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Finding synthetically versatile and common intermediates for multiple useful products with the aid of a synthesis design system

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Abstract—With the aid of a synthesis design system, we searched for common intermediates in routes to sets of target molecules. Finding such common intermediates will be a great help in constructing cost-effective synthetic routes. We tried to look for new common intermediates with 24 investigational or commercially produced antidepressants as target molecules. Most of the common intermediates were usually found to lead to more than two targets.

1. Introduction

Recently, the outsourcing market of pharmaceutical intermediates has been growing rapidly around the world.[1] For pharmaceutical companies, this has the merit of spreading one part of the risk in developing new drugs over to manufacturers of intermediates, which bear the cost of the development of efficient synthetic routes.

Process chemistry has a mission to improve costly routes by optimizing starting materials, reaction conditions, and safety and disposal measures. The choice of starting materials and/or intermediates is one of the most important factors in achieving lower cost routes.

It is especially useful to find common key intermediates because the optimization of their production automatically improves the routes to the various final products for which they are intermediates. In addition trial substances, which are related to the active compounds and may possibly share or exceed their activities, are correspondingly cheaper to make. Deriving diverse compounds from common intermediate thus facilitates both the improvement of routes and the discovery of new drugs and new useful substances in material science.

In the synthetic study of a class of highly complicated natural occurring compounds, it is quite helpful to find common key intermediates, which may be synthesized on a large scale and are relatively close to the targets. For instance, Nicolaou reported that a few intermediate elegantly lead to several endiandric acid derivatives, which were isolated from Australian plant containing several unusual chiral centers and polycyclic structures (Scheme 1).[2]

In finding new common key intermediates, retro-synthetic analyses of targets must be extensively performed. As structures become more complicated and the number of final products of interest increases, the amount of operations increases to the point where manual procedures become impractical. To realize the data extraction, we decided to utilize a synthesis design program, SYNSUP.[3]

The first program for computer-aided organic synthesis (CAOS) has been demonstrated by Corey and Wipke in 1969 with OCSS,[4] whose successor is LHASA.[5] In 1972, Bersohn has published the independent synthesis design program, which evolved into SYNSUP.[6] Besides LHASA and SYNSUP, a number of systems have been reported so far[7] and some of them, such as SYNCHEM,[8] SYNGEN,[9]

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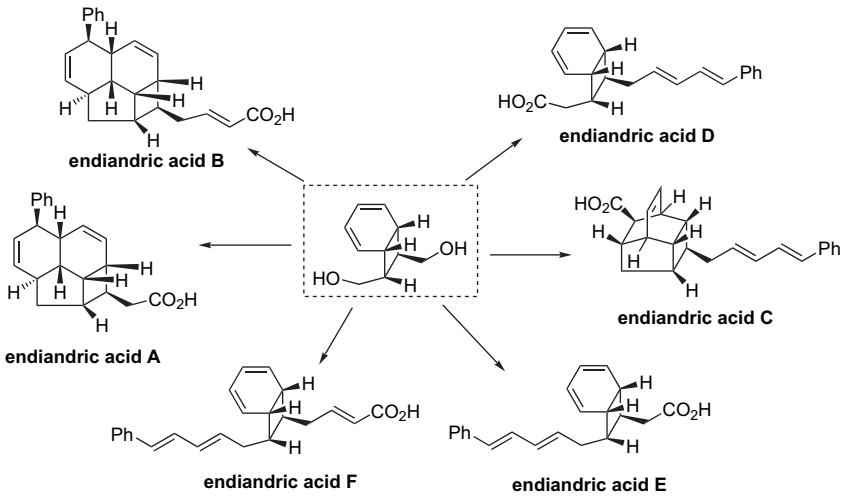


Scheme 1. A reported common intermediate that leads to natural occurring compounds, a series of endiandric acids.

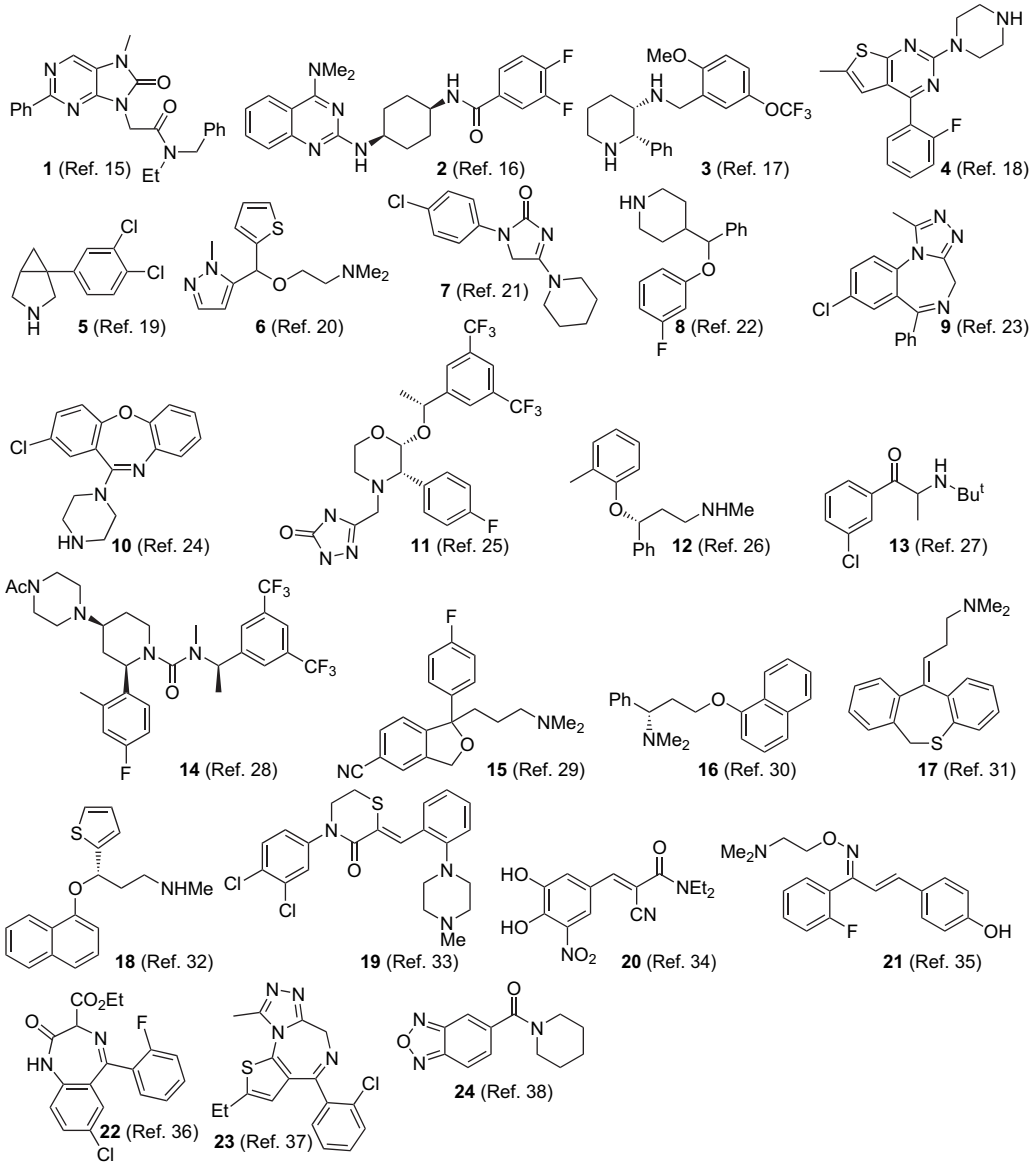


Figure 1. Targets.

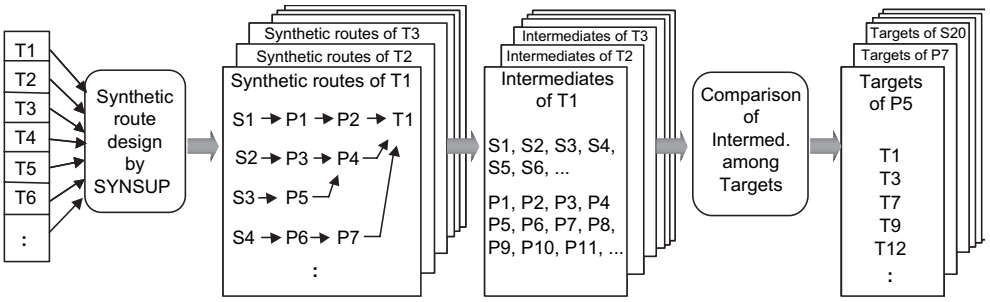


Figure 2. Flow to get common intermediates. T1, T2 and T*n* mean targets, S1, S2, and S*n* are starting materials, and P1, P2, and P*n* are intermediates (precursors).

