Development of a Tripartite Solvent Blend for Sustainable Chromatography

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Supporting Information

1. General

1.1 Reagents

33 compounds were tested (Figure 1): 27 were commercially available and/or marketed drug molecules, and six were compounds that had been previously synthesized in Genentech's Discovery Chemistry laboratories. All 33 compounds met most or all of the following target ranges of properties (as set forth by Lipinski's rules for drug-like compounds, Figure 2): 1) molecular weight between ~180 and 500 g/mol, 2) topological polar surface area (TPSA) smaller than 140 $Å^2$, 3) 10 or fewer rotatable bonds, 4) no more than 5 hydrogen bond donors, 5) no more than 10 hydrogen bond acceptors. All compounds were pure upon utilization for testing and analysis (verified by thin layer chromatography).

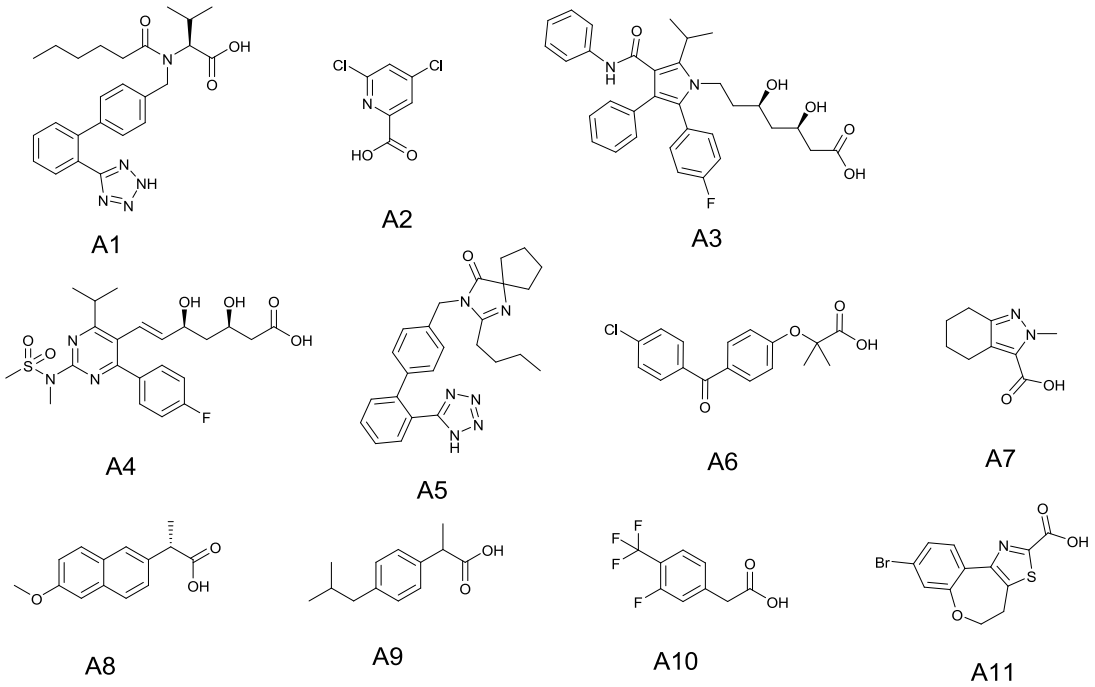


Figure 1a. (Same number in manuscript) Acidic compounds used for testing and analysis (11 total).

Compound identifiers:

A1: valsartan, (*S*)-2-(N-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)hexanamido)-3-methylbutanoic acid, CAS # 137862-53-4

A2: 4,6-dichloropicolinic acid, CAS # 88912-25-8

A3: atorvastatin, (3*R*,5*R*)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid, CAS # 134523-00-5

A4: rosuvastatin, (3*R*,5*S*,*E*)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoic acid, CAS # 287714-41-4

A5: irbesartan, 3-((2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one, CAS # 138402-11-6

A6: fenofibric acid, 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid, CAS # 42017-89-0

A7: 2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-3-carboxylic acid, CAS # 32287-00-6

A8: naproxen, (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid, CAS # 22204-53-1

A9: ibuprofen, 2-(4-isobutylphenyl)propanoic acid, CAS # 15687-27-1

A10: 2-(3-fluoro-4-(trifluoromethyl)phenyl)acetic acid, CAS # 238754-67-1

A11: 8-bromo-4,5-dihydrobenzo[2,3]oxepino[4,5-*d*]thiazole-2-carboxylic acid, CAS # 1189815-93-7

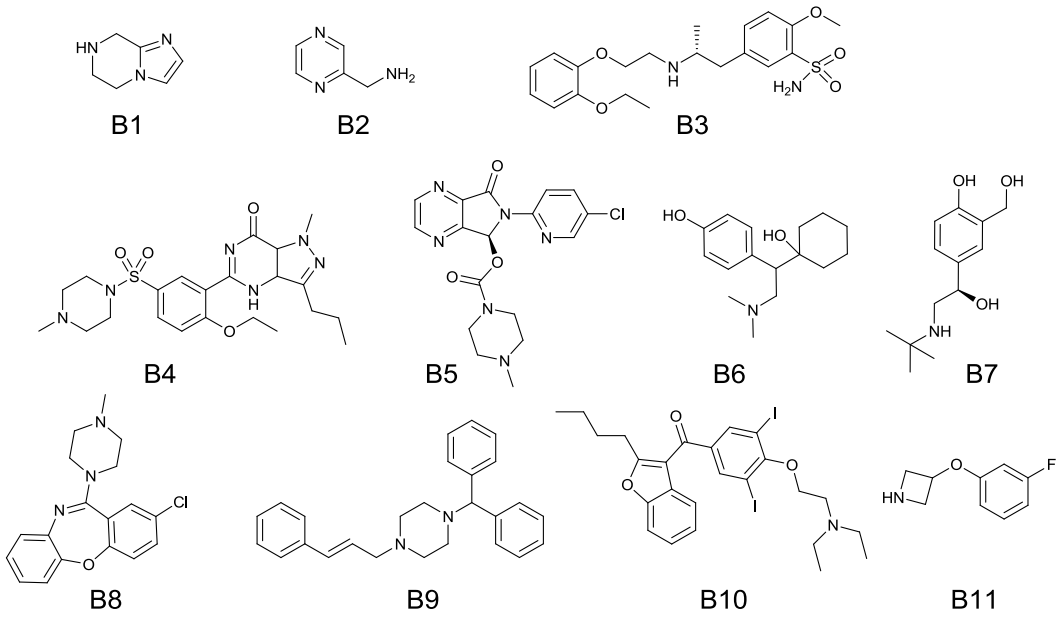


Figure S1b. (Same number in manuscript) Basic compounds used for testing and analysis (11 total).

Compound identifiers:

B1: 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, CAS # 91476-80-1

B2: pyrazin-2-ylmethanamine, CAS # 20010-99-5

B3: tamsulosin, (*R*)-5-(2-((2-(2-ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide, CAS # 106133-20-4

B4: 5-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-1-methyl-3-propyl-3*a*,4-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-7(7aH)-one, CAS # 1319729-37-7

B5: eszopiclone, (*S*)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate, CAS # 138729-47-2

B6: desvenlafaxine, 4-(2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl)phenol, CAS # 93413-62-8

B7: levosalbutamol, (*R*)-4-(2-(tert-butylamino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol, CAS # 34391-04-3

B8: loxapine, 2-chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepine, CAS # 1944-10-2

B9: cinnarizine, 1-benzhydryl-4-cinnamylpiperazine, CAS # 298-57-7

B10: amiodarone, (2-butylbenzofuran-3-yl)(4-(2-(diethylamino)ethoxy)-3,5-diiodophenyl)methanone, CAS # 1951-25-3

B11: 3-(3-fluorophenoxy)azetidine, CAS # 106860-03-1

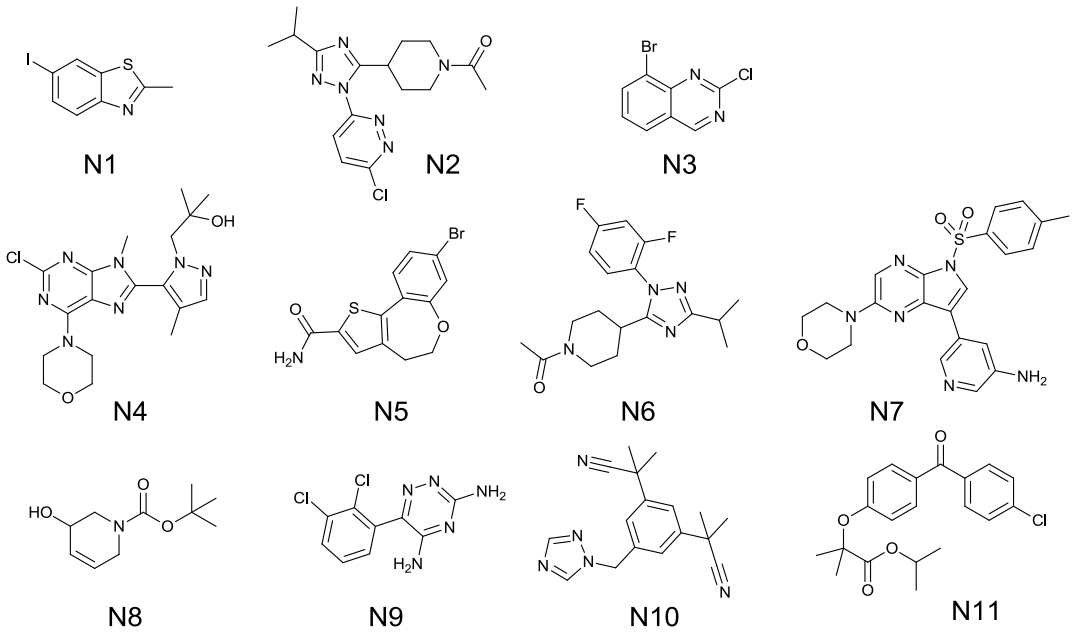


Figure S1c. (Same number in manuscript) Neutral compounds used for testing and analysis (11 total). Compound identifiers:

N1: 6-iodo-2-methylbenzo[*d*]thiazole, CAS # 68867-20-9

N2: 1-(4-(1-(6-chloropyridazin-3-yl)-3-isopropyl-1*H*-1,2,4-triazol-5-yl)piperidin-1-yl)ethanone, CAS #

N3: 8-bromo-2-chloroquinazoline, CAS # 956100-63-3

N4: 1-(5-(2-chloro-9-methyl-6-morpholino-9*H*-purin-8-yl)-4-methyl-1*H*-pyrazol-1-yl)-2-methylpropan-2-ol

N5: 8-bromo-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide, CAS # 1189817-16-0

N6: 1-(4-(1-(2,4-difluorophenyl)-3-isopropyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)ethanone, CAS # 1263816-16-5

N7: 5-(2-morpholino-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)pyridin-3-amine

N8: *tert*-butyl 5-hydroxy-5,6-dihydropyridine-1(2*H*)-carboxylate, CAS # 224779-27-5

N9: lamotrigine, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, CAS # 84057-84-1

N10: anastrozole, 2,2'-(5-((1*H*-1,2,4-triazol-1-yl)methyl)-1,3-phenylene)bis(2-methylpropanenitrile), CAS # 120511-73-1

N11: fenofibrate, isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate CAS # 49562-28-9

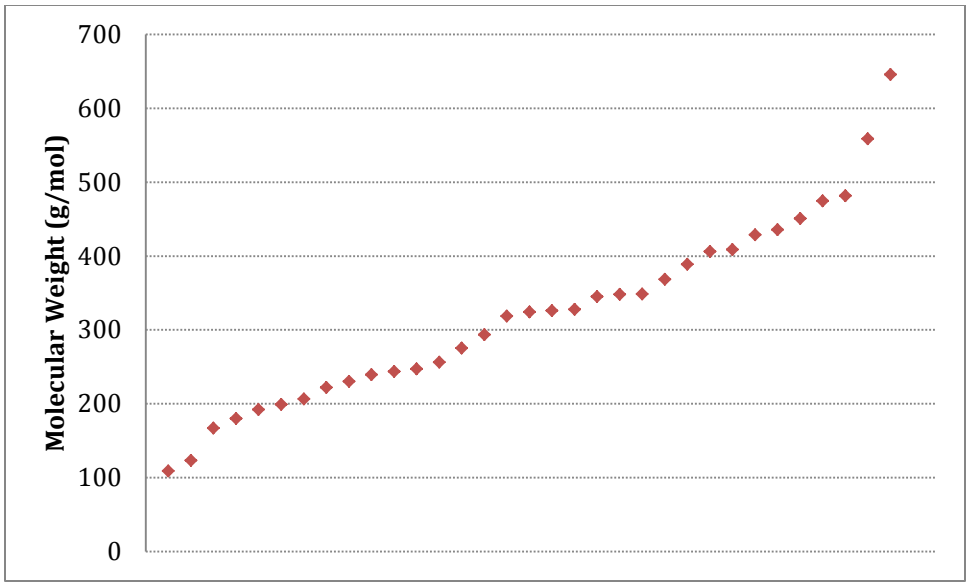


Figure S2a. Distribution of molecular weight of compounds in test set.

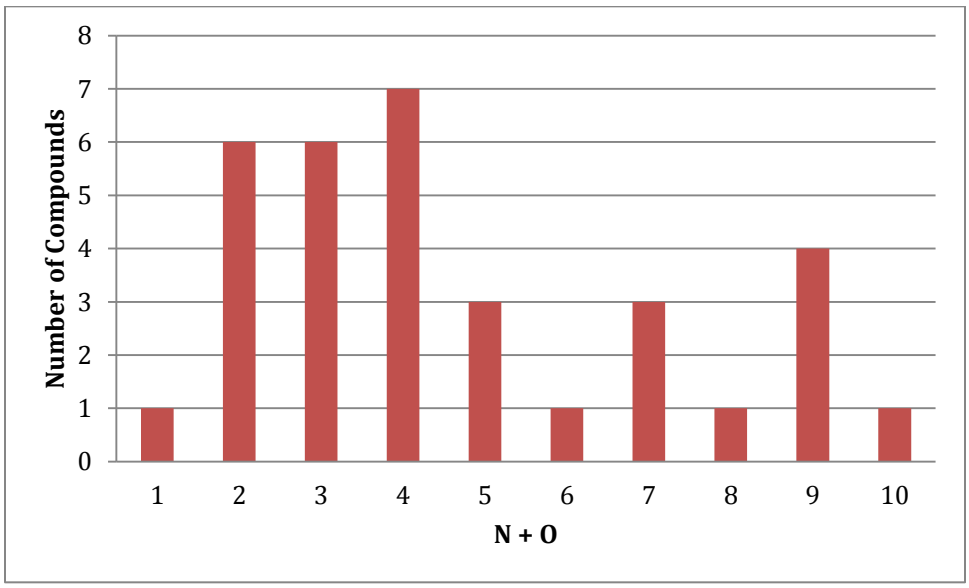


Figure S2b. Number of Hydrogen bond acceptors in compounds in test set.

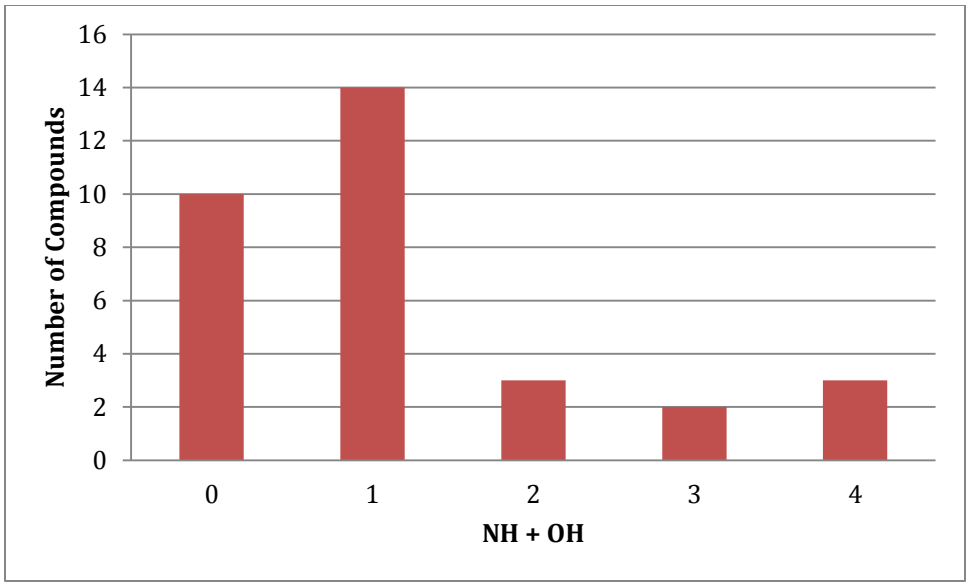


Figure S2c. Number of Hydrogen bond donors in compounds in test set.

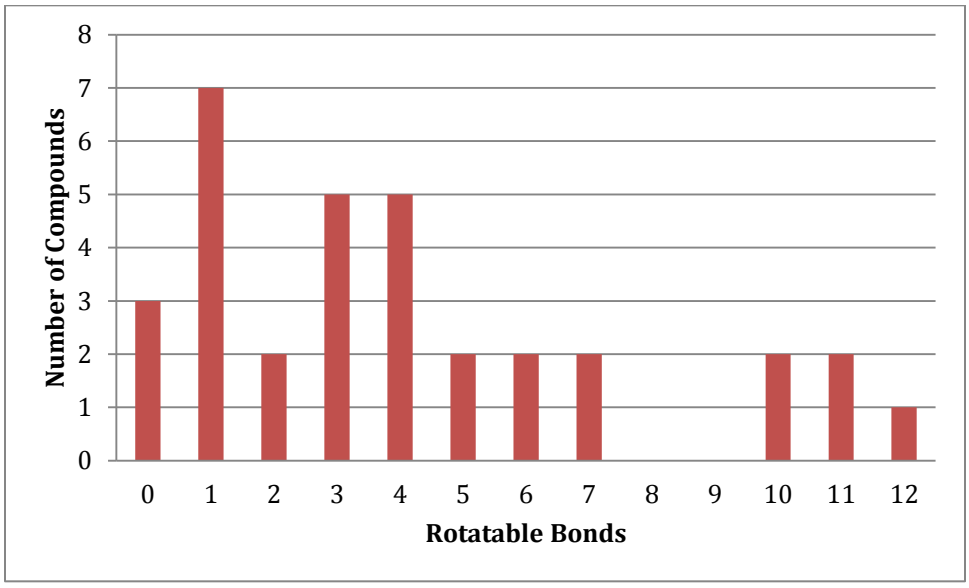


Figure S2d. Number of rotatable bonds in compounds in test set.

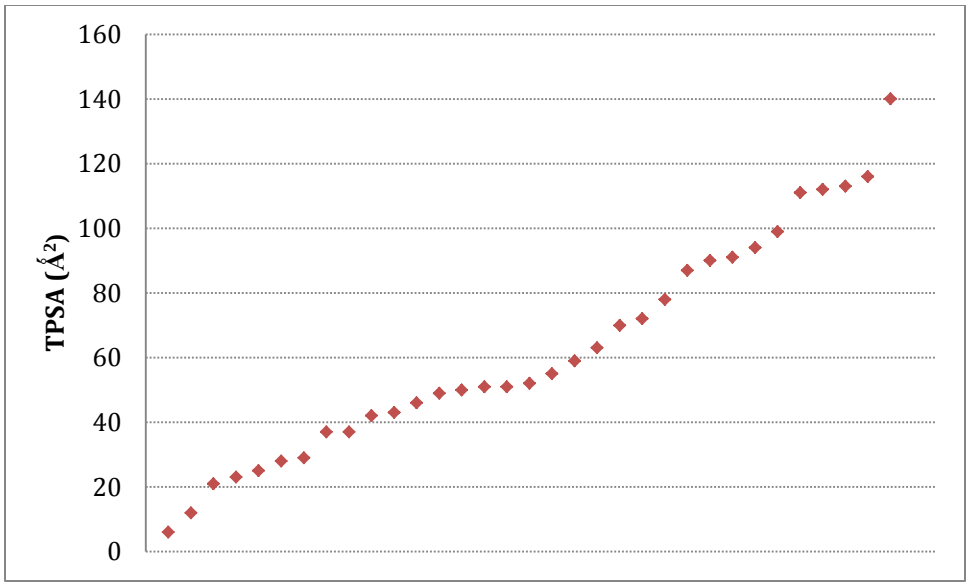


Figure S2e. Distribution of topological polar surface area (TPSA) of compounds in test set.

1.2 Solvent Chemical and Toxicological Information

The six solvents being contrasted within our study are dichloromethane (DCM), hexanes, ethyl acetate (EtOAc), isopropyl acetate (*i*-PrOAc), and heptane, with methanol (MeOH) overlapping between systems. It is well-established – and reflected on several solvent selection guides, including one published by the American Chemical Society Green Chemistry Institute – that DCM and hexanes are less green than the other solvents.[1] In the ACS guide, 5 scores are provided to assess solvents by (1) safety, (2) health, and environment: (3) air, (4) water, and (5) waste. In terms of toxicological data, heptane is considered to be much less toxic and safer than hexane according to concentrations immediately dangerous to life or health (IDLHs) from the Centers for Disease Control and Prevention / National Institute for Occupational Safety and Health (CDC/NIOSH, see Table S1).[2] *i*-PrOAc and EtOAc are considered similar ester solvents, but *i*-PrOAc scores better on environmental scores on the solvent guide as well as from a toxicological point of view.[3] MeOH is widely recognized as a greener solvent, though it must be handled appropriately due to certain level of toxicity.[4] Dichloromethane is the most troubling from an environmental perspective on the solvent guide and also has concerning toxicological effects, hence the great need to replace it as a widely used component in silica gel chromatography.[5]

Table S1. Chemical, green score and toxicological data for solvents under investigation

Solvent	MW	Boiling	Vapor P (mm	Avg. ACS	IDLH (ppm)

[1] http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/acs-gci-pr-solvent-selection-guide.pdf
[2] (a) http://www.cdc.gov/niosh/idlh/142825.html; (b) http://www.cdc.gov/niosh/idlh/110543.html; (c) http://www.cdc.gov/niosh/pel88/hexiso.html
[3] (a) http://www.cdc.gov/niosh/idlh/108214.html; (b) http://www.cdc.gov/niosh/idlh/141786.html
[4] http://www.cdc.gov/niosh/idlh/67561.html
[5] http://www.cdc.gov/niosh/idlh/75092.html

	(g/mol)	point (°C)	Hg, 20 °C)	Green Score[$]	
DCM	**84.93**	**39.8-40.0**	**353**	**6.2**	**2300**
Hexane	**86.18**	**69**	**132**	**5.4**	**2500 (1100*)**
EtOAc	**88.11**	**76.5-77.5**	**73**	**4.6**	**2000**
***i*-PrOAc**	**102.13**	**85-91**	**47**	**3.8**	**1800**
Heptane	**100.20**	**98**	**40**	**4.6**	**750**
MeOH	**32.04**	**64.7**	**97.7**	**4.6**	**6000**

* based on safety considerations (10% of lower exposure limit (LEL) of 1.1%)

[$] Average of five scores for safety, health, and environment (air, water, and waste)

1.3 Equipment Specifications

1.3.1 Thin Layer Chromatography

Thin layer chromatography was performed with EMD TLC Silica gel $60F_{254}$ 2.5x7.5 cm glass plates. Solvent mixtures were made using commercially available solvents in 10 mL graduated cylinders.

1.3.2 Flash Column Chromatography

Flash column chromatography was performed with an automated Teledyne ISCO CombiFlash® Rf 200. Teledyne ISCO 12g RediSep Rf Gold® pre-packed columns were used. Solvent mixtures were made using commercially available solvents in 1000 mL and 100 mL graduated cylinders.

2. Experimental Procedures

2.1 Thin Layer Chromatography

6 compounds were spotted on each TLC plate using commercially available glass capillary tubes. The eluent mixture was eluted to a height of 5 – 6 cm. TLC plates were visualized using 254 nm ultraviolet light, and R_f values were measured in millimeters with a standard ruler.

2.2 Column Chromatography

Mixtures of 3 compounds (~50 mg each) were dissolved in dichloromethane. In cases of insolubility, a few drops of methanol were added to facilitate solubility. The mixtures of 3 compounds were loaded onto pre-packed silica columns either as a liquid or a solid load (in cases of insolubility), and separated.

