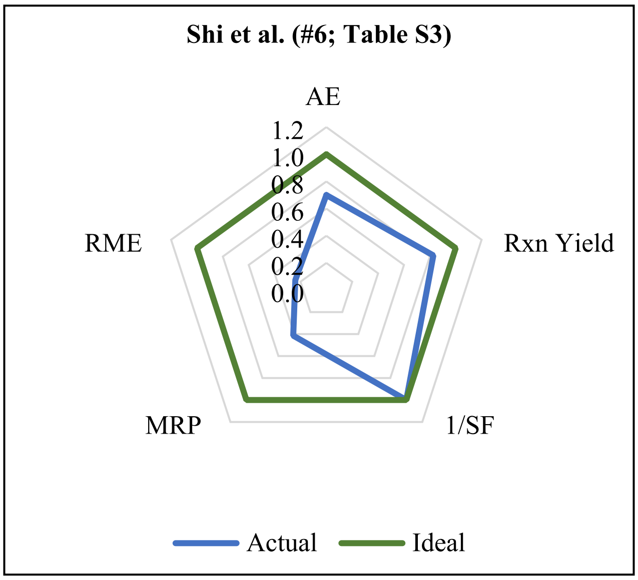
Rxn Yield
1/SF
MRP
RME
Actual
Ideal


Shi et al. (#6; Table S3)
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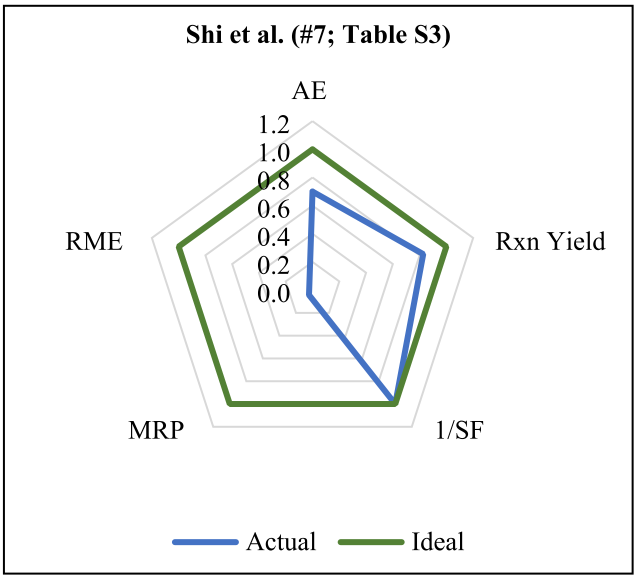
Rxn Yield
1/SF
MRP
RME
Actual
Ideal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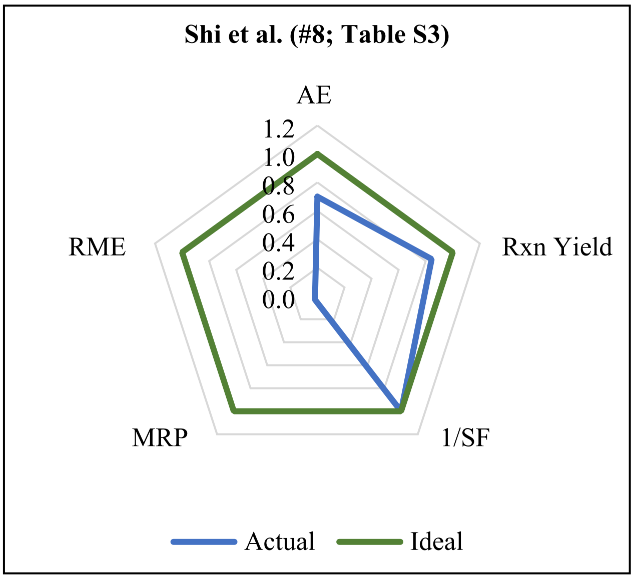
Rxn Yield
1/SF
MRP
RME
Actual
Ideal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Rxn Yield
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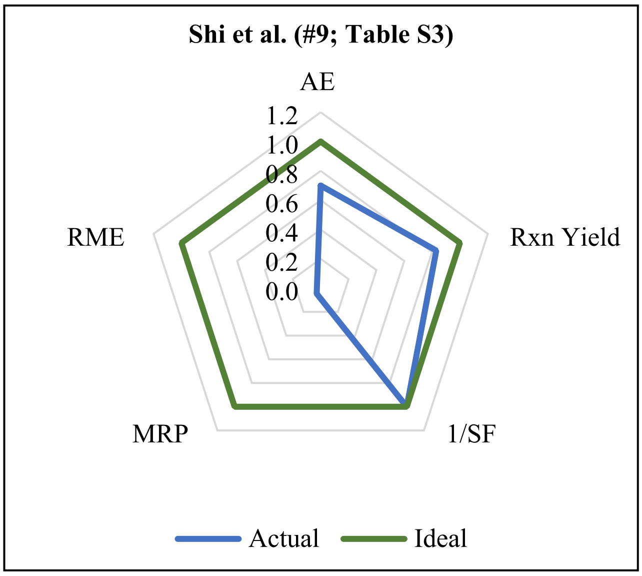
RME
Actual
Ideal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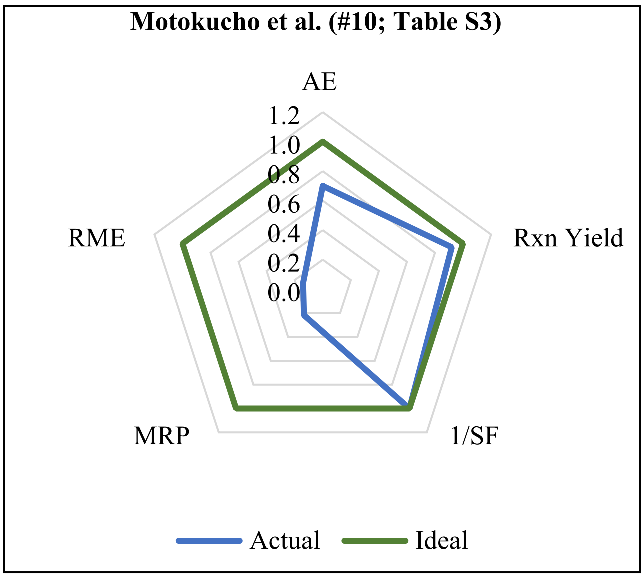
Actual
Ideal


