Directed Synthesis and Retro-Synthesis: In-Silico Exploration of Synthetically Accessible and Medicinally Relevant Chemical Space

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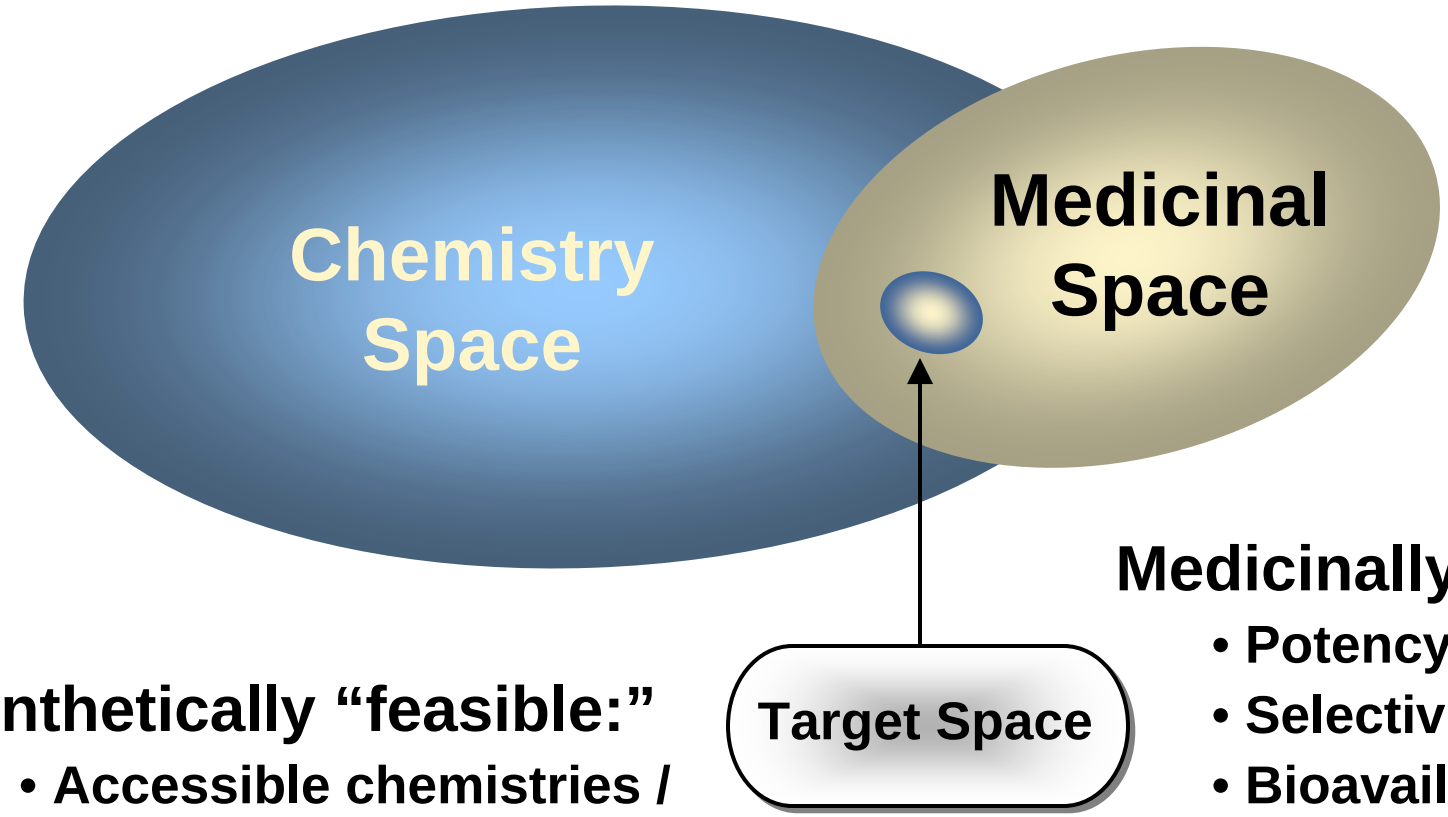
What can be made – What is relevant?



Synthetically "feasible:"

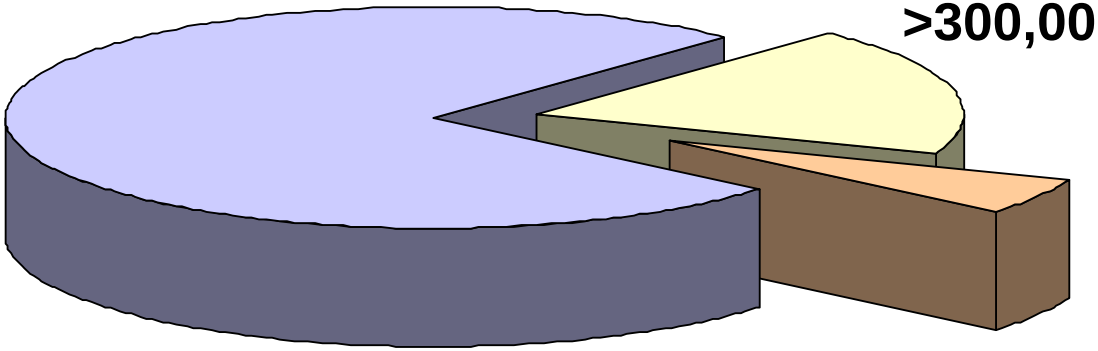
- Accessible chemistries / In-house expertise
- Starting material availability
- Cost / time

Medicinally relevant:

- Potency
- Selectivity
- Bioavailability
- Low toxicity
- Cost effective

SAR and reaction chemistry archive

>4 Million unique structures



>300,000 Unique kinase molecules

>117,000 SAR data points

- >10,000 HTS reactions with experimental procedures
  (>1,500 associated with heterocyclic Kinase inhibitors)
- >8,500 Assay protocols with detailed information
- >45 Kinase target SAR training sets
- >45 Predictive eScreen™ models

Kinase gene family approach

AGC Group

- PKA
- PKG
- PRKCA / PKCa
- PRKCB1 / PCKb
- PRKCD / PCKd
- PRKCE / PKCe
- PRKCG / PKCg
- PRKCH / PKCh

TK-NR

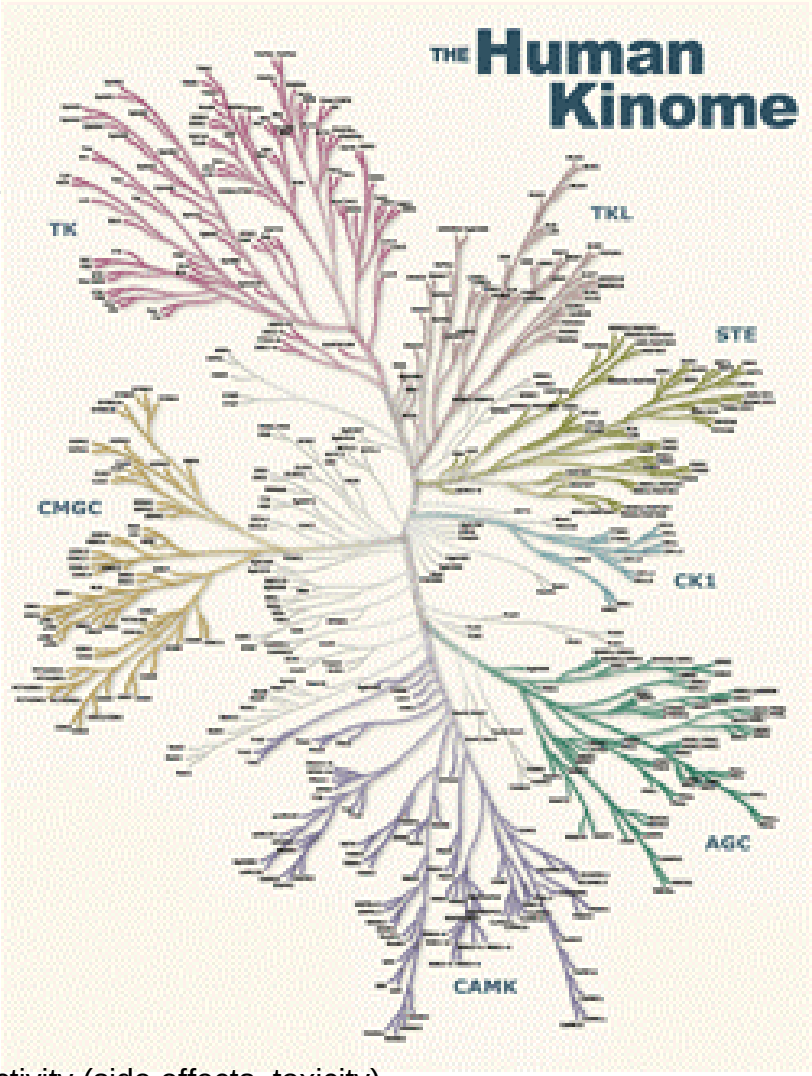
- CSK / c-Src
- SRC / v-Src
- FYN
- LYN
- LCK
- ABL1
- SYK
- ZAP70

TK-R

- EGFR
- ERBB2 / HER2
- FGFR
- CSF1R / FMS
- PDGFRA
- PDGFRB
- FLT1
- KDR
- TEK / TIE2

CMGC Group

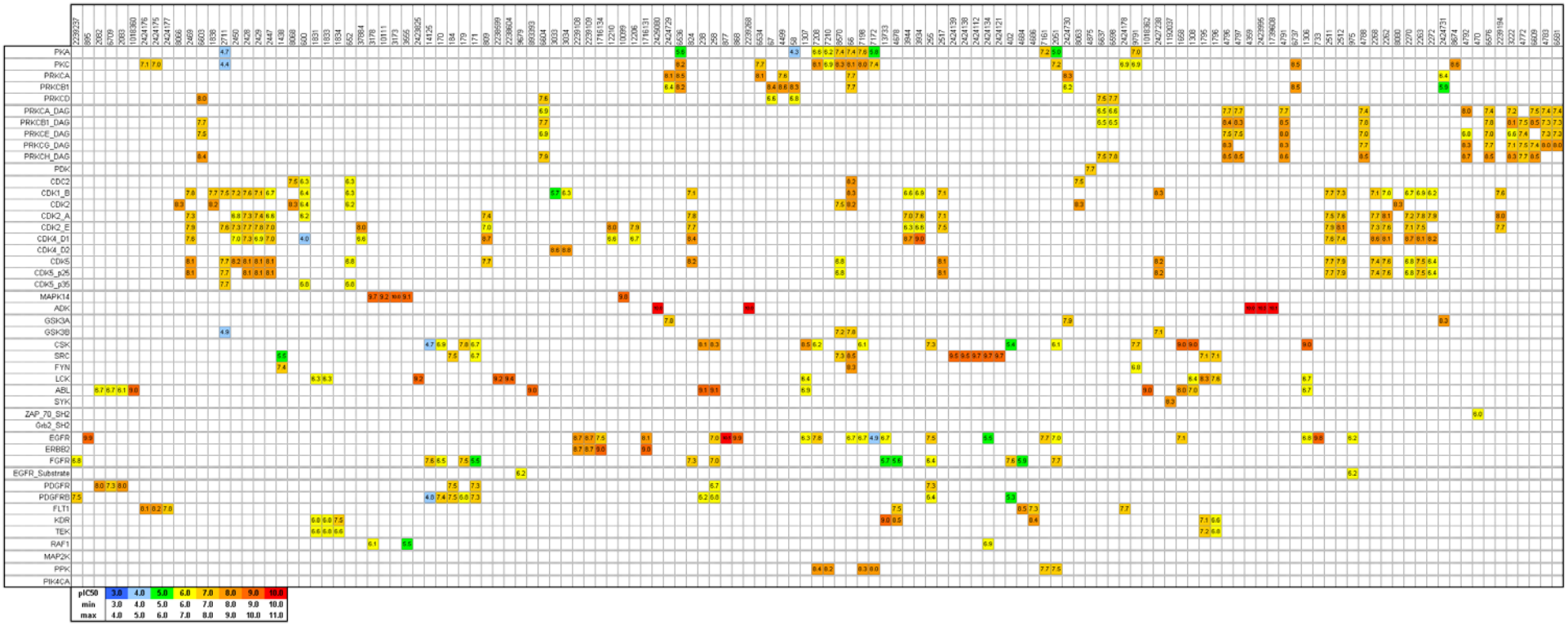
- CDC2 / CDK1
- CDK2
- CDK4
- CDK5
- GSK3A
- GSK3B
- MAPK1 / Erk2
- MAPK3 / Erk1
- MAPK9 / JNK2
- MAPK11 / p38b
- MAPK14 / p38a



