

FIG. 1

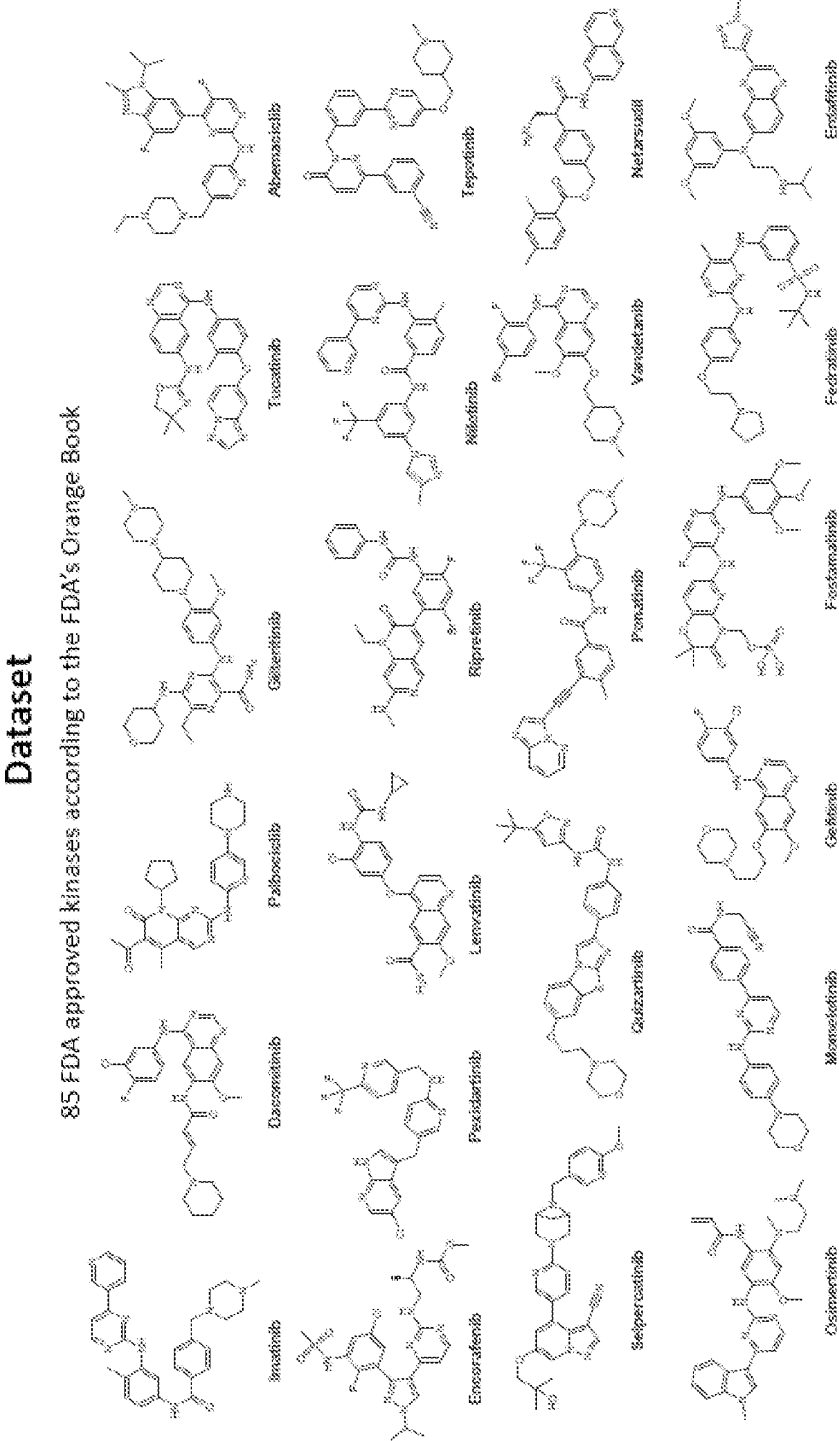


FIG. 2

The LEGO reaction toolkit

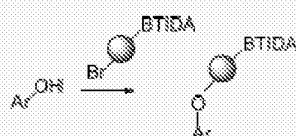
Suzuki coupling:	Buchwald C-N coupling:	Amide coupling
aryl-aryl	aryl Br – aryl amine	Deprotections:
aryl-vinyl	aryl Br- primary amine	BTIDA hydrolysis
vinyl-vinyl	aryl Br- sec unhindered amine	NCbzBTIDA hydrolysis