Motokucho et al. (#10; Table S3)
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RME
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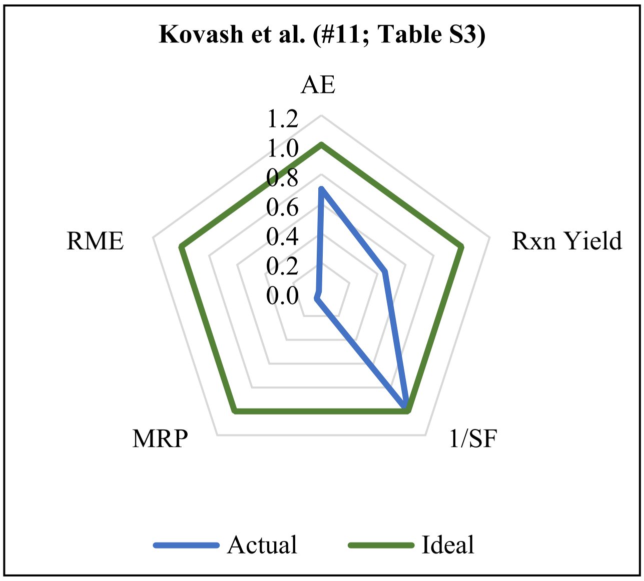
Ideal


Kovash et al. (#11; Table S3)
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RME
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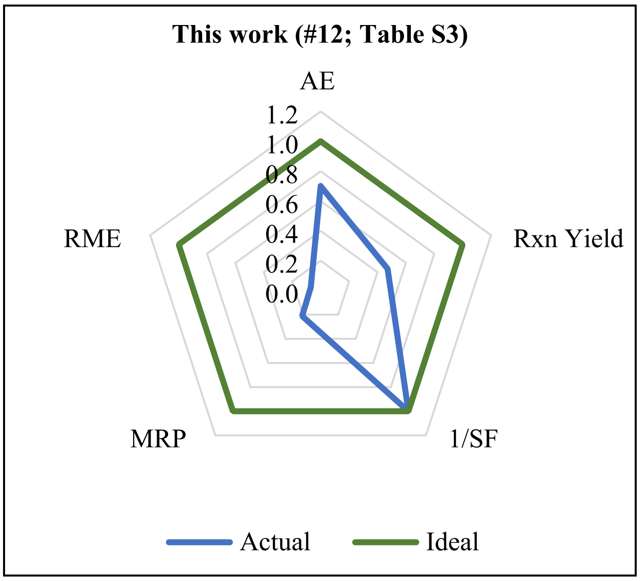
Actual
Ideal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RME
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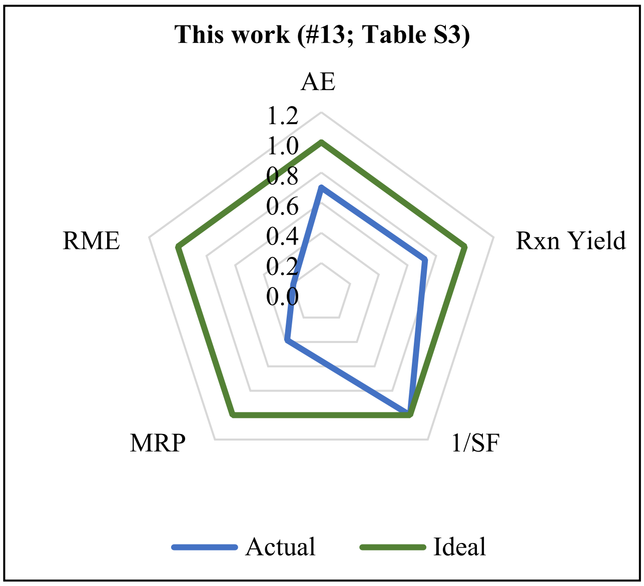
Actual
Ideal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RME
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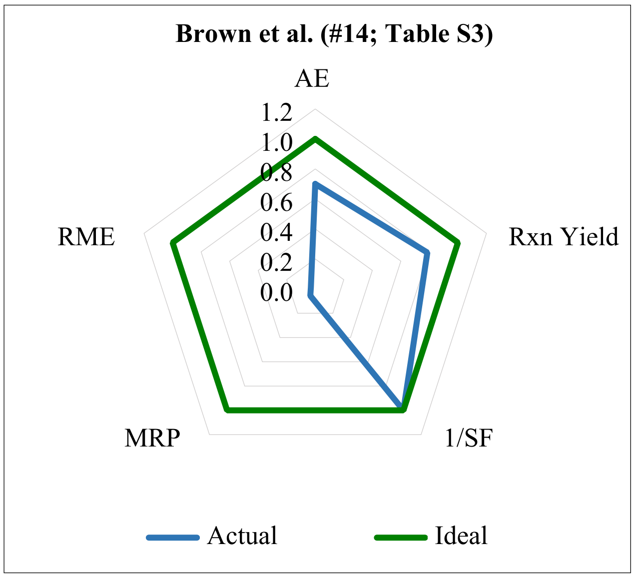
Actual
Ideal