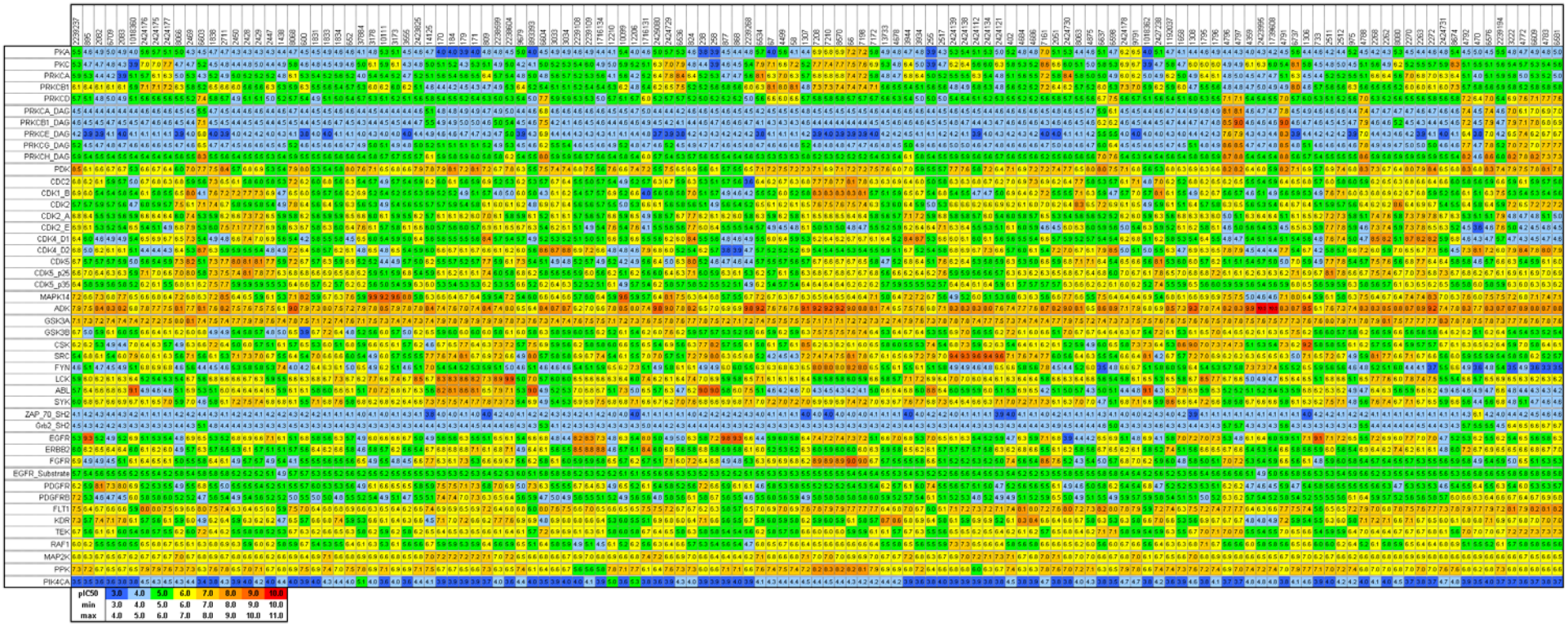
Gene-family-wide approach:

- Analysis of efficacy vs. selectivity (side effects, toxicity)
- Interrelationship between kinases provides additional opportunities for lead compounds (closely related targets)

Observed potency and selectivity

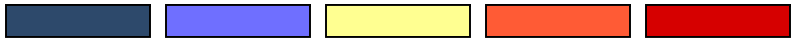


ePotency and eSelectivity



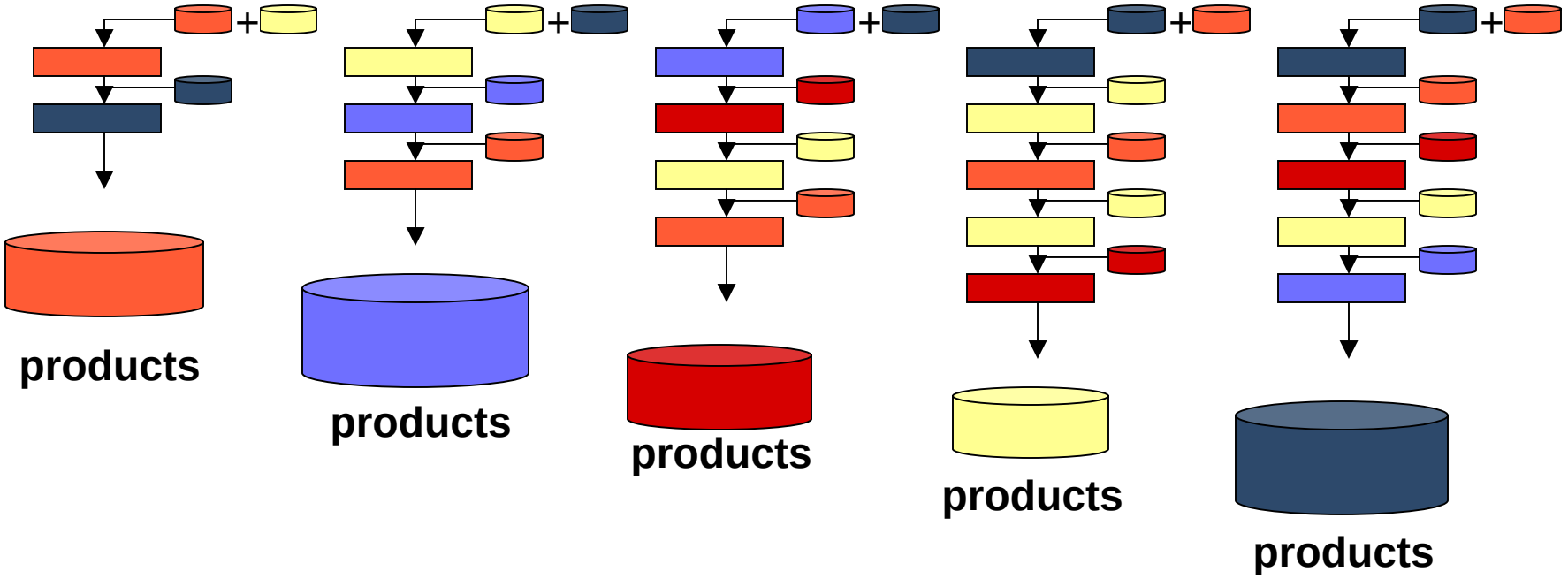
Theoretically accessible chemical space

Chemical transformation types:



Available building blocks:

Potential synthetic strategies:

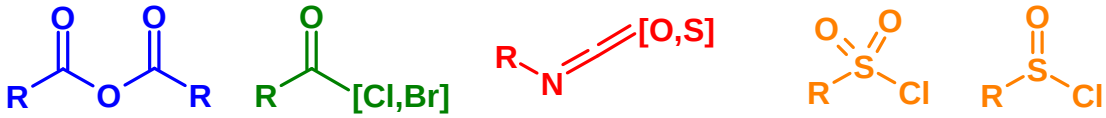


Basic chemistry 101

Chemical (in)-compatibility:

- Cross reactivity of functional groups
- Incompatible functional groups at given reaction type and conditions
- Avoid side reactions, catalyst poisoning, etc.

E.g. Acylators:



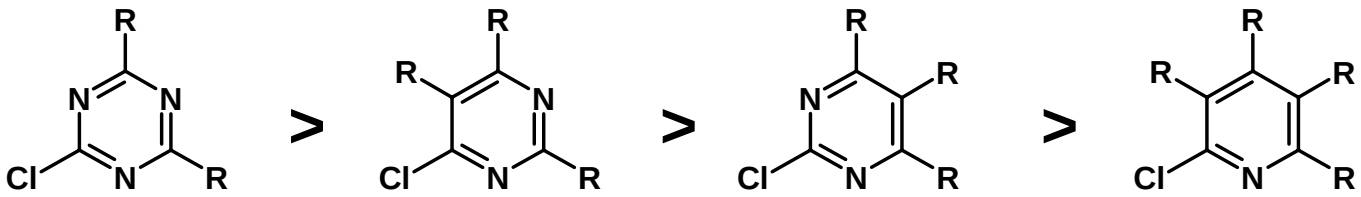

```
C;$(C(=O)OC(=O));!$(C(=O)OC(=O)[!#6]);!$(C(=O)(OC(=O))[!#6])]
OR
C;$(C(=[O,N,S])[F,Cl,Br])]
OR
[C;$(C(=[O,S])=N)]
OR
S;$(S(=O)[Cl,Br,F,I])]
```

Basic chemistry 102

Chemical reactivity:

- Reaction-type specific differences in reactivity
- Usually influenced by reaction center environment
- Definition of the reaction center details

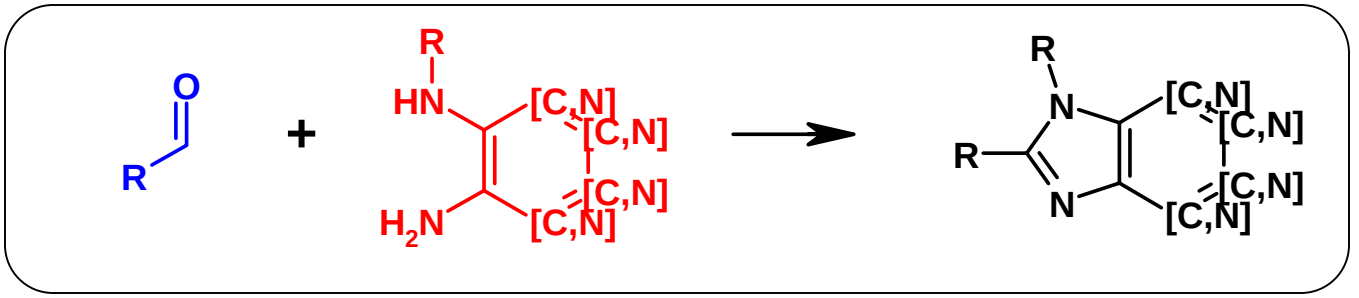
E.g. Nucleophilic aromatic substitution:



Nucleophilicity of aliphatic primary vs. secondary vs. aromatic amines

Introspective filters (transform embedded)