Compounds were eluted with both a 0-20% MeOH / DCM solvent system and a 0-80% 3:1 *i*-PrOAc : MeOH / heptane solvent system, for purposes of comparison. The fractions that exhibited UV activity were co-spotted on TLC plates with the original compounds, to ensure that the compounds were correctly identified upon eluting from the column.

3. Experimental Data

3.1 Thin Layer Chromatography Data

Table S2. Individual R_f values for acidic compounds eluted in MeOH / DCM (+ 2 % AcOH) and 3:1 *i*-PrOAc : MeOH / heptane (+ 2 % AcOH).

Compound	0% MeOH / DCM	1% MeOH / DCM	3% MeOH / DCM	5% MeOH / DCM	10% MeOH / DCM	20% MeOH / DCM	0% 3:1 *i*-PrOAc : MeOH / heptane	10% 3:1 *i*-PrOAc : MeOH / heptane	20% 3:1 *i*-PrOAc : MeOH / heptane	30% 3:1 *i*-PrOAc : MeOH / heptane	40% 3:1 *i*-PrOAc : MeOH / heptane	50% 3:1 *i*-PrOAc : MeOH / heptane	60% 3:1 *i*-PrOAc : MeOH / heptane	70% 3:1 *i*-PrOAc : MeOH / heptane	80% 3:1 *i*-PrOAc : MeOH / heptane	90% 3:1 *i*-PrOAc : MeOH / heptane	100% 3:1 *i*-PrOAc : MeOH / heptane
A1	0.02	0.09	0.33	0.38	0.59	0.81	0	0	0	0.04	0.10	0.25	0.35	0.48	0.58	0.69	0.77
A2	0.04	0.05	0.12	0.18	0.31	0.56	0	0.01	0.02	0.03	0.09	0.16	0.24	0.30	0.33	0.38	0.41
A3	0.05	0.05	0.24	0.33	0.53	0.78	0	0	0	0	0.08	0.20	0.39	0.55	0.67	0.73	0.76
A4	0.05	0.05	0.23	0.32	0.50	0.78	0	0	0	0	0.08	0.19	0.39	0.53	0.66	0.73	0.76
A5	0.05	0.07	0.34	0.48	0.63	0.81	0	0	0	0.02	0.12	0.21	0.40	0.54	0.65	0.72	0.76
A6	0.14	0.24	0.35	0.46	0.59	0.78	0	0.02	0.06	0.17	0.26	0.41	0.49	0.60	0.71	0.76	0.78
A7	0.13	0.22	0.34	0.45	0.56	0.74	0	0.03	0.07	0.17	0.26	0.41	0.48	0.59	0.71	0.72	0.77
A8	0.19	0.25	0.35	0.46	0.58	0.79	0	0.04	0.11	0.21	0.32	0.47	0.55	0.68	0.81	0.84	0.90
A9	0.20	0.27	0.36	0.46	0.60	0.82	0.02	0.12	0.25	0.39	0.47	0.61	0.68	0.79	0.88	0.89	0.92
A10	0.20	0.29	0.37	0.46	0.59	0.76	0	0.03	0.08	0.18	0.29	0.42	0.49	0.61	0.74	0.77	0.83
A11	0.03	0.08	0.16	0.24	0.34	0.59	0	0	0	0.03	0.08	0.18	0.25	0.32	0.38	0.40	0.47

Table S3. Individual R_f values for basic compounds eluted in MeOH / DCM (+ 2 % NH_4OH) and 3:1 *i*-PrOAc : MeOH / heptane (+ 2 % NH_4OH).

Compound	0% MeOH / DCM	1% MeOH / DCM	3% MeOH / DCM	5% MeOH / DCM	10% MeOH / DCM	20% MeOH / DCM	0% 3:1 *i*-PrOAc : MeOH / heptane	10% 3:1 *i*-PrOAc : MeOH / heptane	20% 3:1 *i*-PrOAc : MeOH / heptane	30% 3:1 *i*-PrOAc : MeOH / heptane	40% 3:1 *i*-PrOAc : MeOH / heptane	50% 3:1 *i*-PrOAc : MeOH / heptane	60% 3:1 *i*-PrOAc : MeOH / heptane	70% 3:1 *i*-PrOAc : MeOH / heptane	80% 3:1 *i*-PrOAc : MeOH / heptane	90% 3:1 *i*-PrOAc : MeOH / heptane	100% 3:1 *i*-PrOAc : MeOH / heptane
B1	0	0	0	0	0.23	0.55	0	0	0	0	0.02	0.02	0.04	0.10	N/A	N/A	N/A
B2	0.03	0.03	0.10	0.15	0.33	0.55	0	0	0	0	0.03	0.07	0.09	0.16	0.20	0.22	0.26
B3	0	0.01	0.15	0.20	0.38	0.74	0	0	0	0	0.06	0.11	0.35	0.42	0.55	0.60	0.71
B4	0	0.04	0.20	0.27	0.43	0.83	0	0	0	0	0.09	0.16	0.38	0.42	0.55	0.59	0.69

B5	0	0.03	0.10	0.25	0.60	0.82	0	0	0	0.02	0.05	0.13	0.23	0.39	0.50	0.56	0.65
B6	0	0.02	0.06	0.13	0.36	0.66	0	0	0	0.04	0.10	0.23	0.26	0.44	0.51	0.60	0.65
B7	0	0	0	0.01	0.07	0.40	0	0	0	0	0.01	0.02	0.06	0.17	0.29	0.32	0.42
B8	0.02	0.10	0.22	0.35	0.65	0.86	0	0.03	0.10	0.20	0.29	0.35	0.44	0.60	0.67	0.73	0.78
B9	0	0.19	0.34	0.53	0.88	0.97	0	0.17	0.39	0.54	0.67	0.77	0.80	0.88	0.93	0.95	0.95
B10	0	0.11	0.21	0.33	0.70	0.87	0	0.07	0.25	0.43	0.55	0.71	0.76	0.84	0.89	0.92	0.92
B11	0	0.02	0.06	0.16	0.45	0.65	0	0	0	0.02	0.05	0.13	0.22	0.35	0.43	0.44	0.50

Table S4. Individual R_f values for basic compounds eluted in MeOH / DCM (+ 1 % Et_3N) and 3:1 *i*-PrOAc : MeOH / heptane (+ 1 % Et_3N).

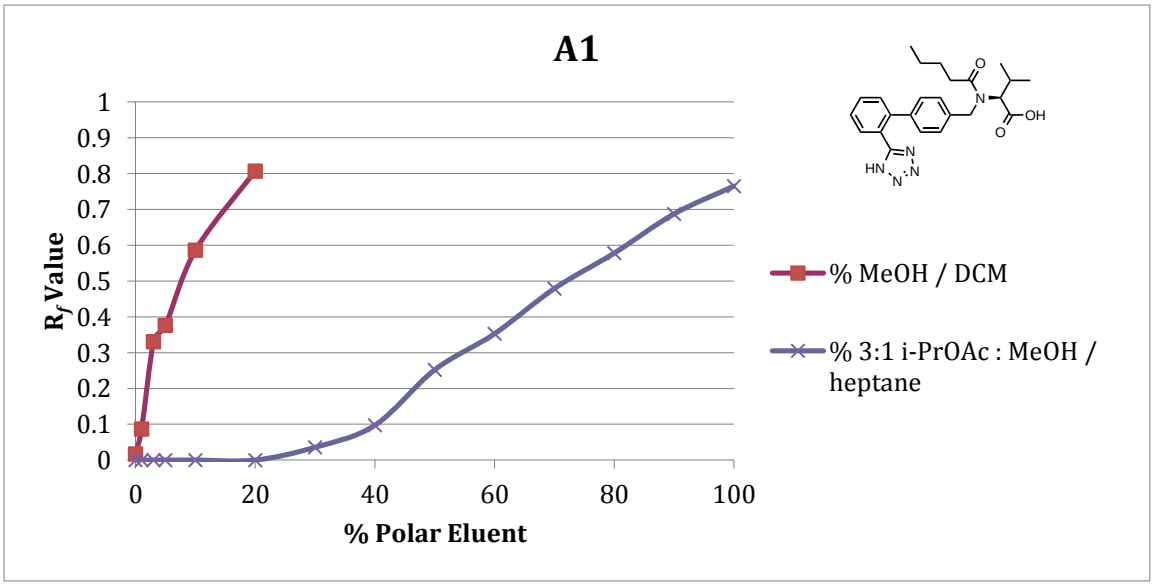
Compound	**0% MeOH / DCM**	**1% MeOH / DCM**	**3% MeOH / DCM**	**5% MeOH / DCM**	**10% MeOH / DCM**	**20% MeOH / DCM**	**0% 3:1 *i*-PrOAc : MeOH / heptane**	**10% 3:1 *i*-PrOAc : MeOH / heptane**	**20% 3:1 *i*-PrOAc : MeOH / heptane**	**30% 3:1 *i*-PrOAc : MeOH / heptane**	**40% 3:1 *i*-PrOAc : MeOH / heptane**	**50% 3:1 *i*-PrOAc : MeOH / heptane**	**60% 3:1 *i*-PrOAc : MeOH / heptane**	**70% 3:1 *i*-PrOAc : MeOH / heptane**	**80% 3:1 *i*-PrOAc : MeOH / heptane**	**90% 3:1 *i*-PrOAc : MeOH / heptane**	**100% 3:1 *i*-PrOAc : MeOH / heptane**
B1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B2	0.02	0.08	0.11	0.16	0.21	0.32	0	0	0	0	0.02	0.04	0.03	0.05	0.06	0.07	0.07
B3	0.04	0.11	0.16	0.24	0.41	0.72	0	0	0	0	0.03	0.07	0.10	0.16	0.21	0.26	0.30
B4	0.04	0.11	0.2	0.31	0.49	0.81	0	0	0	0	0.04	0.08	0.11	0.17	0.21	0.22	0.25
B5	0.04	0.15	0.18	0.20	0.54	0.80	0	0	0	0.01	0.04	0.06	0.07	0.12	0.16	0.18	0.20
B6	0.01	0.09	0.13	0.18	0.30	0.32	0	0	0	0.01	0.05	0.06	0.07	0.08	0.10	0.12	0.13
B7	0	0	0	0	0.08	0.16	0	0	0	0	0	0.02	0.02	0.03	0.07	0.09	0.12
B8	0.02	0.13	0.2	0.25	0.53	0.85	0	0.02	0.03	0.07	0.13	0.21	0.28	0.33	0.38	0.38	0.39
B9	0.02	0.15	0.27	0.31	0.57	0.90	0	0.11	0.21	0.36	0.47	0.59	0.61	0.66	0.68	0.70	0.70
B10	0.02	0.15	0.20	0.22	0.47	0.81	0	0.03	0.04	0.15	0.25	0.32	0.36	0.44	0.45	0.47	0.47
B11	0.01	0.09	0.16	0.19	0.31	0.38	0	0	0	0.02	0.03	0.04	0.04	0.06	0.08	0.09	0.12

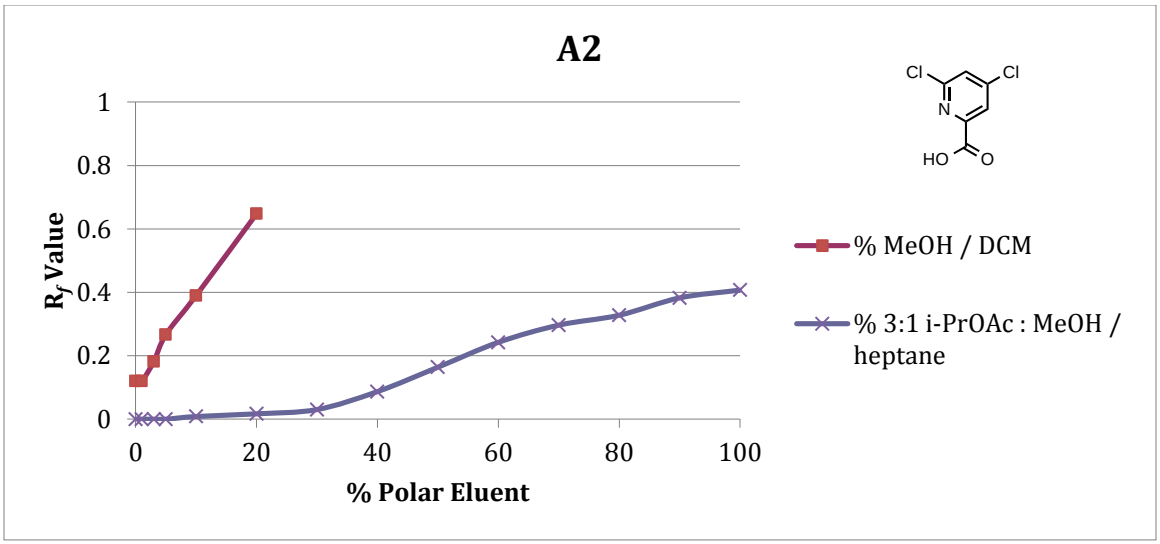
Table S5. Individual R_f values for neutral compounds eluted in MeOH / DCM and 3:1 *i*-PrOAc : MeOH / heptane.

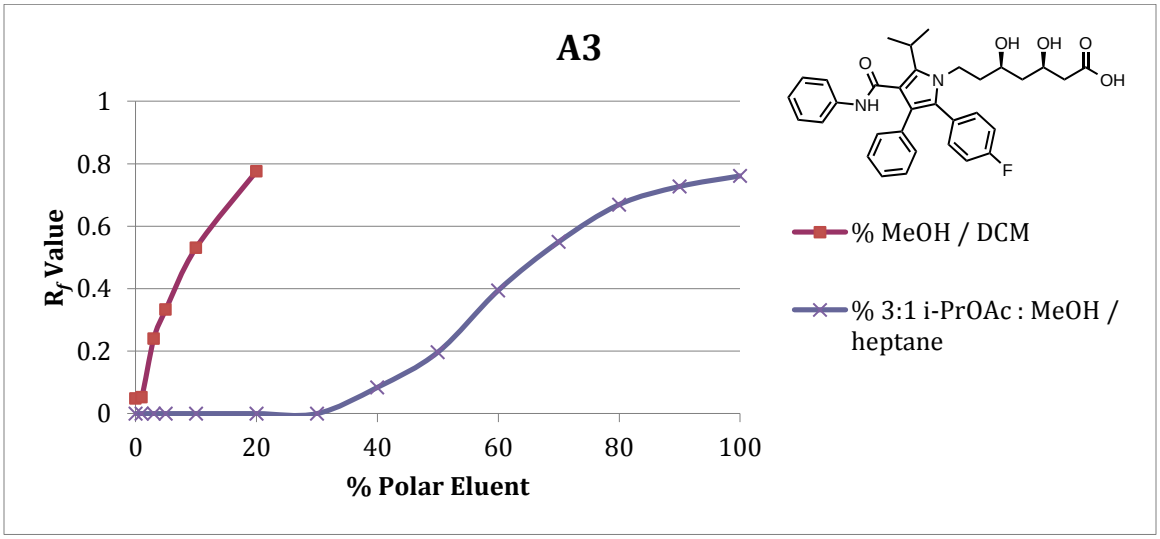
Compound	0% MeOH / DCM	1% MeOH / DCM	3% MeOH / DCM	5% MeOH / DCM	10% MeOH / DCM	20% MeOH / DCM	0% 3:1 *i*-PrOAc : MeOH / heptane	10% 3:1 *i*-PrOAc : MeOH / heptane	20% 3:1 *i*-PrOAc : MeOH / heptane	30% 3:1 *i*-PrOAc : MeOH / heptane	40% 3:1 *i*-PrOAc : MeOH / heptane	50% 3:1 *i*-PrOAc : MeOH / heptane	60% 3:1 *i*-PrOAc : MeOH / heptane	70% 3:1 *i*-PrOAc : MeOH / heptane	80% 3:1 *i*-PrOAc : MeOH / heptane	90% 3:1 *i*-PrOAc : MeOH / heptane	100% 3:1 *i*-PrOAc : MeOH / heptane
N1	0.54	0.63	0.73	0.84	0.93	0.95	0	0.49	0.60	0.64	0.72	0.79	0.84	0.89	0.89	0.91	0.90
N2	0	0.01	0.04	0.28	0.43	0.82	0	0	0.03	0.06	0.16	0.25	0.36	0.51	0.58	0.66	0.69
N3	0.57	0.79	0.88	0.91	0.94	0.95	0	0.21	0.29	0.46	0.55	0.65	0.72	0.82	0.86	0.86	0.87
N4	0	0.087	0.24	0.32	0.57	0.87	0	0.02	0.03	0.12	0.22	0.35	0.45	0.63	0.67	0.76	0.79
N5	0.03	0.10	0.18	0.27	0.45	0.74	0	0	0.01	0.07	0.19	0.34	0.44	0.59	0.65	0.74	0.80
N6	0	0.03	0.26	0.31	0.45	0.77	0	0.01	0.03	0.10	0.11	0.21	0.35	0.46	0.55	0.62	0.67
N7	0	0	0	0.26	0.44	0.82	0	0	0	0.02	0.08	0.17	0.33	0.44	0.58	0.69	0.74
N8	0.02	0.12	0.25	0.36	0.47	0.74	0.01	0.03	0.13	0.24	0.32	0.34	0.49	0.52	0.64	0.67	0.71
N9	0	0	0.04	0.12	0.38	0.67	0	0	0	0	0.04	0.19	0.34	0.40	0.50	0.61	0.69
N10	0.03	0.08	0.21	0.28	0.47	0.77	0	0	0	0	0.07	0.23	0.41	0.46	0.59	0.66	0.76
N11	0.59	0.76	0.88	0.92	0.96	0.97	0	0.45	0.55	0.63	0.75	0.83	0.86	0.91	0.94	0.96	0.95

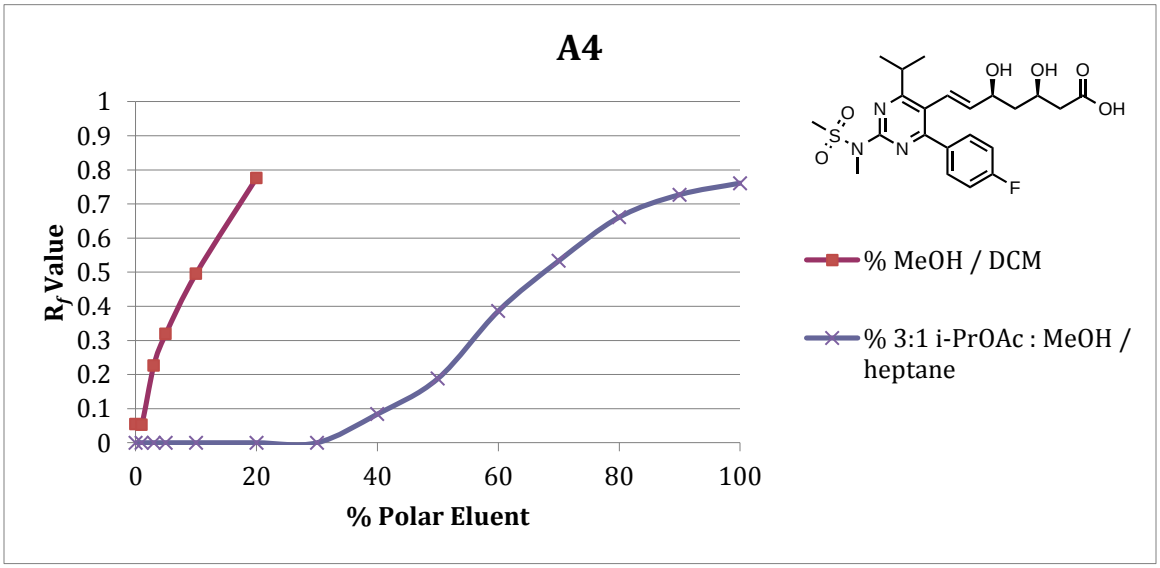
3.2 Graphs depicting % Polar eluent vs. R_f value for all 33 compounds

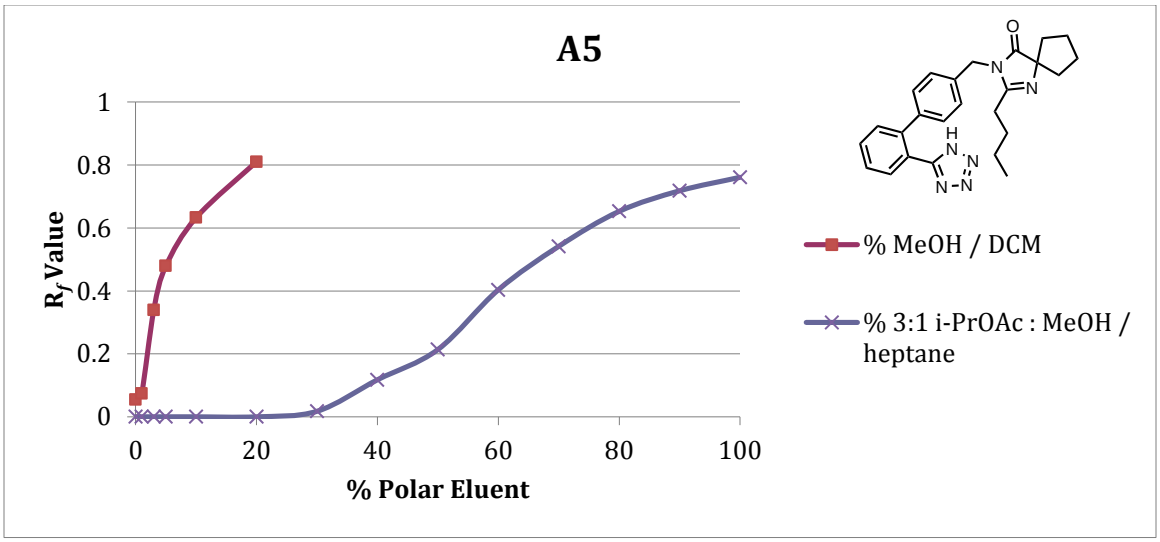
Figure S3a. % Polar eluent vs. R_f value for the 11 acidic compounds. All solutions contain 2 % acetic acid additive.