Brown et al. (#14; Table S3)
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RME
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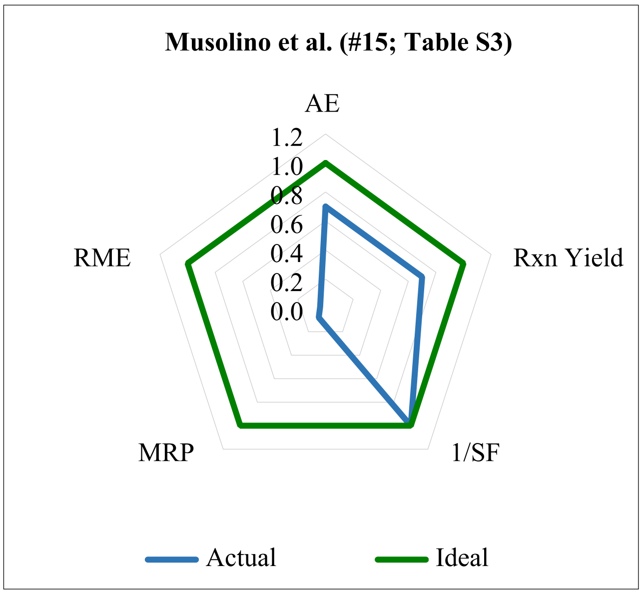
Actual
Ideal


Musolino et al. (#15; Table S3)
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Rxn Yield
1/SF
MRP
RME
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0.8
0.6
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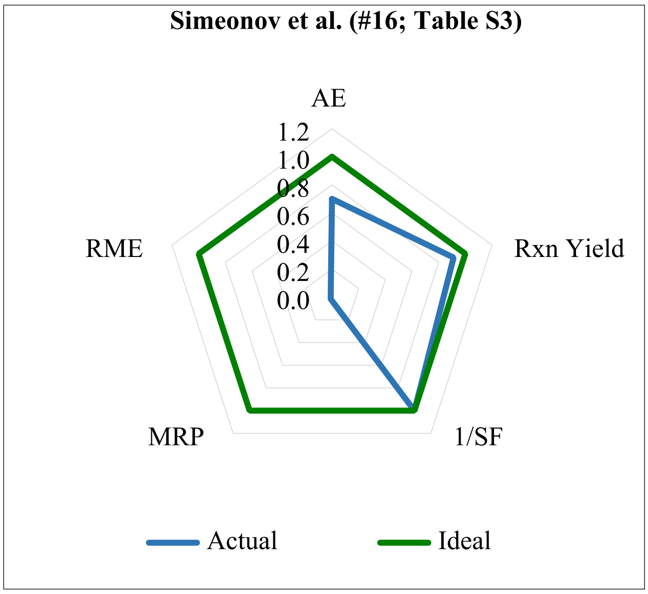
Actual
Ideal