(In)Compatibility filters



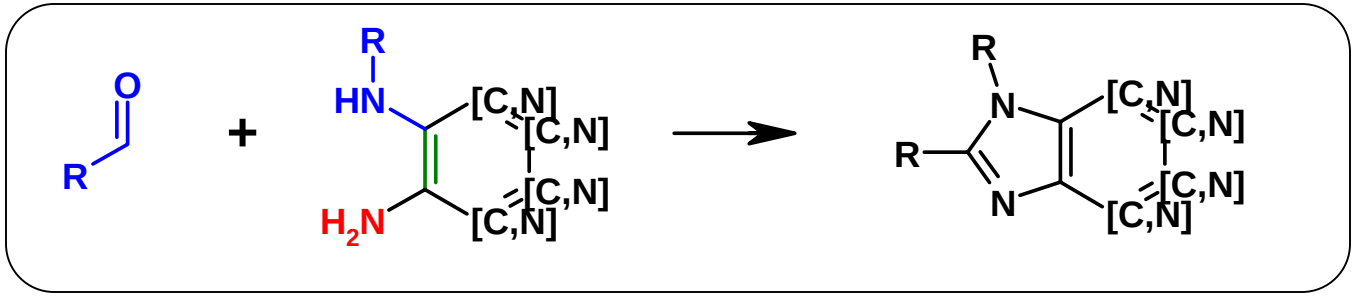
Required: aldehyde; Exclude: >1 aldehyde, amino-2-arylamine, basic nucleophiles, acids, acylators, alkylators, activated aryl halides

```
{[C;!H0;$(C=O);!$(C(=O)[!#6]);!$(C(=O)=[A])]} AND NOT
{{[C;!H0;$(C=O);!$(C(=O)[!#6]);!$(C(=O)=[A])].[C;!H0;$(C=O);!$(C(=O)[!#6]);!$(C(=O)=[A])]} OR
{c(c([NH2;v3])[a])([a])[N;!H0;!$([N+]);!$(NC=,#[!#6]);!$(NC=,#[#6]);!$(N[!#6])]} OR
{[N;!H0;$(NC);!$([N+]);!$(NC=,#[!#6]);!$(NC=,#[#6]);!$(N[!#6]);!$(Nc)] OR [N;!H0;$(N[N;$(N[#6]);!$(NC=,#[!#6])]);!$(NC=,#[!#6])] OR
C([NH2])=[NH] OR [S;$([SH]),$([S-])]} OR {[S;$(S(=O)[OH])] OR [C;$(C(=O)[OH]);!$(C(=O)([OH])[!#6])]} OR
{[C;$(C(=[O,N,S])[O,S]C(=[O,N,S]))] OR [C;$(C(=[O,N,S])[F,Cl,Br])] OR [C;$(C(=[O,S])=N)] OR [S;$(S(=O)[Cl,Br,F,I])]} OR
{[C;$(C[Br,I]);!$(C=,#[A])] OR [C;$(COS(=O)(=O))]} OR {[c;$(c1([Cl,Br,F,I])nc[n,c][c,n][c,n]1)] OR {[c;$(c1([F,Cl])c([N+](=O)[O-
])cccc1),$(c1([F,Cl])ccc([N+](=O)[O-])cc1)] OR c1(c(c([A;$(C#N),$([N+](=O)[O-]),$(C=O),$(C([F,Cl])([F,Cl])[F,Cl]),$(S=O)])cnc1)[F,Cl])}}}
```

Required: amino-2-arylamine; Exclude: basic nucleophiles, aldehydes, acids, acylators, alkylators, activated aryl halides

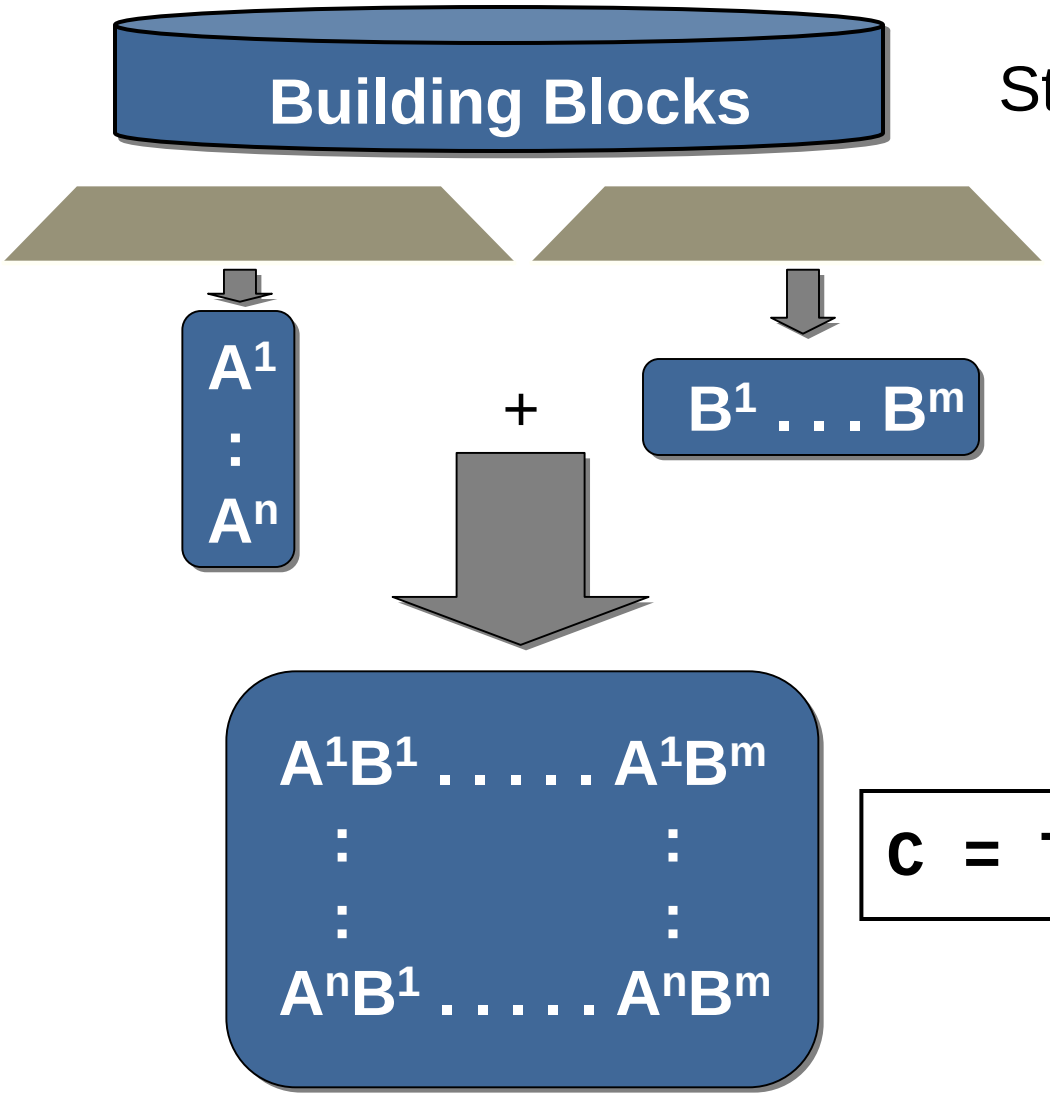
```
{c(c([NH2;v3])[a])([a])[N;!H0;!$([N+]);!$(NC=,#[!#6]);!$(NC=,#[#6]);!$(N[!#6])]} AND NOT
{{[N;!H0;$(NC);!$([N+]);!$(NC=,#[!#6]);!$(NC=,#[#6]);!$(N[!#6]);!$(Nc)] OR {[N;!H0;$(N[N;$(N[#6]);!$(NC=,#[!#6])]);!$(NC=,#[!#6])] OR
C([NH2])=[NH]} OR [S;$([SH]),$([S-])]} OR [C;!H0;$(C=O);!$(C(=O)[!#6]);!$(C(=O)=[A])] OR {[S;$(S(=O)[OH])] OR
[C;$(C(=O)[OH]);!$(C(=O)([OH])[!#6])]} OR {[C;$(C(=[O,N,S])[O,S]C(=[O,N,S]))] OR [C;$(C(=[O,N,S])[F,Cl,Br])] OR [C;$(C(=[O,S])=N)] OR
[S;$(S(=O)[Cl,Br,F,I])]} OR {[C;$(C[Br,I]);!$(C=,#[A])] OR [C;$(COS(=O)(=O))]} OR {[c;$(c1([Cl,Br,F,I])nc[n,c][c,n][c,n]1)] OR
{[c;$(c1([F,Cl])c([N+](=O)[O-])cccc1),$(c1([F,Cl])ccc([N+](=O)[O-])cc1)] OR c1(c(c([A;$(C#N),$([N+](=O)[O-
]),$(C=O),$(C([F,Cl])([F,Cl])[F,Cl]),$(S=O)])cnc1)[F,Cl])}}}
```

Introspective filters and transforms




```
[C;$([C;!H0](=O)[A,a]);!$(C(=O)[!#6]);!$(C(=O)=[A]):5](=O)([A,a:2])[H]
.
[N;$([N;!H0](c1[#6,#7][#6,#7][#6,#7][#6,#7]c1[N;!H0;!H1])[A,a]);!$([N+
]);!$(NC=,#[!#6]);!$(NC=,#[#6]);!$(N[!#6;!H1]):4]([c:11]1[c:10]([N;!H0
;!H1:3]([H])[H])[a:8][a:6][a:7][a:9]1)([A,a:1])[H]
>>
[n:3]1[c:5]([n:4]([c:11]2[c:10]1[a:8][a:6][a:7][a:9]2)[A,a:1])[A,a:2]
```

Chemical transforms and filters



Starting Material Database

Incompatibility Filters

Reaction Input BB

Transform (T) including introspective filters

$C = T(BB^A, BB^B)$

Products

Transforms and filters - cont'd

$$A + B \longrightarrow C$$

$$C + D \longrightarrow E$$

$$C = T_1(BB^A, BB^B)$$

$$E = T_2(C, BB^D)$$

$$= T_2[T_1(BB^A, BB^B), BB^D]$$

Filtration of final products: Lipinski - F^{Lip} , structural filters (undesired functional groups or fragments) - $F^{BadFrag}$, QSAR - F^{QSAR}

$$E^{final} = F^{QSAR}\{F^{BadFrag}\{F^{Lip}(E)\}\}$$

$$= F^{QSAR}\{F^{BadFrag}\{F^{Lip}(T_2[T_1(BB^A, BB^B), BB^D])\}\}$$

ChIP – Chemical intelligence platform

- Forward, prospective exploration of existing and newly coupled synthetic strategies
- Dynamic recombination of synthetic pathways to generate novel synthetically accessible molecules
- Pre- and post-synthesis filtering and prioritization
- Synthesis strategies guided towards novel and medicinally relevant molecules using ePotency, eSelectivity, and eADMEtox models
- Diversity-oriented or directed evolution of molecules

