Supplementary information for manuscript:

Computer-generated "synthetic contingency" plans at times of logistics and supply problems: Scenarios for hydroxychloroquine and remdesivir.

Sara Szymkuć[1+], Ewa P. Gajewska[1+], Karol Molga[1+], Agnieszka Wołos[1], Rafał Roszak[1], Wiktor Beker[1], Martyna Moskal[1], Piotr Dittwald[1] & Bartosz A. Grzybowski[1,2,3]*

[1] Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, Warsaw 02-224, Poland

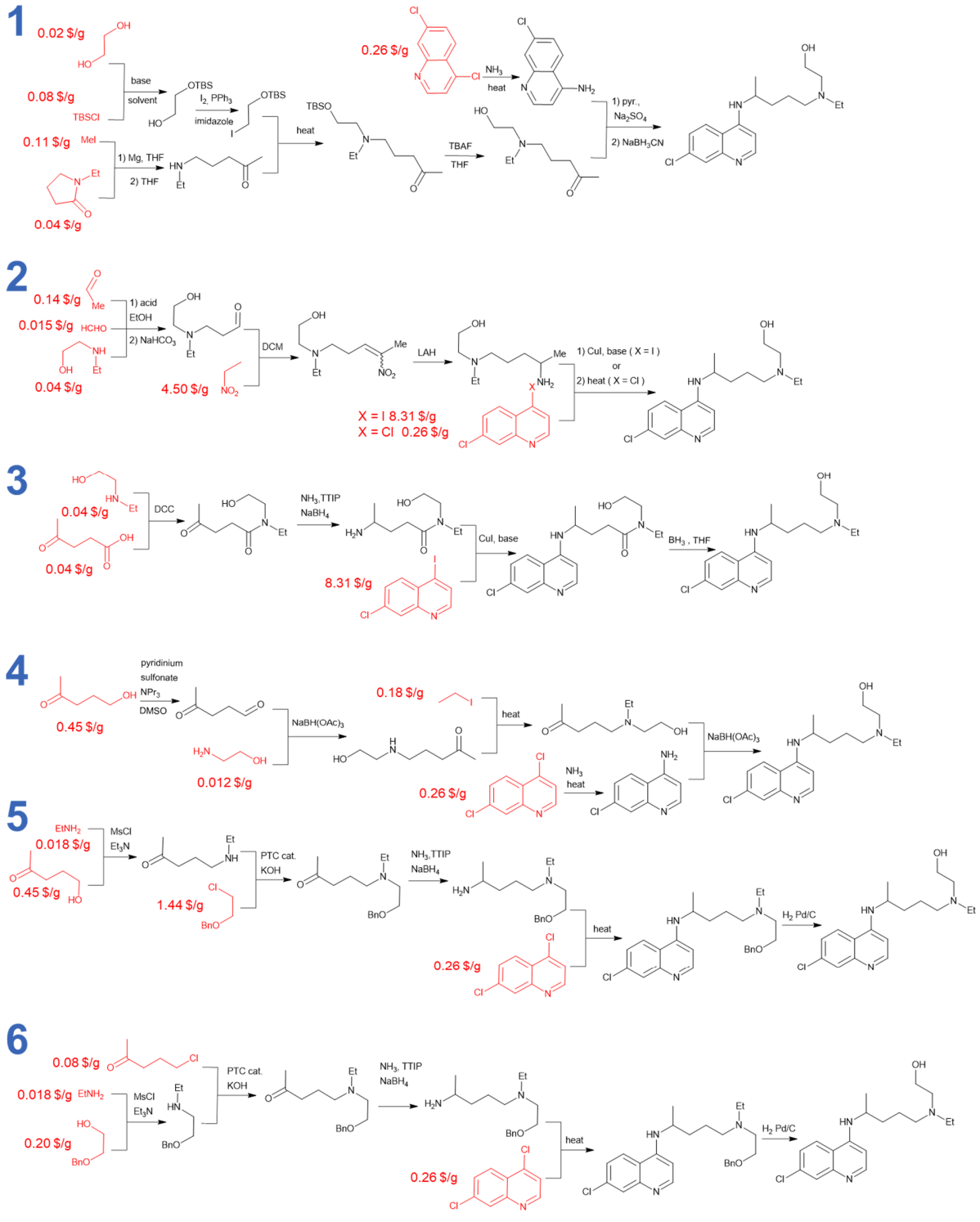
[2] IBS Center for Soft and Living Matter and

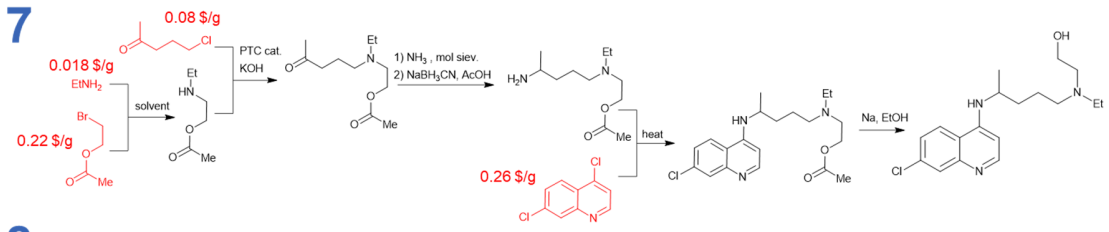
[3] Department of Chemistry, UNIST, 50, UNIST-gil, Eonyang-eup, Ulju-gun, Ulsan, 689-798, South Korea

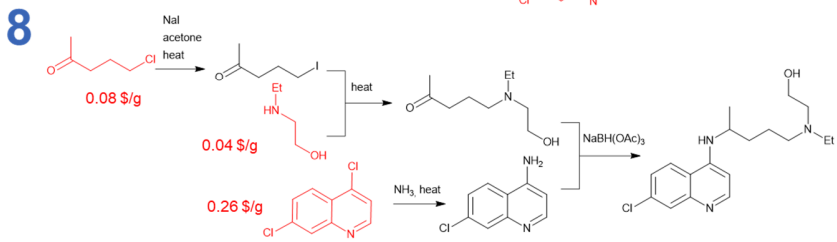
[+]Authors contributed equally

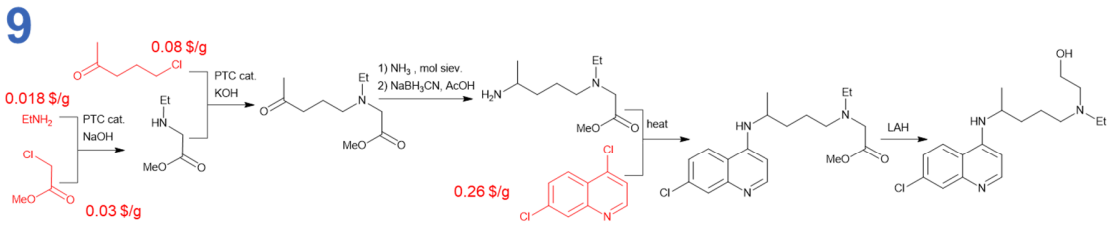
*Correspondence to: nanogrzybowski@gmail.com