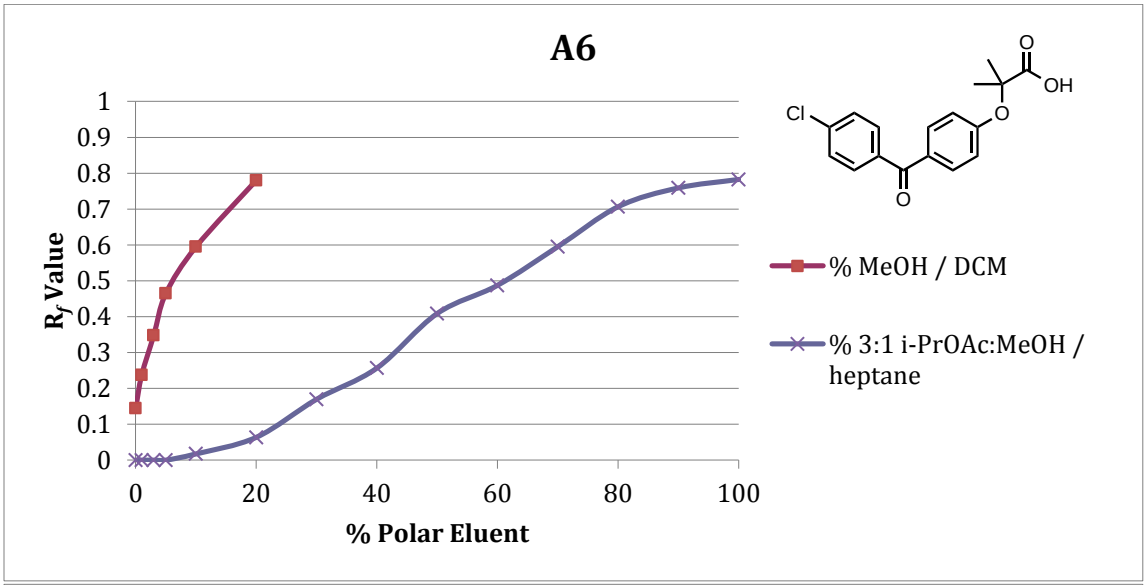


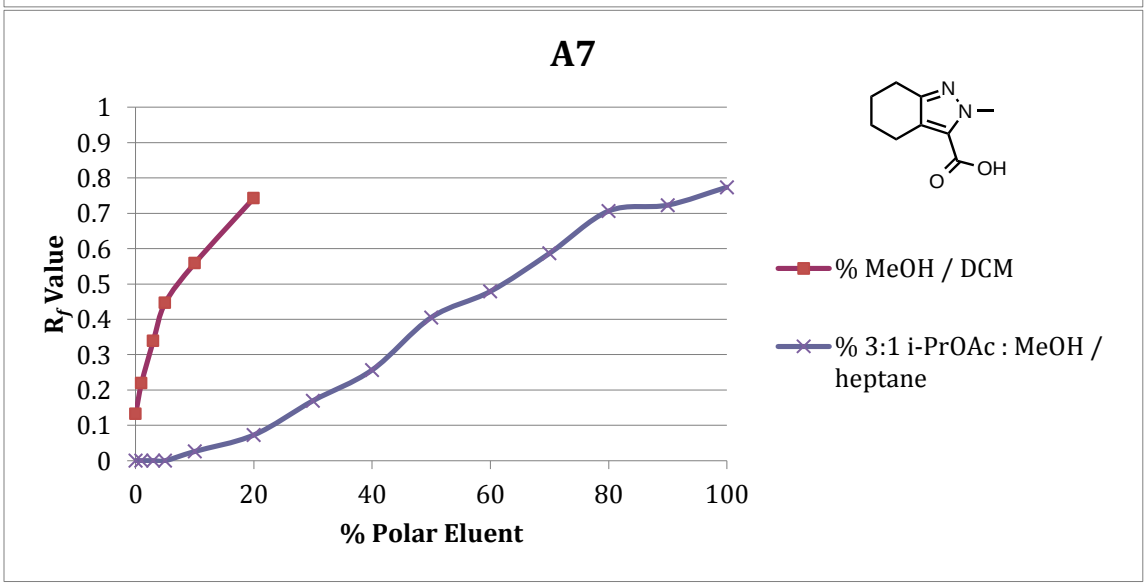

A2
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

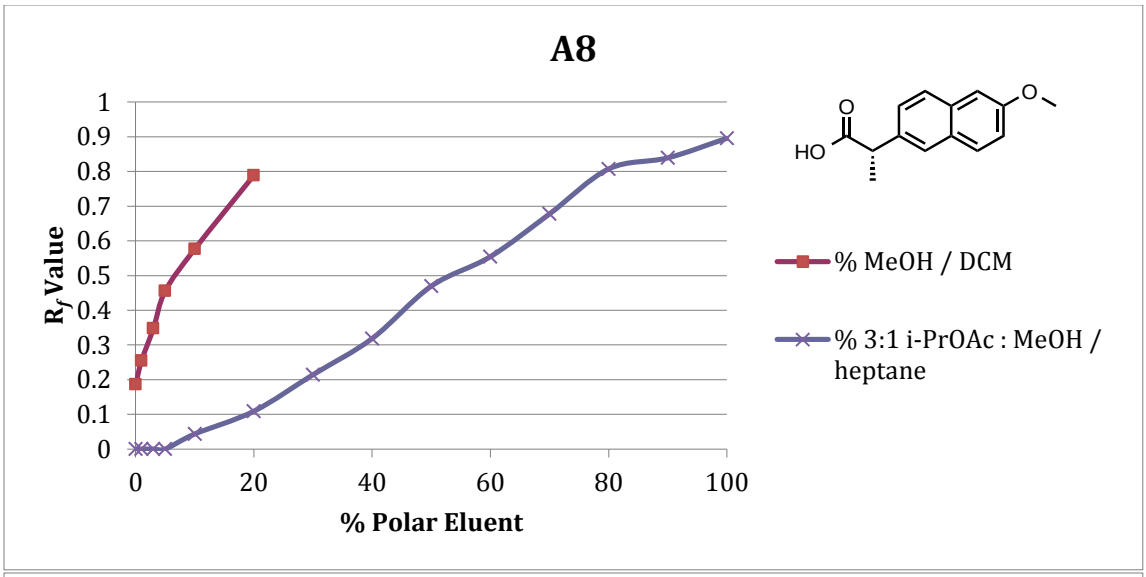

A3
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

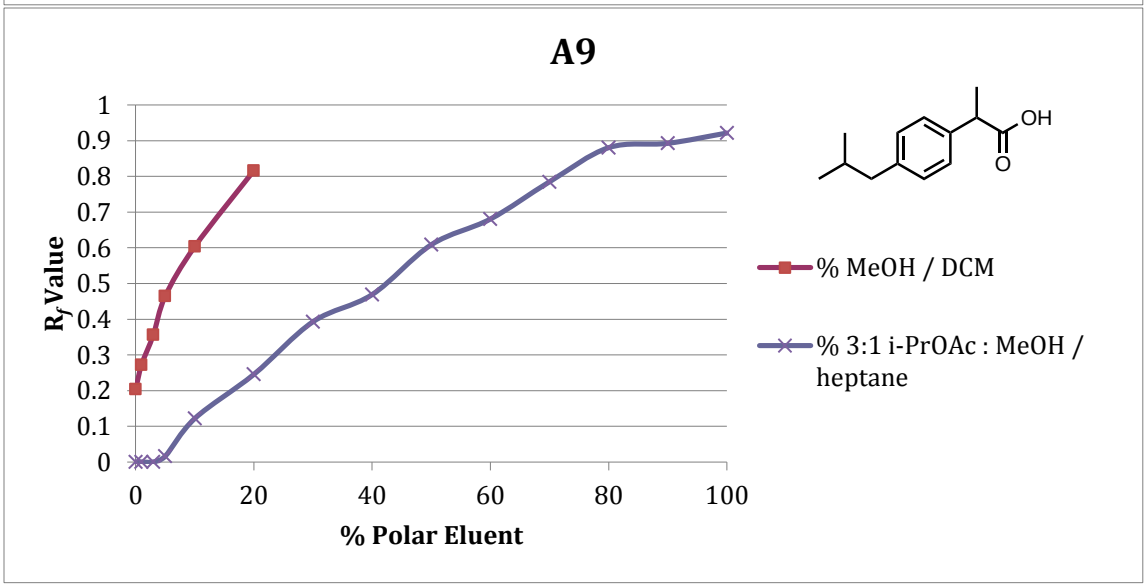

A4
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


A5
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


A6
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc:MeOH / heptane


A7
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


A8
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
HO
O
O
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


A9
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
OH
O
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

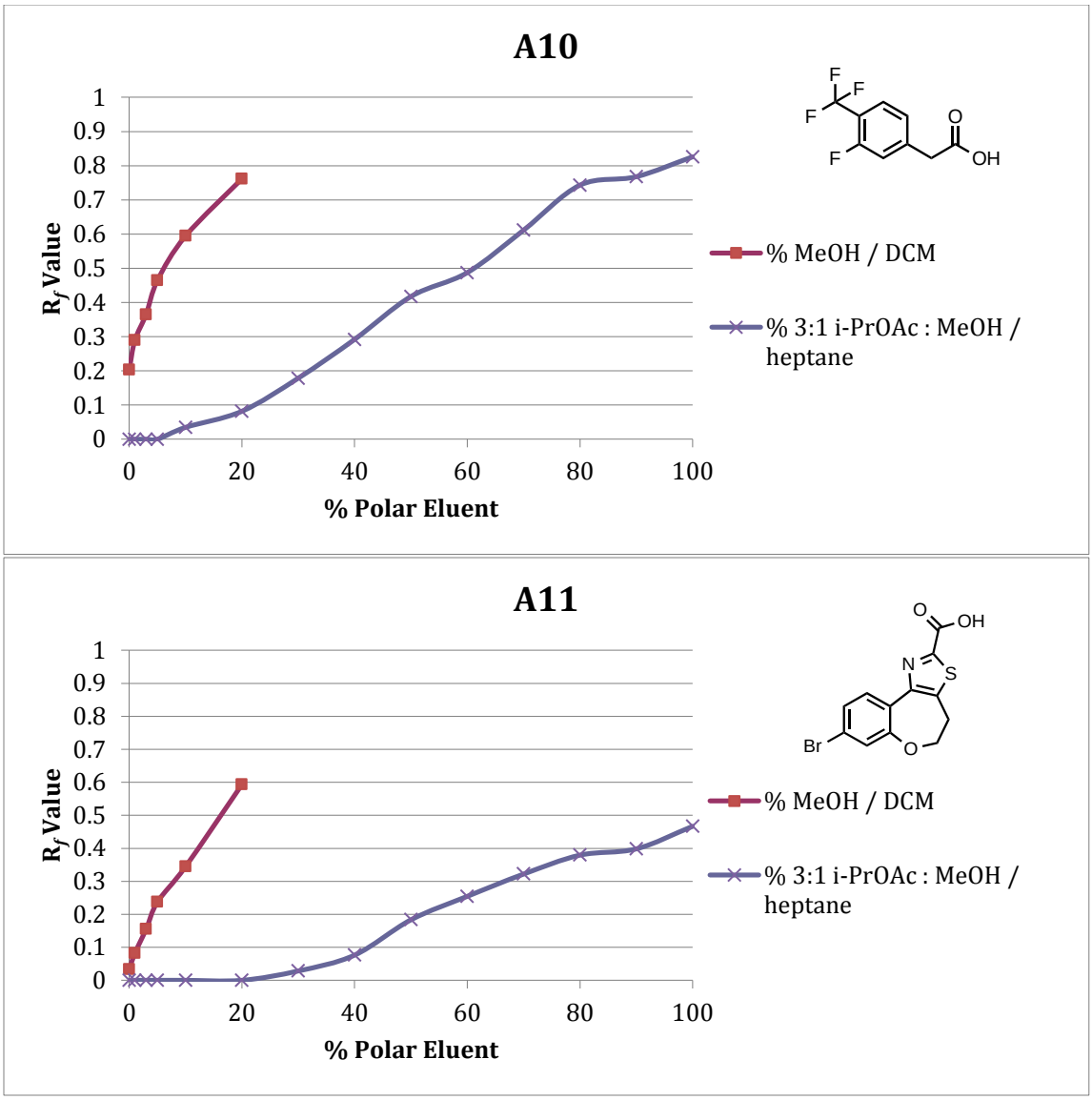
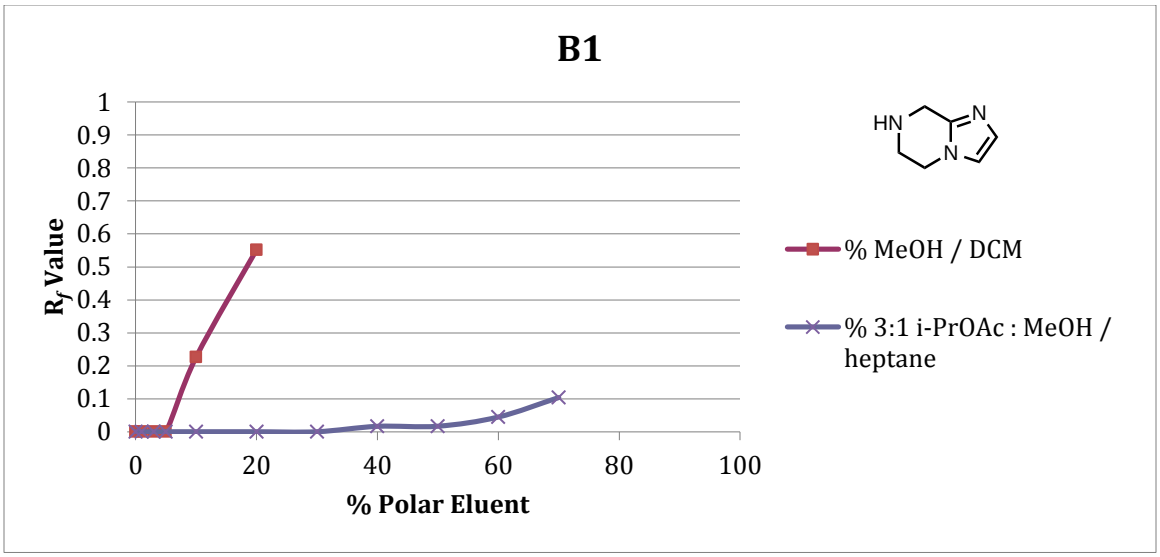
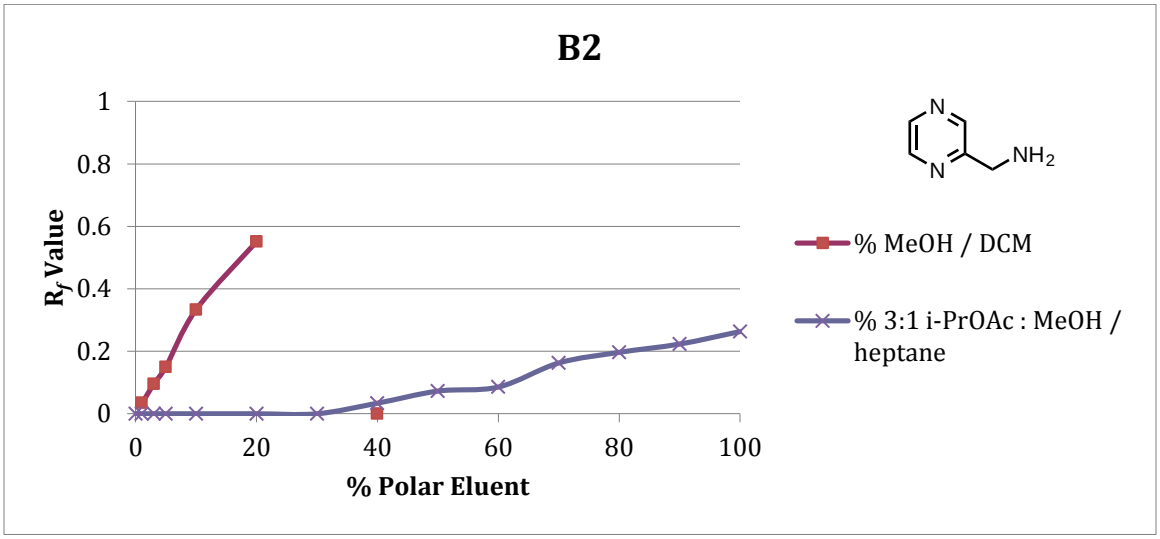
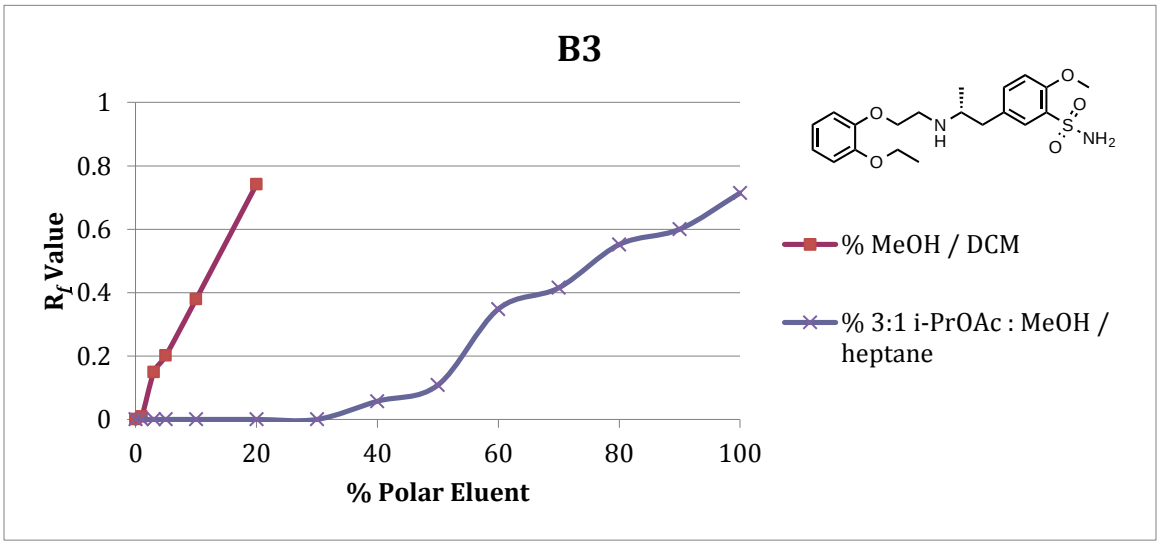
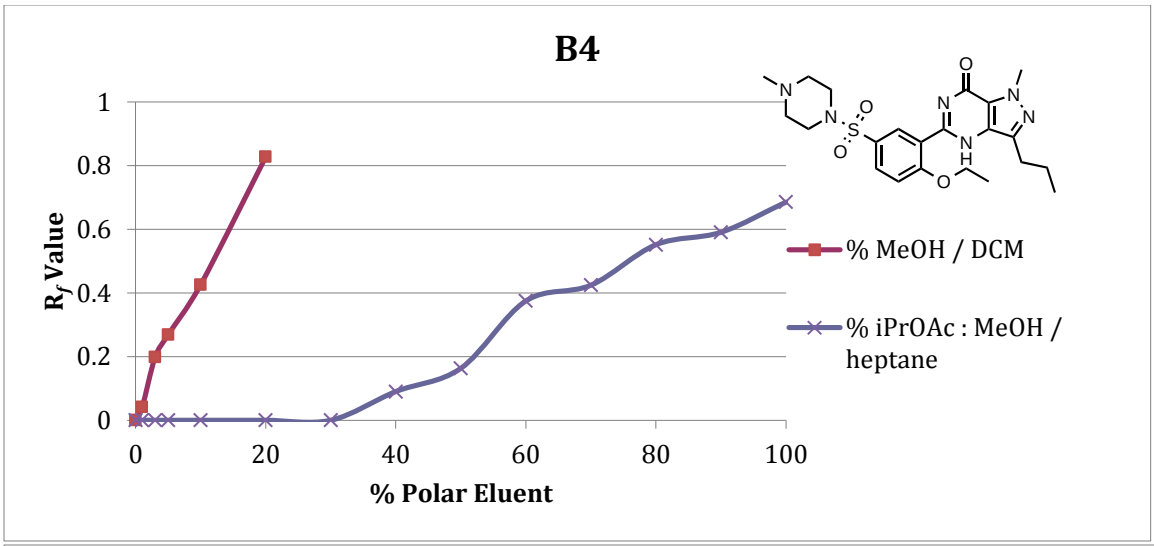


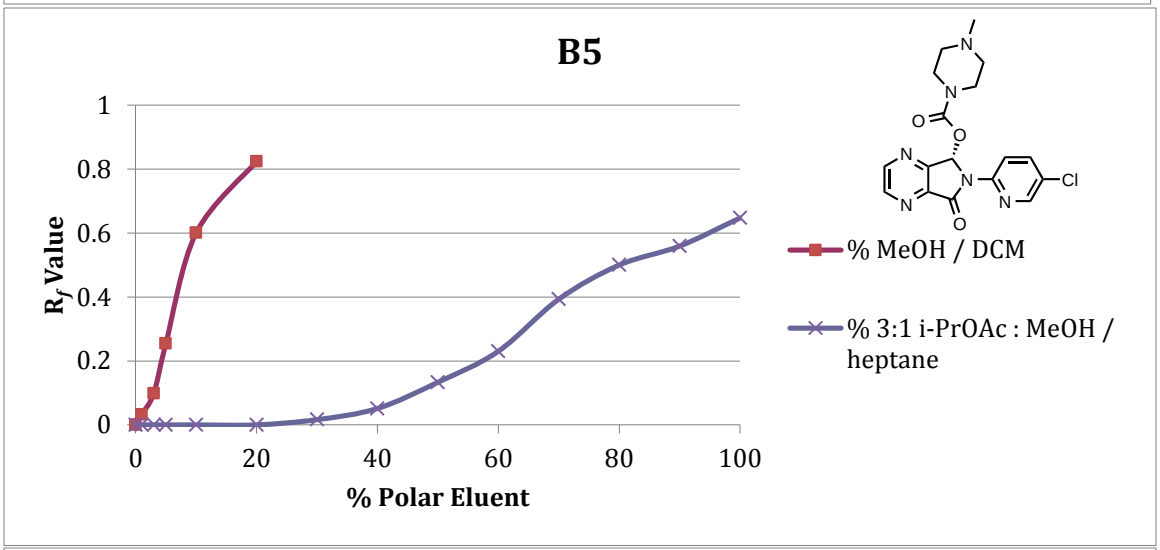
Figure S3b. Graphs of % polar eluent vs. R_f value for the 11 basic compounds. All solutions contain 2 % ammonium hydroxide additive.