Simeonov et al. (#16; Table S3)
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RME
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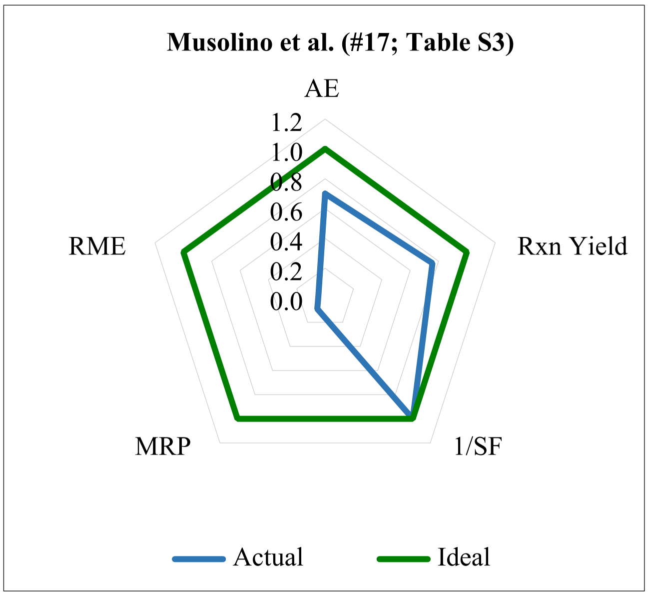
Actual
Ideal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AE
Rxn Yield
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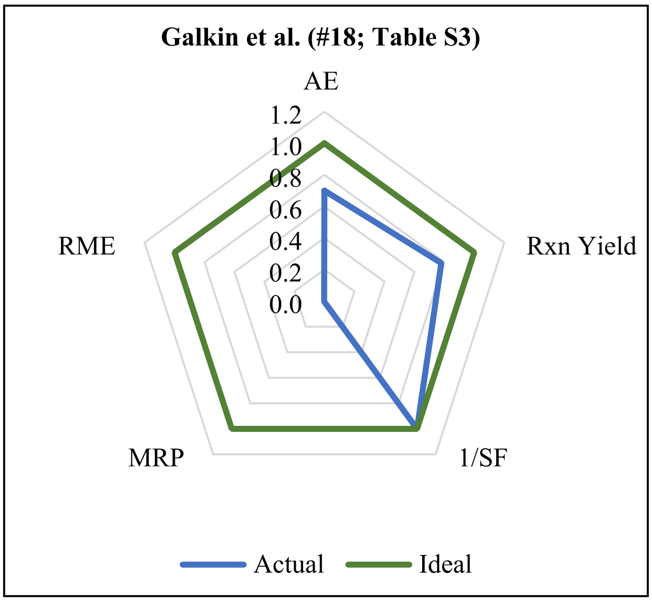
Ideal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RME
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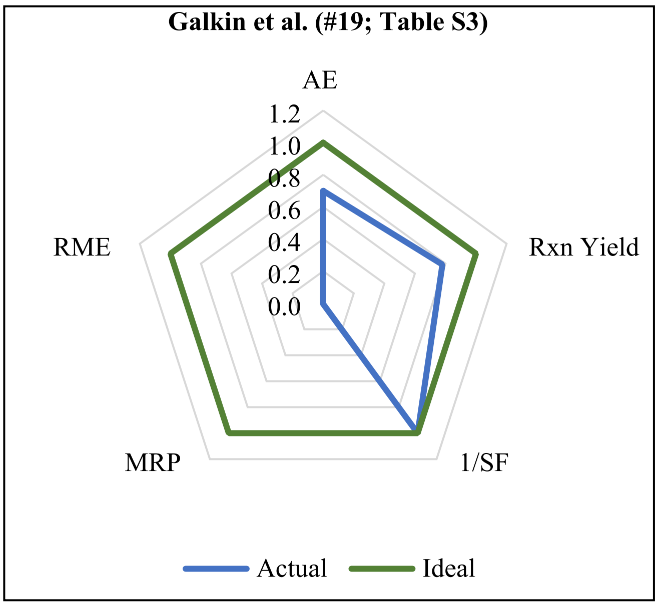
Ideal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RME
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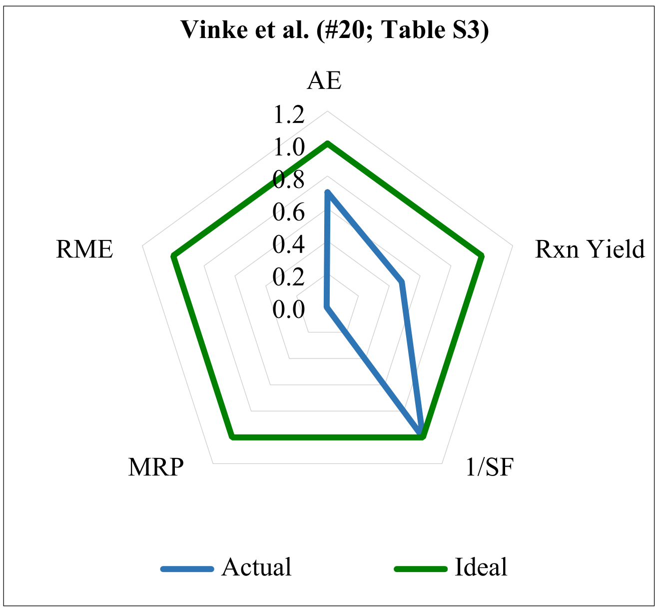
0.0
Actual
Ideal