AIPHOS,[10] WODCA,[11] and WTDWTR,[12] are still being developed. The program SYNSUP generates plausible routes in retro-synthetic fashion after a chemist launches the program with a specific organic molecule. The Sumitomo Chemical Company has taken part in the development of this program since 1984 and now Sumitomo and its group companies use the system. The targets are pharmaceutical and agricultural compounds including their intermediates, electric materials, additive agents, and transition metal ligands at the stage of screening and study of industrial processes.[13] The system has now more than 5500 organic reactions, which number is steadily increasing.

In this field, many concepts and methodologies have been reported, but only a few papers about the examples of utility and application have been reported.[13,14] As one of the advanced examples of utility, we studied searching for common key intermediates from synthetic routes to multiple targets for different groups or purposes.

In this paper, we wish to report the results of extracting common intermediates from 24 targets, which are investigational or commercially produced antidepressants (Fig. 1).[15–38]

2. Computational details

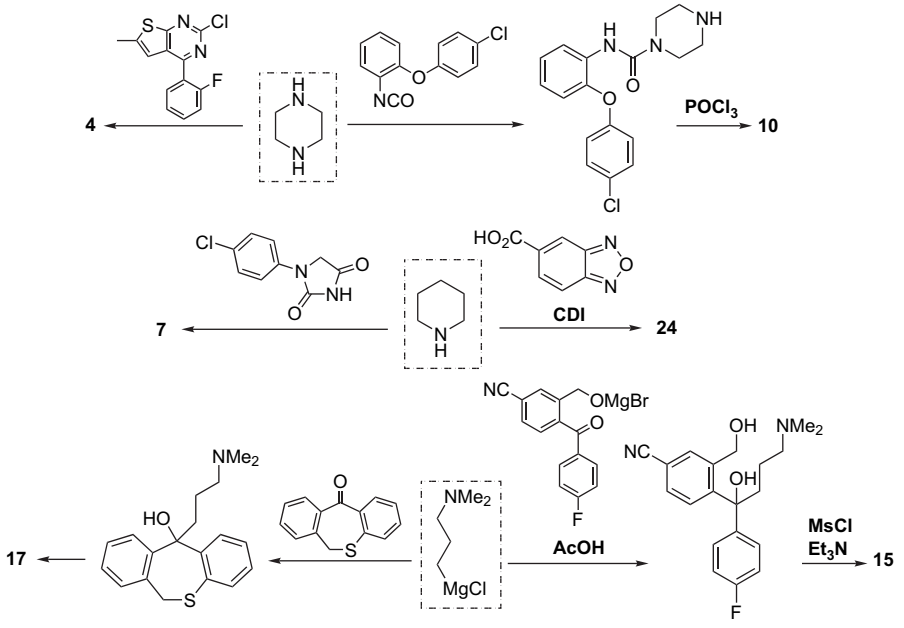
To obtain intermediates of all targets, SYNSUP has been implemented with the following conditions on a route:

(a) The starting materials must be commercially available.
(b) The number of applying functional group interconversion (FGI) reactions must be less than four steps, because FGIs do not contribute to the frame construction.
(c) There must be not more than four reaction steps in the route.

When only less than 10 routes were proposed, the limit on the number of steps is raised to five and the program is rerun.

(d) When more than 1000 routes were proposed, the limit on the number of steps is reduced to three for the rerun of the program.

In fact, the three-step limit on the number of steps was applied to the targets **12**, **17**, **20**, and **21**, and two-step limit was used for the targets **1**, **14**, and **23**.



Scheme 2. Common intermediates extracted from reported synthetic routes of 24 targets.