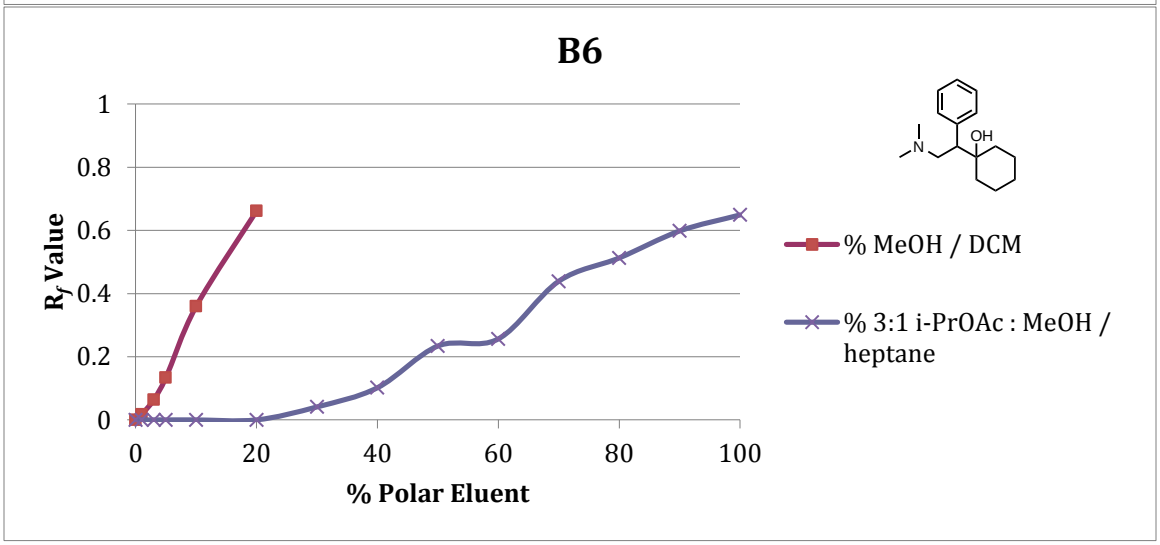

B1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
HN
N
N
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

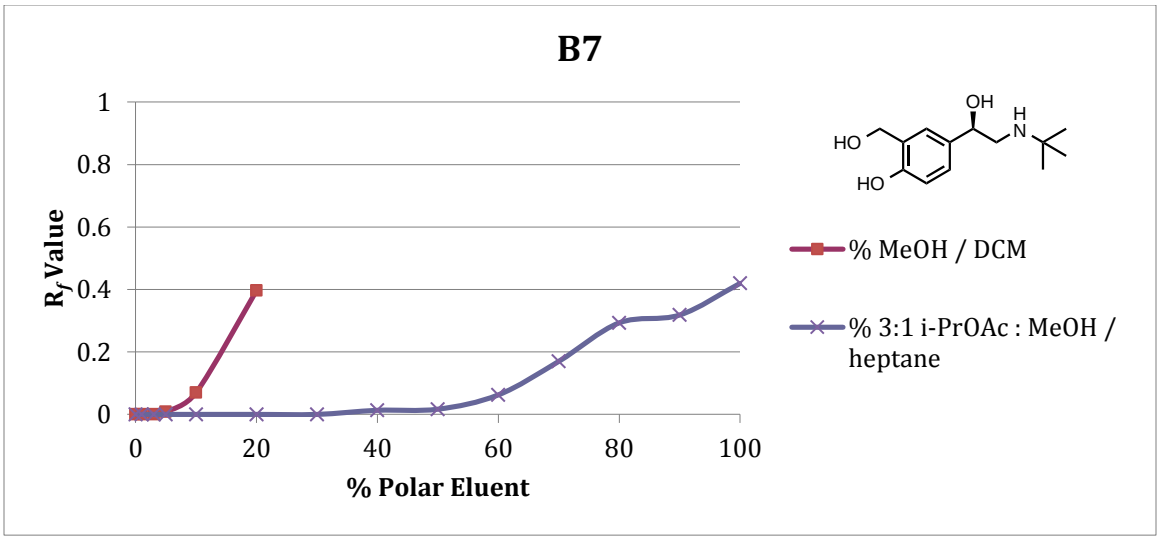

B2
1
0.8
0.6
0.4
0.2
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
N
N
NH2
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

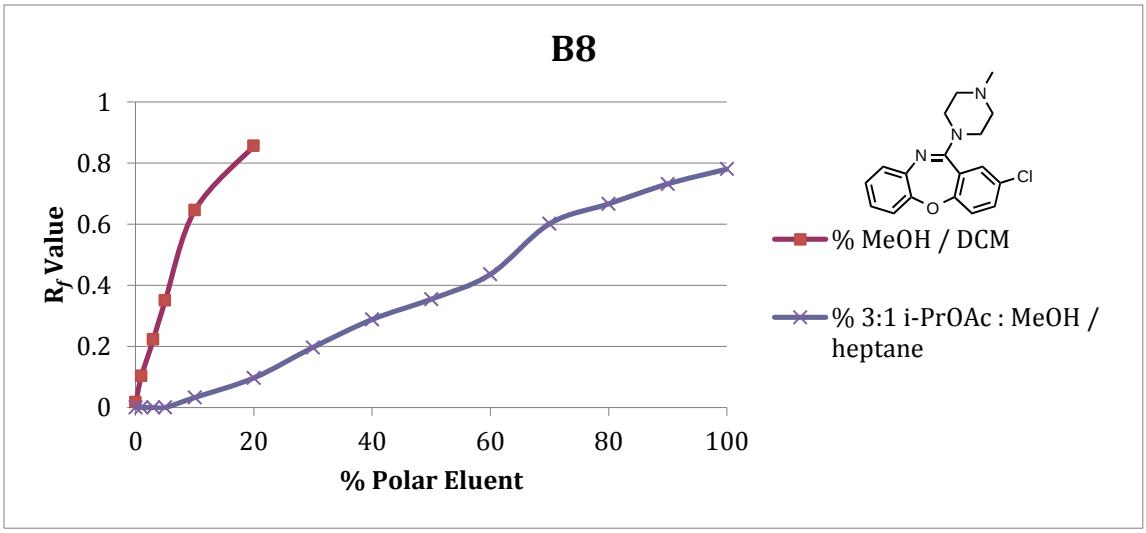

B3
1
0.8
0.6
0.4
0.2
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
O
O
N
H
O
O
S
O
O
NH2
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

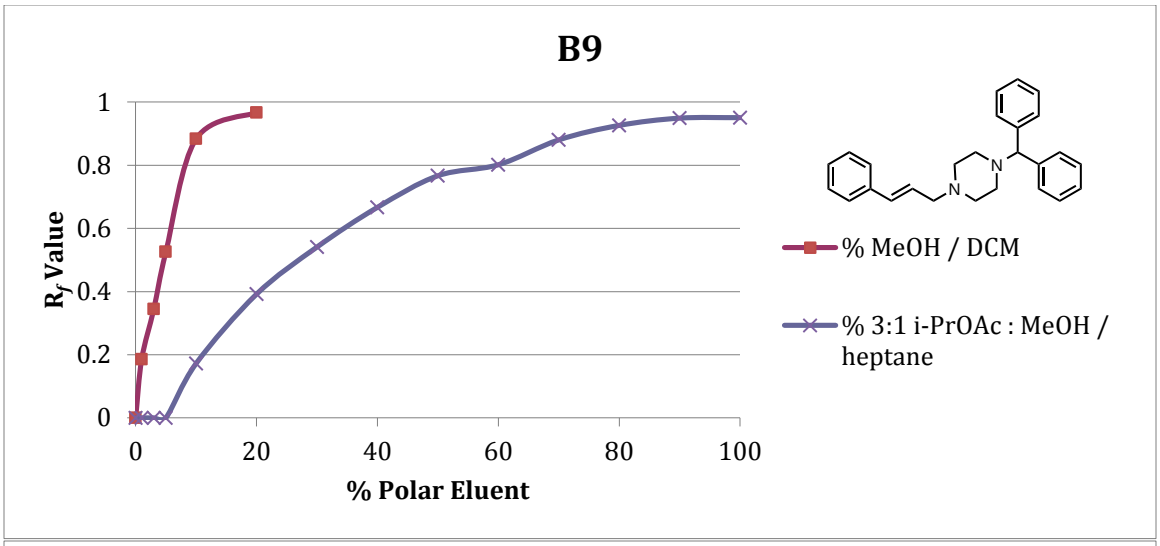

B4
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% iPrOAc : MeOH / heptane

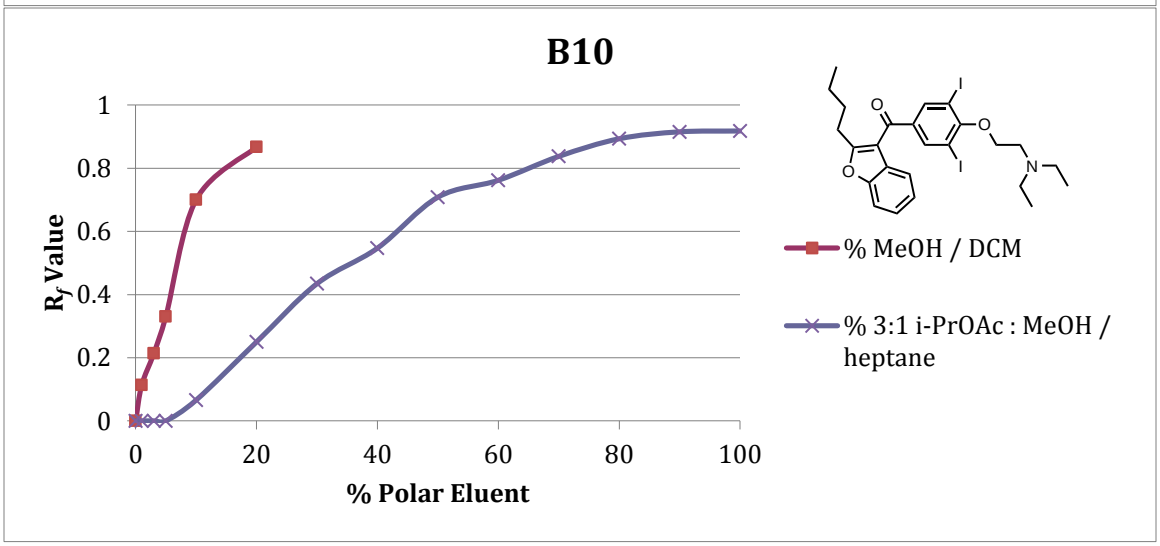

B5
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


B6
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


B7
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
OH
H
N
HO
HO
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


B8
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
N
N
N
Cl
O
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


B9
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


B10
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

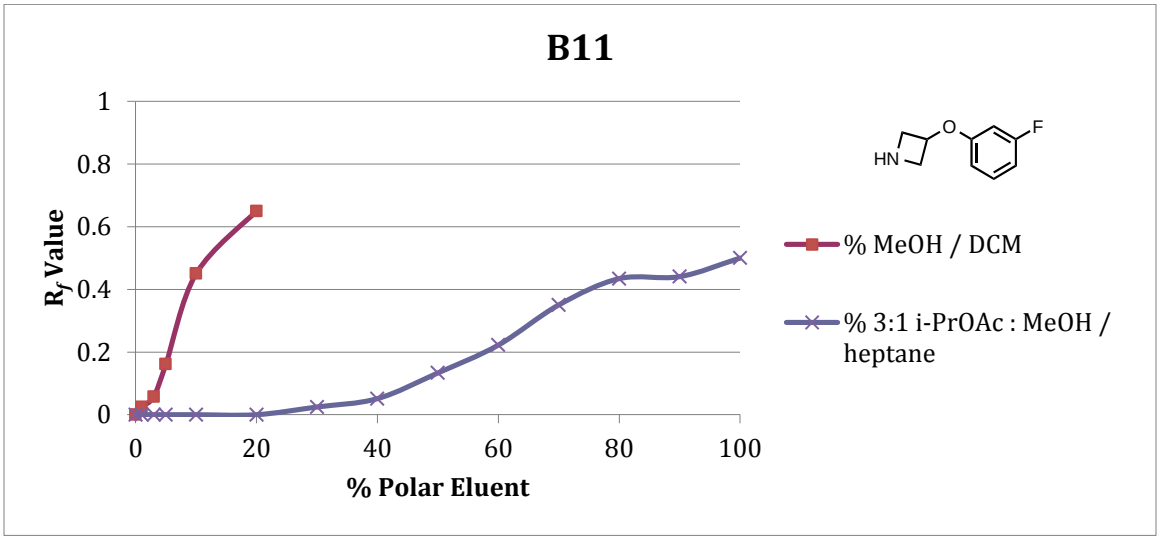
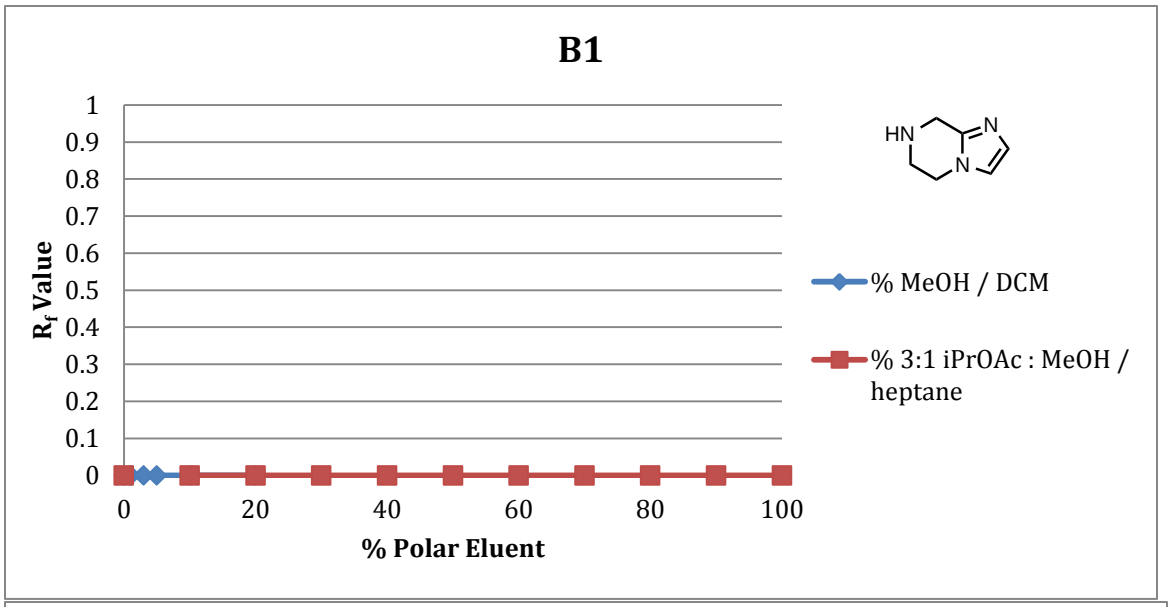
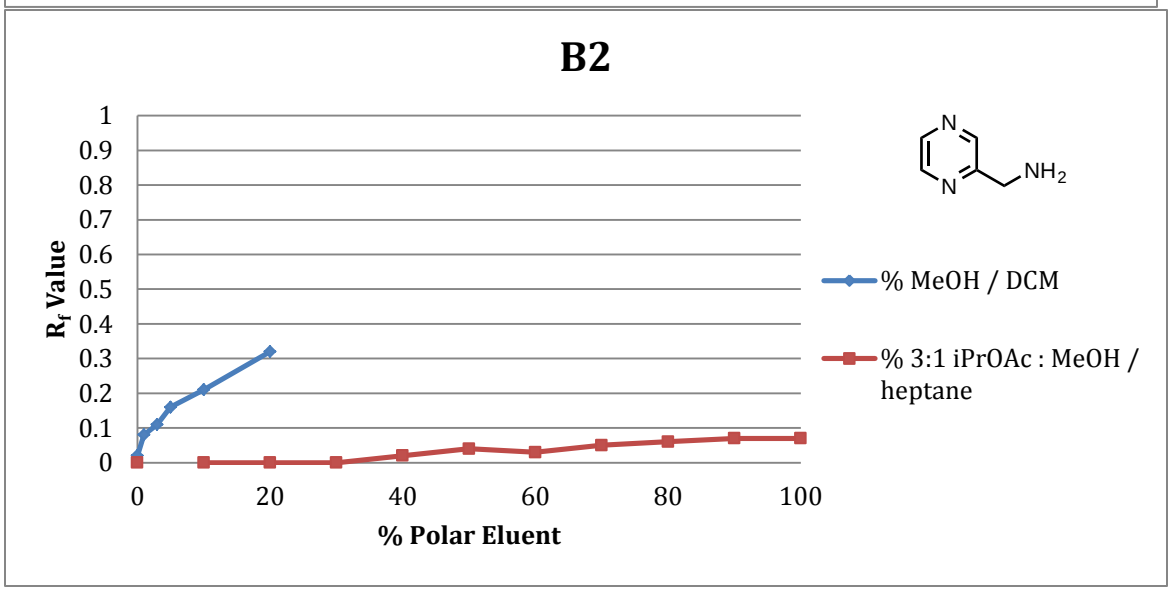
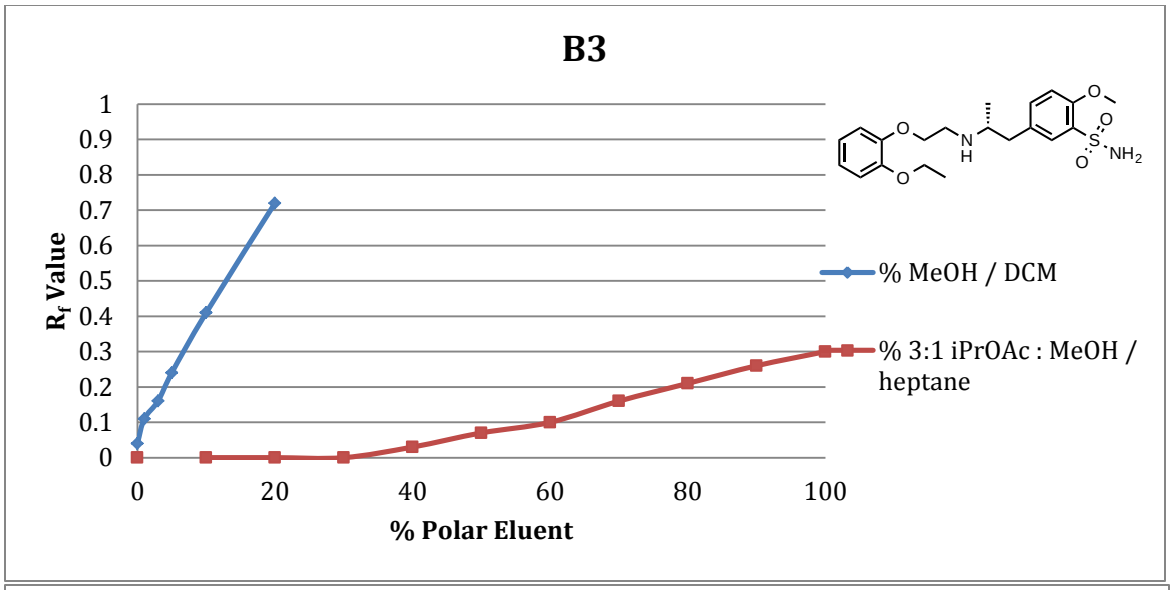
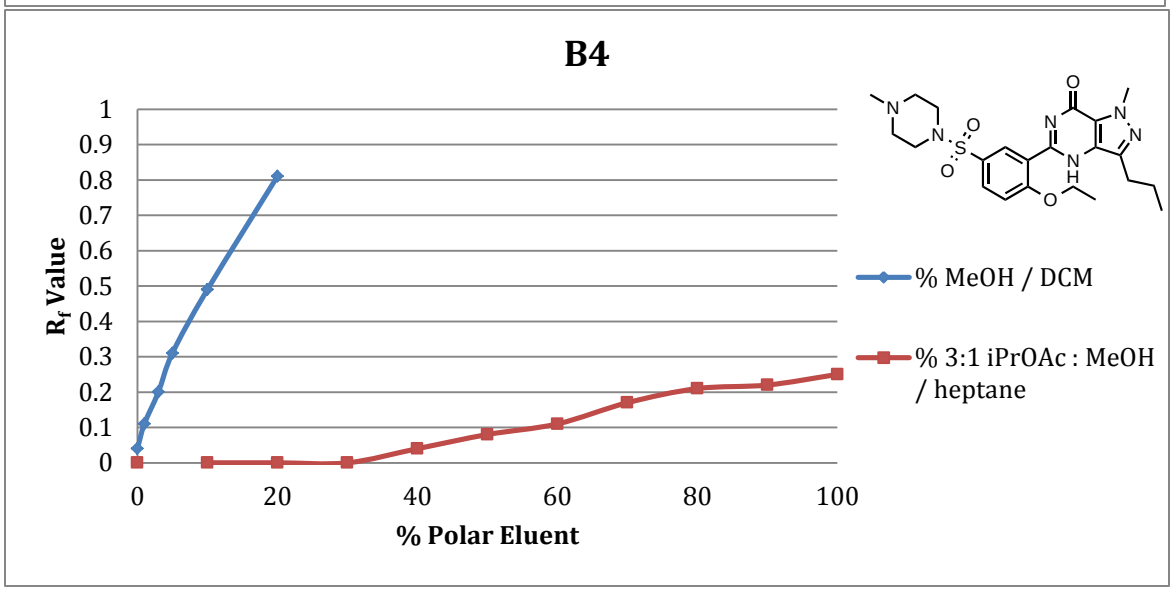

B11
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane

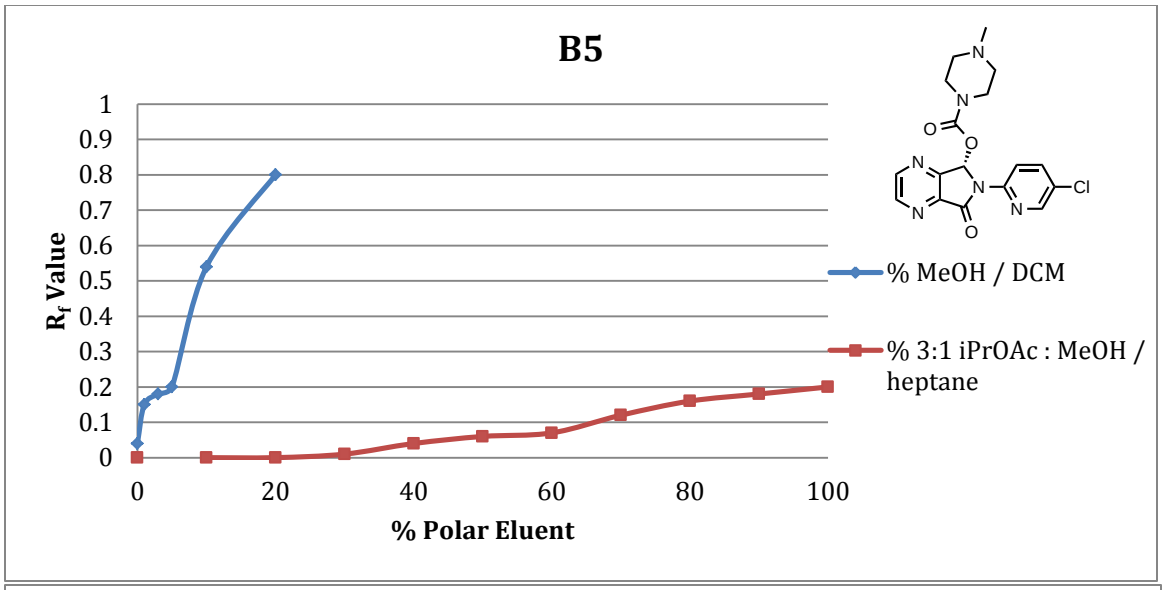
Figure S3c. Graphs of % polar eluent vs. R_f value for the 11 basic compounds. All solutions contain 1 % triethylamine additive.