Vinke et al. (#20; Table S3)
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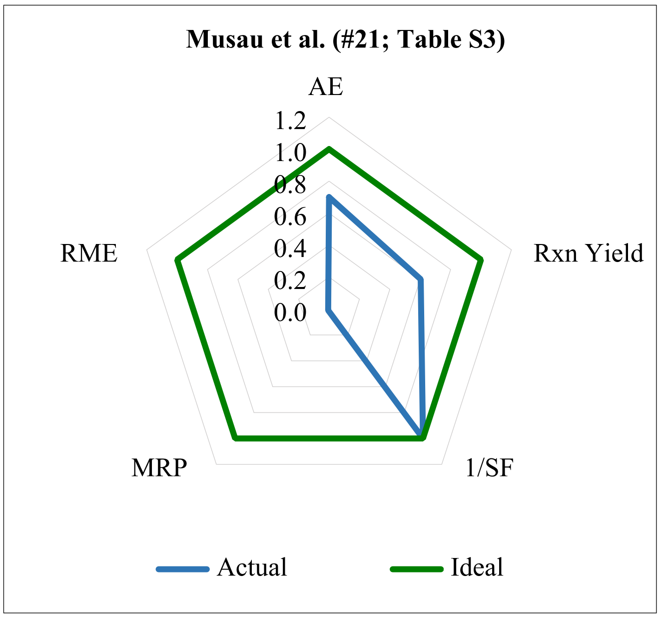
0.0
Actual
Ideal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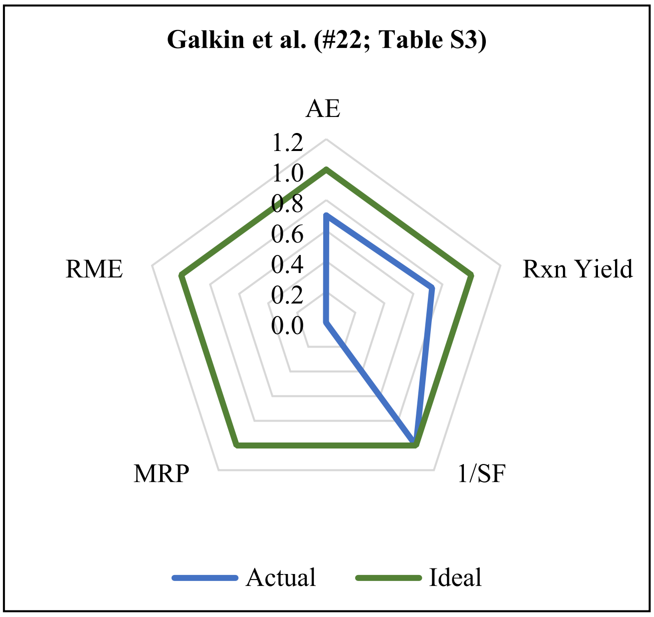
Rxn Yield
1/SF
MRP
RME
Actual
Ideal