Table 1. The list of extracted common intermediates

No.	Name	M.F.	M.W.	N[a]	Targets	No.	Name	M.F.	M.W.	N[a]	Targets
25	Carbon monooxide	CO	28.01	12	**1**,**7**,**10**,**13**,**15**,**16**,**17**,**18**,**20**,**22**,**23**,**24**	**75**	Methylamine	CH_5N	31.06	4	**12**,**16**,**17**,**18**
26	Methanol	CH_4O	32.04	12	**2**,**3**,**6**,**7**,**9**,**10**,**13**,**16**,**18**,**20**,**22**,**24**	**76**	*p*-Toluenesulfonyl chloride	$C_7H_7ClO_2S$	190.65	4	**12**,**13**,**15**,**16**
27	Bromoethane	CH_3Br	94.94	11	**2**,**3**,**6**,**11**,**12**,**13**,**15**,**16**,**17**,**18**,**24**	**77**	Allyl *p*-toluenesulfonate	$C_{10}H_{12}O_3S$	212.27	4	**13**,**15**,**16**,**17**
28	Formaldehyde	CH_2O	30.03	11	**2**,**3**,**5**,**6**,**9**,**12**,**13**,**15**,**16**,**17**,**18**	**78**	Vinyl chloride	C_2H_3Cl	62.50	4	**13**,**18**,**19**,**21**
29	Cyanic acid	CHN	27.03	10	**2**,**6**,**8**,**12**,**13**,**15**,**16**,**18**,**20**,**22**	**79**	Glyoxylic acid	$C_2H_2O_3$	74.04	4	**13**,**16**,**22**,**24**
30	Chloromethane	CH_3Cl	50.49	9	**2**,**3**,**6**,**13**,**14**,**15**,**16**,**17**,**19**	**80**	Allyl bromide	C_3H_5Br	120.98	4	**15**,**16**,**17**,**18**
31	Acetaldehyde	C_2H_4O	44.05	9	**5**,**11**,**12**,**13**,**15**,**16**,**17**,**18**,**21**	**81**	1,3-Dibromopropane	$C_3H_6Br_2$	201.89	4	**15**,**16**,**17**,**18**
32	Methyl *p*-toluenesulfonate	$C_8H_{10}O_3S$	186.23	8	**6**,**12**,**15**,**16**,**17**,**18**,**19**,**24**	**82**	3-Bromopropionitrile	C_3H_4BrN	133.98	4	**15**,**16**,**17**,**18**
33	Methyl formate	$C_2H_4O_2$	60.05	7	**3**,**5**,**6**,**16**,**17**,**18**,**22**	**83**	Cyanoacetic acid	$C_3H_3NO_2$	85.06	4	**16**,**17**,**18**,**20**
34	2-Chloroethyl *p*-toluenesulfonate	$C_9H_{11}ClO_3S$	234.70	7	**4**,**6**,**10**,**12**,**14**,**16**,**18**	**84**	Methyl cyanoformate	$C_3H_3NO_2$	85.06	3	**1**,**13**,**22**
35	Chloroformaldehyde	C_2H_3ClO	78.50	7	**5**,**6**,**12**,**16**,**17**,**18**,**21**	**85**	Glycine methyl ester	$C_3H_7NO_2$	89.09	3	**1**,**13**,**22**
36	Chlorotrimethylsilane	C_3H_9ClSi	108.64	7	**8**,**10**,**13**,**15**,**16**,**18**,**24**	**86**	Bromoacetyl chloride	C_2H_2BrClO	157.39	3	**1**,**14**,**21**
37	Bromoacetonitrile	C_2H_2BrN	119.95	6	**1**,**5**,**6**,**16**,**17**,**18**	**87**	Glycolamide	$C_2H_5NO_2$	75.07	3	**1**,**16**,**23**
38	Methyl iodide	CH_3I	141.94	6	**2**,**3**,**4**,**6**,**7**,**12**	**88**	Chloroacetyl chloride	$C_2H_2Cl_2O$	112.94	3	**1**,**9**,**21**
39	Dimethylamine	C_2H_7N	45.08	6	**2**,**6**,**15**,**16**,**17**,**21**	**89**	4-Nitrophenyl iodoacetate	$C_8H_6INO_4$	307.05	3	**1**,**18**,**22**
40	*N*,*N*-Dimethylformamide	C_3H_7NO	73.10	6	**3**,**6**,**9**,**12**,**18**,**24**	**90**	Iodobenzene	C_6H_5I	204.01	3	**1**,**12**,**16**
41	Bis(tributyltin) oxide	$C_{24}H_{54}OSn_2$	596.08	6	**4**,**5**,**11**,**13**,**17**,**19**	**91**	Chlorobenzene	C_6H_5Cl	112.56	3	**1**,**13**,**16**
42	Tributyltin Chloride	$C_{12}H_{27}ClSn$	325.49	6	**4**,**5**,**11**,**13**,**17**,**19**	**92**	2-Aminobenzonitrile	$C_7H_6N_2$	118.14	3	**2**,**22**,**23**
43	Vinyl bromide	C_2H_3Br	106.95	6	**13**,**15**,**16**,**18**,**19**,**21**	**93**[b]	*N*-Fluorobenzene-sulfonimide	$C_{12}H_{11}FNO_4S_2$	316.35	3	**2**,**15**,**21**
44	Acrolein	C_3H_4O	56.06	6	**13**,**15**,**16**,**17**,**18**,**21**	**94**	2-Bromoanisole	C_7H_7BrO	187.04	3	**2**,**10**,**13**
45	Glycine	$C_2H_5NO_2$	75.07	5	**1**,**5**,**9**,**11**,**23**	**95**	2-Chloroanisole	C_7H_7ClO	142.59	3	**2**,**10**,**13**
46	Ethanol	C_2H_6O	46.07	5	**1**,**5**,**10**,**16**,**22**	**96**	2-Methoxyphenyl-boronic acid	$C_7H_9BO_3$	151.96	3	**2**,**10**,**13**
47	*p*-Nitrophenol	$C_6H_5NO_3$	139.11	5	**2**,**9**,**22**,**23**,**24**	**97**	3,4-Dichlorobenzaldehyde	$C_7H_4Cl_2O$	175.02	3	**2**,**5**,**24**
48	Dimethyl sulfate	$C_2H_6O_4S$	126.13	5	**2**,**3**,**6**,**15**,**16**	**98**	3,4-Dichlorobenzoic acid	$C_8H_6Cl_2O_2$	205.04	3	**2**,**15**,**24**
49	Nitromethane	CH_3NO_2	61.04	5	**3**,**5**,**12**,**16**,**18**	**99**	Benzene	C_6H_6	78.11	3	**3**,**9**,**16**
50	3-Chloropropyl-*p*-toluenesulfonate	$C_{10}H_{13}ClO_3S$	248.73	5	**3**,**15**,**16**,**17**,**18**	**100**	3-Chloropropylamine	C_3H_8ClN	93.56	3	**3**,**15**,**16**
51	1-Bromo-4-chlorobenzene	C_6H_4BrCl	191.46	5	**5**,**7**,**10**,**15**,**22**	**101**	3-Bromopropylamine	C_3H_8BrN	138.01	3	**3**,**16**,**17**
52	Acetonitrile	C_2H_3N	41.05	5	**5**,**12**,**13**,**17**,**18**	**102**	2-Chlorophenylboronic acid	$C_6H_6BClO_2$	156.38	3	**5**,**10**,**19**
53	Succinic semialdehyde	$C_4H_6O_3$	102.09	5	**5**,**15**,**16**,**17**,**18**	**103**[b]	3-Aminopropanal	C_3H_7NO	73.10	3	**5**,**17**,**18**
54	Chloromethyl methyl ether	C_2H_5ClO	80.51	5	**5**,**8**,**16**,**17**,**18**	**104**	2-Aminopropionitrile	$C_3H_6N_2$	70.09	3	**5**,**17**,**18**
55	1,2-Diiodoethane	$C_2H_4I_2$	281.86	5	**6**,**15**,**16**,**17**,**18**	**105**	β-Alanine	$C_3H_7NO_2$	89.09	3	**5**,**17**,**18**
56	Bromoacetic acid	$C_2H_3BrO_2$	138.95	4	**1**,**14**,**16**,**17**	**106**	β-Alanine methyl ester	$C_4H_9NO_2$	103.12	3	**5**,**17**,**18**
57	Methyl bromoacetate	$C_3H_5BrO_2$	152.98	4	**1**,**13**,**16**,**17**	**107**[b]	Malondialdehyde	$C_3H_4O_2$	72.06	3	**5**,**17**,**18**
58	Phosgene	CCl_2O	98.92	4	**1**,**10**,**13**,**22**	**108**	Malononitrile	$C_3H_2N_2$	66.06	3	**5**,**17**,**18**
59	Carbon dioxide	CO_2	44.01	4	**3**,**21**,**22**,**23**	**109**	Methyl acrylate	$C_4H_6O_2$	86.09	3	**5**,**16**,**18**
60	1-Bromo-2-fluorobenzene	C_6H_4BrF	175.00	4	**4**,**10**,**21**,**22**	**110**[b]	2-Iodoethylene-*p*-toluenesulfonate	$C_9H_{11}IO_3S$	326.15	3	**6**,**16**,**18**
61	Glyoxal	$C_2H_2O_2$	58.04	4	**5**,**12**,**17**,**18**	**111**	Ethylene di(*p*-toluenesulfonate)	$C_{16}H_{18}O_6S_2$	370.45	3	**6**,**16**,**18**
62	Methyl acetate	$C_3H_6O_2$	74.08	4	**5**,**13**,**16**,**18**	**112**[b]	2-Iodo-*N*-methyl ethanamide	C_3H_8IN	185.01	3	**6**,**12**,**18**
63	1-Formylpiperidine	$C_6H_{11}NO$	113.16	4	**5**,**15**,**17**,**18**	**113**	2-Dimethyl aminoethanol	$C_4H_{11}NO$	89.14	3	**6**,**15**,**17**
64	3-Chloropropanal	C_3H_5ClO	92.53	4	**5**,**16**,**17**,**18**	**114**	1,2-Dichloroethane	$C_2H_4Cl_2$	98.96	3	**6**,**16**,**19**
65	2-Chloro-*N*,*N*-dimethylethylamine	$C_4H_{10}ClN$	107.58	4	**6**,**15**,**17**,**21**	**115**[b]	2-Bromoacetaldehyde	C_2H_3BrO	122.95	3	**6**,**16**,**17**
66	2-Bromoethyl-*p*-toluenesulfonate	$C_9H_{11}BrO_3S$	279.15	4	**6**,**14**,**16**,**18**	**116**	Chloroacetonitrile	C_2H_2ClN	75.50	3	**6**,**7**,**16**
67	1,2-Dibromoethane	$C_2H_4Br_2$	187.86	4	**6**,**16**,**17**,**18**	**117**	4-Chlorophenylboronic acid	$C_6H_6BClO_2$	156.38	3	**7**,**9**,**10**
68	Cyanomethyl *p*-toluenesulfonate	$C_9H_9NO_3S$	211.24	4	**6**,**7**,**16**,**18**	**118**	Iodoacetamide	C_2H_4INO	184.96	3	**7**,**16**,**23**
69	Iodoacetonitrile	C_2H_2IN	166.95	4	**6**,**7**,**16**,**18**	**119**	Diethyl chlorophosphate	$C_4H_{10}ClO_3P$	172.55	3	**7**,**8**,**23**
70	*p*-Chloroaniline	C_6H_6ClN	127.57	4	**7**,**9**,**15**,**22**	**120**	Benzoyl cyanide	C_8H_5NO	131.14	3	**8**,**9**,**13**
71	Benzaldehyde	C_7H_6O	106.13	4	**8**,**9**,**12**,**16**	**121**	2-Bromo-4-chloroaniline	C_6H_5BrClN	206.47	3	**9**,**22**,**24**
72	Bromobenzene	C_6H_5Br	157.01	4	**8**,**12**,**16**,**17**	**122**	4-Aminophenol	C_6H_7NO	109.13	3	**9**,**10**,**21**
73	*N*-Phenyl-bis(trifluoro-methanesulfonimide)	$C_8H_5F_6NO_4S_2$	357.25	4	**8**,**18**,**19**,**24**	**123**	1,2-Dibromobenzene	$C_6H_4Br_2$	235.91	3	**10**,**17**,**19**
74	Trifluoromethane sulfonic anhydride	$C_2F_6O_5S_2$	282.14	4	**10**,**16**,**17**,**23**	**124**	2-Fluorobenzoic acid	$C_7H_5FO_2$	140.12	3	**10**,**21**,**22**