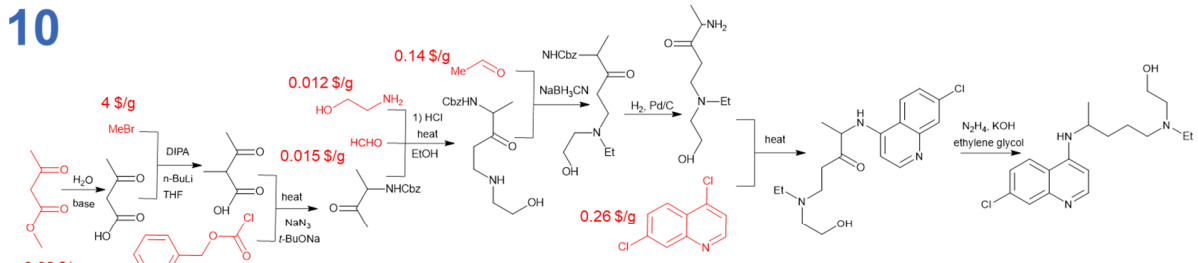
S1. Chematica-designed pathways leading to hydroxychloroquine and presented in a form of a list.

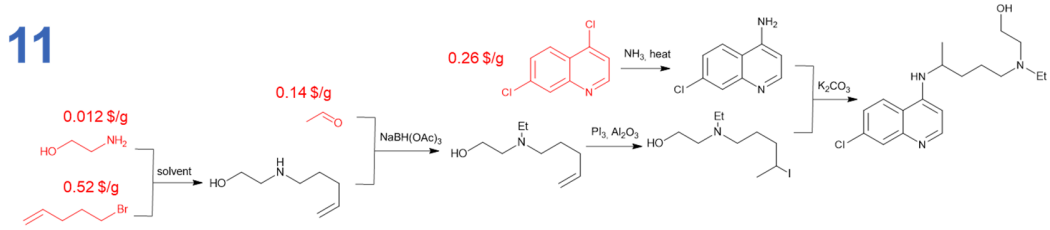



7
0.08 $/g
0.018 $/g
EtNH2
solvent
0.22 $/g
PTC cat.
KOH
1) NH3 , mol siev.
2) NaBH3CN, AcOH
heat
0.26 $/g
Na, EtOH

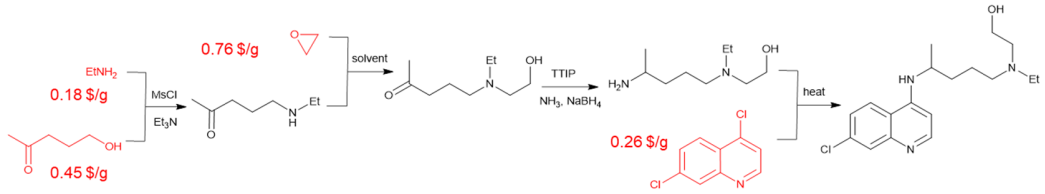

8
NaI
acetone
heat
0.08 $/g
heat
0.04 $/g
0.26 $/g
NH3, heat
NaBH(OAc)3


9
0.08 $/g
0.018 $/g
EtNH2
PTC cat.
NaOH
0.03 $/g
PTC cat.
KOH
1) NH3 , mol siev.
2) NaBH3CN, AcOH
heat
0.26 $/g
LAH

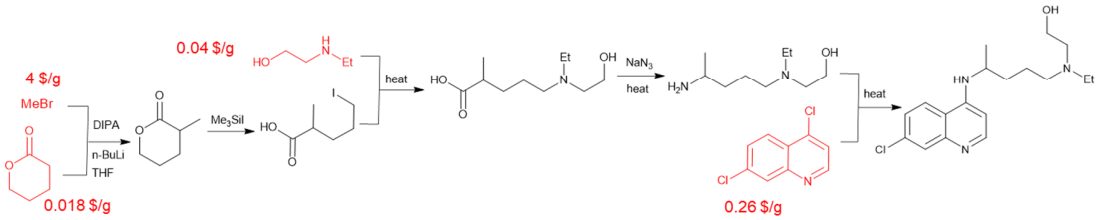

10
4 $/g
MeBr
DIPA
n-BuLi
THF
H2O
base
0.02 $/g
0.012 $/g
HCHO
1) HCl
heat
EtOH
0.015 $/g
0.14 $/g
NaBH3CN
heat
NaN3
t-BuONa
0.19 $/g
H2, Pd/C
0.26 $/g
heat
N2H4, KOH
ethylene glycol


11
0.012 $/g
0.52 $/g
solvent
0.14 $/g
NaBH(OAc)3
0.26 $/g
NH3, heat
PI3, Al2O3
K2CO3