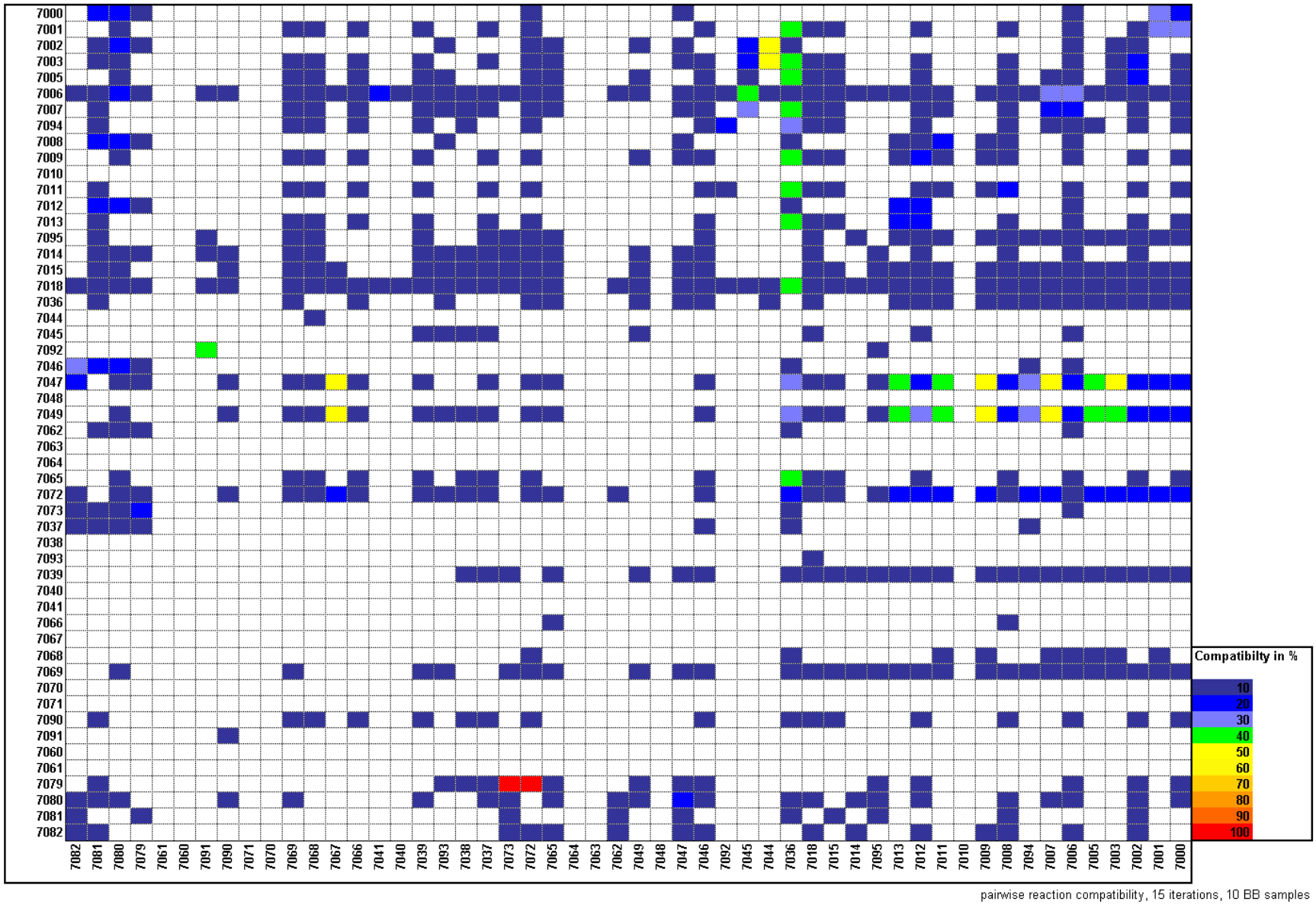
Chemical transformations explored

- Subset 1: Nucleophilic aromatic substitution reactions
- Subset 2: Pd-catalyzed aromatic substitutions
- Subset 3: Functional group transformations
- Subset 4: Amine acylation reactions (amides / carbamates)
- Subset 5: Amine acylation reactions (ureas / thioureas)
- Subset 6: Formation of diverse (annelated) heterocyclic systems (quinazolinones, -diones, benzoimidazoles, -oxazoles, thiazoles)
- Subset 7: Formation of thioimidazoles
- Subset 8: Standard deprotection steps (Fmoc, Boc, *t*-Butyl, Trityl,)

Systematic vs. directed exploration - GA

- Systematic Exploration is not feasible: too many reaction combinations and building blocks – many of them not productive or not relevant
- Directed exploration leveraging a genetic algorithm (GA):
  - Uses text-based representation of reaction step transform
  - Starts with random sequence (starting gene) and generate products for this sequence starting from pre-filtered commercial building blocks
  - Apply Lipinski (MWT, HBA/HBD, ClogP, TPSA, rotBond) and structural filters like reactive functionalities (alkylators / acylators, electrophiles, nucleophiles, etc.) and undesired motifs (non-standard elements, >2 halo or >1 nitro per aryl, thioesters / ureas, un-branched chains, etc.)
  - Evaluate remaining structures by predicted activity (or other scoring function), e.g.: **`100 – 15 * Max (eActivity)`**
  - Optimization of reaction sequences by crossover mutation of highest scoring sequences
- Throughout the simulation best sequences and their products are captured

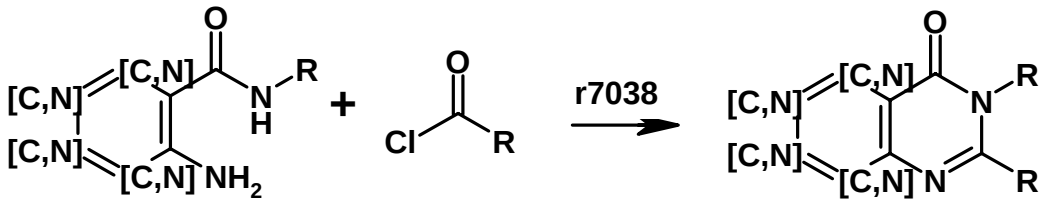
Pair-wise reaction compatibility

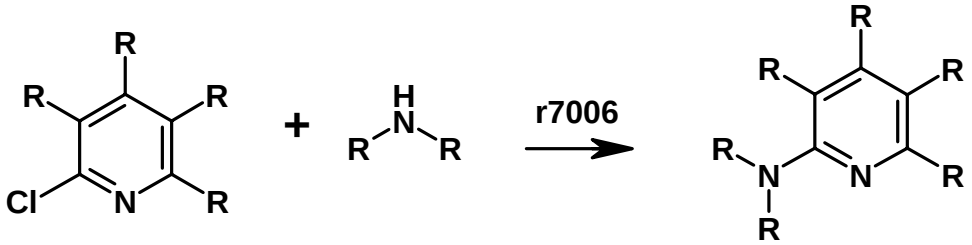


pairwise reaction compatibility, 15 iterations, 10 BB samples

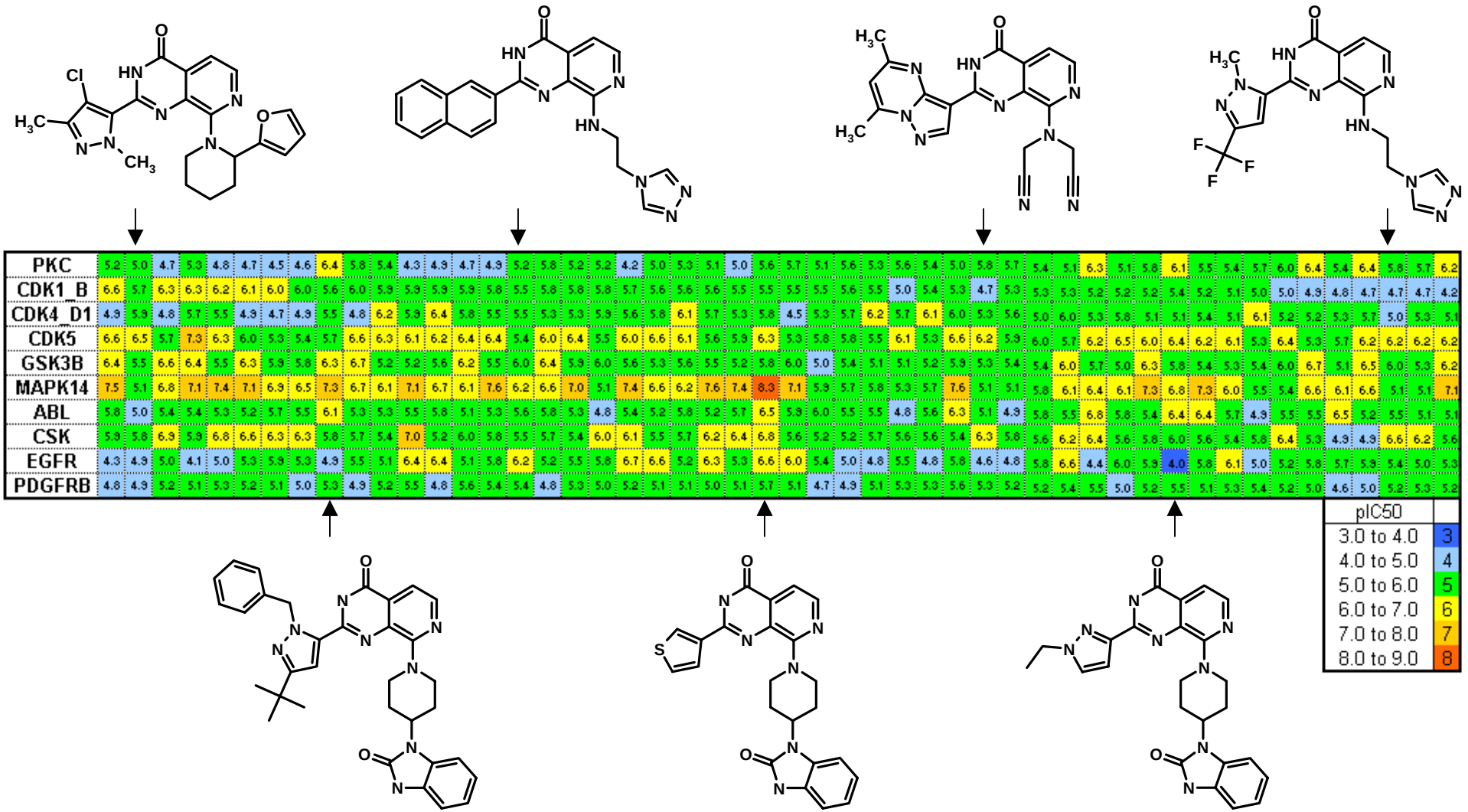
ATP-binding site-directed simulations

vProtocol for the Synthesis of 4-aminopyridopyrimidinones:

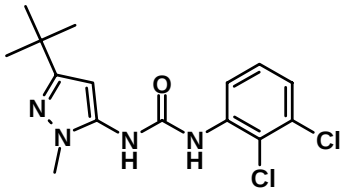




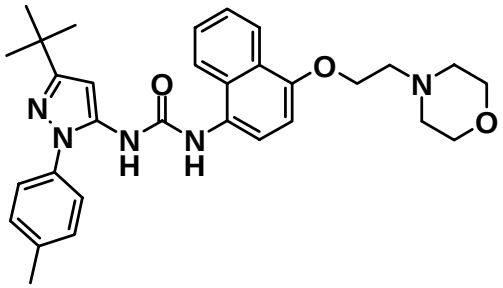
Results


PKC 5.2 5.0 4.7 5.3 4.8 4.7 4.5 4.6 6.4 5.8 5.4 4.3 4.9 4.7 4.9 5.2 5.8 5.2 5.2 4.2 5.0 5.3 5.1 5.0 5.6 5.7 5.1 5.6 5.3 5.6 5.4 5.0 5.8 5.7 5.4 5.1 6.3 5.1 5.8 6.1 5.5 5.4 5.7 6.0 6.4 5.4 6.4 5.8 5.7 6.2
CDK1_B 6.6 5.7 6.3 6.3 6.2 6.1 6.0 6.0 5.6 6.0 5.9 5.9 5.9 5.9 5.8 5.5 5.8 5.6 5.8 5.7 5.6 5.6 5.6 5.5 5.5 5.5 5.5 5.6 5.5 5.0 5.4 5.3 4.7 5.3 5.3 5.3 5.2 5.2 5.2 5.4 5.2 5.1 5.0 5.0 4.9 4.8 4.7 4.7 4.7 4.2
CDK4_D1 4.3 5.9 4.8 5.7 5.5 4.9 4.7 4.9 5.5 4.8 6.2 5.9 6.4 5.8 5.5 5.5 5.3 5.3 5.9 5.6 5.8 6.1 5.7 5.3 5.8 4.5 5.0 5.7 6.2 5.7 6.1 6.0 5.3 5.6 5.0 6.0 5.3 5.8 5.1 5.1 5.4 5.1 6.1 5.2 5.2 5.3 5.7 5.0 5.3 5.1
CDK5 6.6 6.5 5.7 7.3 6.3 6.0 5.3 5.4 5.7 6.6 6.3 6.1 6.2 6.4 6.4 5.4 6.0 6.4 5.5 6.0 6.6 6.1 5.6 5.9 6.3 5.3 5.8 5.8 5.5 6.1 5.3 6.6 6.2 5.9 6.0 5.7 6.2 6.5 6.0 6.4 6.2 6.1 5.3 6.4 5.3 5.7 6.2 6.2 6.2 6.2
GSK3B 6.4 5.5 6.6 6.4 5.5 6.3 5.9 5.8 6.3 6.7 5.2 5.2 5.6 6.2 5.5 6.0 6.4 5.9 6.0 5.6 5.3 5.6 5.5 5.2 5.8 6.0 5.0 5.4 5.1 5.1 5.2 5.9 5.3 5.4 5.4 6.0 5.7 5.0 6.3 5.8 5.4 5.3 5.4 6.0 6.7 5.1 6.5 6.0 5.3 6.2
MAPK14 7.5 5.1 6.8 7.1 7.4 7.1 6.9 6.5 7.3 6.7 6.1 7.1 6.7 6.1 7.6 6.2 6.6 7.0 5.1 7.4 6.6 6.2 7.6 7.4 8.3 7.1 5.9 5.7 5.9 5.3 5.7 7.6 5.1 5.1 5.8 6.1 6.4 6.1 7.3 6.8 7.3 6.0 5.5 5.4 6.6 6.1 6.6 5.1 5.1 7.1
ABL 5.8 5.0 5.4 5.4 5.3 5.2 5.7 5.5 6.1 5.3 5.3 5.5 5.8 5.1 5.3 5.6 5.8 5.3 4.8 5.4 5.2 5.8 5.2 5.7 6.5 5.9 6.0 5.5 5.5 4.8 5.6 6.3 5.1 4.3 5.8 5.5 6.8 5.8 5.4 6.4 6.4 5.7 4.3 5.5 5.5 6.5 5.2 5.5 5.1 5.1
CSK 5.9 5.8 6.9 5.9 6.8 6.6 6.3 6.3 5.8 5.7 5.4 7.0 5.2 6.0 5.8 5.5 5.7 5.4 6.0 6.1 5.5 5.7 6.2 6.4 6.8 5.6 5.2 5.2 5.7 5.6 5.6 5.4 6.3 5.8 5.6 6.2 6.4 5.6 5.8 6.0 5.6 5.4 5.8 6.4 5.3 4.9 4.3 6.6 6.2 5.6
EGFR 4.3 4.9 5.0 4.1 5.0 5.3 5.9 5.3 4.3 5.5 5.1 6.4 6.4 5.1 5.8 6.2 5.2 5.5 5.8 6.7 6.6 5.2 6.3 5.3 6.6 6.0 5.4 5.0 4.8 5.5 4.8 5.8 4.6 4.8 5.8 6.6 4.4 6.0 5.9 4.0 5.8 6.1 5.0 5.2 5.8 5.7 5.9 5.4 5.0 5.3
PDGFRB 4.8 4.9 5.2 5.1 5.0 5.2 5.1 5.0 5.3 4.9 5.2 5.5 4.8 5.6 5.4 5.4 4.8 5.3 5.0 5.2 5.1 5.1 5.0 5.1 5.7 5.1 4.7 4.9 5.1 5.3 5.3 5.6 5.3 5.2 5.2 5.4 5.5 5.0 5.2 5.5 5.1 5.3 5.4 5.2 5.0 4.6 5.0 5.2 5.3 5.2
pIC50
3.0 to 4.0 3
4.0 to 5.0 4
5.0 to 6.0 5
6.0 to 7.0 6
7.0 to 8.0 7
8.0 to 9.0 8