(*continued*)

Table 1. (*continued*)

No.	Name	M.F.	M.W.	N^a	Targets	No.	Name	M.F.	M.W.	N^a	Targets
125	2-Chloroaniline	C_6H_6ClN	127.57	3	**10**,**23**,**24**	**175**	4-Nitrobenzenesulfonic acid	$C_6H_5NO_5S$	203.17	2	**4**,**23**
126	2-Amino-5-chlorobenzoic acid	$C_7H_6ClNO_2$	171.58	3	**10**,**22**,**24**	**176**	Piperazine	$C_4H_{10}N_2$	86.14	2	**4**,**10**
127	2-Chloroethanol	C_2H_5ClO	80.51	3	**11**,**16**,**19**	**177**	Bromopyruvic acid	$C_3H_3BrO_3$	166.96	2	**5**,**24**
128[b]	3-(Methylamino)propanal	C_4H_9NO	87.12	3	**12**,**17**,**18**	**178**	4-Bromo-1,2-dichlorobenzene	$C_6H_3BrCl_2$	225.90	2	**5**,**19**
129	3-Methylaminopropionitrile	$C_4H_8N_2$	84.12	3	**12**,**17**,**18**	**179**	Trimethyltin chloride	C_3H_9ClSn	199.25	2	**5**,**13**
130	α-Vinylbenzyl alcohol	$C_9H_{10}O$	134.18	3	**12**,**13**,**16**	**180**	1-Bromo-3-chlorobenzene	C_6H_4BrCl	191.46	2	**5**,**13**
131	Acetone	C_3H_6O	58.08	3	**13**,**16**,**17**	**181**[b]	*m*-Chlorophenyl-trimethylstannane	$C_9H_{13}ClSn$	275.35	2	**5**,**13**
132	Acetic acid	$C_2H_4O_2$	60.05	3	**13**,**14**,**18**	**182**	Acetyl chloride	C_2H_3ClO	78.50	2	**5**,**14**
133	Allyltrimethylsilane	$C_6H_{14}Si$	114.26	3	**13**,**16**,**17**	**183**	*N*-Acetylglycine	$C_4H_7NO_3$	117.11	2	**5**,**14**
134	Acrylic acid	$C_3H_4O_2$	72.06	3	**13**,**17**,**18**	**184**	*N*-(Cynanomethyl)acetamide	$C_4H_6N_2O$	98.11	2	**5**,**14**
135	*N*,*o*-Dimethyl-hydroxylamine	C_2H_7NO	61.08	3	**13**,**15**,**17**	**185**	1-Chloro-4-iodobenzene	C_6H_4ClI	238.46	2	**5**,**10**
136	Fluorobenzene	C_6H_5F	96.11	3	**15**,**21**,**22**	**186**	3-Iodophenol	C_6H_5IO	220.01	2	**5**,**13**
137	3-Bromopropionyl chloride	C_3H_4BrClO	171.42	3	**15**,**16**,**17**	**187**	1-Chloro-3-iodobenzene	C_6H_4ClI	238.46	2	**5**,**13**
138	3-Bromopropanol	C_3H_7BrO	138.99	3	**16**,**17**,**18**	**188**	2-Chlorophenol	C_6H_5ClO	128.56	2	**5**,**10**
139[b]	3-Bromopropanal	C_3H_5BrO	136.98	3	**16**,**17**,**18**	**189**	4-Amino-2-chlorophenol	C_6H_6ClNO	143.57	2	**5**,**20**
140	4-Bromo-1-butene	C_4H_7Br	135.00	3	**16**,**17**,**18**	**190**	*p*,*p*-Dimethyl-phosphonoacetate	$C_4H_9O_5P$	168.09	2	**5**,**18**
141	3-Bromopropionic acid	$C_3H_5BrO_2$	152.98	3	**16**,**17**,**18**	**191**	Methyl malonate	$C_4H_6O_4$	118.09	2	**5**,**16**
142	Methyl 3-bromopropionate	$C_4H_7BrO_2$	167.00	3	**16**,**17**,**18**	**192**	3-Amino-4-chlorobenzoic acid	$C_7H_6ClNO_2$	171.58	2	**5**,**24**
143	3-Hydroxypropionitrile	C_3H_5NO	71.08	3	**16**,**17**,**18**	**193**	4-Bromo-2-chloroaniline	C_6H_5BrClN	206.47	2	**5**,**24**
144[b]	3-(4-Methylphenyl-sulfonyloxy)-propanal	$C_{10}H_{12}O_4S$	228.27	3	**16**,**17**,**18**	**194**	Ethyl acrylate	$C_5H_8O_2$	100.12	2	**5**,**16**
145	2-Bromoethanol	C_2H_5BrO	124.97	3	**16**,**17**,**19**	**195**	Furfural	$C_5H_4O_2$	96.09	2	**6**,**18**
146	3-Iodopropionic acid	$C_3H_5IO_2$	199.98	3	**16**,**17**,**18**	**196**[b]	2-Dimethylaminoethyl iodide	$C_4H_{10}IN$	199.04	2	**6**,**15**
147	Acrylamide	C_3H_5NO	71.08	3	**16**,**17**,**18**	**197**[b]	2-Bromofuran	C_4H_3BrO	146.97	2	**6**,**18**
148	3-Chloropropionamide	C_3H_6ClNO	107.54	3	**16**,**17**,**18**	**198**[b]	2-(Dimethylamino)ethyl bromide	$C_4H_{10}BrN$	152.04	2	**6**,**17**
149	3-Chloropropionitrile	C_3H_4ClN	89.53	3	**16**,**17**,**18**	**199**	2-Thiophenecarboxaldehyde	C_5H_4OS	112.15	2	**6**,**18**
150	Acetone oxide	C_3H_7NO	73.10	3	**16**,**18**,**21**	**200**	2-Bromothiophene	C_4H_3BrS	163.04	2	**6**,**18**
151	Methyl cyanoacetate	$C_4H_5NO_2$	99.09	3	**16**,**18**,**20**	**201**	Thiophene	C_4H_4S	84.14	2	**6**,**18**
152	Bromoethane	C_2H_5Br	108.97	3	**20**,**22**,**23**	**202**	2-Chlorothiophene	C_4H_3ClS	118.59	2	**6**,**18**
153	3,3,4-Trimethyl-2-oxazolinium iodide	$C_6H_{12}NO$	114.17	3	**20**,**22**,**24**	**203**	2-Thiophenecarbonitrile	C_5H_3NS	109.15	2	**6**,**18**
154	2-Amino-4-chlorophenol	C_6H_6ClNO	143.57	3	**20**,**22**,**24**	**204**[c]	2-Methylamino-ethyl *p*-toluenesulfonate	$C_{10}H_{15}NO_3S$	229.30	2	**6**,**18**
155	Ethyl bromoacetate	$C_4H_7BrO_2$	167.00	2	**1**,**22**	**205**[b]	2-Bromo-*N*-methylethylamine	C_3H_8BrN	138.01	2	**6**,**18**
156	Phenyl bromoacetate	$C_8H_7BrO_2$	215.05	2	**1**,**14**	**206**[b]	2-Iodoethylamine	C_2H_6IN	170.98	2	**6**,**18**
157	Glycolic acid	$C_2H_4O_3$	76.05	2	**1**,**16**	**207**	2-Chloroethylamine	C_2H_6ClN	79.53	2	**6**,**19**
158	Methyl glycolate	$C_3H_6O_3$	90.08	2	**1**,**16**	**208**	2-Bromoethylamine	C_2H_6BrN	123.98	2	**6**,**18**
159	Iodoacetic acid	$C_2H_3IO_2$	185.95	2	**1**,**18**	**209**[b]	2-Oxo-ethyl *p*-toluenesulfonate	$C_9H_{10}O_4S$	214.24	2	**6**,**16**
160	Iodoacetic anhydride	$C_4H_4I_2O_3$	353.88	2	**1**,**18**	**210**[b]	(Methoxymethyl)dimethylamine	$C_4H_{11}NO$	89.14	2	**6**,**15**
161	Ethyl iodoacetate	$C_4H_7IO_2$	214.00	2	**1**,**22**	**211**	Piperidine	$C_5H_{11}N$	85.15	2	**7**,**24**
162	Phenylboronic acid	$C_6H_7BO_2$	121.93	2	**1**,**10**	**212**	2-Chloroacetamide	C_2H_4ClNO	93.51	2	**7**,**16**
163	Urea	CH_4N_2O	60.06	2	**1**,**7**	**213**	1,4-Dichlorobenzene	$C_6H_4Cl_2$	147.00	2	**7**,**15**
164	Dimethyl carbonate	$C_3H_6O_3$	90.08	2	**2**,**22**	**214**	2-Chloro-1,1,1-trimethoxyethane	$C_5H_{11}ClO_3$	154.59	2	**7**,**9**
165	(Trimethylsilyl)diazomethane	$C_4H_{10}N_2Si$	114.22	2	**2**,**24**	**215**	Aminoacetonitrile	$C_2H_4N_2$	56.07	2	**7**,**22**
166	3,4-Dichlorobenzoic acid	$C_7H_4Cl_2O_2$	191.01	2	**2**,**24**	**216**	3-Carboxyphenylboronic acid	$C_7H_7BO_4$	165.94	2	**7**,**10**
167	2-Fluoroaniline	C_6H_6FN	111.12	2	**2**,**10**	**217**	4-Iodophenylboronic acid	$C_6H_6BIO_2$	247.83	2	**7**,**10**
168	Chlorosulfonyl isocyanate	$CClNO_3S$	141.53	2	**2**,**10**	**218**	4-Hydroxyphenylboronic acid	$C_6H_7BO_3$	137.93	2	**7**,**10**
169	4-Amino-3-chlorobenzonitrile	$C_7H_5ClN_2$	152.58	2	**2**,**24**	**219**[b]	Trimethylsilane	$C_3H_{10}Si$	74.20	2	**8**,**16**
170	3-Amino-3-phenylpropionic acid	$C_9H_{11}NO_2$	165.19	2	**3**,**16**	**220**	Nitrosobenzene	C_6H_5NO	107.11	2	**8**,**22**
171	Gentisic acid	$C_7H_6O_4$	154.12	2	**3**,**10**	**221**[b]	Methyl ethanehydrazonate	$C_3H_8N_2O$	88.11	2	**9**,**23**
172	Methyl chloroformate	$C_2H_3ClO_2$	94.50	2	**3**,**16**	**222**	Methoxylamine	CH_5NO	47.06	2	**9**,**16**
173	Methyl 2,5-dihydroxybenzoate	$C_8H_8O_4$	168.15	2	**3**,**10**	**223**	4-Nitrophenyl 4-toluenesulfonate	$C_{13}H_{11}NO_5S$	293.30	2	**9**,**22**
174	Diethylenetriamine	$C_4H_{13}N_3$	103.17	2	**4**,**10**	**224**	2,4-Dichlorophenylboronic acid	$C_6H_5BCl_2O_2$	190.82	2	**9**,**22**