AUXILIARY REACTIONS

(can act only as the first or the last reaction in a squence)

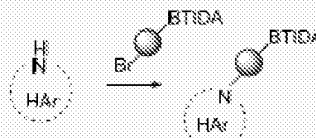
Buchwald C-O coupling: *

aryl Br – phenols

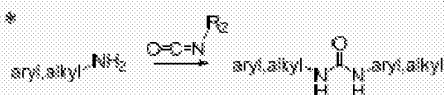


Buchwald C-N coupling: *

aryl Br – heterocyclic amine



Reaction of amines** with isocyanides



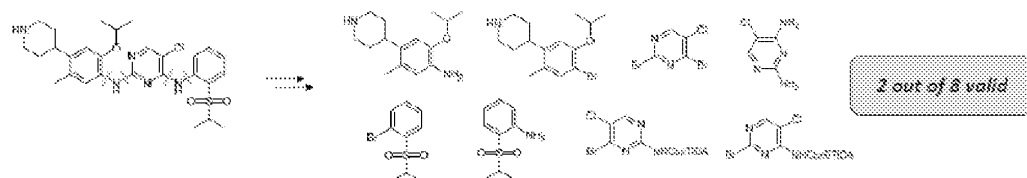
* Only as the first reaction

** Only as the final reaction

RXNs ACCOMPANIED BY ~400 INCOMPATIBLE GROUPS

FIG. 3

"Modularization" is trivial ...



...but not if it also has to ensure compatibility with automated synthesis!