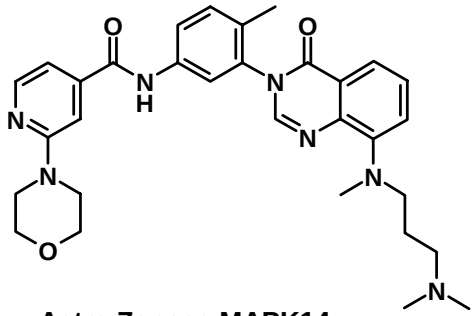
Tanimoto similarities



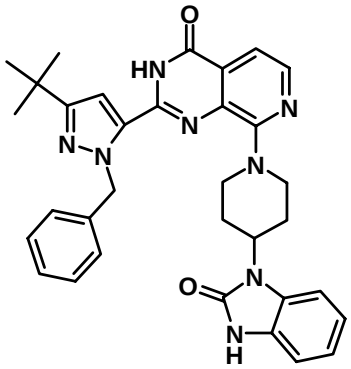
Bayer MAPK14 inhibitor
IC50 = 53 nM



Boehringer Ingelheim MAPK14
IC50 = 18 nM



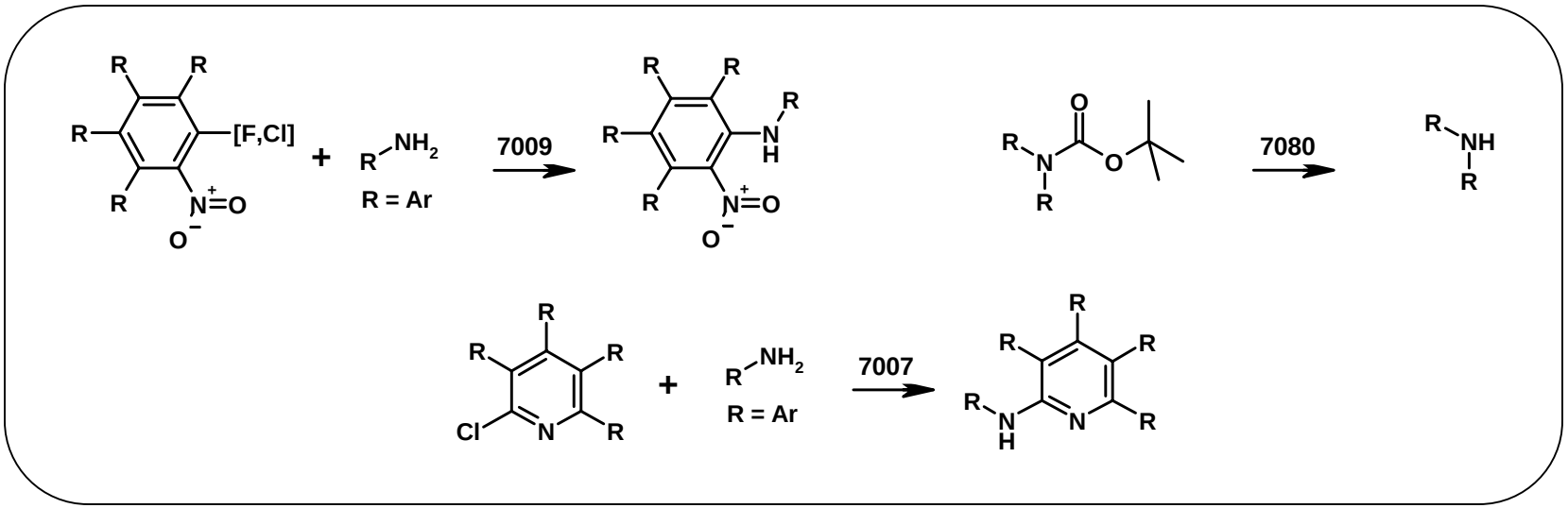
Astra Zeneca MAPK14
IC50 = 100 nM

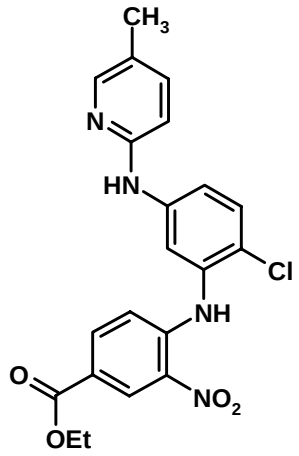


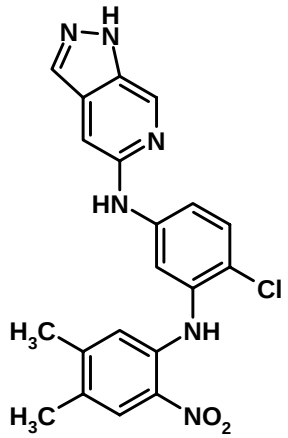
Simulation result MAPK14

0.40	0.49	0.62	structural
0.28	0.64	0.44	pharmacophoric

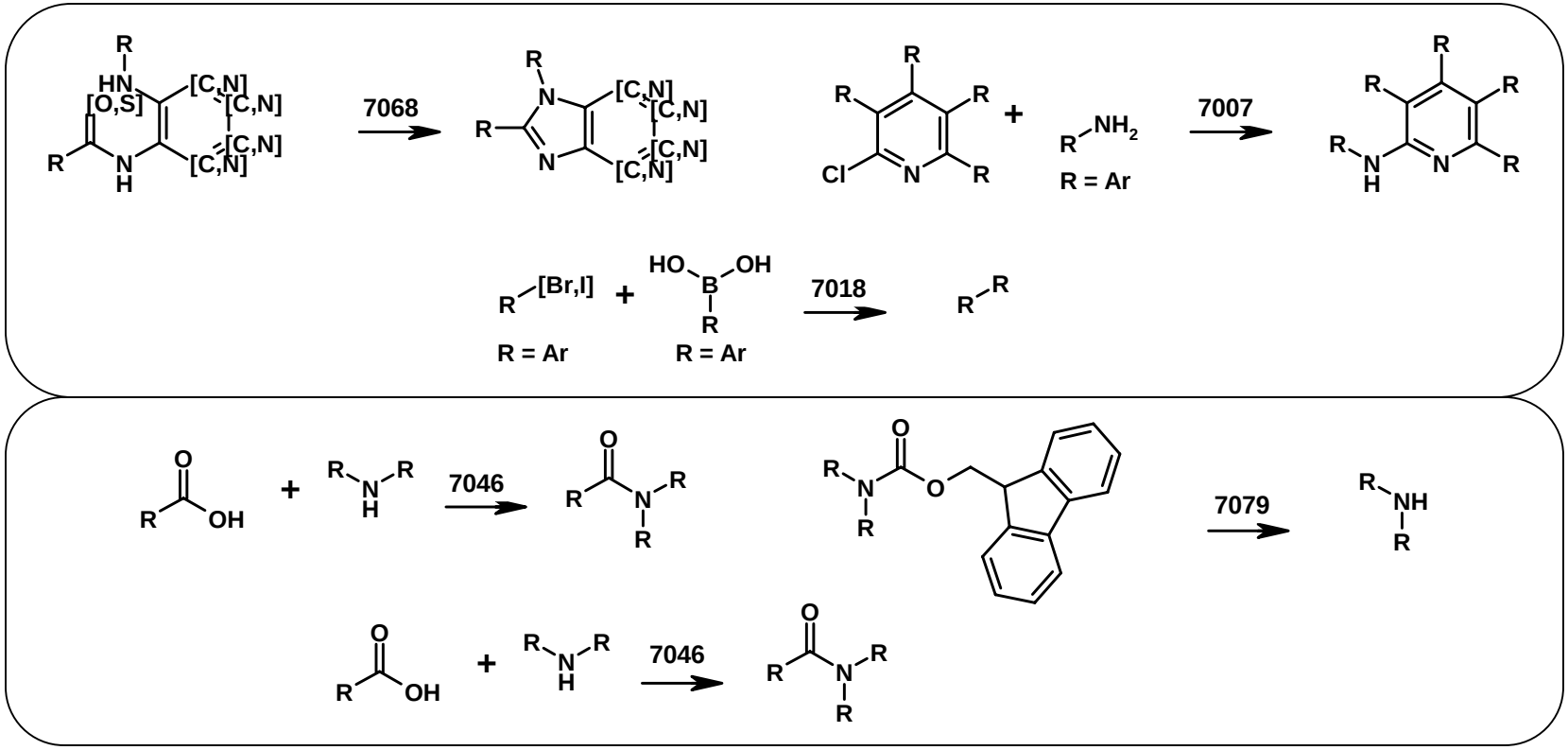
Similarity-directed simulations I

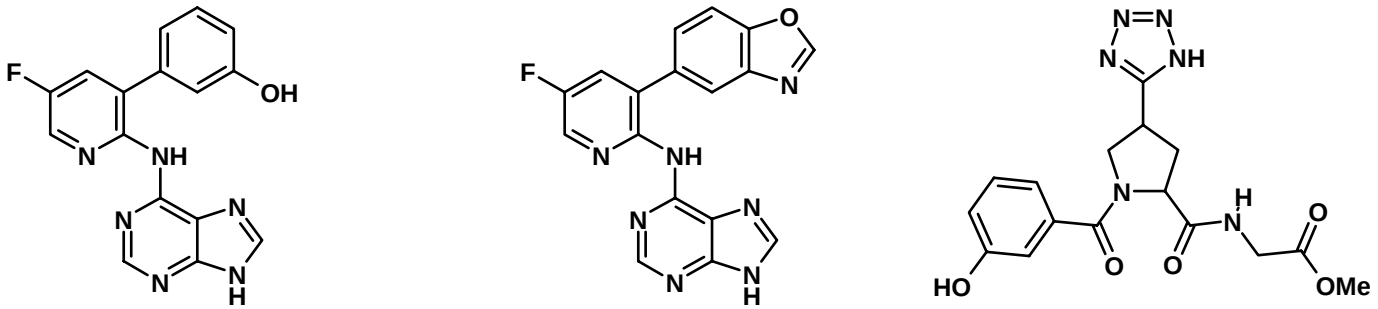






Similarity-directed simulations I - cont'd



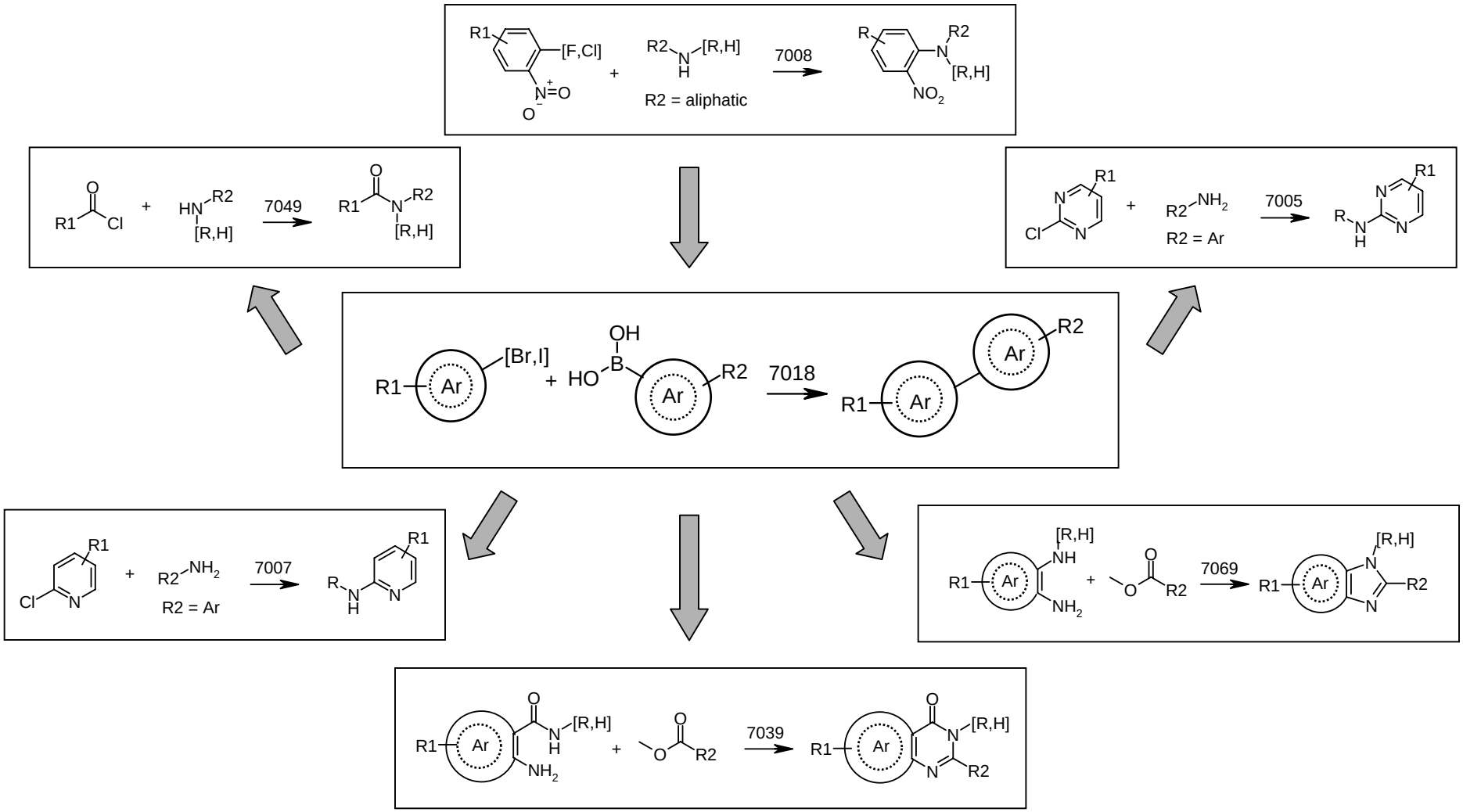


Results – predicted activity matrix

		PKA	PKC	PRKCA	PRKCB1	PRKCD	PRKCA_DAG	PRKCB1_DAG	PRKCE_DAG	PRKCG_DAG	PRKCH_DAG	PDK	CDC2	CDK1_B	CDK2	CDK2_A	CDK2_E	CDK4_D1	CDK4_D2	CDK5	CDK5_p25	CDK5_p35	MAPK14	ADK	GSK3A	GSK3B	CSK	SRC	FYN	LCK	ABL	SYK	ZAP_70_SH2	Grb2_SH2	EGFR	ERBB2	FGFR	EGFR_Substrate	PDGFR	PDGFRB	FLT1	KDR	TEK	RAF1	MAP2K	PPK	PIK4CA
	10557855	4.9	4.7	5.6	6.6	5.0	4.4	4.4	4.0	4.6	5.4	5.7	7.0	6.4	6.2	6.3	6.2	6.1	5.8	7.0	7.2	6.3	7.5	7.8	7.7	6.1	5.2	6.4	5.2	6.0	5.4	6.8	4.2	4.4	6.1	5.8	5.1	5.5	5.2	5.0	6.7	6.5	5.8	5.8	6.8	7.0	3.8
	10557857	4.8	4.6	5.2	6.8	5.2	4.5	4.5	4.0	4.6	5.4	6.4	6.1	5.7	5.6	6.5	6.4	5.7	5.0	6.5	7.3	6.5	7.6	7.4	7.5	5.7	6.4	5.3	5.0	6.0	5.7	5.9	4.2	4.4	6.4	5.4	5.6	5.6	5.3	5.2	6.5	6.0	5.7	5.9	6.6	7.3	3.8
r7009	10557860	4.8	4.6	5.8	6.1	5.1	4.5	4.4	4.0	4.6	5.5	7.0	6.3	5.7	5.9	6.1	6.1	6.1	6.8	5.5	6.6	6.6	7.3	7.2	7.4	5.5	5.7	6.2	4.7	6.3	5.6	6.2	4.2	4.4	5.9	5.9	6.0	5.6	5.4	5.0	7.0	6.1	6.1	6.3	7.0	6.8	3.4
r7080	10557864	5.1	4.9	6.0	6.1	5.3	4.5	4.4	3.9	4.7	5.5	6.9	6.8	6.2	6.7	6.2	6.7	6.7	6.5	6.7	7.4	6.5	7.1	8.2	8.0	6.0	6.0	5.9	4.6	6.6	5.5	6.3	4.1	4.4	7.1	6.1	6.2	5.6	5.3	5.3	7.3	6.1	6.5	6.3	7.0	7.2	4.0
r7007	10557865	5.0	5.2	5.3	5.9	5.5	4.6	4.6	4.1	4.6	5.4	6.5	6.8	7.0	6.8	5.9	6.9	5.9	6.3	7.2	7.4	6.5	6.1	8.5	7.7	6.3	5.5	6.2	5.2	6.1	5.5	6.2	4.1	4.4	5.6	6.0	5.6	5.6	5.0	5.3	7.3	6.2	6.4	6.3	6.9	7.3	4.4
	10557866	4.9	5.3	5.9	5.5	5.4	4.6	4.4	4.1	4.7	5.6	7.1	6.7	6.6	6.7	6.3	7.2	6.4	6.8	6.6	7.2	6.5	7.2	8.5	7.8	6.1	5.4	6.3	5.1	6.8	5.4	6.6	4.1	4.4	6.1	6.6	6.0	5.5	4.7	5.1	7.5	5.9	6.6	6.1	7.1	7.0	3.9
	10557858	5.0	5.0	6.3	6.1	5.1	4.5	4.5	4.0	4.7	5.7	8.1	6.0	5.3	5.9	5.9	5.9	5.8	7.0	5.4	6.4	6.5	7.9	7.8	7.4	5.4	5.6	6.2	4.5	6.7	5.7	6.5	4.2	4.4	5.9	6.4	5.8	5.6	5.5	5.0	7.2	6.1	6.3	6.3	7.1	6.7	3.6
	10557859	4.9	5.2	6.1	6.3	5.1	4.6	4.4	4.0	4.8	5.5	7.1	6.9	6.2	5.6	6.2	5.8	6.1	7.3	5.7	6.4	6.5	7.1	7.8	7.6	5.7	5.6	6.2	4.3	6.4	5.1	6.3	4.3	4.4	5.8	6.3	5.4	5.6	5.1	4.7	7.4	6.4	6.4	6.2	7.2	6.6	3.6
	10557861	4.8	4.7	5.5	6.5	5.0	4.4	4.4	4.0	4.6	5.4	5.7	6.8	5.8	6.1	6.2	5.8	5.8	5.9	6.3	6.8	6.3	7.6	7.5	7.7	5.9	5.1	6.5	5.3	6.0	5.6	6.8	4.2	4.4	5.6	5.7	5.3	5.5	5.2	4.9	6.7	6.7	5.8	5.8	6.7	7.0	3.8
	10557856	5.2	5.5	5.6	6.8	5.0	4.3	4.4	3.8	4.5	5.3	5.7	6.2	5.6	5.5	6.2	5.6	5.8	4.8	5.3	6.8	5.9	7.4	7.9	7.5	5.8	5.7	6.1	5.2	5.9	5.9	6.5	4.2	4.3	6.4	5.9	5.1	5.4	5.5	5.1	6.5	5.7	5.6	5.9	6.7	7.0	3.8
	10557862	4.7	5.4	6.8	5.9	5.0	4.5	4.5	4.0	4.7	5.6	6.2	7.4	6.3	7.3	5.5	6.1	5.7	6.8	6.4	6.4	6.5	7.0	8.9	8.0	6.4	5.6	6.6	4.9	7.0	5.5	7.3	4.1	4.3	4.8	6.2	5.3	5.5	4.8	4.6	7.4	6.5	6.4	6.3	7.2	6.8	3.9
	10557853	5.1	4.8	5.3	6.2	5.0	4.6	4.6	4.0	4.8	5.6	6.1	6.5	5.8	5.7	5.8	5.2	5.6	6.7	4.7	6.2	5.8	7.6	7.8	7.4	6.5	4.7	6.5	4.7	5.0	6.1	6.0	4.4	4.2	5.9	6.5	4.5	5.6	6.4	4.8	6.9	6.7	6.3	5.5	6.6	6.5	3.4
	10557863	4.9	4.9	4.9	5.8	5.2	4.5	4.5	4.1	4.5	5.3	6.8	7.2	6.5	6.0	6.3	6.2	5.8	5.7	6.8	7.1	6.2	6.9	7.1	7.2	6.3	5.8	6.1	5.8	5.9	5.4	6.7	4.1	4.3	5.8	5.8	5.4	5.3	5.8	5.0	6.6	5.7	5.8	6.2	7.0	7.2	4.5
	10557854	4.7	4.3	5.0	6.1	5.0	4.5	4.5	4.1	4.6	5.3	6.2	5.9	5.3	5.1	5.7	5.7	5.5	6.0	5.1	6.5	5.8	7.6	6.9	7.4	5.7	5.5	6.0	5.1	5.8	6.4	6.0	4.3	4.3	6.9	6.1	5.3	5.5	6.2	5.1	6.4	6.6	5.9	5.3	6.6	6.7	3.8
	10557881	4.4	4.5	4.6	5.8	5.1	4.5	4.5	4.1	4.5	5.4	5.1	5.7	5.0	5.2	6.7	5.4	5.1	3.9	5.5	6.1	5.4	6.7	7.5	7.2	5.6	6.5	6.5	6.4	5.6	6.4	7.0	4.2	4.3	6.1	5.5	5.1	5.1	5.4	5.2	6.2	5.4	5.3	5.5	6.4	7.0	4.0
	10557879	4.4	4.7	5.0	5.9	5.2	4.6	4.6	4.1	4.6	5.5	6.1	6.2	5.4	5.4	6.7	5.4	5.1	3.8	5.4	6.5	5.6	7.1	7.9	7.2	5.9	6.5	6.0	6.6	5.7	6.1	6.9	4.1	4.3	5.9	5.8	5.4	5.2	5.3	5.3	6.7	5.8	5.6	5.7	6.5	7.4	4.2