225	4-Chlorophenol	C_6H_5ClO	128.56	2	**10**,**22**	**273**[b]	4-Dimethylamino-*N*-methoxy-*N*-methylbutyramide	$C_8H_{18}N_2O_2$	174.24	2	**15**,**17**
226	2-Iodoaniline	C_6H_6IN	219.03	2	**10**,**19**	**274**[b]	(3-Bromopropyl)dimethylamine	$C_5H_{12}BrN$	166.06	2	**15**,**17**
227	2-Bromophenyl	C_6H_5BrO	173.01	2	**10**,**19**	**275**	3-Dimethylamino-1-propanol	$C_5H_{13}NO$	103.17	2	**15**,**17**
228	Salicylic acid	$C_7H_6O_3$	138.12	2	**10**,**23**	**276**	1,3-Diiodopropane	$C_3H_6I_2$	295.89	2	**15**,**16**
229	Phenol	C_6H_6O	94.11	2	**10**,**13**	**277**	3-Dimethylamino-1-propylchloride	$C_5H_{12}ClN$	121.61	2	**15**,**17**
230	1-Bromo-2-iodobenzene	C_6H_4BrI	282.91	2	**10**,**19**	**278**	4-Bromobenzaldehyde	C_7H_5BrO	185.02	2	**15**,**21**
231	2-Bromobenzoic acid	$C_7H_5BrO_2$	201.02	2	**10**,**17**	**279**	*N*,*N*-Dimethylacetamide	C_4H_9NO	87.12	2	**15**,**17**
232	2-Bromophenylboronic acid	$C_6H_6BBrO_2$	200.83	2	**10**,**19**	**280**	Allyltributylstannane	$C_{15}H_{32}Sn$	331.11	2	**15**,**18**
233	2-Bromoaniline	C_6H_6BrN	172.03	2	**10**,**17**	**281**	2-Chlorobenzyl chloride	$C_7H_6Cl_2$	161.03	2	**15**,**17**
234	2-Iodophenol	C_6H_5IO	220.01	2	**10**,**19**	**282**	1-Naphthol	$C_{10}H_8O$	144.17	2	**16**,**18**
235	2-Fluorobenzamide	C_7H_6FNO	139.13	2	**10**,**22**	**283**	1-Fluoronaphthalene	$C_{10}H_7F$	146.17	2	**16**,**18**
236	*o*-Anisidine	C_7H_9NO	123.16	2	**10**,**13**	**284**	1-Iodonaphthalene	$C_{10}H_7I$	254.07	2	**16**,**18**
237	Methyl 2,5-dichlorobenzoate	$C_8H_6Cl_2O_2$	205.04	2	**10**,**15**	**285**	2-(Diethylamino)acetonitrile	$C_6H_{12}N_2$	112.18	2	**16**,**17**
238	Trifluoromethanesulfonyl chloride	$CClF_3O_2S$	168.52	2	**10**,**17**	**286**[b]	1-Bromo-3-tosyloxypropane	$C_{10}H_{13}BrO_3S$	293.18	2	**16**,**17**
239	4-Chlorocatechol	$C_6H_5ClO_2$	144.56	2	**10**,**20**	**287**	Acetamide	C_2H_5NO	59.07	2	**16**,**18**
240	3-Chlorobenzoic acid	$C_7H_5ClO_2$	156.57	2	**10**,**13**	**288**	2-Bromoacetamide	C_2H_4BrNO	137.96	2	**16**,**17**
241	5-Chlorosalicylaldehyde	$C_7H_5ClO_2$	156.57	2	**10**,**22**	**289**	Methyl malonate monoamide	$C_4H_7NO_3$	117.11	2	**16**,**22**
242	2,5-Dichlorotoluene	$C_7H_6Cl_2$	161.03	2	**10**,**15**	**290**	3-Chloropropionic acid	$C_3H_5ClO_2$	108.53	2	**16**,**17**
243	Methyl 2-amino-5-chlorobenzoate	$C_8H_8ClNO_2$	185.61	2	**10**,**22**	**291**	2-Chloroethoxytrimethylsilane	$C_5H_{13}ClOSi$	152.70	2	**16**,**18**
244	*N*-(2-Hydroxyphenyl)-*p*-toluenesulfonamide	$C_{13}H_{13}NO_3S$	263.32	2	**10**,**23**	**292**	1-Bromo-2-chloroethane	C_2H_4BrCl	143.41	2	**16**,**17**
245	4-Nitrophenyl chloroformate	$C_7H_4ClNO_4$	201.57	2	**10**,**22**	**293**	1,3-Dichloropropane	$C_3H_6Cl_2$	112.99	2	**16**,**17**
246	*o*-Phenylenediamine	$C_6H_8N_2$	108.14	2	**10**,**24**	**294**	3-Iodo-1-propanol	C_3H_7IO	185.99	2	**16**,**17**
247	1-Bromo-2-chlorobenzene	C_6H_4BrCl	191.46	2	**10**,**19**	**295**	*N*,*N*-Dimethylformamide dimethyl acetal	$C_5H_{13}NO_2$	119.16	2	**16**,**19**
248	1-Bromo-4-fluorobenzene	C_6H_4BrF	175.00	2	**11**,**15**	**296**	Propargyl *p*-toluenesulfonate	$C_{10}H_{10}O_3S$	210.25	2	**16**,**18**
249	2-Bromo-4-fluoroacetophenone	C_8H_6BrFO	217.04	2	**11**,**15**	**297**	Propargyl chloride	C_3H_3Cl	74.51	2	**16**,**18**
250	Ethanolamine	C_2H_7NO	61.08	2	**11**,**18**	**298**	5,6,7,8-Tetrahydro-1-naphthol	$C_{10}H_{12}O$	148.21	2	**16**,**18**
251[b]	3-Hydroxy-3-phenyl-propyl-toluenesulfonate	$C_{16}H_{18}O_4S$	306.38	2	**12**,**16**	**299**	Formamide	CH_3NO	45.04	2	**16**,**17**
252	(*R*)-1-Phenyl-1,3-propanediol	$C_9H_{12}O_2$	152.19	2	**12**,**16**	**300**	Acrylonitrile	C_3H_3N	53.06	2	**16**,**18**
253	(*R*)-3-Chloro-1-phenyl-1-propanol	$C_9H_{11}ClO$	170.64	2	**12**,**16**	**301**	Phenyl vinyl sulfone	$C_8H_8O_2S$	168.22	2	**16**,**18**
254	Acetophenone	C_8H_8O	120.15	2	**12**,**16**	**302**	2-Chloroethyl phenyl sulfone	$C_8H_9ClO_2S$	204.68	2	**16**,**18**
255	Vinyl phenyl ketone	C_9H_8O	132.16	2	**12**,**16**	**303**	1-Methoxy-1,3,3-trimethylurea	$C_5H_{12}N_2O_2$	132.16	2	**16**,**17**
256	(2-Hydroxyethyl)methylamine	C_3H_9NO	75.11	2	**12**,**18**	**304**	*N*,*N*-Dimethylacrylamide	C_5H_9NO	99.13	2	**16**,**17**
257	(*S*)-Styrene oxide	C_8H_8O	120.15	2	**12**,**16**	**305**	1-Chloronaphthalene	$C_{10}H_7Cl$	162.62	2	**16**,**18**
258	Allylalcohol	C_3H_6O	58.08	2	**13**,**16**	**306**	Methyl propiolate	$C_4H_4O_2$	84.08	2	**16**,**19**
259	Hydroxyacetone	$C_3H_6O_2$	74.08	2	**13**,**16**	**307**	Methyl malonyl chloride	$C_4H_5ClO_3$	136.54	2	**16**,**22**
260	Methyl pyruvate	$C_4H_6O_3$	102.09	2	**13**,**19**	**308**	Phenyl trifluoromethanesulfonate	$C_7H_5F_3O_3S$	226.18	2	**16**,**17**
261	Vinyl methyl ketone	C_4H_6O	70.09	2	**13**,**16**	**309**	2-Bromobenzaldehyde	C_7H_5BrO	185.02	2	**17**,**19**
262	Methylglyoxal	$C_3H_4O_2$	72.06	2	**13**,**24**	**310**[b]	Cyanoacetaldehyde	C_3H_3NO	69.06	2	**17**,**18**
263	Dimethyl malonate	$C_5H_8O_4$	132.12	2	**13**,**16**	**311**	Cyanoacetamide	$C_3H_4N_2O$	84.08	2	**17**,**18**
264	3-Butenoic acid	$C_4H_6O_2$	86.09	2	**13**,**16**	**312**	Trimethyl phosphonoacetate	$C_5H_{11}O_5P$	182.11	2	**17**,**18**
265	(Trimethylsiloxy)ethylene	$C_5H_{12}OSi$	116.24	2	**13**,**15**	**313**	2-Chlorobenzaldehyde	C_7H_5ClO	140.57	2	**19**,**23**
266	Acryl chloride	C_3H_3ClO	90.51	2	**13**,**21**	**314**	2-Fluorobenzoyl chloride	C_7H_4ClFO	158.56	2	**21**,**22**
267	4-(Methylamino)butyric acid	$C_5H_{11}NO_2$	117.15	2	**15**,**17**	**315**	2-Fluorobenzonitrile	C_7H_4FN	121.12	2	**21**,**22**
268	1-Bromo-3-chloropropane	C_3H_6BrCl	157.44	2	**15**,**16**	**316**	2-Fluorobenzaldehyde	C_7H_5FO	124.12	2	**21**,**22**
269	4-(Dimethylamino)butyric acid	$C_6H_{13}NO_2$	131.18	2	**15**,**17**	**317**	2-Chloroacetophenone	C_8H_7ClO	154.60	2	**21**,**23**
270[b]	4-(Dimethylamino)butanoyl chloride	$C_6H_{12}ClNO$	149.62	2	**15**,**17**	**318**	Methyl 2-fluorobenzoate	$C_8H_7FO_2$	154.14	2	**21**,**22**
271	4-(Dimethylamino)butyronitrile	$C_6H_{12}N_2$	112.18	2	**15**,**17**	**319**	2-Amino-4-chlorobenzoic acid	$C_7H_6ClNO_2$	171.58	2	**22**,**24**
272	*N*,*N*-Dimethylallylamine	$C_5H_{11}N$	85.15	2	**15**,**17**	**320**	4-Chloro-2-iodoaniline	C_6H_5ClIN	253.47	2	**22**,**24**