Galkin et al. (#22; Table S3)
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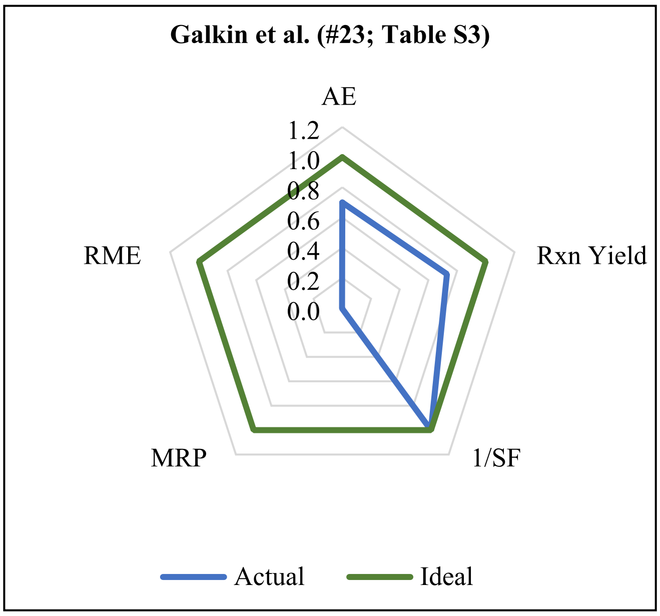
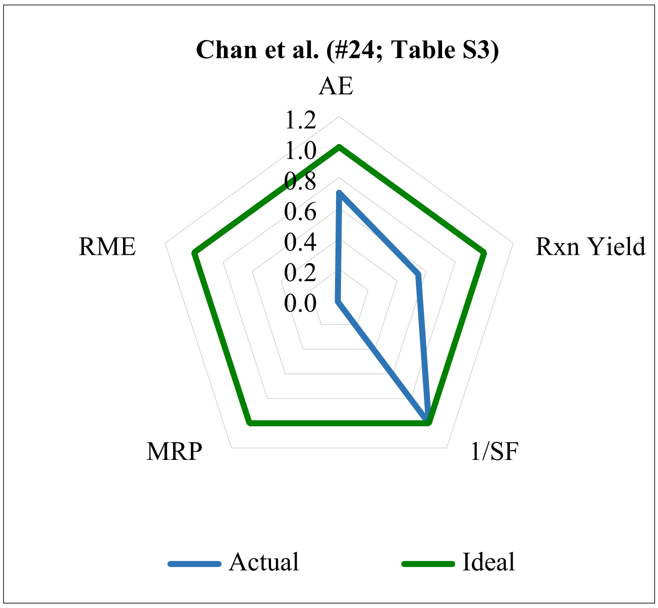
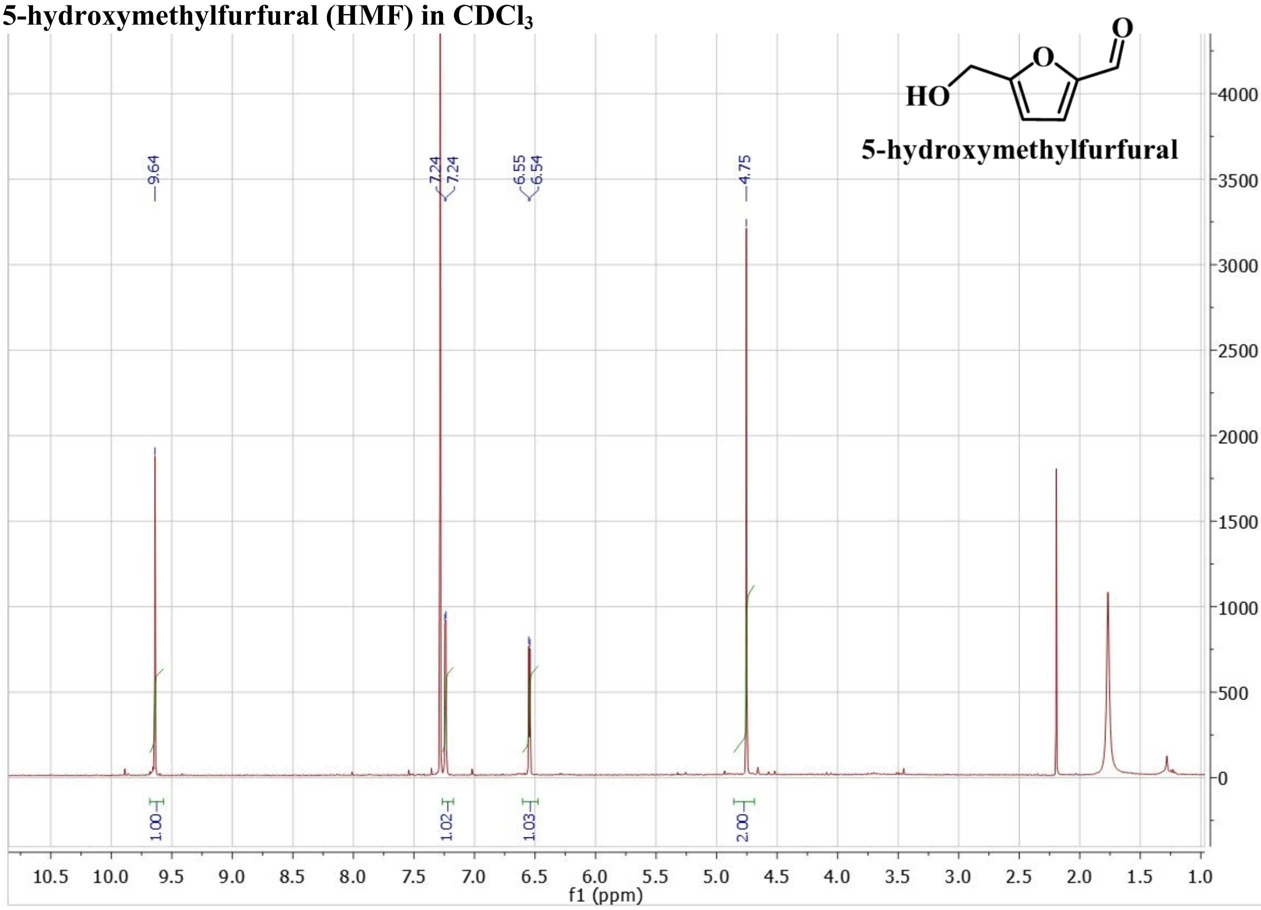
0.0
Rxn Yield
1/SF
MRP
RME
Actual
Ideal