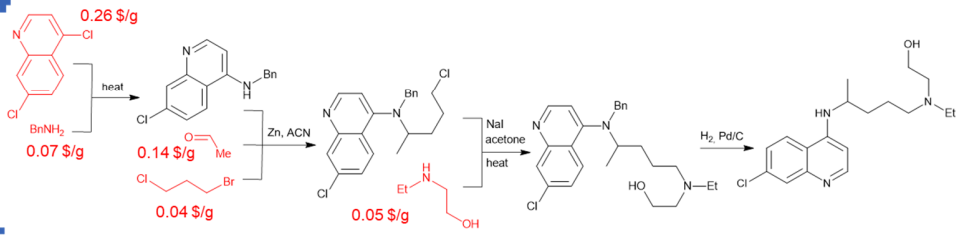
12



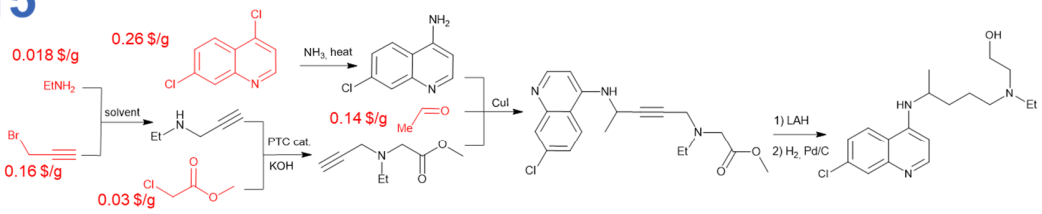
13



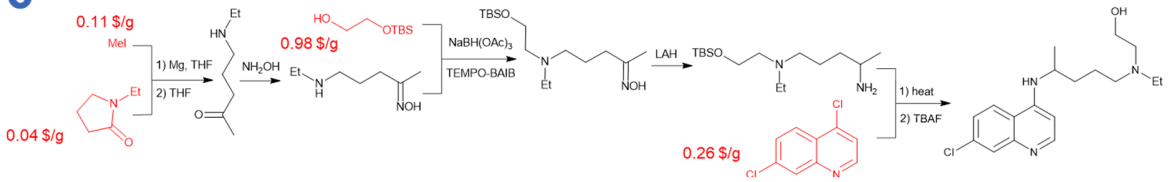
14



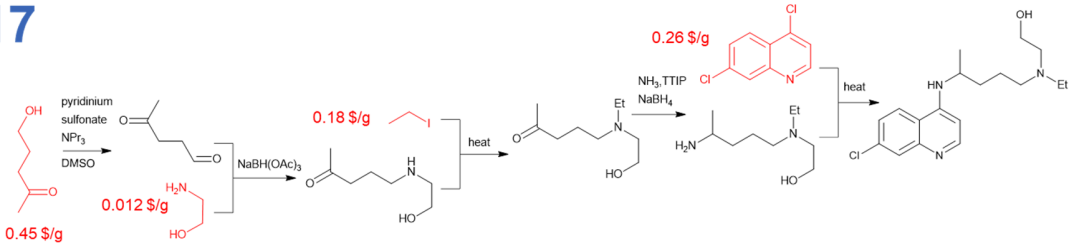
15



16



17



S2. Details of *Chematica* searches.

The search details are structured in the following manner: (i) stop conditions (threshold prices and/or synthetic popularities), (ii) details of scoring functions, and (iii) additional parameters. Whereas most of these settings were discussed in detail in our earlier publications (see refs.S1-S4), some functionalities are new and merit brief description:

(a) Increasing the value of either "**minimum search width**" or "**max reactions per product**" increases the "breadth" of possible reactions considered at each step and, typically, yields more diverse results at the expense of longer time to complete calculations.

(b) Similarly, last five parameters for pathway 14 (cf. below) aim at increasing the diversity of results. If a certain transformation repeats in a given number of the top-scoring pathways and is identified as a "**key-step**," it becomes disallowed after user-specified number of iterations. The key-transformation is defined as a reaction generating (in the retro direction) the highest simplification of the structure according to the specified chemical scoring function. Such reaction, in order to be identified as a "key-step," has to be applied to an intermediate having certain percentage of the target's mass.

(c) Four options, "**Apply_tunnels**", **Apply_FGI**, **FGI_with_protections** and **Multirx**, are designed to strategize over multiple steps and to navigate around intermediates presenting reactive and conflicting groups. In addition, their use in combination with large penalty for protection steps (in the Reaction Scoring Function) yields pathways with complete protection/deprotection strategy (as opposed to implicit treatment of protection chemistries in the earlier versions of *Chematica*).

(c) If "**Cut all Heterocycles**" filter is "on," all aromatic heterocycles present in a molecule have to be synthesized rather than supplied as starting materials.

(d) The "**remove_diast**" option excludes from the search all reactions yielding mixtures of diastereoisomers. Although it does not apply here for HCQ, we usually left this option on.

All the settings used for designing synthetic routes described in the text are listed below.

Pathways: 2 (from 8-chloro-4-iodoquinoline), 3, 5, 6, 7, 9
Stop points:
Buyable molecules: 1000 g/mol, 200 $/g
Known molecules: 1000 g/mol, 50 popularity
Scoring Functions:
Chemical Scoring Function: SMALLER**3, SMALLER**1.5
Reaction Scoring Function: 60 + 120000 * PROTECT + 1000000 * (CONFLICT + NON_SELECTIVITY + FILTERS)
Additional parameters:
Minimum search width = 400
Max reactions per product = 60
remove_diast = True

Macrocycles filter: ON

Pathways: 2 (from dichloroquinoline), 4, 8, 17
Stop points:
Buyable molecules: 1000 g/mol, 200 $/g
Known molecules: 1000 g/mol, 50 popularity
Scoring Functions:
Chemical Scoring Function: SMALLER**3, SMALLER**1.5
Reaction Scoring Function: 60 + 120000 * PROTECT + 1000000 * (CONFLICT + NON_SELECTIVITY + FILTERS) + 50000 * HIDE_SEEK_NAME(['Pd'])
Additional parameters:
Minimum search width = 400
Max reactions per product = 60
remove_diast = True
Macrocycles filter: ON

Pathways: 1,15
Stop points:
Buyable molecules: 1000 g/mol, 1000 $/gram
Known molecules: 1000 g/mol, 5 popularity
Scoring Functions:
Chemical Scoring Function: HOOD**3, HOOD**1.5
Reaction Scoring Function: TUNNEL_COEF * FGI_COEF *60 + 10000000*(CONFLICT +NON_SELECTIVITY+FILTERS+PROTECT)
Additional parameters:
Macrocycles filter: ON
Minimum search width = 200
Max reactions per product = 30
apply_tunnels = True
apply_FGI = True
FGI_with_protections = True
multirx = True
remove_diast = True

Pathways: 13, 16
Stop points:
Buyable molecules: 1000 g/mol, 200 $/gram
Known molecules: 1000 g/mol, 10 popularity
Scoring Functions:
Chemical Scoring Function: HOOD**3, HOOD**1.5
Reaction Scoring Function **(for pathway 13)**: TUNNEL_COEF * FGI_COEF * 60+10000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)+10000000*HIDE_SEEK_NAME(['Ozonolysis','Amination of aryl iodides','Synthesis of haloarenes via triflates'])+10000000*HIDE_SEEK_SMILES([' Fc1ccnc2cc(Cl)ccc12'])
Reaction Scoring Function **(for pathway 16)**: TUNNEL_COEF * FGI_COEF * 60+10000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)+10000000*HIDE_SEEK_NAME(['Ozonolysis','Amination of aryl iodides','Synthesis of haloarenes via triflates'])

Additional parameters:
Macrocycles filter: ON
Minimum search width = 200
Max reactions per product = 30
apply_tunnels = True
apply_FGI = True
FGI_with_protections = True
multirx = True
remove_diast = True

Pathways: 10,11,12
Stop points:
Buyable molecules: 1000 g/mol , 50 $/gram
Known molecules: 1000 g/mol , 40 popularity
Scoring Functions:
CSF: HOOD**3, HOOD**1.5
RSF: TUNNEL_COEF * FGI_COEF *60+10000000*(CONFLICT + NON_SELECTIVITY+FILTERS+PROTECT)+10000000*HIDE_SEEK_NAME(['Ozonolysis','Amination of aryl iodides','Synthesis of haloarenes via triflates','Decarboxylative alkylation',' Photocatalytic','Amination of aryl tosylates','Coupling of Ammonia with Aryl Sulfonates','Hydroaminomethylation','Tandem Ni/Ir'])
Additional parameters:
Macrocycles filter: ON
Minimum search width = 200
Max reactions per product = 30
apply_tunnels = True
apply_FGI = True
FGI_with_protections = True
multirx = True
remove_diast = True