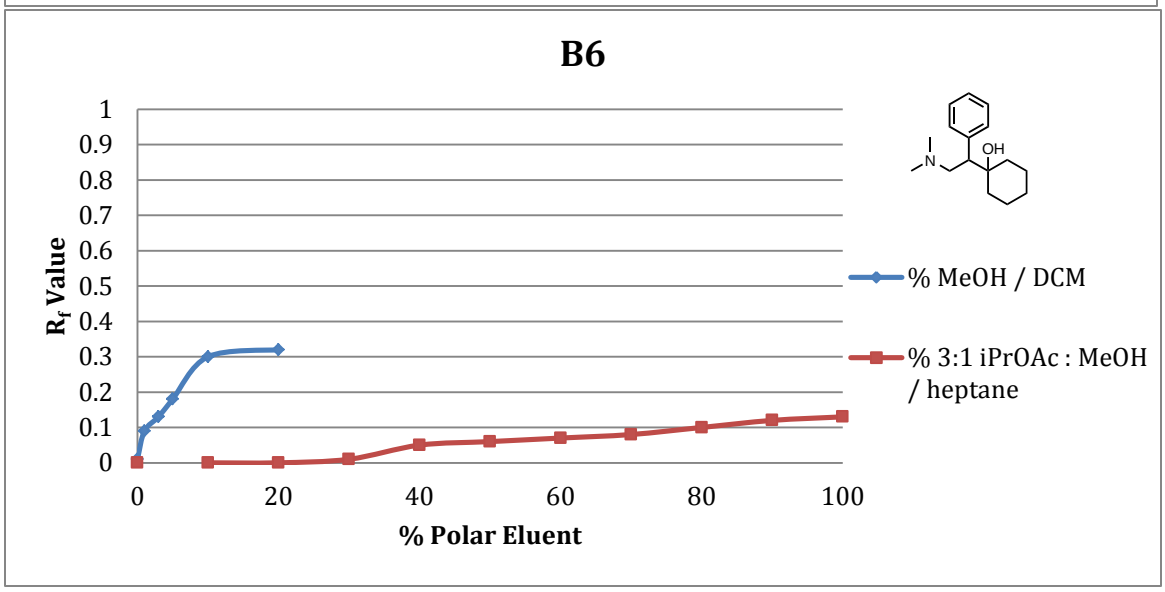


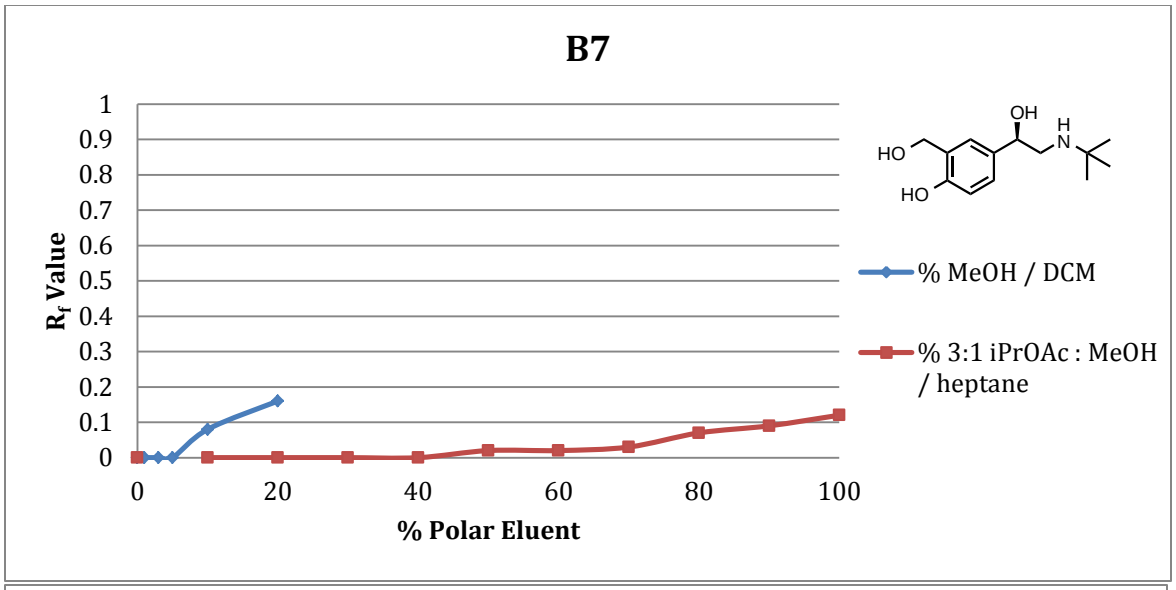


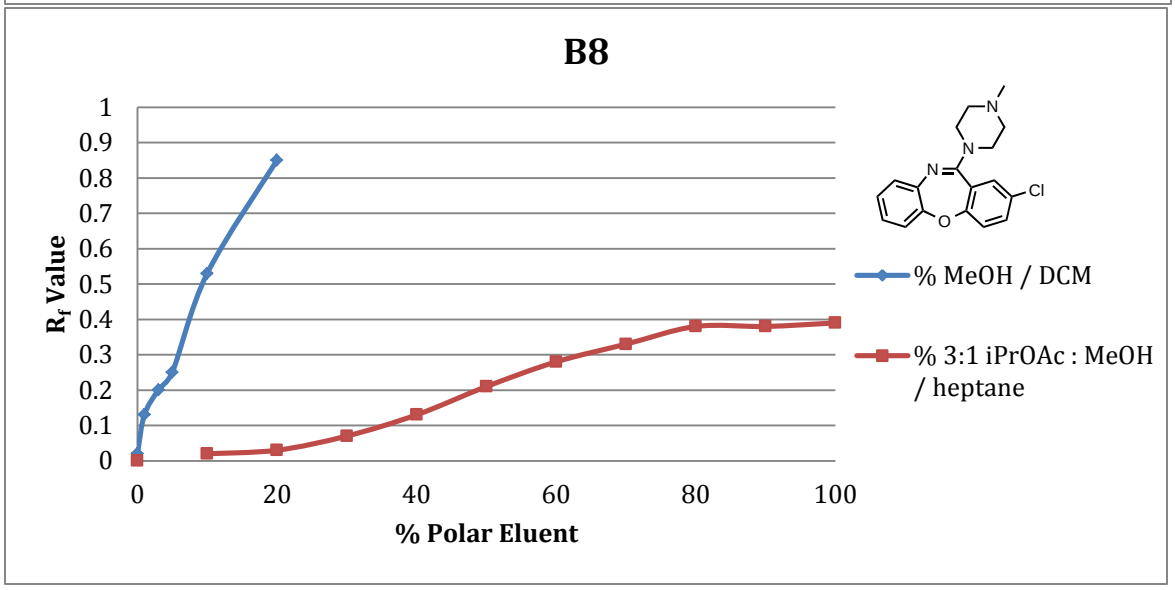

B3
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane

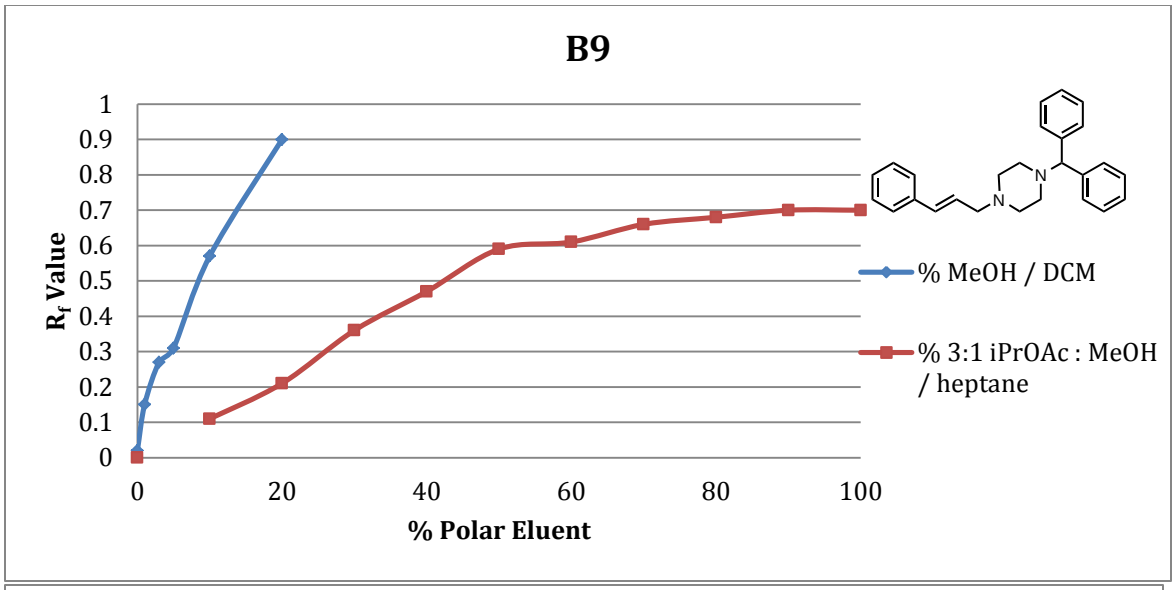

B4
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane

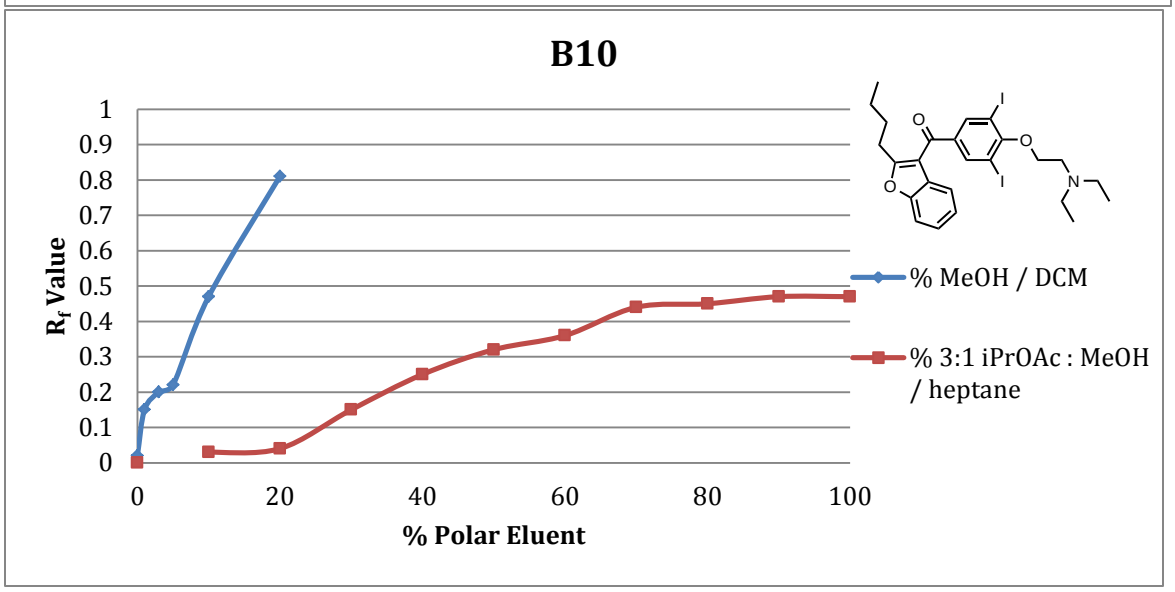

B5
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane
N
N
O
O
N
N
N
N
Cl
O


B6
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane
N
OH


B7
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
OH
H
N
HO
HO
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane


B8
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
N
N
N
O
Cl
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane


B9
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane


B10
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Rf Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 iPrOAc : MeOH / heptane

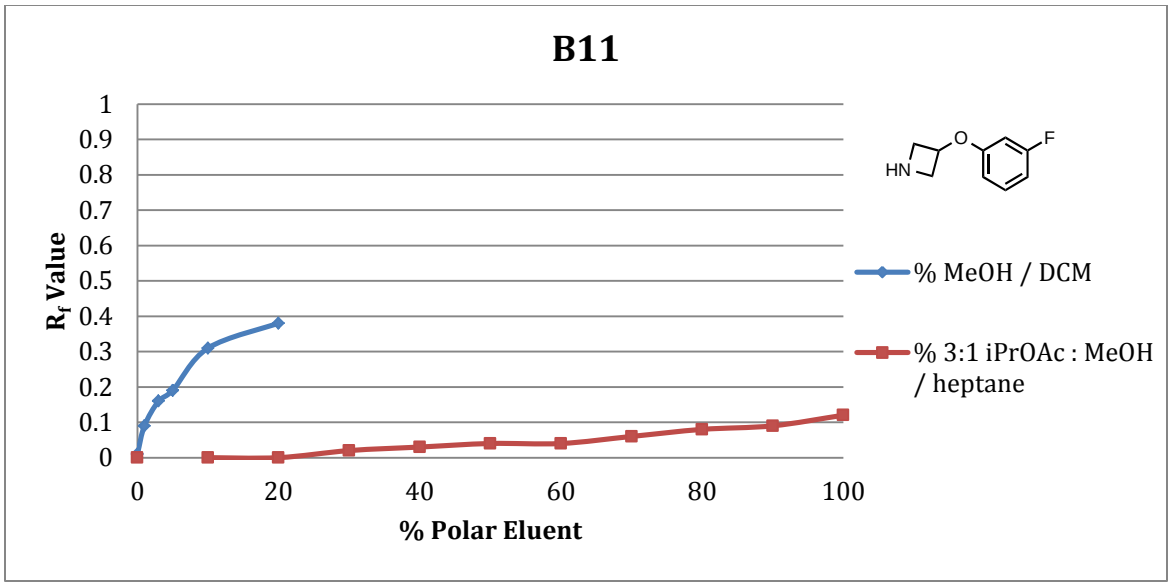
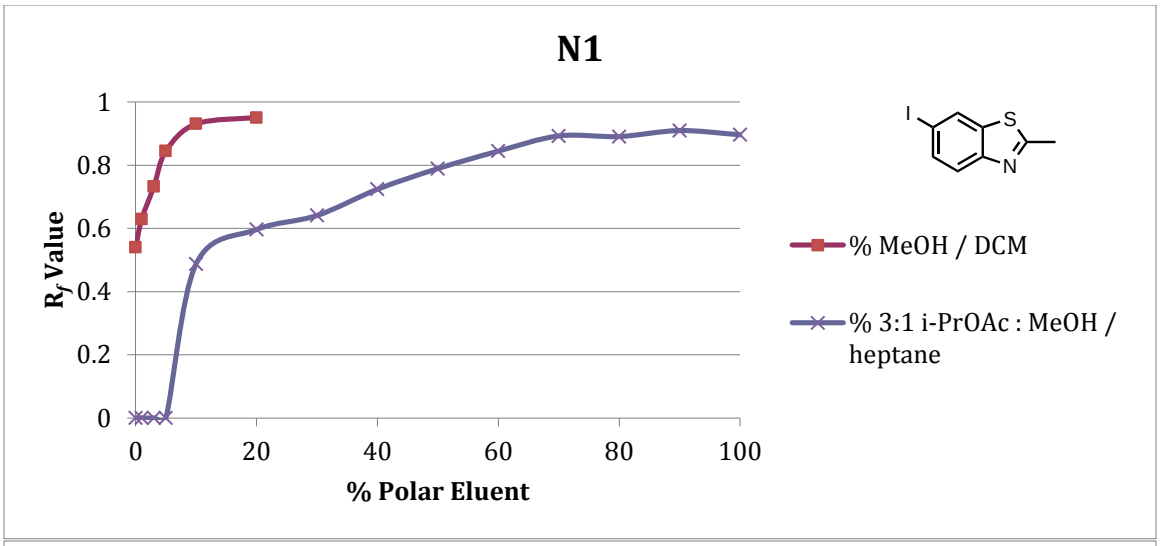
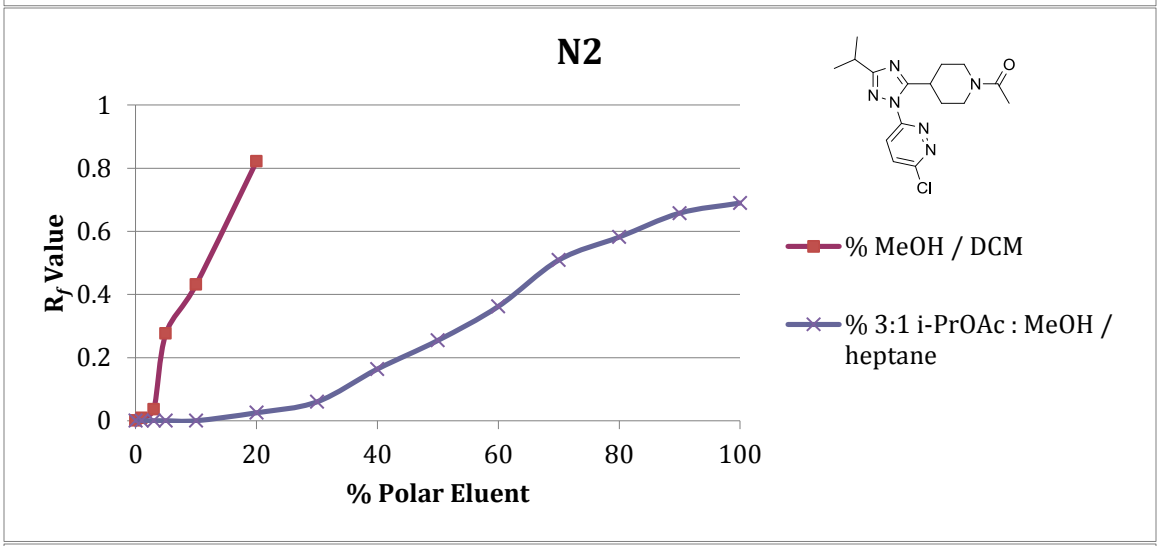
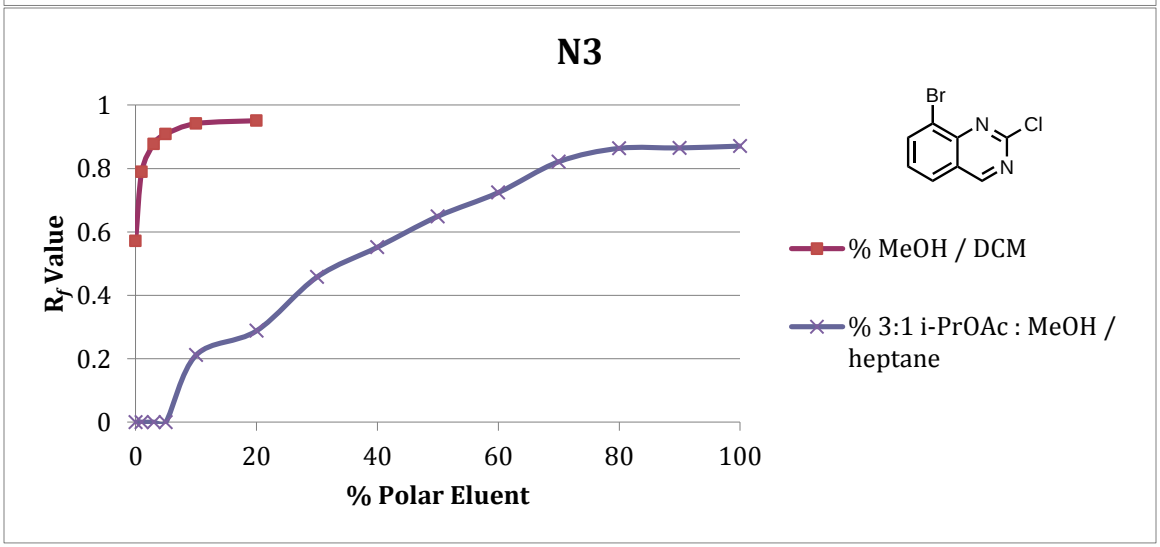


Figure S3d. Graphs of % polar eluent vs. R_f value for the 11 neutral compounds.


N1
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane
I
S
N


N2
1
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane
N
O
Cl


N3
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0.8
0.6
0.4
0.2
0
R_f Value
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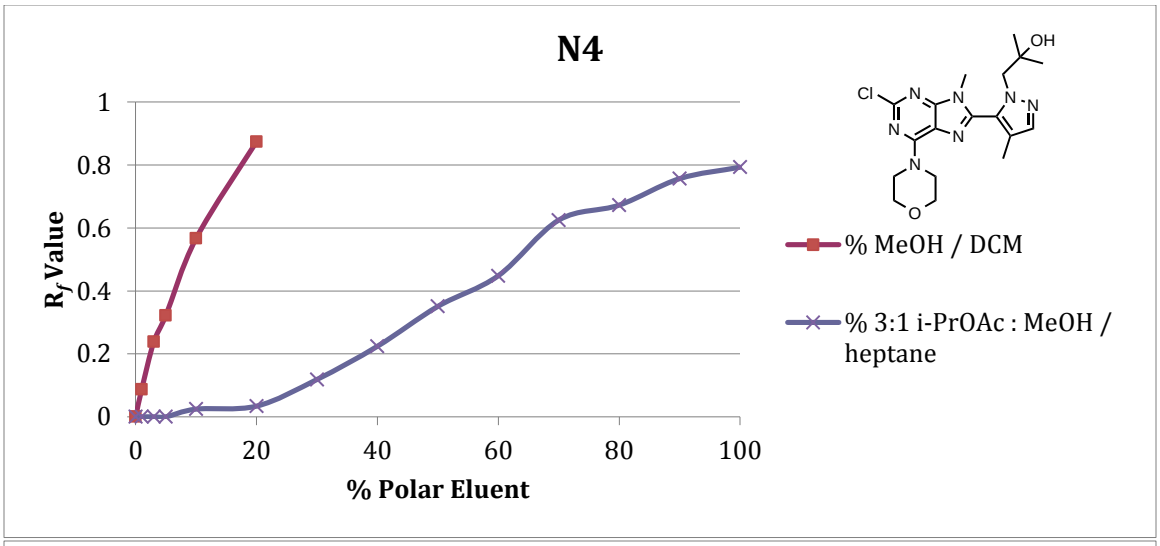
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane
Br
N
Cl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0.6
0.4
0.2
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Rf Value
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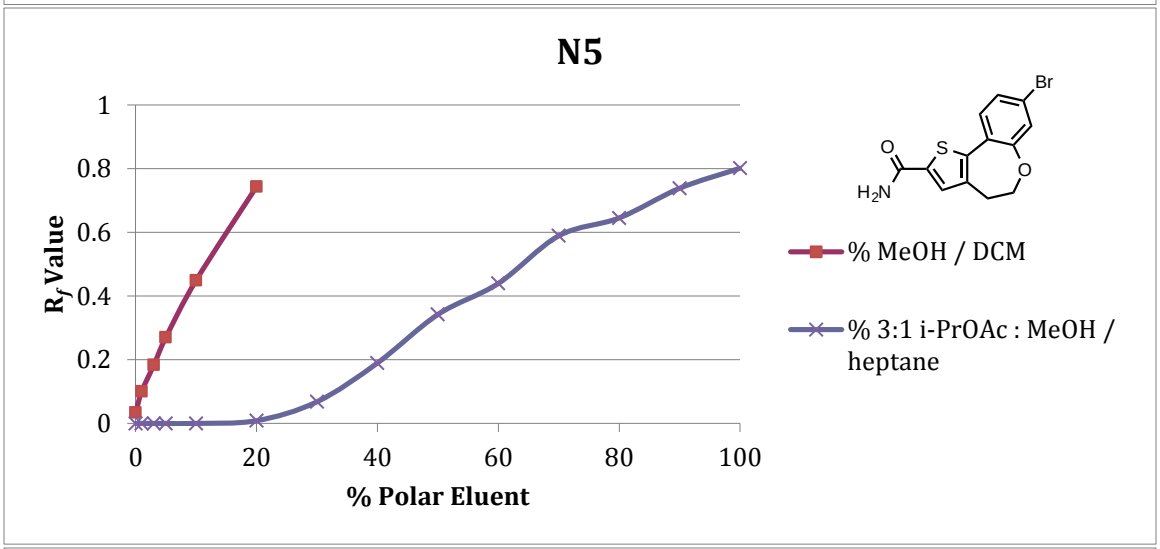
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane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0.6
0.4
0.2
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Rf Value
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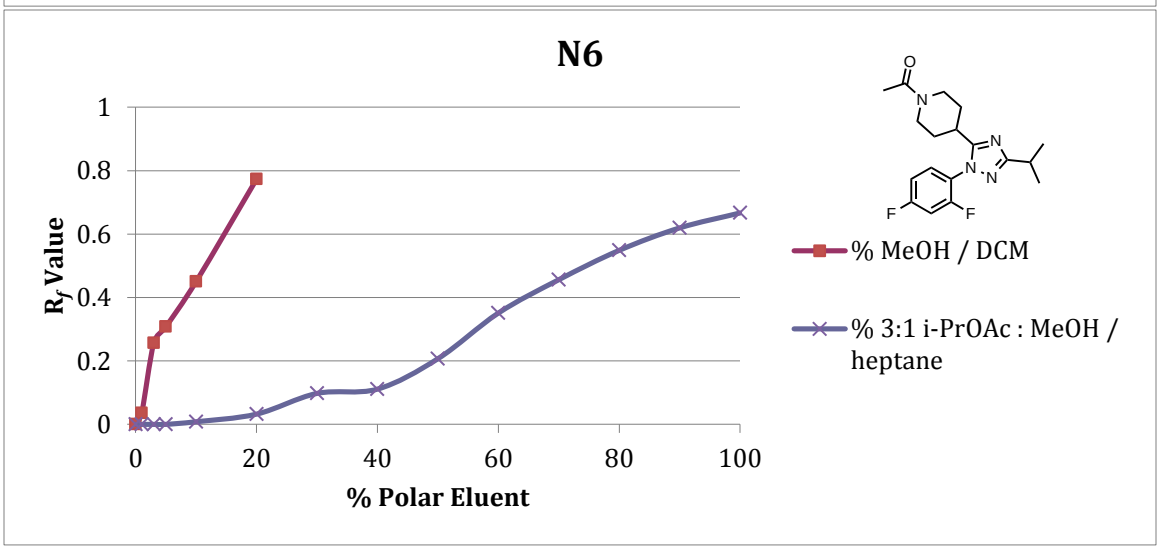
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane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0.6
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0.2
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Rf Value
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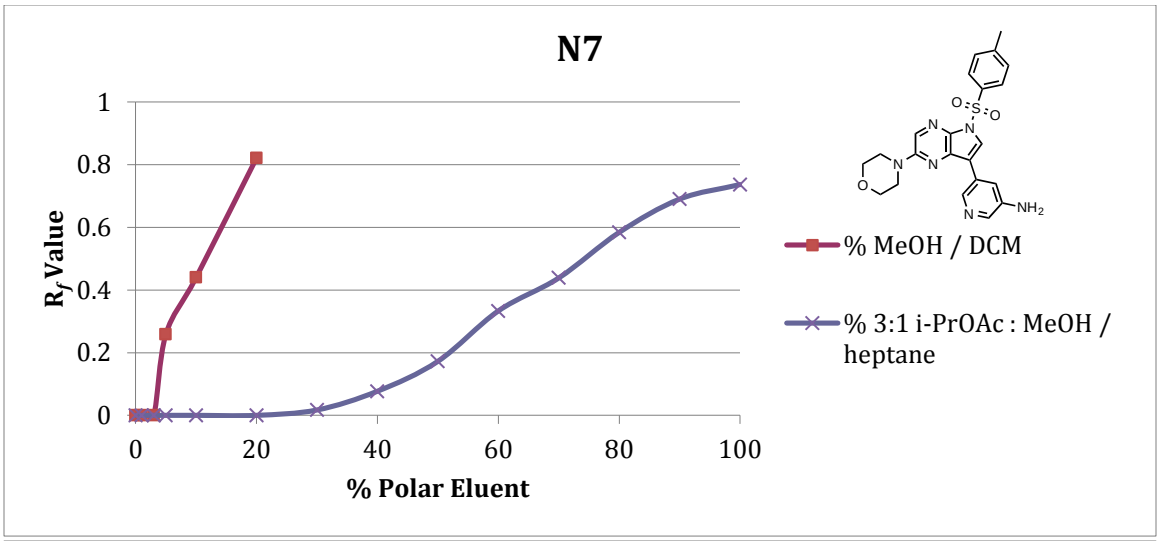
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