[a] The number of the corresponding targets.
[b] Not commercially available compound.
[c] No CAS registry number.

Figure 2 shows the procedures to collect common intermediates. At first, SYNSUP is executed for 24 targets one after another. Next, from the proposed routes, intermediates and starting materials are collected. Finally, common intermediates are extracted by comparison of intermediates among targets. SYNSUP is written in C++ and a small script to extract common intermediates by comparison among synthetic routes is written in PERL.[39] Both of them have been executed on Linux machines.

3. Results and discussion

At first, we looked for the common intermediates in the reported synthetic routes of 24 targets. Piperazine, piperidine, and 3-dimethylaminopropyl magnesium chloride were found as common intermediates. Piperazine is found in the routes for **4**[18] and **10**,[24] piperidine for **7**[21] and **24**,[38] and 3-dimethylaminopropyl magnesium chloride for **15**[29] and **17**[31] as shown in Scheme 2.

In the known routes of 24 targets, there was no common intermediate leading to more than two targets. However using the proposed routes of the synthesis design system enabled us to find such common intermediates for routes to various targets.

In this study, we considered the common intermediates containing at least one carbon atom. Table 1 is a list of all common intermediates extracted by comparison among the result of SYNSUP executions. In addition, Table 2 summarizes the number of proposed routes, intermediates, common intermediates, the number of steps in the routes, and the execution times of SYNSUP on a Xeon/2.8 GHz. It took only a few minutes for the PERL script to find common intermediates from proposed synthetic routes of all targets.

From the result of executions, all targets were found to have some common intermediates. The number of common intermediates of each target was roughly proportional to the number of proposed routes and the intermediates involved in the routes (Figs. 3 and 4). The correlation coefficients were 0.872 and 0.842, respectively.

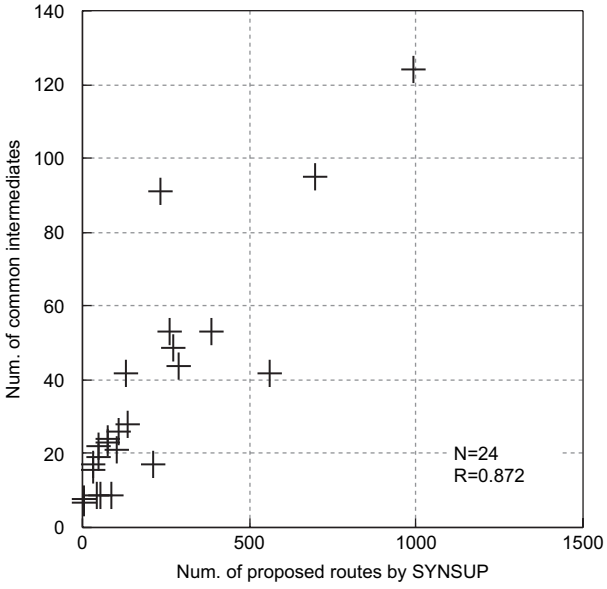


Figure 3. Dependence of the number of the common intermediates on the number of the proposed routes by SYNSUP.