Pathway 14

Stop points:
Buyable molecules: 1000 g/mol, 30 $/gram
Known molecules: 1000 g/mol, 20 popularity
Scoring Functions:
CSF: HOOD**3, HOOD**1.5
RSF: TUNNEL_COEF * FGI_COEF * 120+10000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)+10000000*HIDE_SEEK_NAME(['Ozonolysis','Amination of aryl iodides','Synthesis of haloarenes via triflates','Decarboxylative','Photocatalytic','Amination of aryl tosylates','Coupling of Ammonia with Aryl Sulfonates','Hydroaminomethylation','Tandem Ni/Ir'])
Additional parameters:
Macrocycles filter: ON
Minimum search width = 400
Max reactions per product = 60

apply_tunnels = True
apply_FGI = True
FGI_with_protections = True
multirx = True
remove_diast = True
algo_mode = restart_search
key_rx_prod_target_fraction = 0.5
restart_search_num_same_paths = 3
restart_search_expanded_spiders_same_paths = 800
restart_search_csf = SMALLER**3
restart_search_csf_fraction_bound = 0.8

Pathways avoiding usage of dichloroquinine

Pathway 23

Stop points:

Buyable molecules: 1000 g/mol, 200 $/gram
Known molecules: 1000 g/mol , 15 popularity

Scoring Functions:

Chemical Scoring Function: HOOD**3, HOOD**1.5
Reaction Scoring Function: TUNNEL_COEF * FGI_COEF *60+10000000*(CONFLICT +NON_SELECTIVITY+FILTERS+PROTECT+HIDE_SEEK_SMARTS(['[Cl,I]c1ccc2c([Cl,I])c cnc2c1'])+HIDE_SEEK_NAME(['Synthesis of haloarenes via triflates','Coupling of Ammonia with Aryl Sulfonates','Amination of aryl tosylates','Buchwald-Hartwig type reaction','Ir/Ni','Rh-cat']))

Additional parameters:

Macrocycles filter: ON
beam_width = 200
max_reactions_per_product = 30
apply_tunnels = True
apply_FGI = True
FGI_with_protections = True
multirx = True
remove_diast = True

Pathway 24

Stop points:

Buyable molecules: 1000 g/mol, 50 $/gram
Known molecules: 1000 g/mol, 15 popularity

Scoring Functions:

Chemical Scoring Function: HOOD**3, HOOD**1.5
Reaction Scoring Function: TUNNEL_COEF * FGI_COEF * 60+10000000*(CONFLICT +NON_SELECTIVITY+FILTERS+PROTECT+HIDE_SEEK_SMARTS(['[Cl,I]c1ccc2c([Cl,I])c cnc2c1'])+HIDE_SEEK_NAME(['Synthesis of haloarenes via triflates','Coupling of Ammonia with Aryl Sulfonates','Amination of aryl tosylates','Buchwald-Hartwig type reaction','Ir/Ni','Rh-cat','Pfitzinger Reaction']))

Additional parameters:

Macrocycles filter: ON
beam_width = 200
max_reactions_per_product = 30
apply_tunnels = True
apply_FGI = True
FGI_with_protections = True
multirx = True
remove_diast = True
selection_method = yield_rsf_millimole_selection
sort_results_by = fully_penalized_cost
selection_penalty = 100

Search details for the synthetic pathways leading to dichloroquinoline (the same for pathways 18-22):

Chemical Scoring Function: HOOD**1.2+50*RINGS+50*STEREO
Reaction Scoring Function: TUNNEL_COEF * FGI_COEF * 60 + 10000000 * (CONFLICT + NON_SELECTIVITY+FILTERS+PROTECT+HIDE_SEEK_SMARTS(['[Cl,I]c1ccc2c([Cl,I])ccnc2c1']) + HIDE_SEEK_NAME(['Synthesis of haloarenes via triflates','Coupling of Ammonia with Aryl Sulfonates','Amination of aryl tosylates','Buchwald-Hartwig type reaction','Ir/Ni','Rh-cat']))
Additional parameters:
selection_method = yield_rsf_millimole_selection
sort_results_by = fully_penalized_cost
selection_penalty = 100
Cut all Heterocycles filter: ON
Macrocycles filter: ON
Buyable molecules: 1000 g/mol, 10 $/g for pathways **1**,**3-5** ; 20 $/g for pathway **2**
Known molecules: 1000 g/mol, 5 popularity

Search details for the synthetic pathways leading to: levulinic aldehyde, 3-oxo-butanoic acid 7-chloro-quinolin-4-ylamine and N-ethyl-N-propargylamine (stop points on pathways 1,4,10,17)

Stop points:
Buyable molecules: 1000 g/mol, 20 $/gram
Known molecules: 1000 g/mol , 60 popularity
Scoring Functions:
Chemical Scoring Function: HOOD**3, HOOD**1.5
Reaction Scoring Function: FGI_COEF * 60+10000000* (CONFLICT +NON_SELECTIVITY+ FILTERS+PROTECT)
Additional parameters:
beam_width = 100
max_reactions_per_product = 30
apply_FGI = True
FGI_with_protections = True
multirx = True

remove_diast = True

Search details for the synthetic pathways leading to remdesivir:
Stop points:
Buyable molecules: 1000 g/mol, 100 $/gram
Known molecules: 1000 g/mol, 20 popularity
Scoring Functions:
Chemical Scoring Function: HOOD**3, HOOD**1.5
Reaction Scoring Function: TUNNEL_COEF*FGI_COEF*20+400000000*PROTECT+1000000*(CONFLICT+NON_SELECTIVITY+FILTERS)
Additional parameters:
Macrocycles filter: ON
apply_tunnels = True
beam_width = 200
max_reactions_per_product = 30
apply_FGI = True
FGI_with_protections = True
multirx = True
remove_diast = True

S3. References cited in the main text for Figure 1

a) T. R. Ward, B. J. Turunen, T. Haack, B. Neuenswander, W. Shadrick and G. I. Georg, *Tetrahedron Lett.*, 2009, **50**, 6494–6497.

b) N. Al-Awadi, I. Abdelhamid, I. Abdelhamid, A. Al-Etaibi and M. Elngadi, *Synlett*, 2007, **2007**, 2205–2208.

c) R. A. Bunce, N. R. Cain and J. G. Cooper, *Org. Prep. Proced. Int.*, 2013, **45**, 28–43.

d) E. S. Ibrahim, M. O. A. Orabi, M. El-Badawi and M.T. Omar, *Egypt. J. Chem.*, 1991, **34**, 459–465.

e) M. Baudouin and H. Linares, US4421918, January 15, 1982.

f) M. Baudouin and D. Michelet, US4412076, January 15, 1982.

g) Y. Asano, T. Kojima, O. Kurasawa, T.-T. Wong, Y. Hirata, N. Iwamura, B. Saito, Y. Tanaka, R. Arai, S. Imamura, K. Yonemori, Y. Miyamoto, S. Kitamura and O. Sano, EP3287441, April 19, 2016.