N7
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0.8
0.6
0.4
0.2
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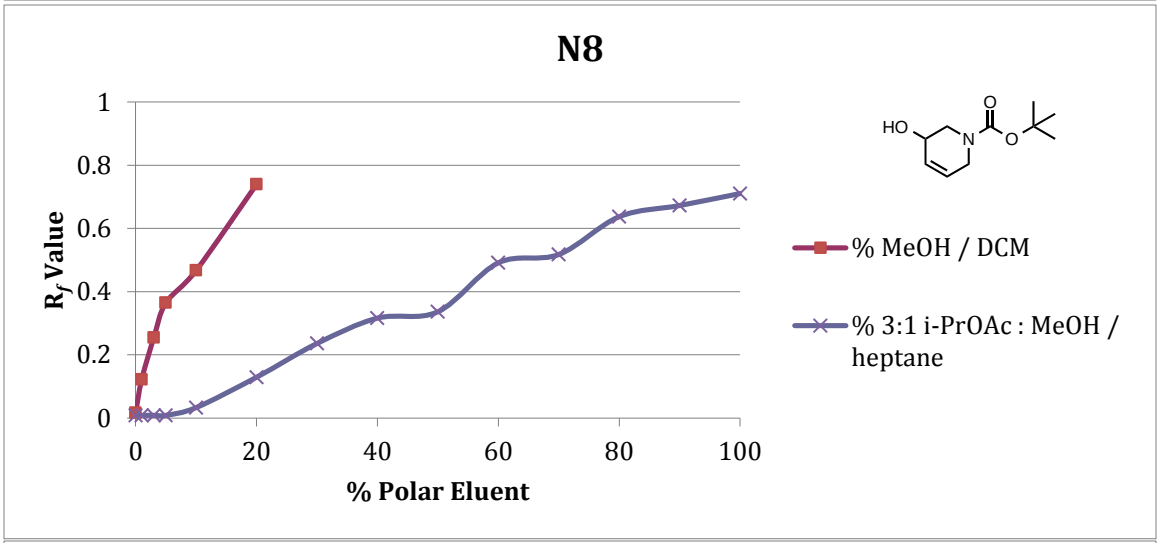
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


N8
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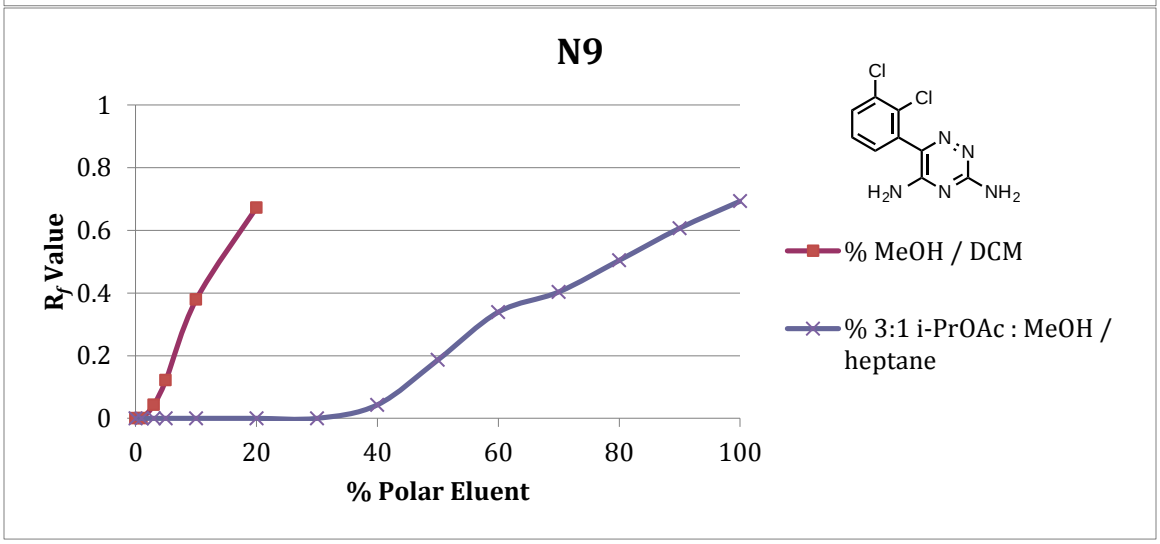
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane


N9
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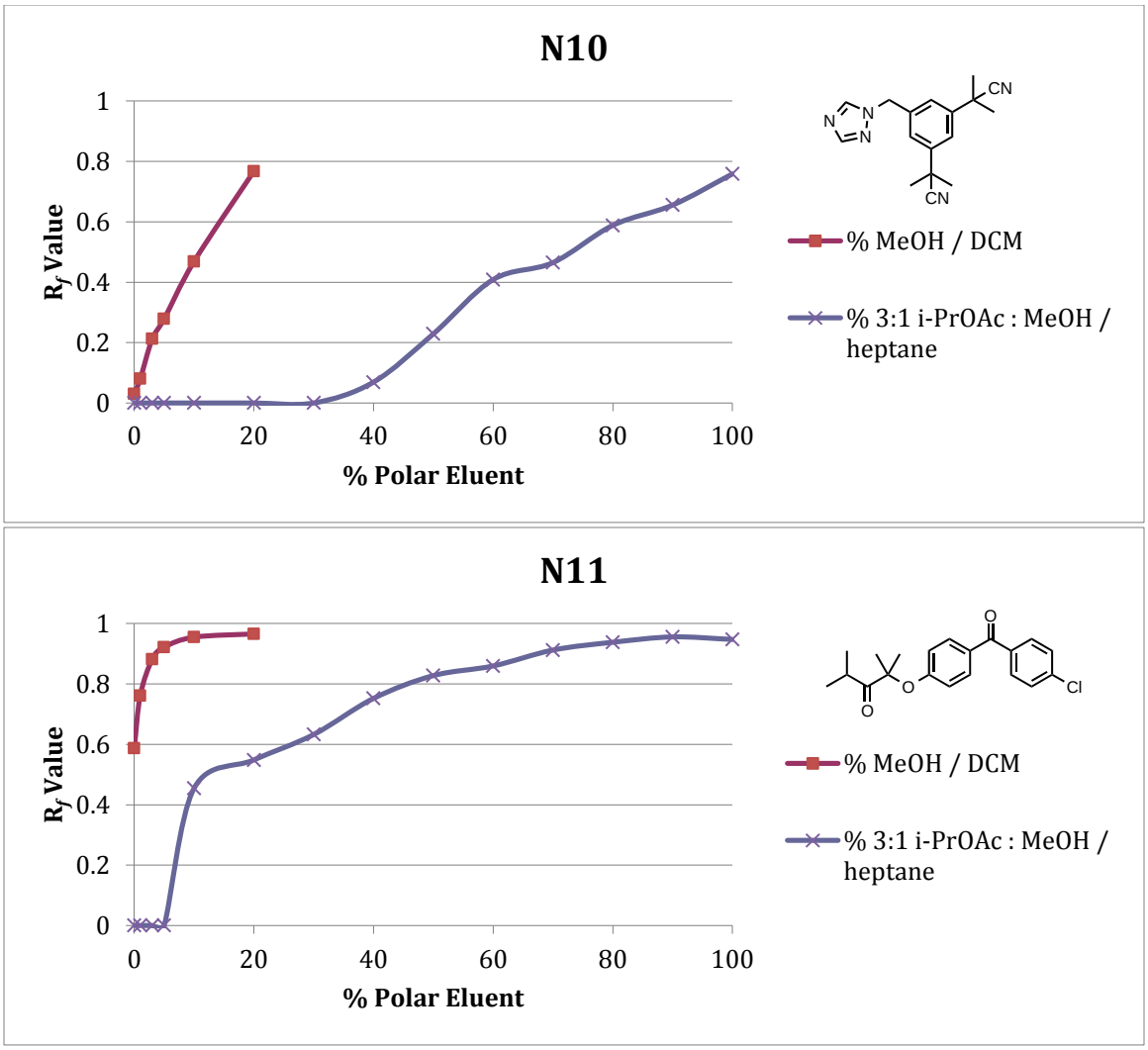
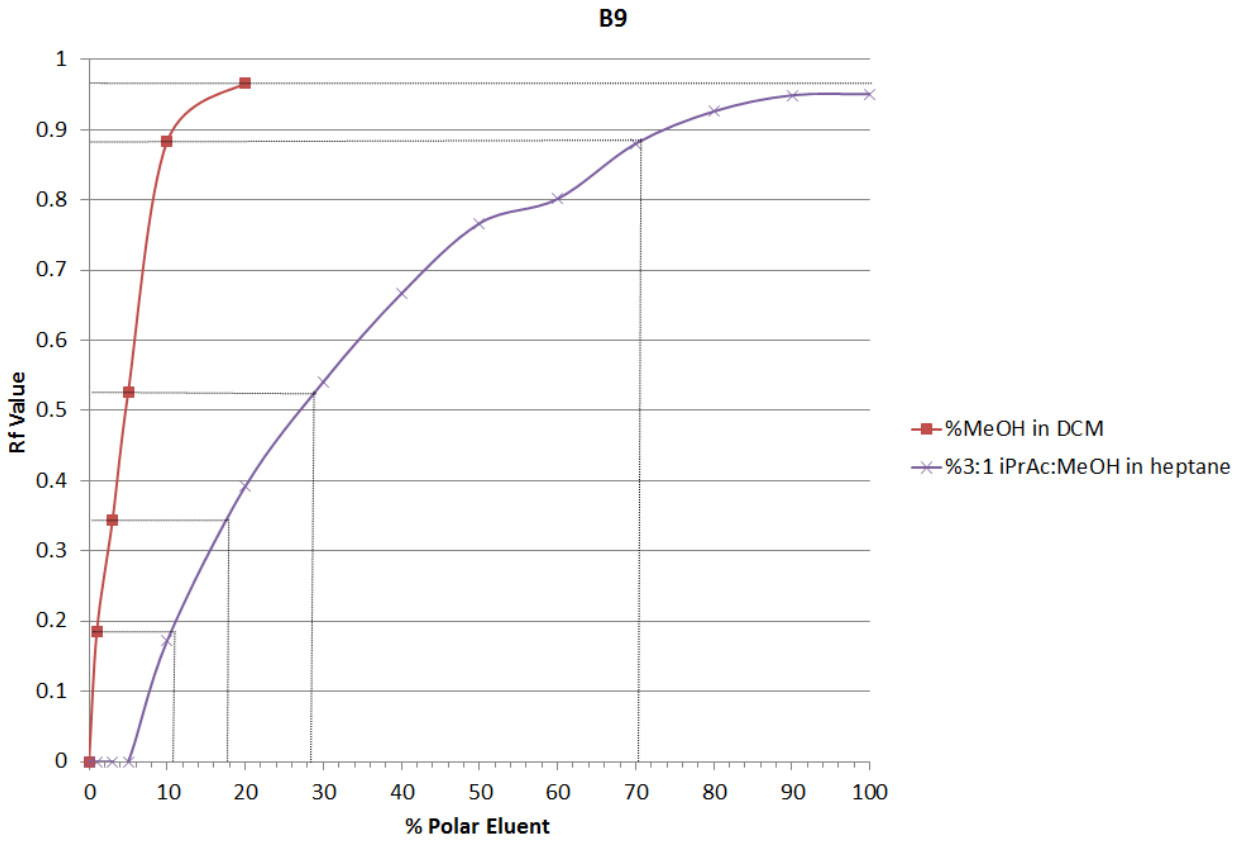
0.8
0.6
0.4
0.2
0
R_f Value
0
20
40
60
80
100
% Polar Eluent
% MeOH / DCM
% 3:1 i-PrOAc : MeOH / heptane



3.3 Graphs representing two different solvent systems to attain equivalent R_f values

3.3.1 Method for generating Figures S4a – c: For each compound within a set, the point at which the R_f values were equivalent in 3:1 *i*-PrOAc : MeOH / heptane to different compositions of MeOH / DCM (0, 1, 3, 5, 10 and 20 %) were measured using the graphs in Figures 3a, 3b, and 3d. For example, compound B9 in Figure 3b:



%MeOH in DCM	Rf	**Corresponding % 3 : 1 *i*-PrOAc : MeOH**
0	0	**0**
1	0.19	**10.2**
3	0.35	**17.5**
5	0.53	**28.3**
10	0.88	**70.7**
20	0.97	-

The values of corresponding % 3:1 iPrOAc : MeOH were calculated for each compound and averaged to create Figures S4a – c.

Figure S4a. (Figure 2a in manuscript) Graph depicting corresponding polarity of solvent mixtures with 2 % acetic acid additive based on equivalent R_f values of a set of 10 acidic compounds. Error bars correspond to one standard deviation.

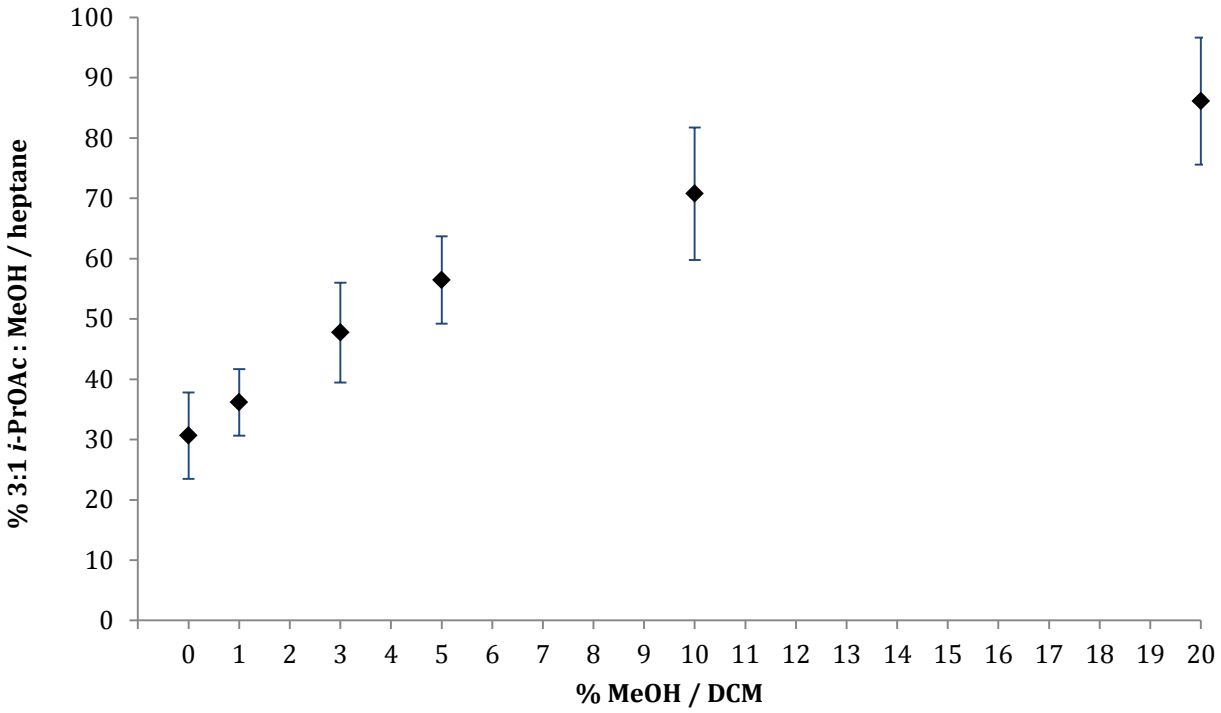


Figure S4b. (Figure 2b in manuscript) Graph depicting corresponding polarity of solvent mixtures with 2 % ammonium hydroxide additive based on equivalent R_f values of a set of 10 basic compounds. Error bars correspond to one standard deviation.

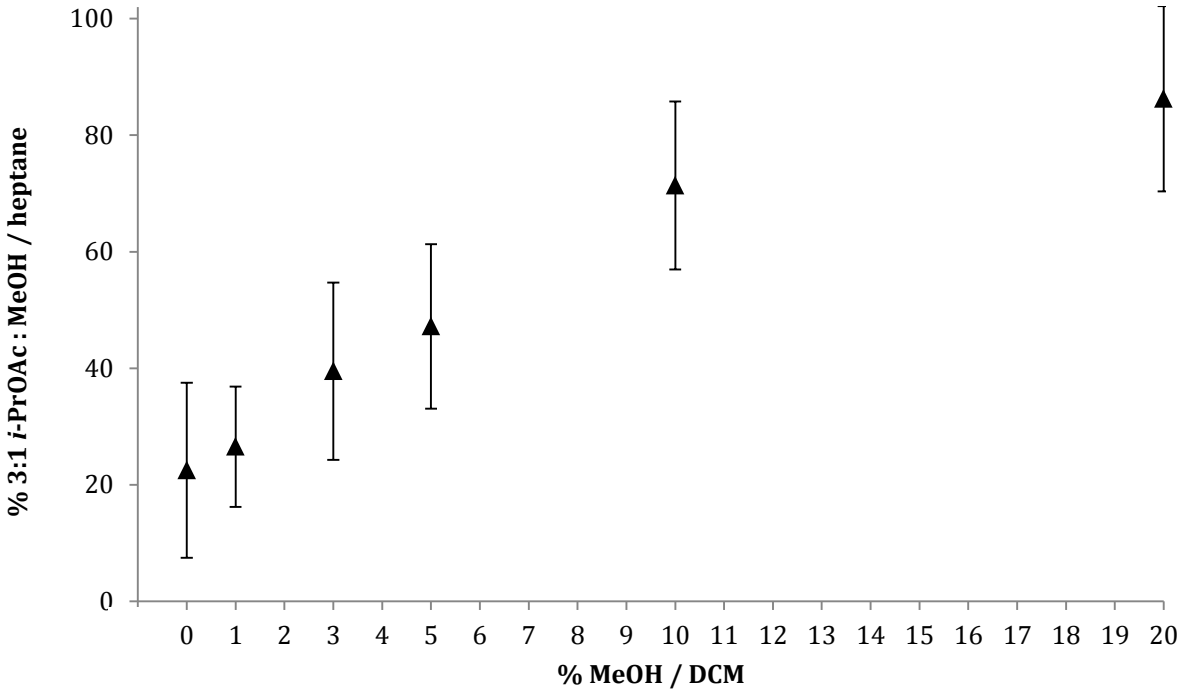


Figure S4c. (Figure 2c in manuscript) Graph depicting corresponding polarity of solvent mixtures based on equivalent R_f values of a set of 10 neutral compounds. Error bars correspond to one standard deviation.

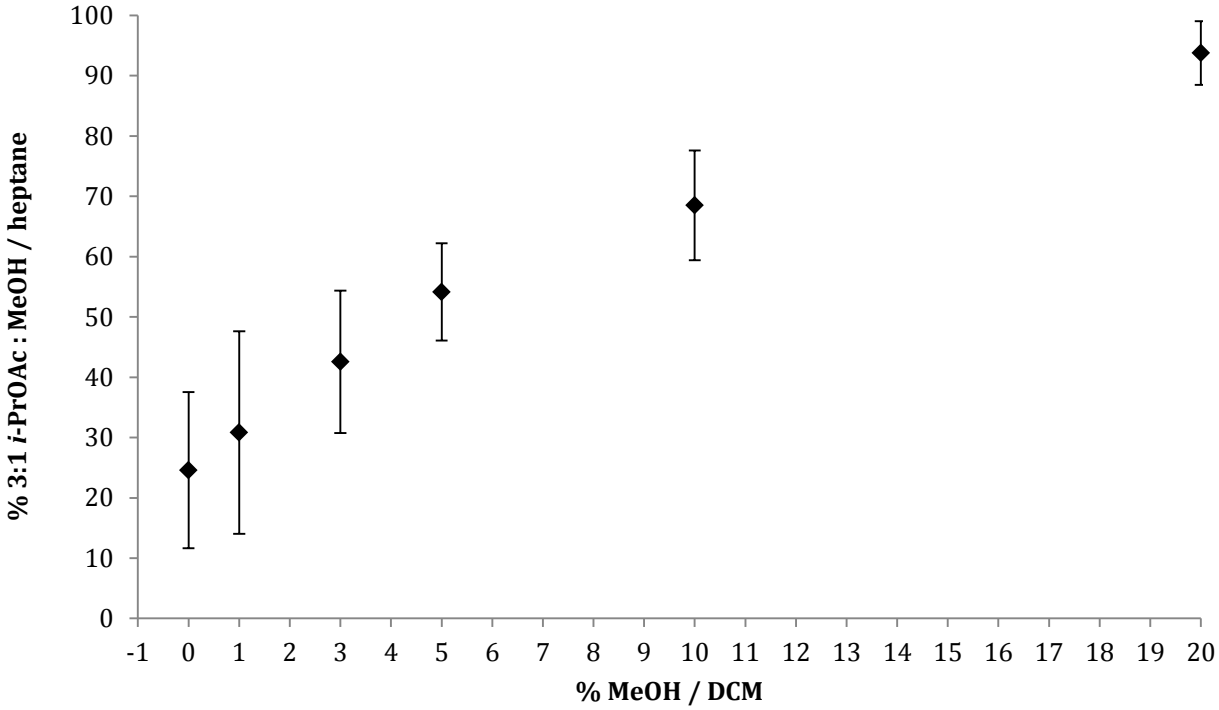
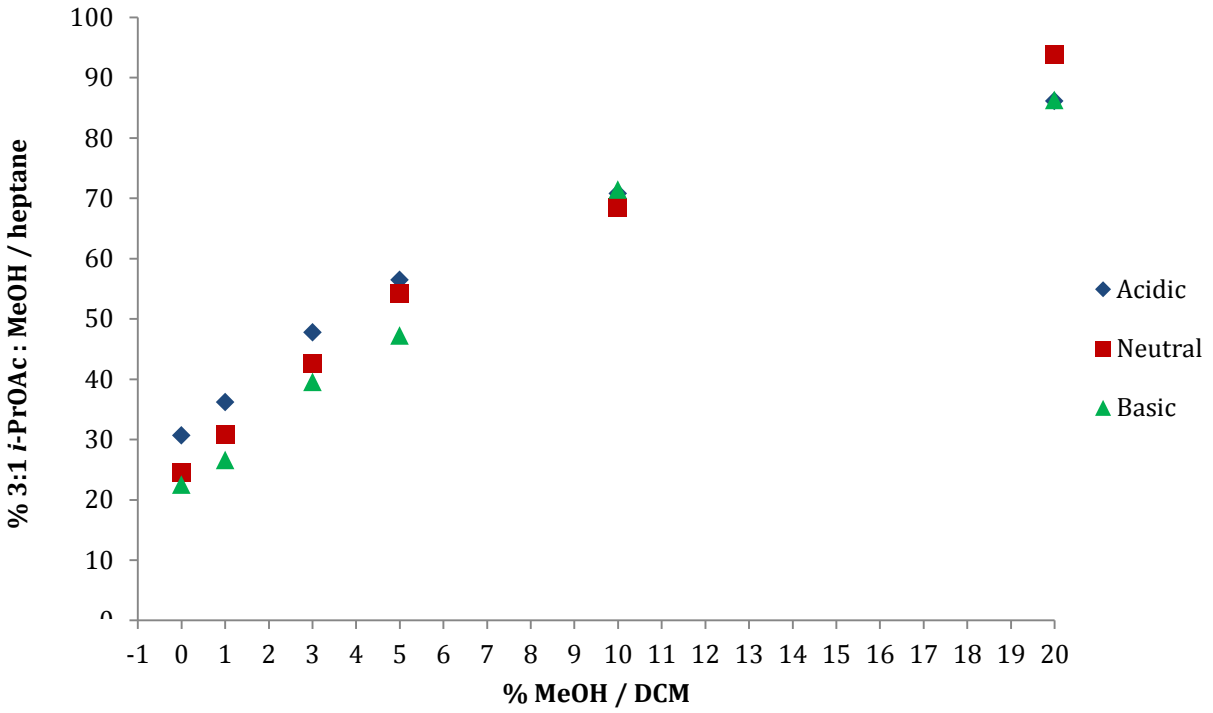


Figure S5. (Figure 2d in manuscript) Graph depicting corresponding polarity of solvent mixtures based on equivalent R_f values of a set of representative compounds.