r7068	10557886	4.6	4.9	5.2	5.9	5.3	4.6	4.6	4.1	4.6	5.5	6.6	6.4	5.9	5.4	7.1	6.0	5.9	4.3	6.0	7.1	6.0	7.2	7.5	7.2	5.6	6.7	6.3	6.6	6.2	5.8	6.7	4.1	4.3	6.2	5.8	5.8	5.3	5.4	5.4	7.0	5.5	5.7	6.2	6.5	7.5	4.1
r7007	10557885	4.8	5.5	5.2	5.7	5.4	4.6	4.5	4.1	4.5	5.4	6.5	6.5	5.7	5.8	6.4	6.2	5.6	4.7	6.2	6.8	5.9	5.8	6.9	7.2	6.0	5.8	6.6	6.9	6.1	5.4	6.9	4.1	4.3	6.0	5.9	5.7	5.3	5.3	5.5	6.7	5.4	5.8	5.8	6.9	7.3	4.4
r7018	10557874	4.7	5.2	5.1	5.5	5.1	4.5	4.5	4.0	4.5	5.4	6.5	6.0	5.7	5.6	6.7	6.5	5.7	4.8	5.8	6.8	5.9	7.4	7.7	7.1	5.3	6.0	6.8	6.5	6.9	6.1	7.1	4.1	4.3	6.4	6.0	5.6	5.3	5.2	5.1	6.6	5.1	5.8	6.0	6.8	7.3	4.2
	10557888	4.5	4.6	5.0	6.3	5.1	4.4	4.4	3.9	4.5	5.4	5.8	5.6	5.2	5.6	6.7	5.8	5.6	4.4	5.6	6.4	5.7	6.2	7.6	7.0	4.8	6.5	5.9	5.5	6.6	6.4	6.8	4.2	4.3	6.5	5.5	4.8	5.3	5.6	5.2	6.3	5.6	5.5	5.9	6.6	7.2	3.6
	10557877	4.5	4.4	4.8	6.1	5.1	4.5	4.5	4.1	4.6	5.5	5.4	5.7	5.0	5.3	6.7	5.6	5.2	4.0	5.3	6.1	5.5	6.4	7.6	7.1	5.3	6.2	6.7	5.9	6.1	6.4	7.0	4.2	4.3	6.3	5.5	4.8	5.2	5.3	5.2	6.2	5.6	5.4	5.5	6.4	7.0	3.7
	10557880	4.3	4.3	4.6	5.8	5.2	4.6	4.6	4.1	4.6	5.5	6.0	6.3	5.7	5.6	6.7	5.8	4.9	4.0	5.4	6.4	5.7	6.9	7.5	7.3	6.0	6.8	5.9	6.6	5.8	6.4	6.8	4.1	4.3	5.9	5.5	5.4	5.1	5.3	5.3	6.5	5.9	5.5	5.5	6.6	7.3	4.2
	10557883	4.8	4.9	4.8	5.8	5.2	4.5	4.5	4.1	4.5	5.4	6.2	5.7	5.7	5.5	6.9	6.3	5.7	4.3	5.8	6.7	5.8	6.9	7.4	7.0	5.5	6.0	6.1	6.4	6.3	6.2	7.0	4.1	4.3	6.5	5.8	5.5	5.2	5.2	5.1	6.5	5.4	5.6	5.9	6.6	7.3	4.4
	10557878	4.9	4.8	5.1	6.1	5.2	4.6	4.5	4.1	4.6	5.5	6.3	5.6	5.6	5.4	7.0	6.2	5.6	4.2	5.6	6.8	5.7	6.4	7.4	7.1	5.3	6.0	6.5	5.9	6.4	6.1	6.8	4.2	4.3	6.6	5.8	5.3	5.3	5.2	5.5	6.4	5.4	5.5	5.9	6.4	7.3	4.0
	10557884	4.4	4.7	4.9	5.7	5.1	4.5	4.5	4.1	4.5	5.4	5.5	5.6	5.1	5.6	6.5	5.9	5.2	4.2	5.3	6.1	5.6	7.2	7.8	6.9	5.3	5.9	6.1	6.5	6.5	6.3	7.2	4.1	4.3	6.3	5.6	5.2	5.2	5.2	5.0	6.3	5.5	5.6	5.4	6.7	7.1	4.3
	10557876	4.6	5.7	5.0	5.8	5.4	4.6	4.5	4.1	4.5	5.4	6.4	6.6	6.0	5.6	6.6	5.7	5.8	5.0	6.1	6.7	5.8	5.6	6.7	7.6	6.2	6.2	6.9	6.9	5.7	5.0	6.6	4.2	4.3	5.9	5.8	5.8	5.2	5.1	5.7	6.8	5.0	5.8	6.0	6.7	7.2	4.1
	10557887	4.6	4.9	5.2	6.3	5.1	4.4	4.4	3.8	4.6	5.5	8.1	5.5	5.5	5.4	6.2	6.6	5.8	5.3	5.8	6.8	5.9	7.0	7.9	7.0	4.6	5.6	6.1	4.6	7.4	6.5	6.5	4.2	4.3	6.8	6.0	4.8	5.6	5.9	4.8	6.5	5.4	6.0	6.2	6.6	7.1	3.6
	10557875	5.0	5.5	5.4	6.3	5.1	4.4	4.5	3.8	4.7	5.5	7.8	5.4	5.9	5.6	5.9	6.2	5.9	6.8	5.9	6.9	5.7	7.6	8.4	7.3	5.2	5.9	5.5	4.6	7.2	6.3	6.4	4.2	4.3	6.9	6.7	5.0	5.6	6.1	4.9	6.8	5.9	6.2	6.5	6.4	7.1	3.5
	10557882	4.9	4.8	5.3	6.7	5.1	4.4	4.4	3.9	4.5	5.4	5.5	5.5	5.7	5.0	6.0	5.8	6.1	4.9	5.7	6.6	5.3	5.9	7.2	7.6	5.7	5.2	5.6	5.5	5.9	5.6	6.5	4.2	4.3	6.4	5.7	5.1	5.3	5.6	5.3	6.2	6.0	5.4	5.8	6.2	6.7	4.1
	10557871	4.9	4.3	4.8	6.4	6.1	5.0	4.4	4.0	5.1	5.4	8.0	7.3	6.8	6.1	5.7	5.3	5.3	6.2	6.5	7.1	7.0	5.8	7.0	7.3	5.4	6.9	5.4	4.4	6.6	4.8	5.2	4.4	5.2	5.3	5.2	6.0	5.8	5.3	6.0	7.7	6.8	6.4	6.5	6.6	7.6	4.1
	10557869	4.4	4.6	4.4	5.0	6.0	4.9	4.4	4.1	4.7	5.5	7.1	6.6	5.9	6.0	5.3	5.1	4.5	6.6	6.1	6.5	6.5	5.4	7.3	7.6	5.2	5.6	6.1	6.0	5.9	4.1	6.2	4.2	5.1	3.9	5.9	5.8	5.4	4.9	5.6	7.5	6.2	6.4	6.0	7.0	7.1	4.2
r7046	10557873	4.5	4.9	5.1	6.0	6.3	5.1	4.7	4.2	5.3	5.7	7.1	7.0	6.5	7.0	5.1	5.8	4.9	6.9	7.6	7.2	7.0	6.6	8.6	7.6	5.7	6.0	5.7	4.6	6.5	4.2	5.7	4.2	5.5	4.7	5.8	5.1	5.8	4.6	6.1	8.0	6.7	6.8	6.7	7.0	7.6	3.9
r7079	10557867	4.3	4.2	4.0	5.4	6.2	5.1	4.6	4.3	5.1	5.6	8.4	5.5	7.4	5.5	5.5	5.4	4.4	5.4	5.7	6.4	6.2	4.9	6.7	7.3	5.0	5.4	5.1	5.7	6.1	4.0	5.8	4.2	5.1	4.4	4.8	5.5	5.3	4.7	6.0	6.9	6.0	6.1	6.0	6.7	7.4	5.6
r7046	10557870	4.6	5.2	4.7	5.0	6.6	4.6	4.2	3.9	5.5	5.4	7.8	7.2	5.8	6.1	5.5	5.3	5.3	7.0	6.3	6.2	6.9	6.1	8.7	7.4	5.2	6.4	6.0	4.9	6.0	4.7	5.3	4.4	5.4	5.4	5.2	6.5	5.8	5.2	5.8	7.9	6.7	6.8	6.4	6.6	7.0	4.1
	10557868	4.1	4.4	4.2	5.4	6.4	5.3	5.0	4.6	5.4	6.1	8.3	5.3	6.9	6.1	5.4	5.5	4.7	5.6	6.0	6.6	6.1	5.2	7.3	7.5	5.1	5.5	5.6	5.8	5.7	3.5	6.3	4.1	5.4	4.3	4.9	5.3	5.3	4.4	5.5	7.1	5.9	6.1	6.2	6.8	7.4	5.0
	10557872	4.4	4.6	4.5	5.0	6.0	4.9	4.4	4.1	4.7	5.5	7.2	6.6	5.9	6.0	5.2	5.1	4.5	6.6	6.0	6.5	6.4	5.5	7.4	7.6	5.3	5.7	6.1	6.0	6.0	4.2	6.2	4.2	5.1	3.8	6.0	5.8	5.4	4.9	5.7	7.5	6.1	6.4	6.0	7.0	7.1	4.2