h) H. Muñoz, J. Tamariz, H. S. Zamora, M. Lázaro and F. Labarrios, *Synth. Commun.*, 1987, **17**, 549–554.

i) X. Simeone, M. T. Iorio, D. C. B. Siebert, S. Rehman, M. Schnürch, M. D. Mihovilovic and M. Ernst, *Bioorg. Med. Chem.*, 2019, **27**, 3167–3178.

j) L. Forezi, N. Tolentino, A. de Souza, H. Castro, R. Montenegro, R. Dantas, M. Oliveira, F. Silva, Jr., L. Barreto, R. Burbano, B. Abrahim-Vieira, R. de Oliveira, V. Ferreira, A. Cunha, F. Boechat and M. de Souza, *Molecules*, 2014, **19**, 6651–6670.

k) S.T. Gangadharaiah, G. Sambasivam, S. Eswaran, S. Narayanan, Rk. Shandil, Rk, ; P. Kaur, V. and Potluri, WO2019243971, June 14, 2019.

l) Z. Wang; R. Cao; X. Zhang; Z. Rong; X. Chen; X. Zhang; H. Huang; Z. Li; M. Xu; Z. Wang; J. Li and Z. Ren, CN105017145, December 12, 2012.

m) T. G. Shruthi, S. Eswaran, P. Shivarudraiah, S. Narayanan and S. Subramanian, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 97–102.

n) C. C. Price and R. M. Roberts, *Org. Synth.*, 1955, **CVIII**, 272-274.

o) C. Theeraladanon, M. Arisawa, A. Nishida and M. Nakagawa, *Tetrahedron*, 2004, **60**, 3017–3035.

p) L. C. Bannen, D. S-M. Chan, J. Chen, L. E. Dalrymple, T. P. Forsyth, T. P. Huynh, V. Jammalamadaka, R. G. Khoury, J. W. Leahy, M. B. Mac, G. Mann, L. W. Mann, J. M. Nuss, J. J. Parks, C. S. Takeuchi, Y. Wang and W. Xu, WO2005030140, September 24, 2004.

q) T. P. Forsyth; M. B. Mac; J. W. Leahy; J. M. Nuss and W. Xu, WO2006108059, April 6, 2006.

r) T. Su, J. Zhu, R. Sun, H. Zhang, Q. Huang, X. Zhang, R. Du, L. Qiu and R. Cao, *Eur. J. Med. Chem.*, 2019, **178**, 154–167.

s) Z. Wang, R. Cao, S. Zhang, F. Mo, F. Hu, S. Zhang, Z. Rong, X. Zhang, G. Yang; Z. Luo; S. Xia; C. Sun; R. Zhang and L. Xiong, CN105037266, December 12, 2012.

t) P. Shi, L. Wang, K. Chen, J. Wang and J. Zhu, *Org. Lett.*, 2017, **19**, 2418–2421.

u) V. Bizet and C. Bolm, *European J. Org. Chem.*, 2015, **2015**, 2854–2860.

v) K. Al-Zaydi and R. Borik, *Molecules*, 2007, **12**, 2061–2079.

w) M. V. N. de Souza, K. C. Pais, C. R. Kaiser, M. A. Peralta, M. de L. Ferreira and M. C. S. Lourenço, *Bioorg. Med. Chem.*, 2009, **17**, 1474–1480.

x) G. Bringmann, M. Loedige, A. Kronhardt, C. Beitzinger, H. Barth and R. Benz, WO2012041493, September 28, 2011.

y) V. Ferey, J. Mateos-Caro, R. Mondiere, P. Vayron and S. Vigne, WO2011154923, June 10, 2011.

z) V. Ferey, J. Mateos-Caro, R. Mondiere, P. Vayron and S. Vigne, US2013096306, December 10, 2012.

aa) A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, 1950, **72**, 1814–1815.

ab) E. F. Elslager, S. Marie-Jo, US2902403, December 3, 1956.

ac) E. Yu, H. P. R. Mangunuru, N. S. Telang, C. J. Kong, J. Verghese, S. E. Gilliland III, S. Ahmad, R. N. Dominey and B. F. Gupton, *Beilstein J. Org. Chem.*, 2018, **14**, 583–592.

ad) B.F. Gupton, S. Ahmad, H. P. R. Mangunuru and N. S. Telang, WO2019165337, February 25, 2019.

ae) F. Chen; B. Hou; X. Ma; P. Gong and C. Hou, CN105693606, March 9, 2016.

af) H. Qiang, Q. Xu and Y. Yin, CN109456266, November 12, 2018.

ag) X. Li, G. Yan, J. Wei, P. Zhu, K. Yu, Y. Ding, W. Yu and Y. Ding, CN108689929, July 5, 2018.

ah) Y. Zhang, K. Yu, Q. Huang, Z. Zhang, W. Yu, Y. Ding, J. Wei and P. Zhu, CN108658858, June 27, 2017.

ai) X. Li, G. Yan, J. Wei, P. Zhu, K. Yu, Y. Ding, W. Yu and Y. Ding, CN108727263, July 5, 2018.

aj) M. Tang, D. Gong, Z. Yang, Y. Liu, J. Yang, Z. Cai, Z. Zha, Y. Wang, CN104230803, August 28, 2014.

ak) J. Huang, Z. Li, J. Ran, Z. Wang, Z. Wang and F. Wu, CN109280029, December 11, 2018.

al) J. Zhao, C. Chen, K. Yu, W. Qiu, G. Yan, W. Yu, J. Li, T. Liu, F. Liu, Z. Liu and X. Xu, CN110283121, August 6, 2019.

am) J. Pi, Y. Ding, R. Yue, J. Wei, W. Pan and G. Xie, CN103724261, December 13, 2013.

an) J. S. Glenn and E. A. Pham, WO2017004454, June 30, 2016.

ao) T. K. Olszewski, C. Bomont, P. Coutrot and C. Grison, *J. Organomet. Chem.*, 2010, **695**, 2354–2358.

ap) R. Nisal, G. P. Jose, C. Shanbhag and J. Kalia, *Org. Biomol. Chem.*, 2018, **16**, 4304–4310.

aq) Z. Huang, CN107721835, August 13, 2016.

ar) E. Mizushima, T. Hayashi, K. Sato and M. Tanaka, US2005143597, March 6, 2003.

as) E. Mizushima, D.-M. Cui, D. C. Deb Nath, T. Hayashi and M. Tanaka, *Org. Synth.*, 2006, **83**, 55-60.

at) J. Ning, X. Wu, W. Xu, H. Zhang, Z. Zhang, D. Zheng and J. Zhou, CN103694094.

au) X. Li, CN108586214, December 1, 2018.

av) C. Zhang, K. Yuan, L. Fan, X. Xu, D. Lu, J. Qin and P. Ju, CN109748783, January 31, 2019.