Table 2. The results of SYNSUP jobs and the extracted common intermediates

Target	Number			Min. steps	Max. steps	CPU time
	Proposed routes	Intermediates	Common intermediates			
1	82	71	24	5	5	3 h 31 min 24 s
2	109	109	22	3	4	2 h 26 min 48 s
3	217	161	18	3	4	1 h 24 min 46 s
4	13	25	8	3	4	59 min 11 s
5	292	262	45	3	4	47 min 27 s
6	570	115	43	3	4	25 min 44 s
7	57	55	20	3	4	10 min 51 s
8	59	74	10	2	4	16 min 10 s
9	37	87	18	2	4	3 min 23 s
10	394	310	54	3	4	44 min 32 s
11	11	27	9	3	4	10 min 10 s
12	140	85	29	2	3	30 s
13	279	242	50	2	4	2 min 2 s
14	51	70	10	5	5	22 h 22 min 27 s
15	267	162	54	3	4	1 h 4 min 13 s
16	998	409	125	2	4	9 min 11 s
17	239	196	92	2	3	3 min 59 s
18	702	258	96	3	4	31 min 22 s
19	83	72	25	4	4	4 h 38 s
20	90	84	10	2	3	2 min 24 s
21	54	71	23	2	3	3 min 39 s
22	137	158	43	3	4	13 min 32 s
23	40	77	17	5	5	8 h 31 min 42 s
24	117	189	27	1	4	45 h 25 min 54 s
Av	209.9	140.4	36.3			

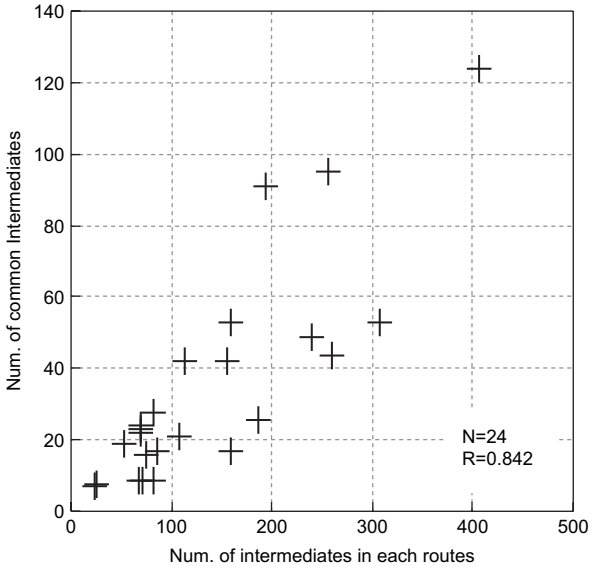


Figure 4. Dependence of the number of the common intermediates on the number of the intermediates included in the proposed routes.

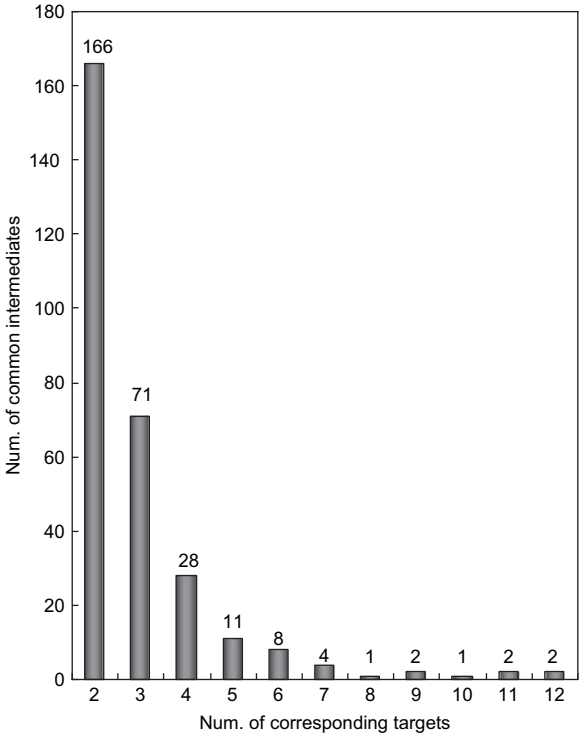


Figure 5. Distribution of the number of the common intermediates against the number of the corresponding targets.

In all, 296 kinds of common intermediates were found. Table 3 is a matrix of the number of common intermediates between two targets. Most of the pairs of targets share some common intermediates, especially, **16**, **17**, and **18** share more than 40 common intermediates because many proposed routes for each have the same substructure, the dimethylamino group. The targets with identical substructures tend to have more common intermediates, for example, targets **6** and **18** share 29 common intermediates because they both have a thiophene ring.

The distribution of the number of common intermediates versus the corresponding targets shows that many common intermediates lead to more than two targets, though more than half of the common intermediates led to just two targets (Fig. 5). The common intermediates for 12 targets, which are maximum, are carbon monoxide and methanol. Carbon monoxide is used for a carbonyl insertion reaction in the presence of transition metals. Broadly speaking, these common intermediates were classified into carbonyl, aromatic, amine, and alkyl halide derivatives and chiral compounds.

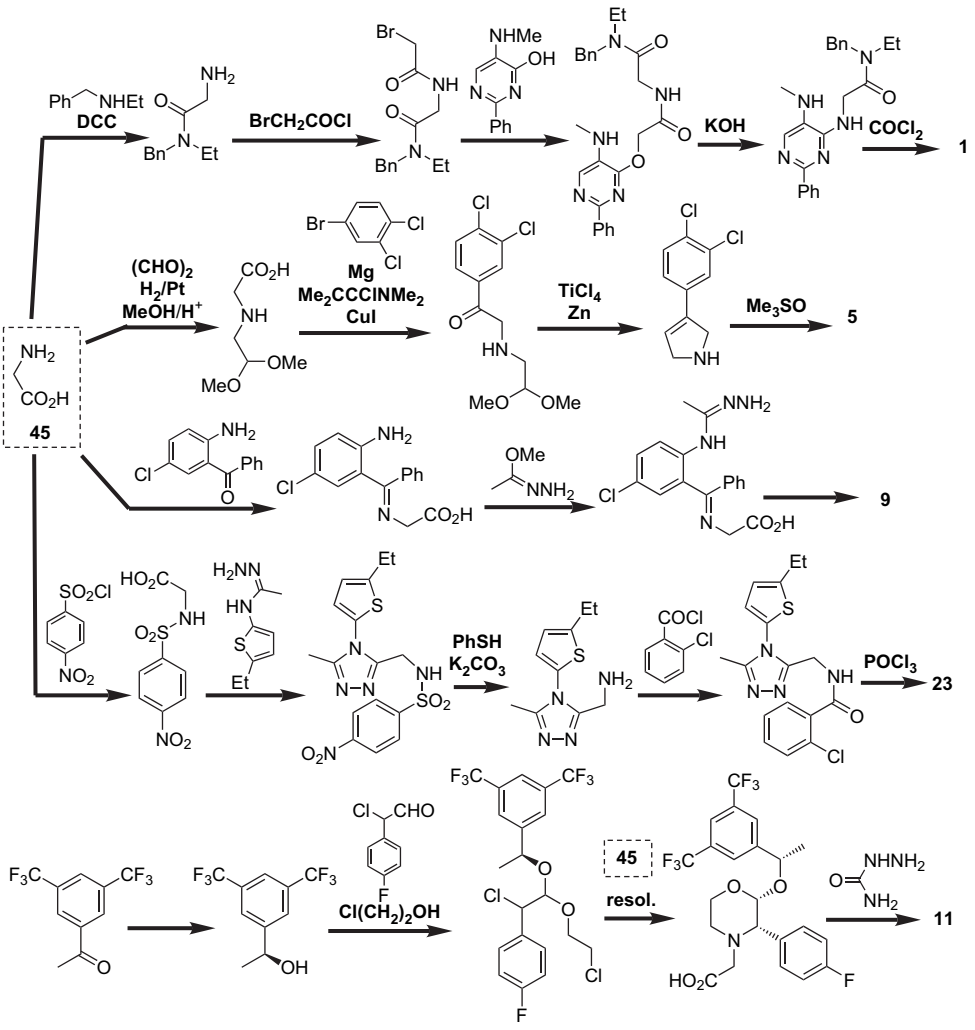
Among the common intermediates, 26 compounds have not been found in chemical catalogs. But 25 compounds of these 26 have CAS registry numbers, so it is evident that SYNSUP did not generate chemically erroneous molecules.