3.4 Chromatograms from separations of mixtures of compounds

Figure S6a. (Figure 3a in manuscript) Separation of three basic molecules (B6, B7, and B9) employing a gradient of 0-20% MeOH / DCM spiked with triethylamine as the solvent system.

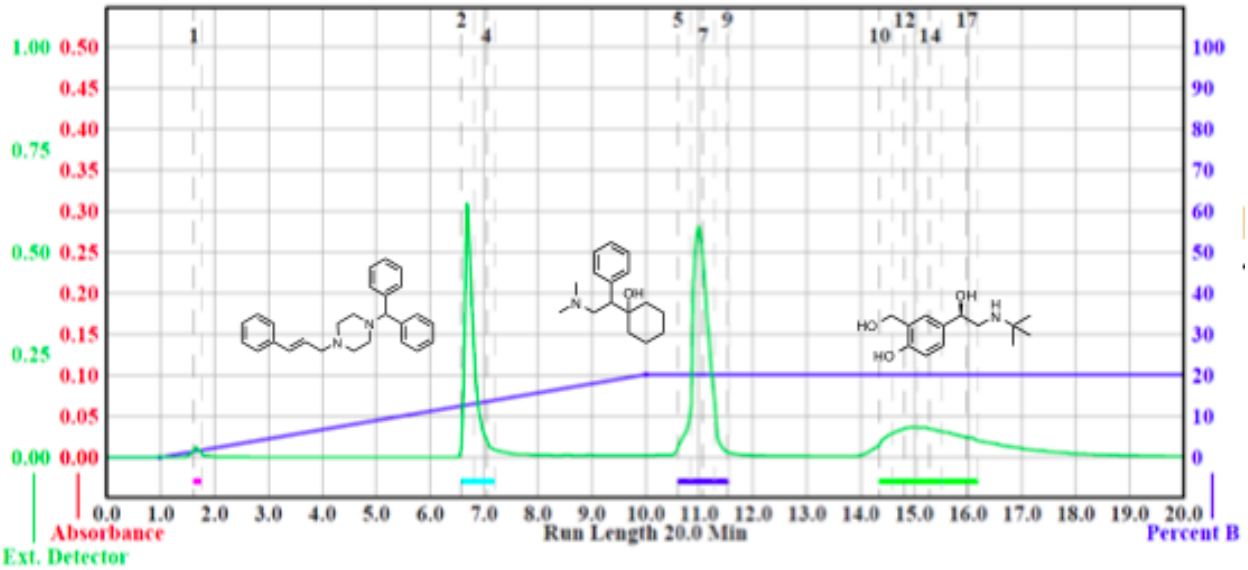


Figure S6b. (Figure 3b in manuscript) Separation of the same three basic molecules (B6, B7, B9) employing a gradient of 0-80% 3:1 *i*-PrOAc : MeOH / heptane spiked with triethylamine as the solvent system.

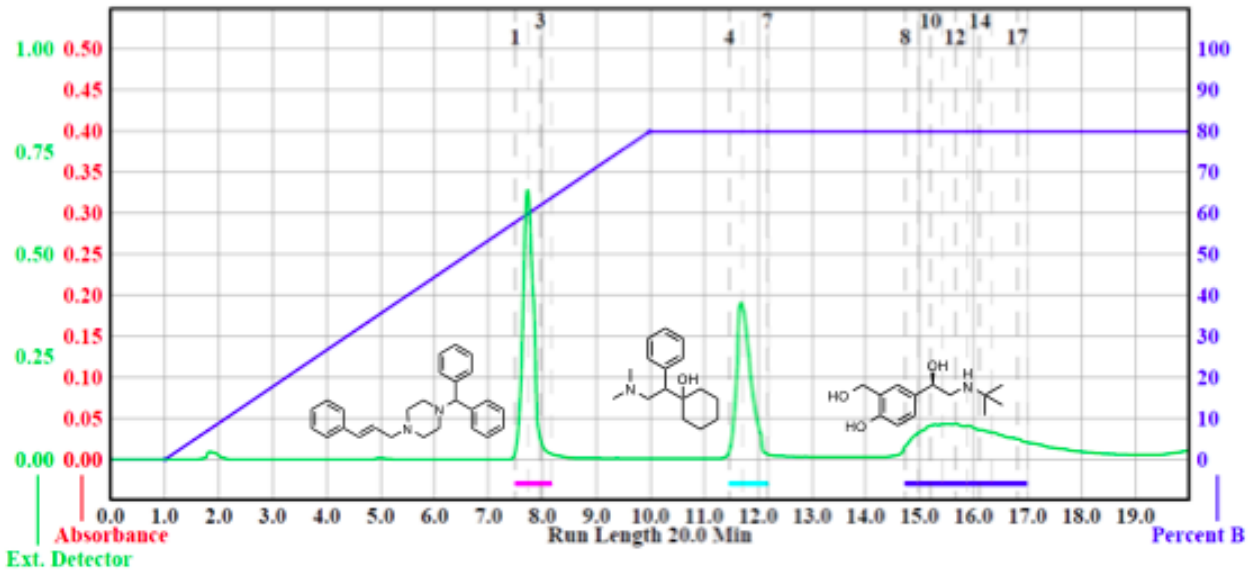


Figure S7a. Separation of three basic molecules (B5, B7, B10) employing a gradient of 0-20% MeOH / DCM spiked with triethylamine as the solvent system.

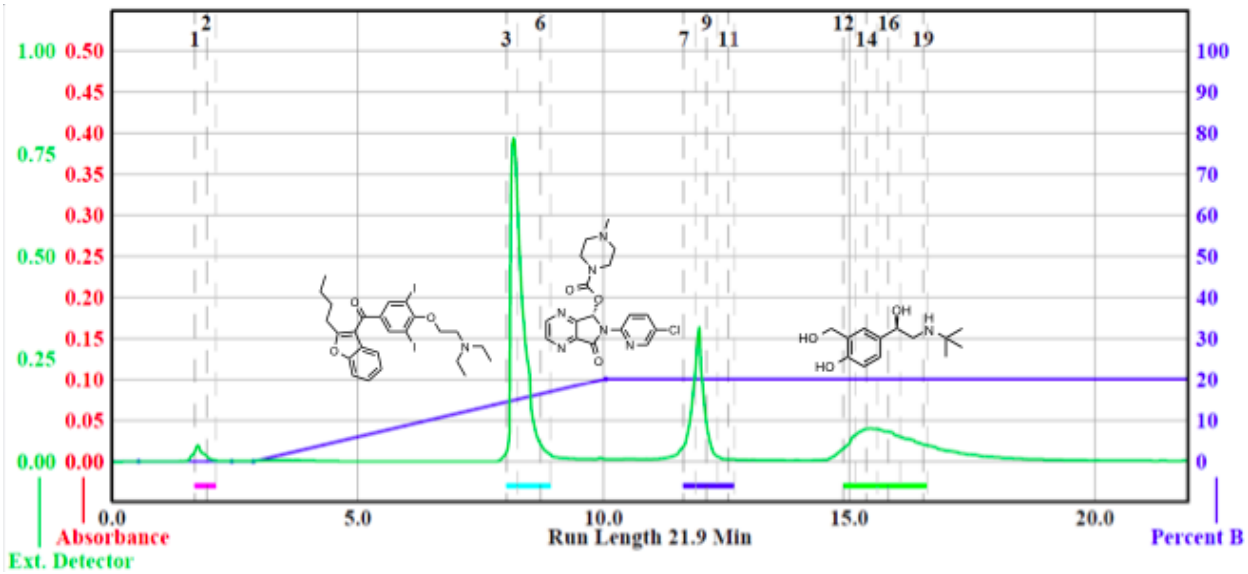
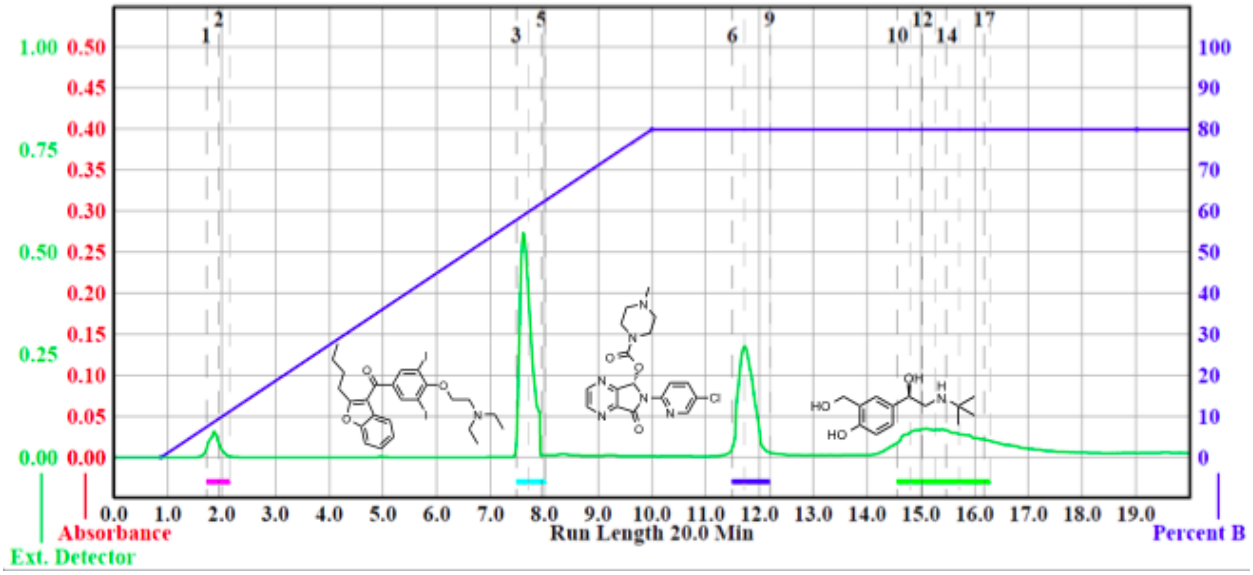


Figure S7b. Separation of the same three basic molecules (B5, B7, B10) employing a gradient of 0-80% 3:1 *i*-PrOAc : MeOH / heptane spiked with triethylamine as the solvent system.



3.5 Relative cost comparison between two solvent systems

In order to compare relative costs between the two solvent systems, we calculated volumes (areas above and below the curve) of all solvents used for the separation of compounds B6, B7, and B9 (see Figures S8a and S8b). Since flow rate and run times were identical between the runs, total volumes were as well and these items cancel when the two systems are compared (Table S6). Next, we determined the relative cost of the solvent inputs and the disposal costs of halogenated vs. non-halogenated solvent waste. Based on our internal pricing data, we learned that the cost of using our greener solvents (*i*-PrOAc, MeOH, and heptane) is 46% higher (1.46:1) than the non-green solvents (DCM and MeOH). However, we also learned that waste disposal costs for the halogenated waste are 179% higher (2.79:1). Consequently, the overall relative cost of using the non-green solvent system is 91% higher (1.91:1). In other words, costs can be cut by nearly half with the greener solvent system (3:1 *i*-PrOAc / MeOH and heptane).

Figure S8a. (modified Figure S6a) Area over/under curve for MeOH / DCM separation (B6, B7, B9).

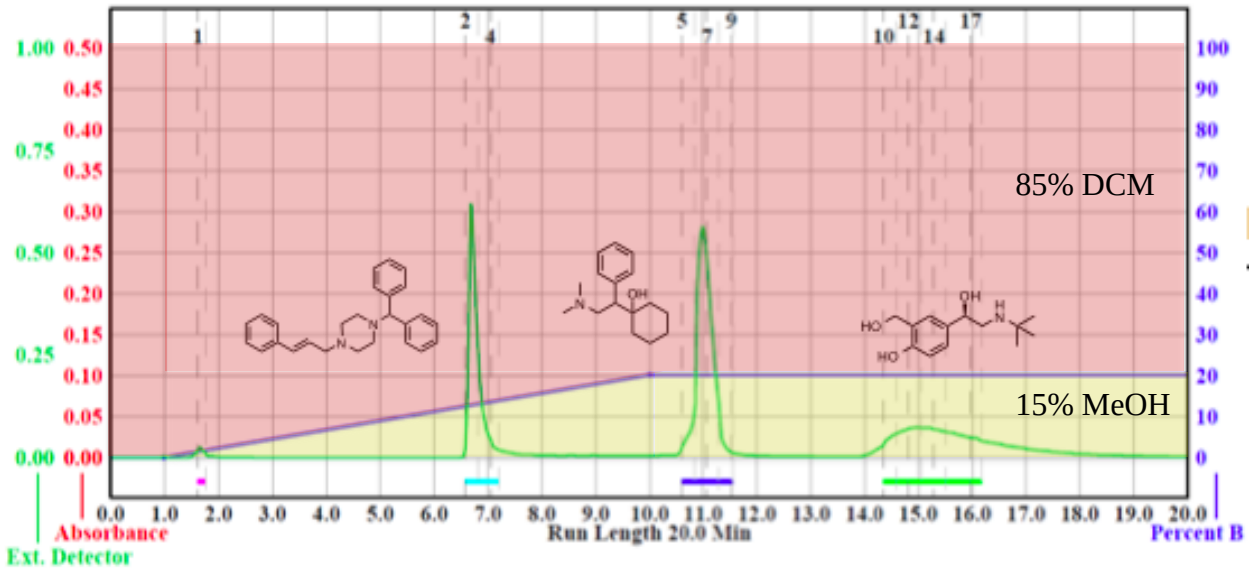


Figure S8b. (modified Figure S6b) Area over/under curve, 3:1 *i*-PrOAc : MeOH / hept separation (B6, B7, B9).

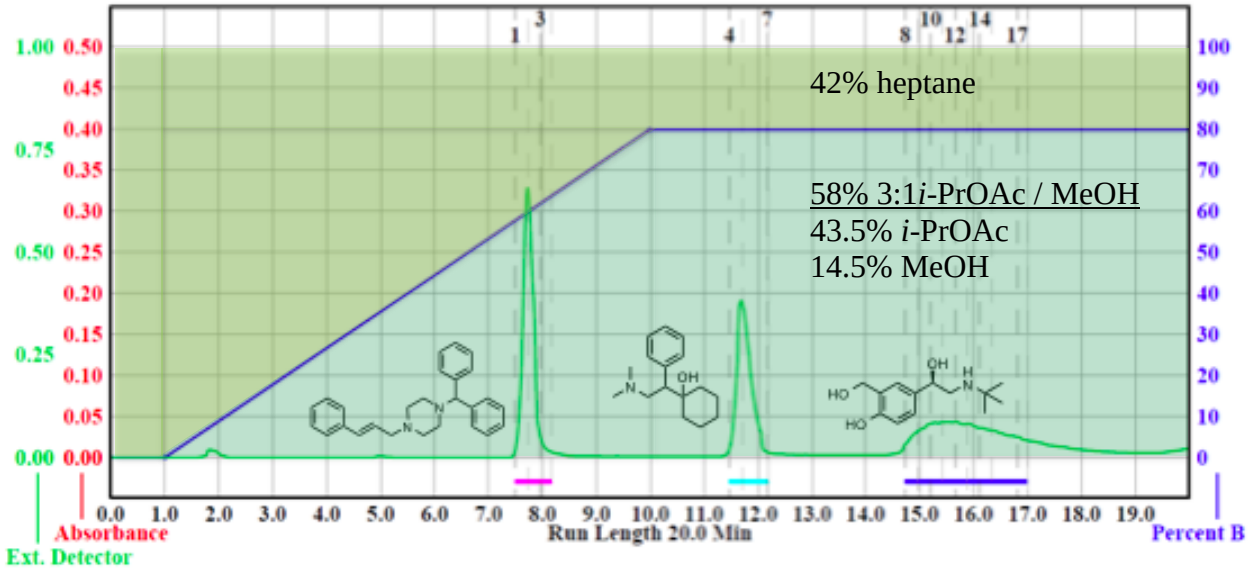


Table S6: Cost comparison: solvent input vs. waste disposal

Figure/ Expt	Composition, mobile phase	Relative run time	Relative volumes	Relative cost solvent input	Relative cost waste disposal	Overall relative cost
S8a	85% DCM 15% MeOH	1	1	1	2.79	1.91
S8b	42% heptane 43.5% *i*-PrOAc 14.5% MeOH	1	1	1.46	1	1

3.6 HSGC Analysis of mobile phase solutions

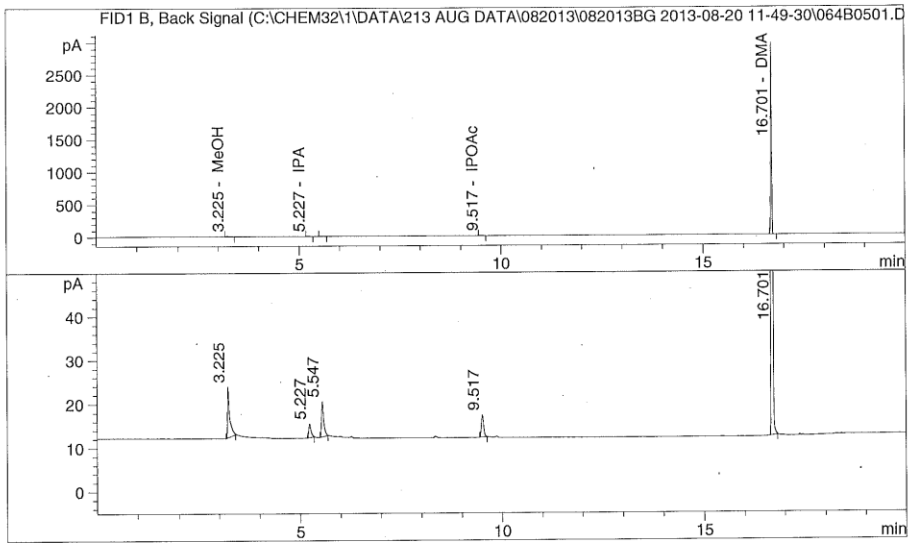
Table S7: Solutions analyzed by HSGC for stability

Vial	Contents	Time Range	Date Prepared	Date Tested
1	3:1 *i*-PrOAc : MeOH	60 d	June 21, 2013	August 20, 2013
2	3:1 *i*-PrOAc : MeOH (with 2% NH_4OH)	60 d	June 21, 2013	August 20, 2013
3	3:1 *i*-PrOAc : MeOH (with 2% CH_3COOH)	60 d	June 21, 2013	August 20, 2013
4	3:1 *i*-PrOAc : MeOH	42 d	July 9, 2013	August 20, 2013
5	3:1 *i*-PrOAc : MeOH	7 d	August 13, 2013	August 20, 2013
6	3:1 *i*-PrOAc : MeOH (with 1% $N(CH_2CH_3)_3$)	7 d	August 13, 2013	August 20, 2013
7	3:1 *i*-PrOAc : MeOH	1 d	August 19, 2013	August 20, 2013
8	3:1 *i*-PrOAc : MeOH (with 1% $N(CH_2CH_3)_3$)	1 d	August 19, 2013	August 20, 2013
9	Standard: methyl acetate (MeOAc)	1 d	August 19, 2013	August 20, 2013
10	Standard: isopropyl alcohol (*i*-PrOH)	1 d	August 19, 2013	August 20, 2013
11	Standard: methanol (MeOH)	1 d	August 19, 2013	August 20, 2013
12	Standard: isopropyl acetate (*i*-PrOAc)	1 d	August 19, 2013	August 20, 2013

Figure S8. HSGC analysis of solvent mixtures

```
Data file  : C:\CHEM32\1\DATA\213 AUG DATA\082013\082013BG 2013-08-20 11->
Sample Name: Stock Soln MeOH, IPA. MeOAC, IsoProOAc                    1
Sample Info: Stock Soln, (0.77107g MeOH 28496KM, 0.77289g IPA SHBC2648V. 0.
             87327g MeOAc 56696MV, 0.85091g IsoProOAc B0518676) QS to 100
             mL with DMA Sigma LN: BCBG6468V, made 081913
 ============================================================================
Acq Operator     : RGJr                          Location   :     Vial 64
Seq Line   :           5  Injection Date  : Tue, 20. Aug. 2013
Inj. No.   :           1
Acq. Method      : C:\Chem32\1\DATA\082013\082013BG 2013-08-20 11-49-30\
                   Q12690V2.M
Analysis Method :  C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

 Q12690v2
 Method for Determination of Residual Solvents in API by Headspace GC
 J&W DB-624 30m, 0.32mm, 1.8um
```



Signal 1: FID1 B, Back Signal

Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.225	12	44.11	0.8	0.054	BB	10.3636	MeOH
2	5.227	3	12.60	0.2	0.059	BB	8.3357	IPA
3	5.547	8	30.76	0.6	0.057	BB	9.1639	MeOAc
4	9.517	5	19.46	0.4	0.061	BB	8.5613	IPOAc
5	16.701	2942	5355.52	98.0	0.028	BB	0.0000	DMA

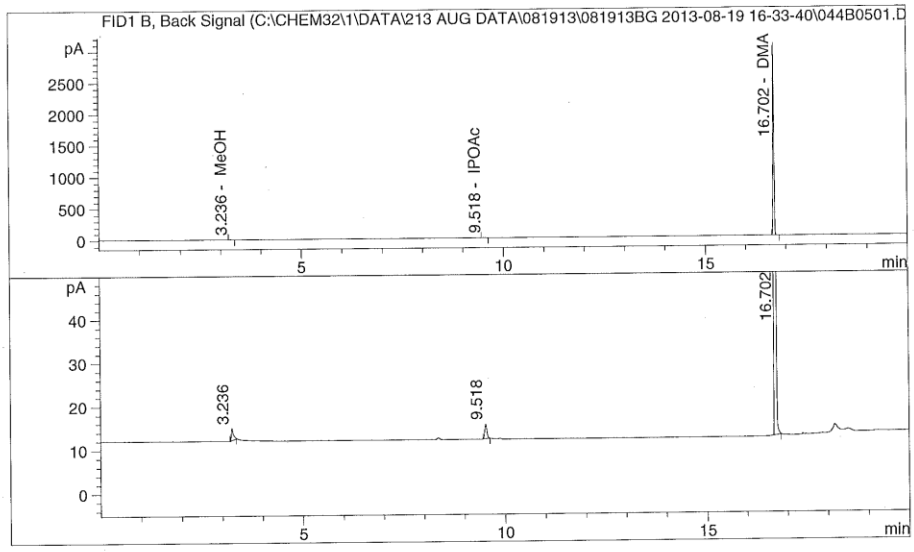
```
*** End of Report ***

143-X-9893 GMP GC        Report Style: Koenig Area%          Page   1 of 1
```

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Sample #1, 1:100 dil 1
Sample Info: Sample #1 (3:1 iProOAc:MeOH neutral 062113) 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 44
Seq Line : 5 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.236	3	9.57	0.2	0.052	BB	2.2495	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.518	3	13.32	0.2	0.062	BB	5.8591	IPOAc
5	16.702	3048	5520.55	99.6	0.029	BB	0.0000	DMA

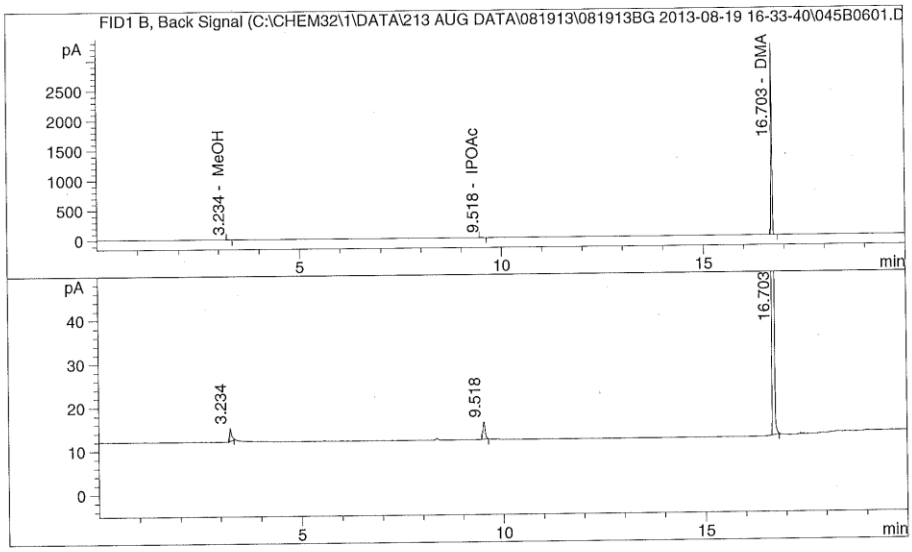
*** End of Report ***

143-X-9893 GMP GC Report Style: Koenig Area% Page 1 of 1

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Sample #2, 1:100 dil 1
Sample Info: Sample #2 (3:1 iProOAc:MeOH basic w 2% NH4OH, 062113) 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 45
Seq Line : 6 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