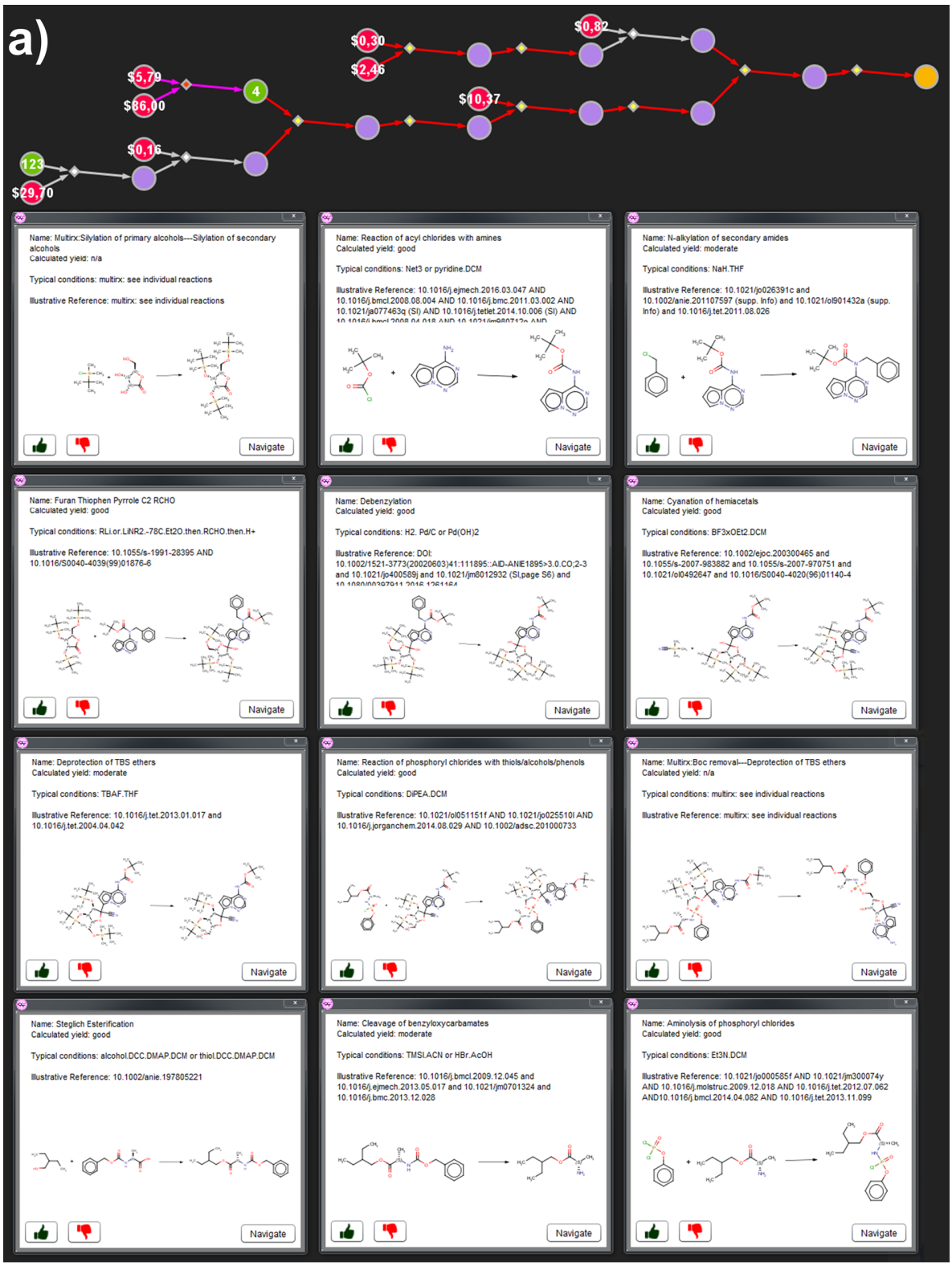
aw) T. J. Fleck, J. J. Chen, C. V. Lu and K. J. Hanson, *Org. Process Res. Dev.*, 2006, **10**, 334–338.

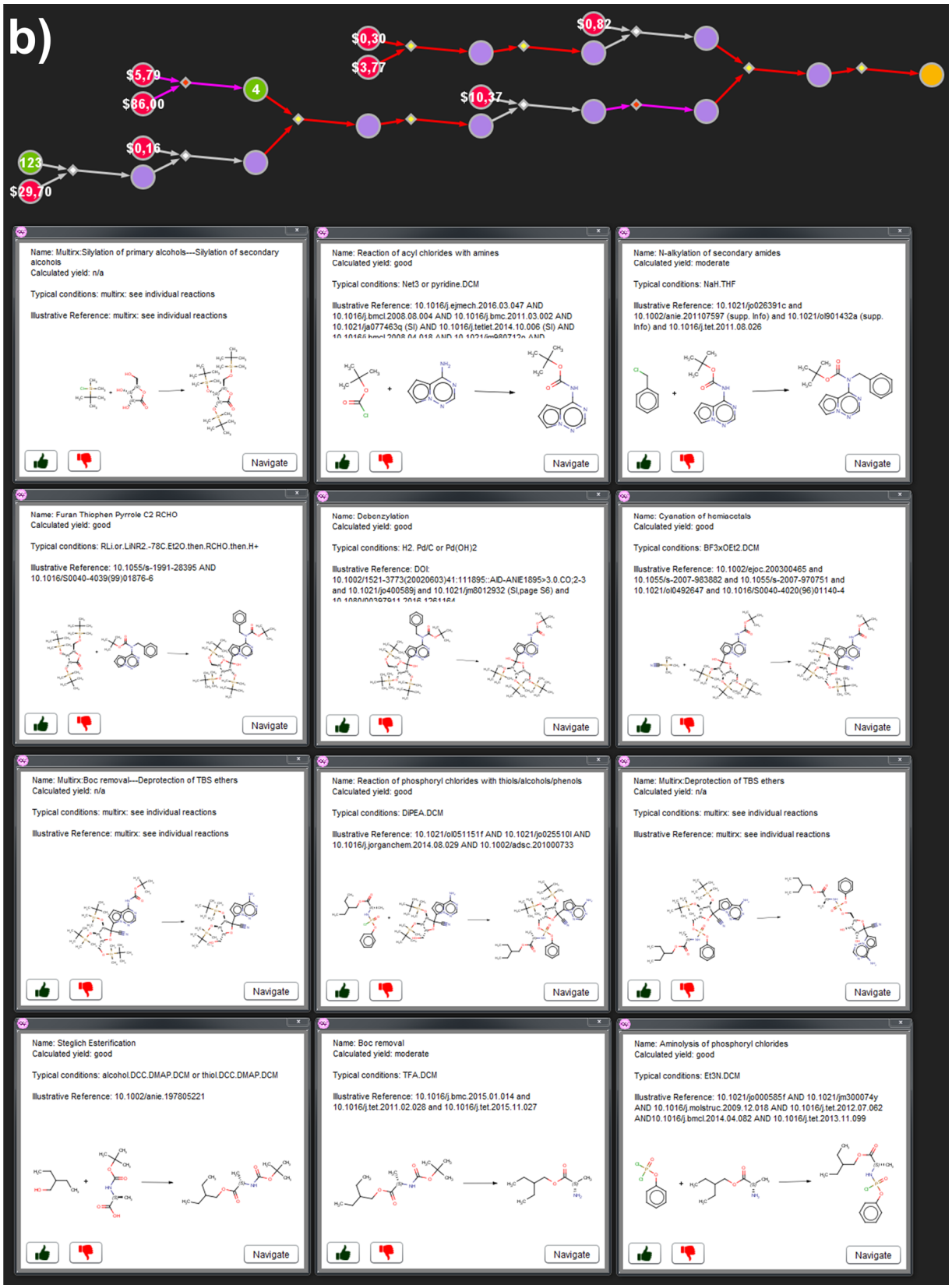
ax) X. Gao, J. Zhou and X. Peng, *Catal. Commun.*, 2019, **122**, 73–78.