The proposed routes including common intermediates, a carbonyl derivative, glycine **45**, an aromatic derivative,

Table 3. The list of the number of common intermediates between two targets

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
1		0	0	0	3	1	2	0	2	4	1	1	6	3	1	10	4	5	0	1	2	8	3	1
2	0		6	1	2	8	2	1	3	6	1	4	8	1	8	7	4	4	1	2	2	5	2	8
3	0	6		1	3	8	2	0	4	3	1	5	4	1	6	13	6	7	1	1	1	3	1	3
4	0	1	1		2	2	1	0	0	4	2	2	2	1	0	1	2	1	2	0	1	1	1	0
5	3	2	3	2		4	1	1	2	5	4	6	11	3	5	14	19	21	4	1	2	3	1	4
6	1	8	8	2	4		5	1	3	2	1	9	5	3	12	23	14	29	4	2	3	3	0	4
7	2	2	2	1	1	5		1	4	7	0	1	2	0	4	7	1	4	0	2	0	5	3	3
8	0	1	0	0	1	1	1		2	1	0	3	3	0	2	6	2	4	1	1	0	2	1	2
9	2	3	4	0	2	3	4	2		3	1	3	3	0	2	5	1	3	0	1	2	6	3	4
10	4	6	3	4	5	2	7	1	3		0	1	10	1	5	6	6	4	8	3	3	13	5	6
11	1	1	1	2	4	1	0	0	1	0		2	4	0	4	3	4	3	3	0	1	0	1	1
12	1	4	5	2	6	9	1	3	3	1	2		7	1	6	20	11	16	1	1	2	1	0	3
13	6	8	4	2	11	5	2	3	3	10	4	7		2	13	24	15	14	6	3	5	7	1	6
14	3	1	1	1	3	3	0	0	0	1	0	1	2		1	4	2	3	1	0	1	0	0	0
15	1	8	6	0	5	12	4	2	2	5	4	6	13	1		24	31	17	3	2	8	5	1	5
16	10	7	13	1	14	23	7	6	5	6	3	20	24	4	24		55	58	8	5	6	8	4	6
17	4	4	6	2	19	14	1	2	1	6	4	11	15	2	31	55		46	7	2	5	2	2	3
18	5	4	7	1	21	29	4	4	3	4	3	16	14	3	17	58	46		4	5	6	5	1	7
19	0	1	1	2	4	4	0	1	0	8	3	1	6	1	3	8	7	4		0	2	0	1	2
20	1	2	1	0	1	2	2	1	1	3	0	1	3	0	2	5	2	5	0		0	6	2	4
21	2	2	1	1	2	3	0	0	2	3	1	2	5	1	8	6	5	6	2	0		8	2	0
22	8	5	3	1	3	3	5	2	6	13	0	1	7	0	5	8	2	5	0	6	8		5	10
23	3	2	1	1	1	0	3	1	3	5	1	0	1	0	1	4	2	1	1	2	2	5		3
24	1	8	3	0	4	4	3	2	4	6	1	3	6	0	5	6	3	7	2	4	0	10	3	

10～19, 20～39, > 39.

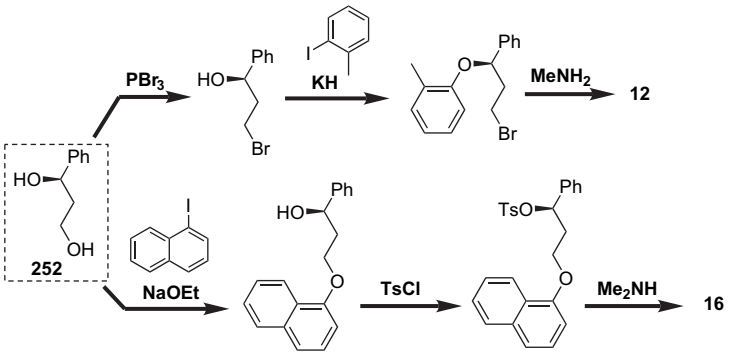


Scheme 3. Proposed synthetic routes of **1**, **5**, **9**, **11**, and **23** from **45** by SYNSUP.

3,4-dichlorobenzaldehyde **97**, and a chiral compound, (*R*)-1-phenyl-1,3-propanediol **252**, are shown in Schemes 3–5, respectively. In this paper, we display computer proposed routes with bold arrows, to distinguish them from experimentally reported schemes.

Compound **45** is a common intermediate of five targets, **1**, **5**, **9**, **11**, and **23**, and plays a role in a component of their heterocyclic rings (Scheme 3). The synthetic routes of **9** and **23** are interesting due to different and effective ring closure steps from the reported routes.

Scheme 4. Proposed routes of **2**, **5**, and **24** from **97** by SYNSUP.



Scheme 5. Proposed routes of **12** and **16** from **252** by SYNSUP.

As shown in Scheme 4, **97** must not be a realistic intermediate for targets **2**, **5**, and **24**. A cyclopropanation leading to **5** is doubtful. Amidation in the routes of **2** and **24** is also generally unused. Actually SYNSUP has some other type of amidation reactions from an amine with a carbonyl such as an acid chloride,[40] methyl ester,[41] carboazide,[42] 4-nitrophenyl ester,[43] or acid anhydride,[44] because the variation is sometimes helpful to avoid patented routes or intermediates.

The chiral diol **252** leading to **12** and **16** is a suitable chiral source, i.e., retention for **12** and inversion for **16** at the chiral center (Scheme 5). In fact, **252** is reportedly a starting material of **16**.[30] Although SYNSUP sometimes proposed chemically doubtful or erroneous reactions, many of the proposed synthetic routes and related common intermediates were interesting and practical.

To characterize the size of common intermediates, the distribution of molecular weight between targets and common intermediates has been investigated (Fig. 6). The maximum molecular weights of common intermediates with six targets are outstandingly large, because of including bis(tributyltin) oxide **41** to take advantage of the Stille coupling.[45] The average molecular weights of common intermediates with two to eight targets are almost constant as about 150, which correspond to five to seven carbons in the molecules. The average molecular weight of 24 targets and 296 common intermediates were 337.53 and 142.86, respectively. In other words the common intermediates had on an average about 40% of the molecular weights of the ultimate targets.

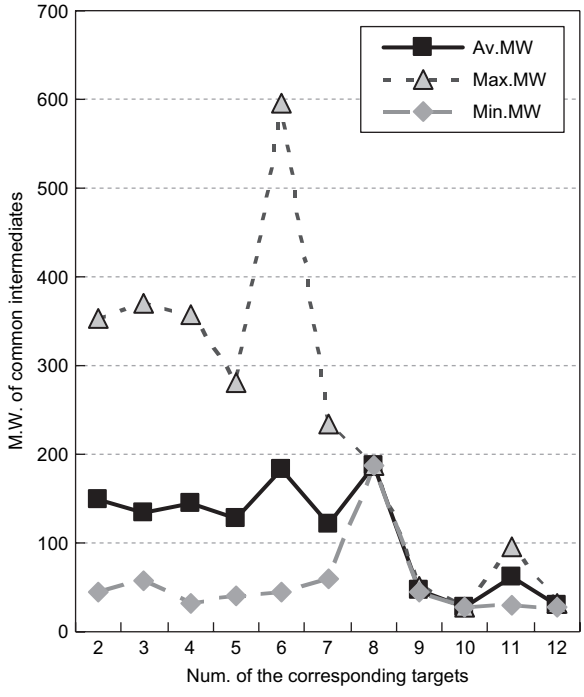


Figure 6. Dependence of molecular weights of the common intermediates on the number of the corresponding targets.

In summary, we tried to find, automatically, versatile and common intermediates leading to multiple target molecules with the aid of the synthesis design system SYNSUP. Many common intermediates for more than two corresponding targets were found, and they generally had about 40% of the molecular weight of the targets.

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