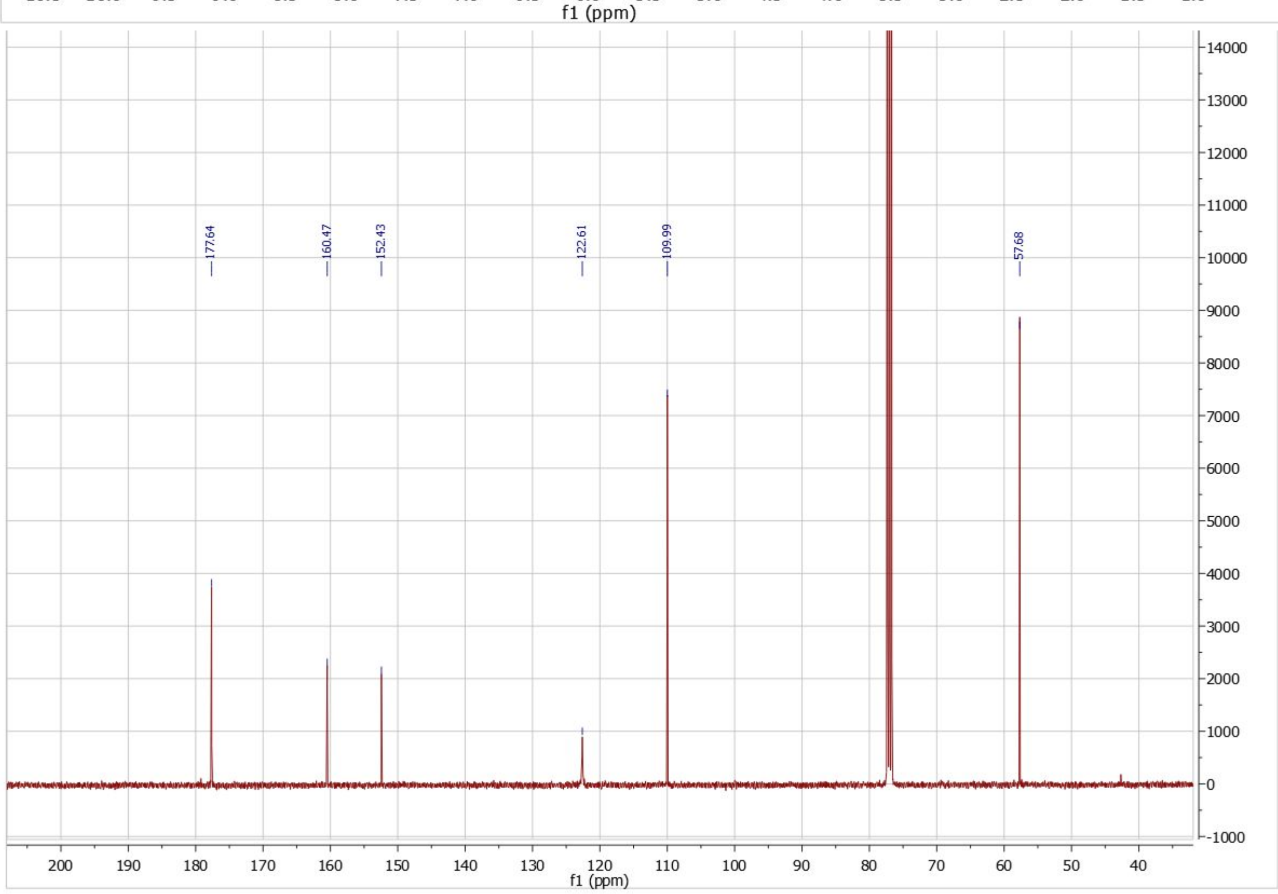

Galkin et al. (#23; Table S3)
AE
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Rxn Yield
1/SF
MRP
RME
Actual
Ideal


Chan et al. (#24; Table S3)
AE
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Rxn Yield
1/SF
MRP
RME
Actual
Ideal