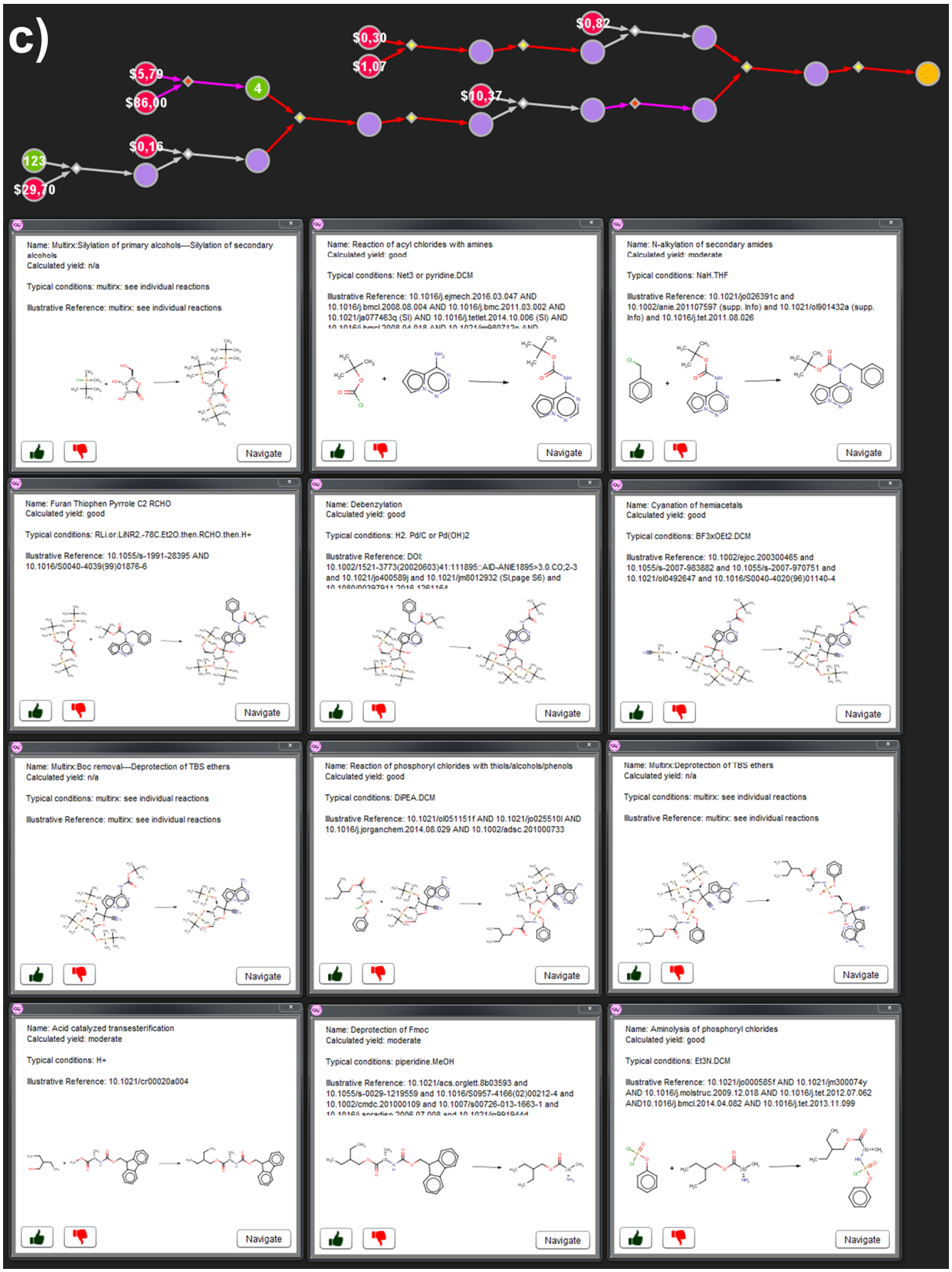
ay) A. R. Surrey, US2546658, July 23 1949.

az) T. Deng, T. Liu, N. Peng and H. You, CN107266323, July 18, 2018.