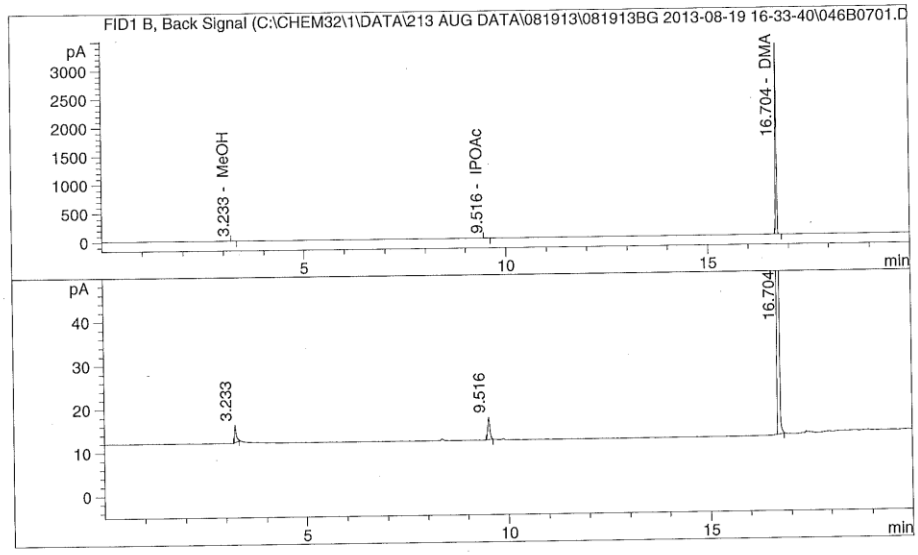
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.234	3	9.89	0.2	0.048	BB	2.3236	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.518	4	15.44	0.3	0.061	BB	6.7926	IPOAc
5	16.703	3186	5885.02	99.6	0.030	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Sample #3, 1:100 dil 1
Sample Info: Sample #3 (3:1 iProOAc:MeOH acidic w/ 2% CH3COOH, 062113) 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 46
Seq Line : 7 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.233	4	12.21	0.2	0.046	BB	2.8694	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.516	5	19.37	0.3	0.058	BB	8.5224	IPOAc
5	16.704	3334	6245.16	99.5	0.030	BB	0.0000	DMA

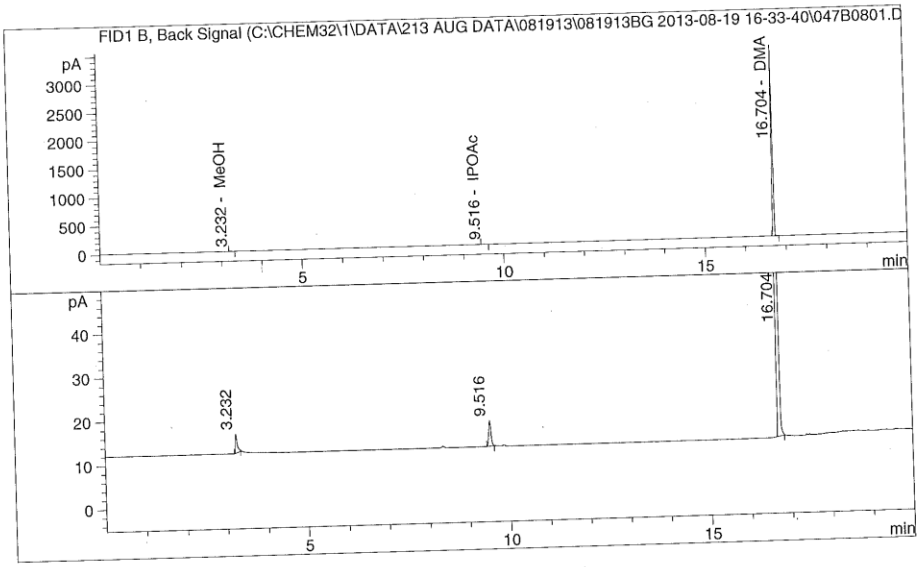
*** End of Report ***

143-X-9893 GMP GC Report Style: Koenig Area% Page 1 of 1

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16-> 1
Sample Name: Sample #4, 1:100 dil
Sample Info: Sample #4 (3:1 iProOAc:MeOH neutral 070913) 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 47
Seq Line : 8 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.232	4	13.31	0.2	0.045	BB	3.1277	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.516	6	21.58	0.3	0.059	BB	9.4940	IPOAc
5	16.704	3361	6320.79	99.5	0.030	BB	0.0000	DMA

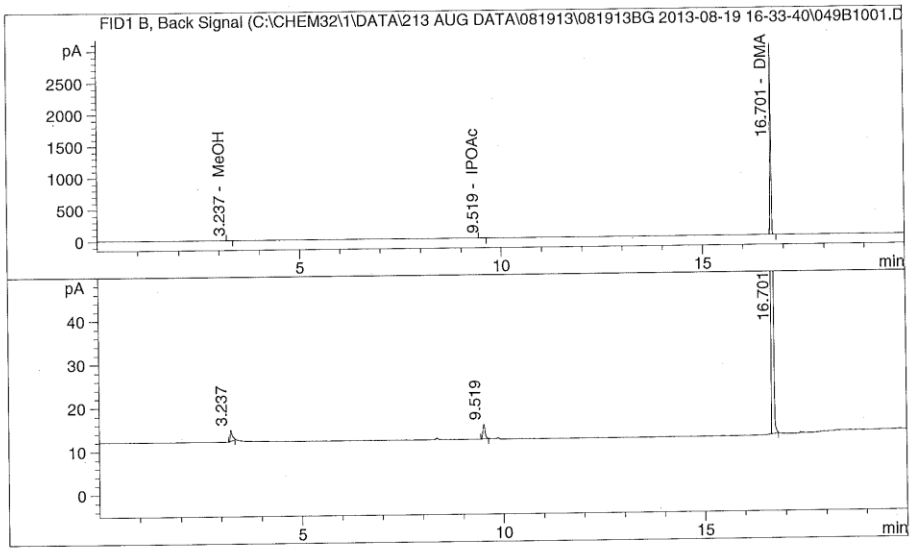
*** End of Report ***

143-X-9893 GMP GC Report Style: Koenig Area% Page 1 of 1

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Sample #5, 1:100 dil 1
Sample Info: Sample #5 (3:1 iProOAc:MeOH neutral 081313) 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 49
Seq Line : 10 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

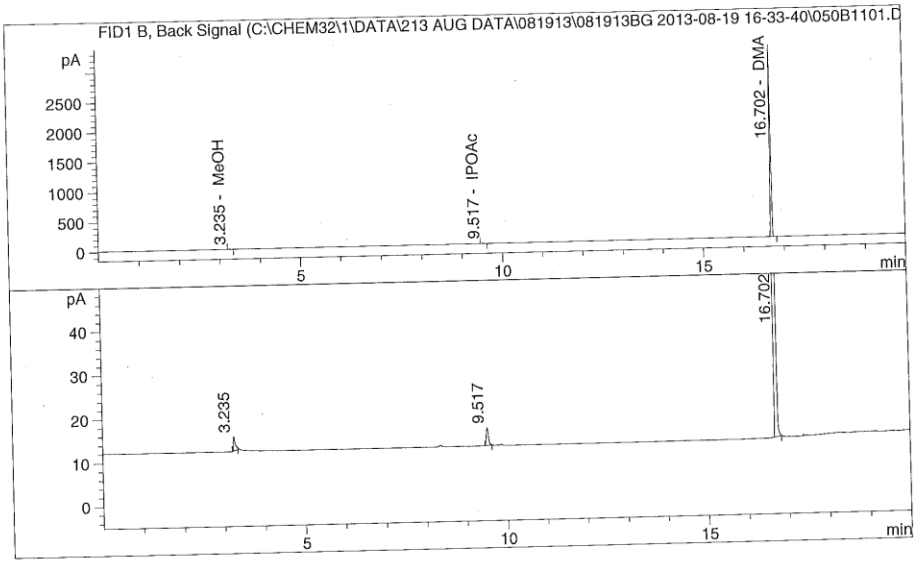
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.237	3	9.39	0.2	0.052	BB	2.2069	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.519	3	13.25	0.2	0.062	BB	5.8306	IPOAc
5	16.701	3002	5458.42	99.6	0.028	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16-> 1
Sample Name: Sample #6, 1:100 dil
Sample Info: Sample #6 (3:1 iProOAc:MeOH basic w 1% TEA, 081313) 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 50
Seq Line : 11 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

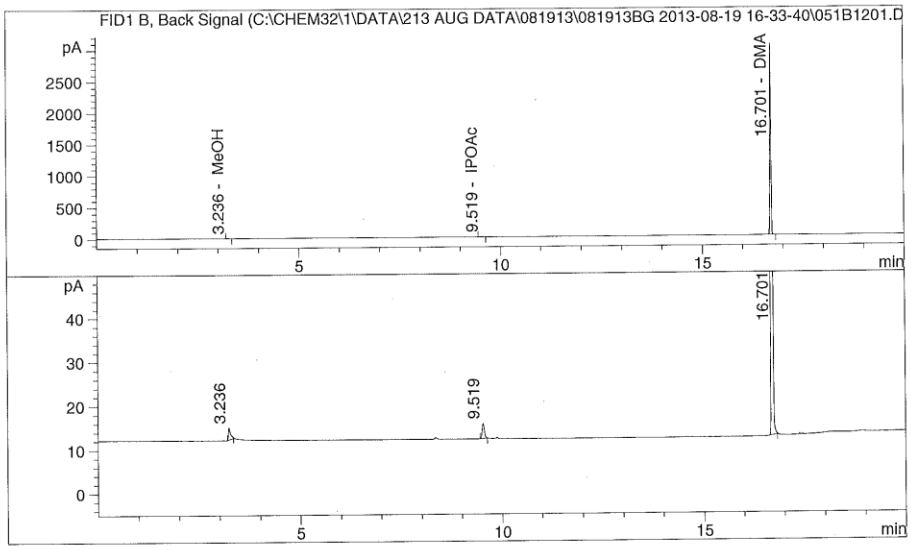
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.235	3	10.89	0.2	0.048	BB	2.5586	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.517	4	15.70	0.3	0.060	BB	6.9047	IPOAc
5	16.702	3215	5868.44	99.5	0.028	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Sample #7, 1:100 dil 1
Sample Info: Sample #7 (3:1 iProOAc:MeOH neutral 081913) 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 51
Seq Line : 12 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

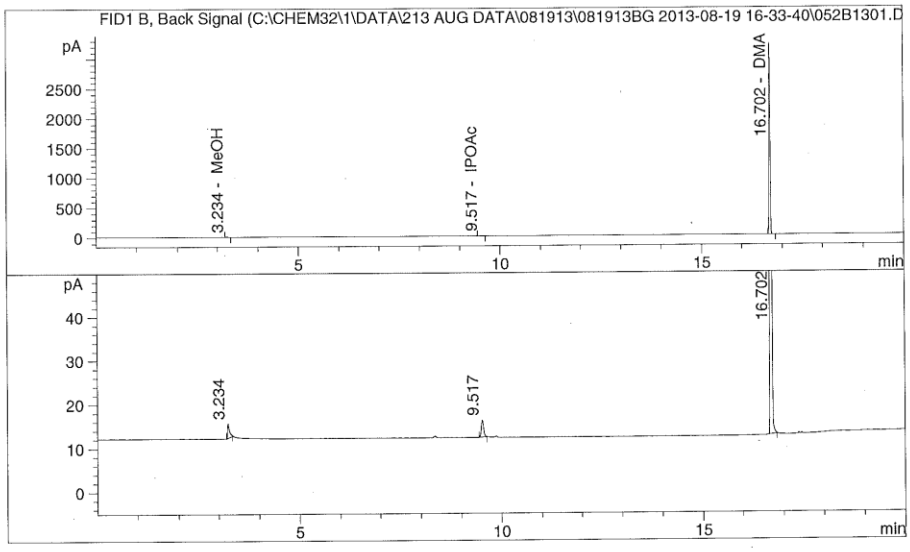
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.236	3	9.84	0.2	0.052	BB	2.3120	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.519	3	13.66	0.2	0.062	BB	6.0092	IPOAc
5	16.701	3025	5541.67	99.6	0.029	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Sample #8, 1:100 dil 1
Sample Info: Sample #8 (3:1 iProOAc:MeOH basic w/1% TEA 081913) 10 uL in
990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 52
Seq Line : 13 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\
Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

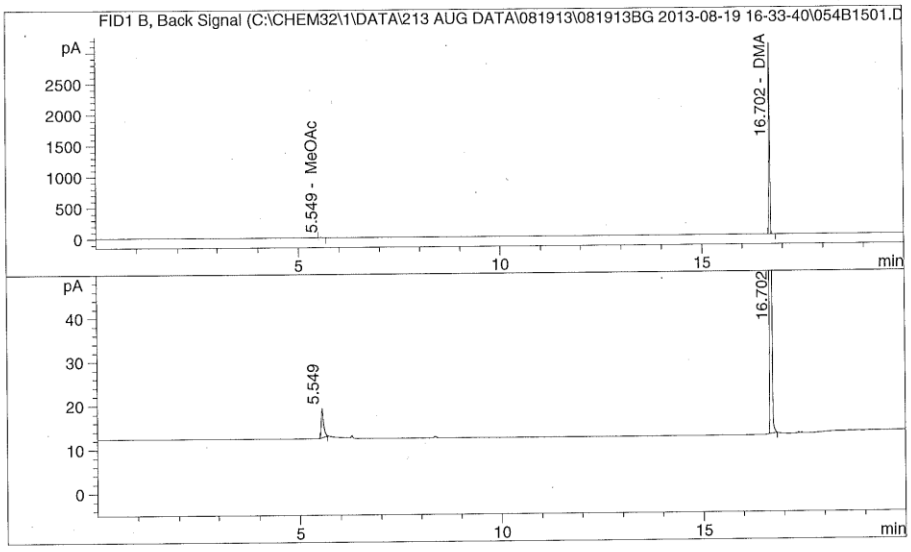
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.234	3	10.69	0.2	0.047	BB	2.5118	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.517	4	14.85	0.3	0.060	BB	6.5306	IPOAc
5	16.702	3211	5841.64	99.6	0.028	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Methyl Acetate, 1:100 dil 1
Sample Info: Methyl Acetate, 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 54
Seq Line : 15 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

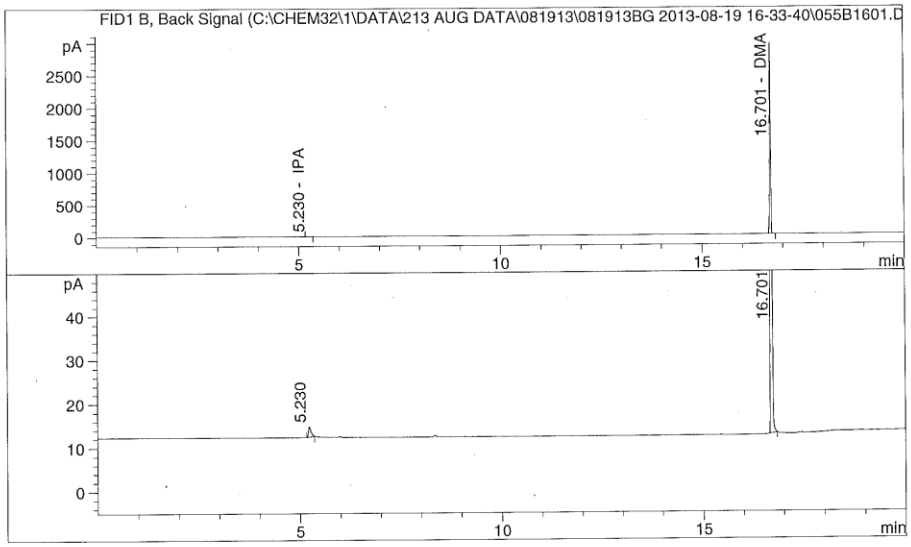
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	0.000	0	0.00	0.0	0.000		0.0000	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	5.549	7	27.35	0.5	0.061	BB	8.1473	MeOAc
4	0.000	0	0.00	0.0	0.000		0.0000	IPOAc
5	16.702	3082	5549.06	99.5	0.028	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Isopropyl alcohol, 1:100 dil 1
Sample Info: Isopropyl alcohol, 10 uL in 990 uL of DMA Sigma LN:
BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 55
Seq Line : 16 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\
Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

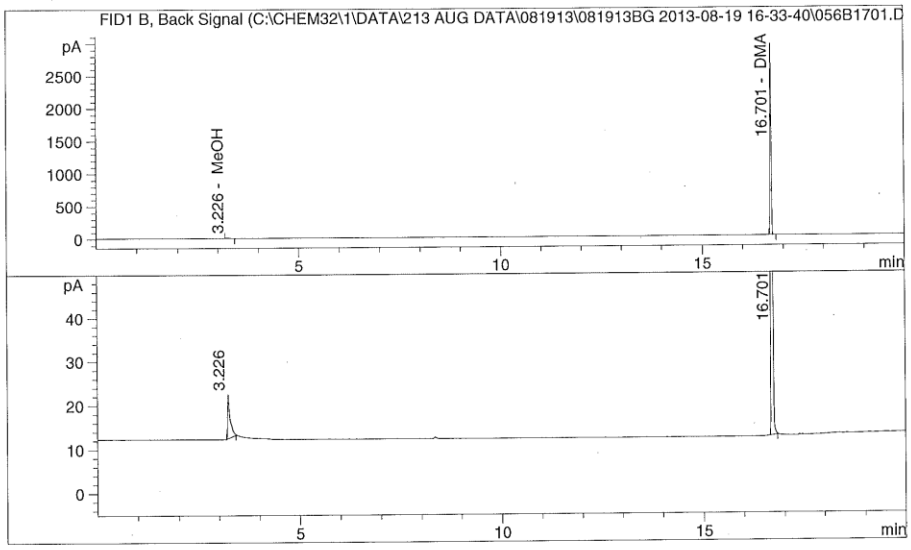
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	0.000	0	0.00	0.0	0.000		0.0000	MeOH
2	5.230	2	10.57	0.2	0.064	BB	6.9924	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	0.000	0	0.00	0.0	0.000		0.0000	IPOAc
5	16.701	2940	5292.78	99.8	0.028	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16-> 1
Sample Name: Methanol, 1:100 dil
Sample Info: Methanol, 10 uL in 990 uL of DMA Sigma LN: BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 56
Seq Line : 17 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

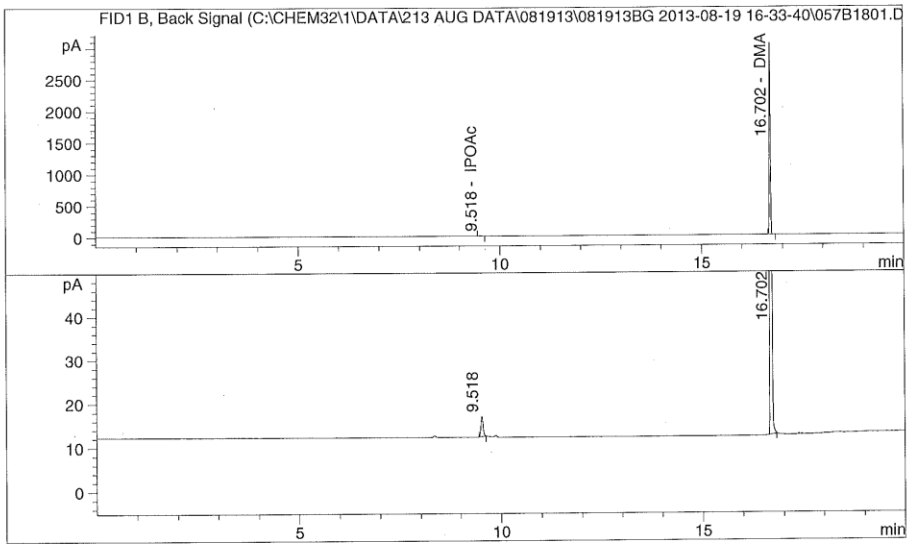
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	3.226	10	43.65	0.8	0.061	BB	10.2565	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	0.000	0	0.00	0.0	0.000		0.0000	IPOAc
5	16.701	2928	5319.68	99.2	0.028	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: Isopropyl Acetate, 1:100 dil 1
Sample Info: Isopropyl Acetate, 10 uL in 990 uL of DMA Sigma LN:
BCBG6468Vmade 081913

Acq Operator : RGJr Location : Vial 57
Seq Line : 18 Injection Date : Tue, 20. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\
Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

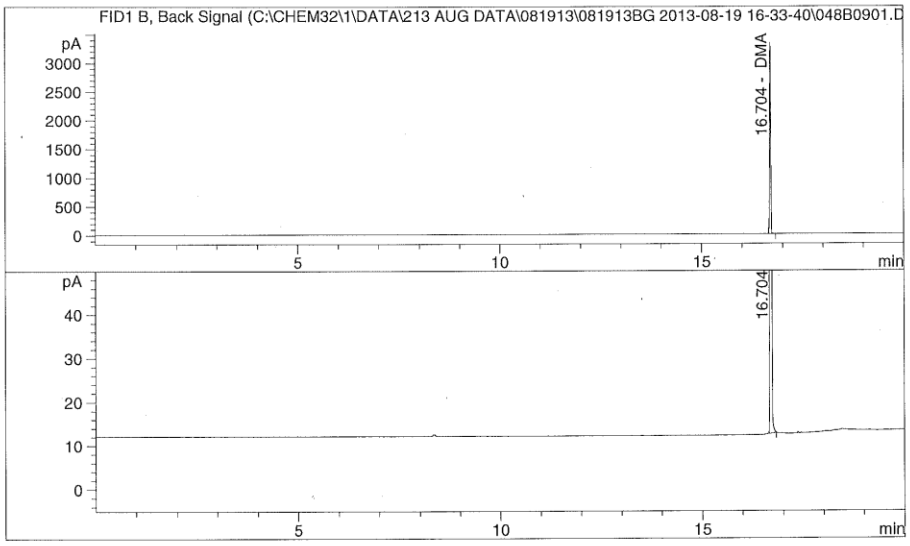
Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	0.000	0	0.00	0.0	0.000		0.0000	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	9.518	5	18.38	0.3	0.061	BB	8.0862	IPOAc
5	16.702	3042	5591.58	99.7	0.029	BB	0.0000	DMA

*** End of Report ***

Data file : C:\CHEM32\1\DATA\213 AUG DATA\081913\081913BG 2013-08-19 16->
Sample Name: DMA Blank #4 1
Sample Info: DMA Sigma LN: BCBG6468V

Acq Operator : RGJr Location : Vial 48
Seq Line : 9 Injection Date : Mon, 19. Aug. 2013
Inj. No. : 1
Acq. Method : C:\Chem32\1\DATA\081913\081913BG 2013-08-19 16-33-40\
Q12690V2.M
Analysis Method : C:\CHEM32\1\METHODS\GMP_METHODS\Q12690V2.M

Q12690v2
Method for Determination of Residual Solvents in API by Headspace GC
J&W DB-624 30m, 0.32mm, 1.8um



Signal 1: FID1 B, Back Signal

Peak #	RT [min]	Height	Area	Area %	Width [min]	Type	Amount w/w%	Name
1	0.000	0	0.00	0.0	0.000		0.0000	MeOH
2	0.000	0	0.00	0.0	0.000		0.0000	IPA
3	0.000	0	0.00	0.0	0.000		0.0000	MeOAc
4	0.000	0	0.00	0.0	0.000		0.0000	IPOAc
5	16.704	3316	6144.32	100.0	0.029	BB	0.0000	DMA

*** End of Report ***