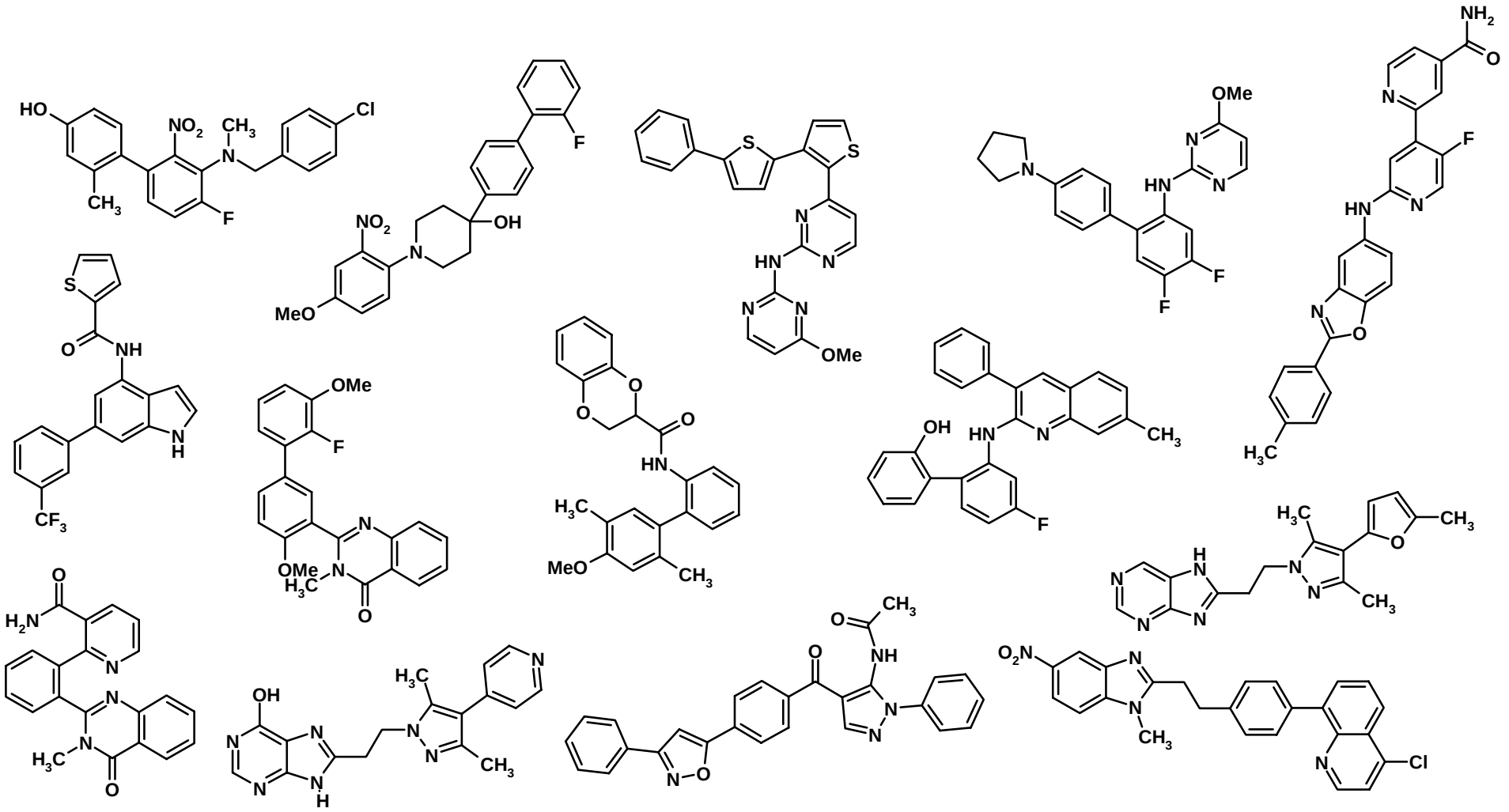
pIC50	3.0	4.0	5.0	6.0	7.0	8.0
min	3.0	4.0	5.0	6.0	7.0	8.0
max	4.0	5.0	6.0	7.0	8.0	9.0

Simulations II - selected reaction sequences

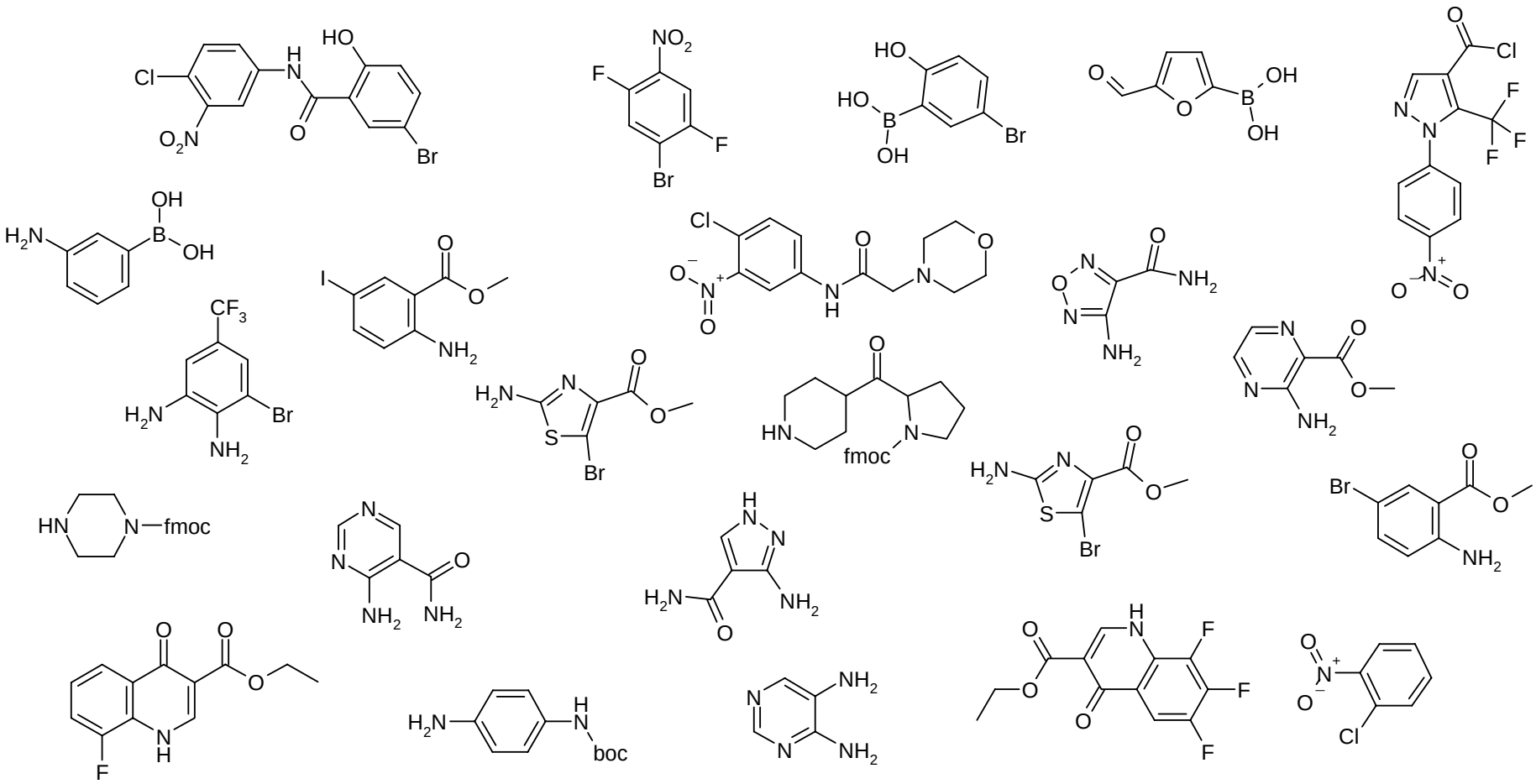


orthogonal building blocks and cross compatibility

Simulations II - selected compounds



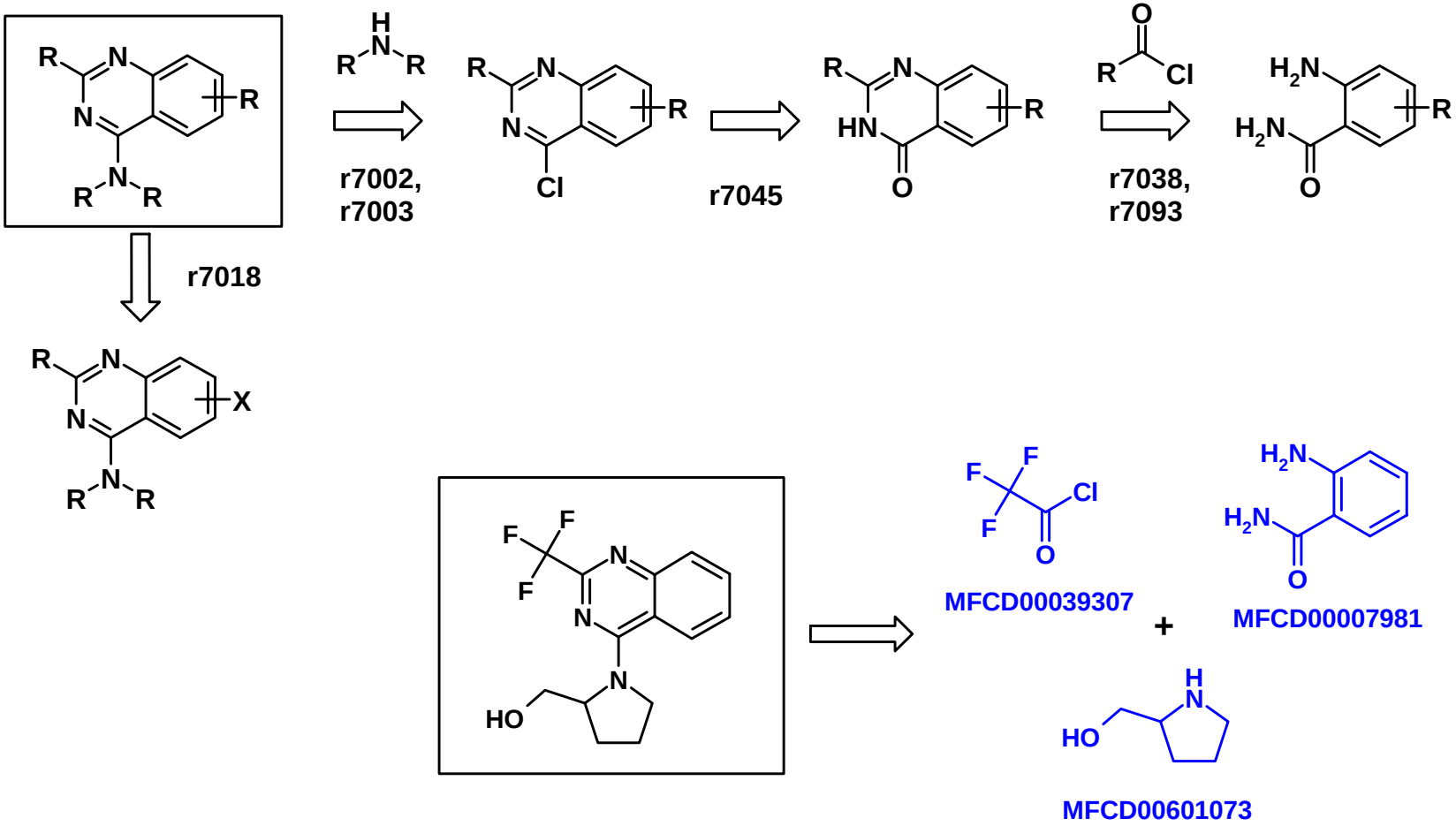
Privileged building blocks



selected examples of bi-functional and most frequent building blocks

Retro-synthesis (example)

Retro-protocol r7038r7045r7002:



ChIP partnerships

Chip Strategic Partnership Program

- Early collaborative applications of the technology
- Experimental proof of concept studies
- “Personalized” ChIP – developed around proprietary chemistries of collaborator
- Early access to ChIP technology
- Access to current LUCIA system (ChIP precursor)

Acknowledgements

National Institute of Standards and Technology – funding of ChIP in the ATP program

Steve Muskal and Sertanty's software and content development teams

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