S4. Screenshots of *Chematica*'s syntheses of remdesivir




b)
$0,30
$3,77
$0,82
$5,79
$86,00
4
$10,37
$0,16
123
$29,70
Name: Multirx:Silylation of primary alcohols---Silylation of secondary alcohols
Calculated yield: n/a
Typical conditions: multirx: see individual reactions
Illustrative Reference: multirx: see individual reactions
Navigate
Name: Reaction of acyl chlorides with amines
Calculated yield: good
Typical conditions: Net3 or pyridine.DCM
Illustrative Reference: 10.1016/j.ejmech.2016.03.047 AND 10.1016/j.bmcl.2008.08.004 AND 10.1016/j.bmc.2011.03.002 AND 10.1021/ja077463q (SI) AND 10.1016/j.tetlet.2014.10.006 (SI) AND
Navigate
Name: N-alkylation of secondary amides
Calculated yield: moderate
Typical conditions: NaH.THF
Illustrative Reference: 10.1021/jo026391c and 10.1002/anie.201107597 (supp. Info) and 10.1021/ol901432a (supp. Info) and 10.1016/j.tet.2011.08.026
Navigate
Name: Furan Thiophen Pyrrole C2 RCHO
Calculated yield: good
Typical conditions: RLi.or.LiNR2.-78C.Et2O.then.RCHO.then.H+
Illustrative Reference: 10.1055/s-1991-28395 AND 10.1016/S0040-4039(99)01876-6
Navigate
Name: Debenzylation
Calculated yield: good
Typical conditions: H2. Pd/C or Pd(OH)2
Illustrative Reference: DOI: 10.1002/1521-3773(20020603)41:111895::AID-ANIE1895>3.0.CO;2-3 and 10.1021/jo400589j and 10.1021/jm8012932 (SI,page S6) and
Navigate
Name: Cyanation of hemiacetals
Calculated yield: good
Typical conditions: BF3xOEt2.DCM
Illustrative Reference: 10.1002/ejoc.200300465 and 10.1055/s-2007-983882 and 10.1055/s-2007-970751 and 10.1021/ol0492647 and 10.1016/S0040-4020(96)01140-4
Navigate
Name: Multirx:Boc removal---Deprotection of TBS ethers
Calculated yield: n/a
Typical conditions: multirx: see individual reactions
Illustrative Reference: multirx: see individual reactions
Navigate
Name: Reaction of phosphoryl chlorides with thiols/alcohols/phenols
Calculated yield: good
Typical conditions: DiPEA.DCM
Illustrative Reference: 10.1021/ol051151f AND 10.1021/jo025510l AND 10.1016/j.jorganchem.2014.08.029 AND 10.1002/adsc.201000733
Navigate
Name: Multirx:Deprotection of TBS ethers
Calculated yield: n/a
Typical conditions: multirx: see individual reactions
Illustrative Reference: multirx: see individual reactions
Navigate
Name: Steglich Esterification
Calculated yield: good
Typical conditions: alcohol.DCC.DMAP.DCM or thiol.DCC.DMAP.DCM
Illustrative Reference: 10.1002/anie.197805221
Navigate
Name: Boc removal
Calculated yield: moderate
Typical conditions: TFA.DCM
Illustrative Reference: 10.1016/j.bmc.2015.01.014 and 10.1016/j.tet.2011.02.028 and 10.1016/j.tet.2015.11.027
Navigate
Name: Aminolysis of phosphoryl chlorides
Calculated yield: good
Typical conditions: Et3N.DCM
Illustrative Reference: 10.1021/jo000585f AND 10.1021/jm300074y AND 10.1016/j.molstruc.2009.12.018 AND 10.1016/j.tet.2012.07.062 AND10.1016/j.bmcl.2014.04.082 AND 10.1016/j.tet.2013.11.099
Navigate


c)
$0,30
$1,07
$0,82
$5,79
$86,00
4
$10,37
$0,16
123
$29,70
Name: Multirx:Silylation of primary alcohols---Silylation of secondary alcohols
Calculated yield: n/a
Typical conditions: multirx: see individual reactions
Illustrative Reference: multirx: see individual reactions
Navigate
Name: Reaction of acyl chlorides with amines
Calculated yield: good
Typical conditions: Net3 or pyridine.DCM
Illustrative Reference: 10.1016/j.ejmech.2016.03.047 AND 10.1016/j.bmcl.2008.08.004 AND 10.1016/j.bmc.2011.03.002 AND 10.1021/ja077463q (SI) AND 10.1016/j.tetlet.2014.10.006 (SI) AND
Navigate
Name: N-alkylation of secondary amides
Calculated yield: moderate
Typical conditions: NaH.THF
Illustrative Reference: 10.1021/jo026391c and 10.1002/anie.201107597 (supp. Info) and 10.1021/ol901432a (supp. Info) and 10.1016/j.tet.2011.08.026
Navigate
Name: Furan Thiophen Pyrrole C2 RCHO
Calculated yield: good
Typical conditions: RLi.or.LiNR2.-78C.Et2O.then.RCHO.then.H+
Illustrative Reference: 10.1055/s-1991-28395 AND 10.1016/S0040-4039(99)01876-6
Navigate
Name: Debenzylation
Calculated yield: good
Typical conditions: H2. Pd/C or Pd(OH)2
Illustrative Reference: DOI: 10.1002/1521-3773(20020603)41:111895::AID-ANIE1895>3.0.CO;2-3 and 10.1021/jo400589j and 10.1021/jm8012932 (SI,page S6) and
Navigate
Name: Cyanation of hemiacetals
Calculated yield: good
Typical conditions: BF3xOEt2.DCM
Illustrative Reference: 10.1002/ejoc.200300465 and 10.1055/s-2007-983882 and 10.1055/s-2007-970751 and 10.1021/ol0492647 and 10.1016/S0040-4020(96)01140-4
Navigate
Name: Multirx:Boc removal---Deprotection of TBS ethers
Calculated yield: n/a
Typical conditions: multirx: see individual reactions
Illustrative Reference: multirx: see individual reactions
Navigate
Name: Reaction of phosphoryl chlorides with thiols/alcohols/phenols
Calculated yield: good
Typical conditions: DiPEA.DCM
Illustrative Reference: 10.1021/ol051151f AND 10.1021/jo025510l AND 10.1016/j.jorganchem.2014.08.029 AND 10.1002/adsc.201000733
Navigate
Name: Multirx:Deprotection of TBS ethers
Calculated yield: n/a
Typical conditions: multirx: see individual reactions
Illustrative Reference: multirx: see individual reactions
Navigate
Name: Acid catalyzed transesterification
Calculated yield: moderate
Typical conditions: H+
Illustrative Reference: 10.1021/cr00020a004
Navigate
Name: Deprotection of Fmoc
Calculated yield: moderate
Typical conditions: piperidine.MeOH
Illustrative Reference: 10.1021/acs.orglett.8b03593 and 10.1055/s-0029-1219559 and 10.1016/S0957-4166(02)00212-4 and 10.1002/cmdc.201000109 and 10.1007/s00726-013-1663-1 and
Navigate
Name: Aminolysis of phosphoryl chlorides
Calculated yield: good
Typical conditions: Et3N.DCM
Illustrative Reference: 10.1021/jo000585f AND 10.1021/jm300074y AND 10.1016/j.molstruc.2009.12.018 AND 10.1016/j.tet.2012.07.062 AND10.1016/j.bmcl.2014.04.082 AND 10.1016/j.tet.2013.11.099
Navigate

Chematica's syntheses of Remdesivir mimic the known approach relying on the addition of appropriate metalated heterocycle to a protected ribolactone and subsequent cyanation of the obtained hemiacetal. The side chain is constructed via sequential functionalization of phenylphosphoryl dichloride.

Supplementary references:

S1. S. Szymkuć, E. P. Gajewska, T. Klucznik, K. Molga, P. Dittwald, M. Startek, M. Bajczyk and B. A. Grzybowski, *Angew. Chemie Int. Ed.*, 2016, **55**, 5904–5937.
S2. T. Klucznik, B. Mikulak-Klucznik, M. P. McCormack, H. Lima, S. Szymkuć, M. Bhowmick, K. Molga, Y. Zhou, L. Rickershauser, E. P. Gajewska, A. Toutchkine, P. Dittwald, M. P. Startek, G. J. Kirkovits, R. Roszak, A. Adamski, B. Sieredzińska, M. Mrksich, S. L. J. Trice and B. A. Grzybowski, *Chem*, 2018, **4**, 522–532.
S3. K. Molga, E. P. Gajewska, S. Szymkuć and B. A. Grzybowski, *React. Chem. Eng.*, 2019, **4**, 1506–1521.
S4. T. Badowski, K. Molga and B. A. Grzybowski, *Chem. Sci.*, 2019, **10**, 4640–4651.