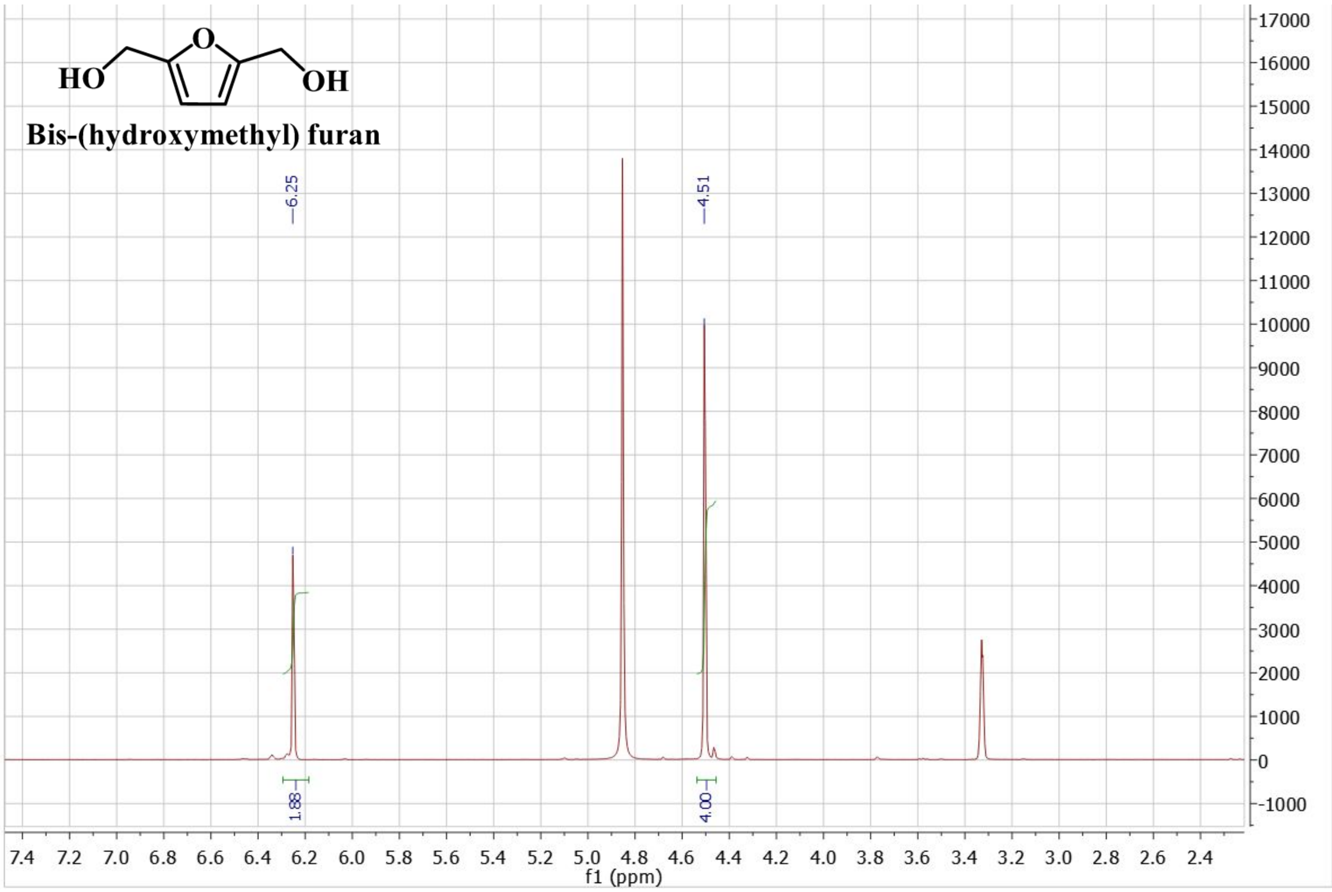
^{1}NMR and ^{13}C-NMR spectra

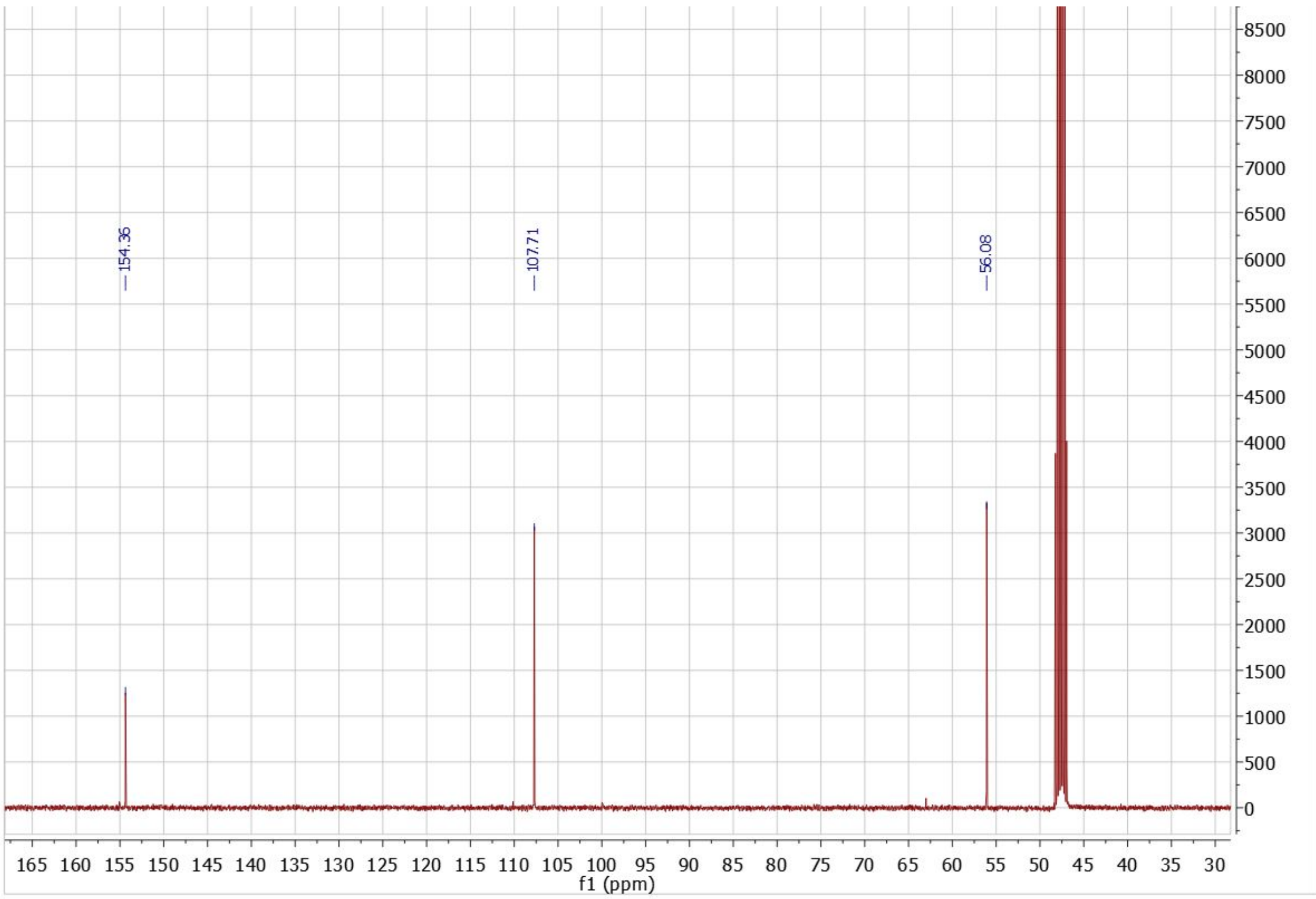
5-hydroxymethylfurfural (HMF) in $CDCl_3$





Bis-(hydroxymethyl)furan (BHMF) in MeOD





Dark-brown HMF-rich oil in $CDCl_3$