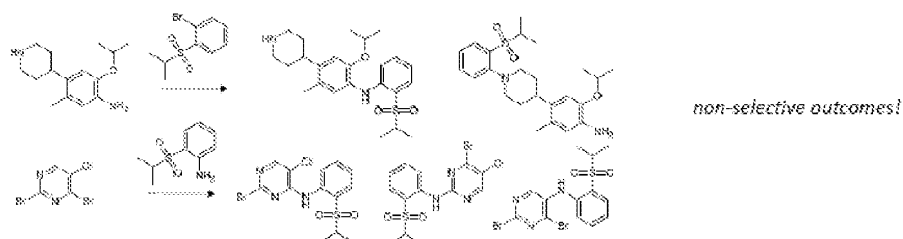


FIG. 4

Modularization compatible with subsequent automated synthesis

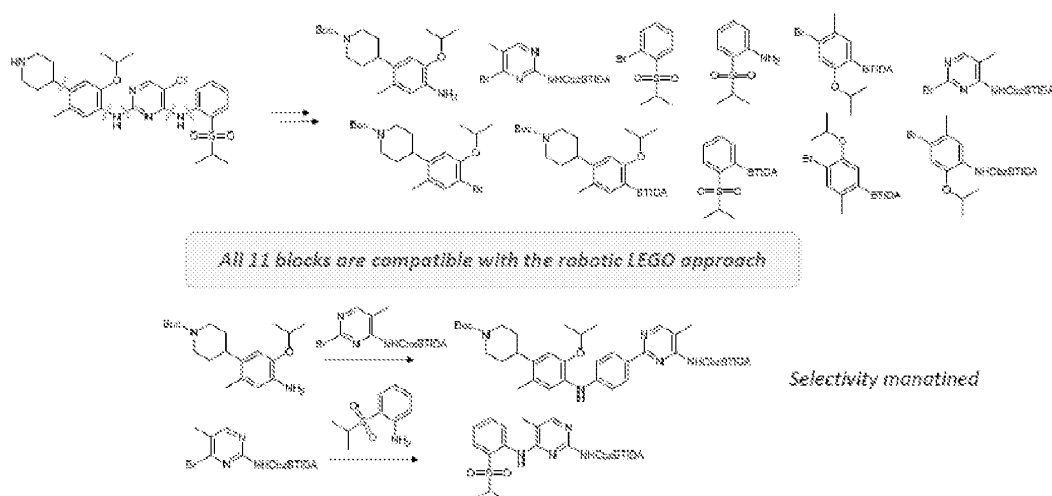


FIG. 5

The overall logic for the synthesis-oriented categorization of building blocks

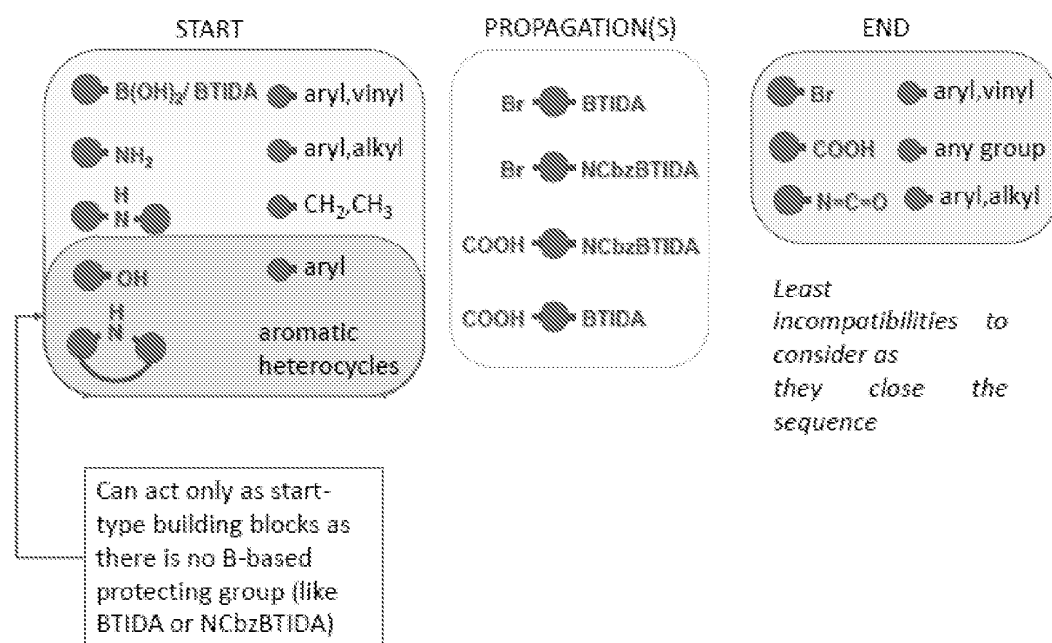


FIG. 6A

The logic of smart modularization

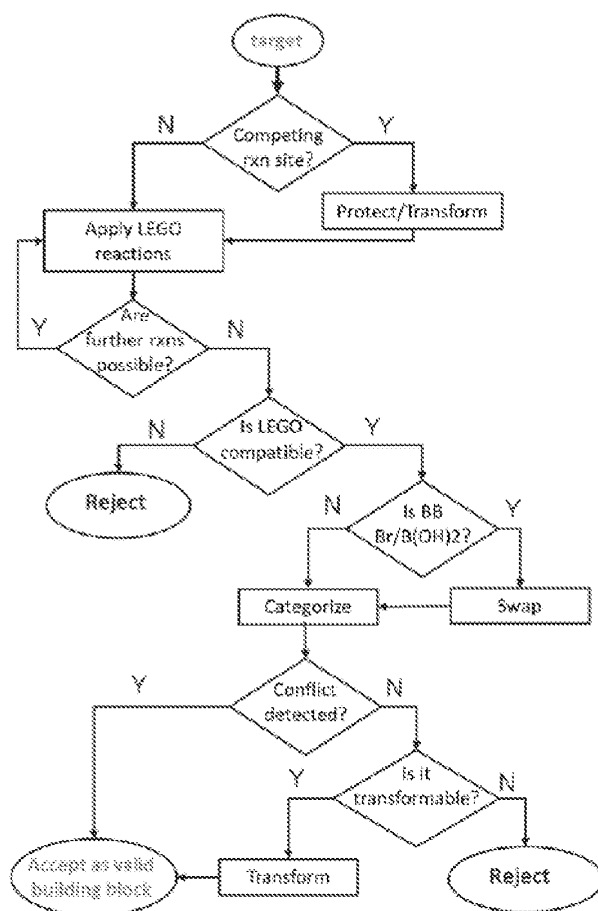


FIG. 6B

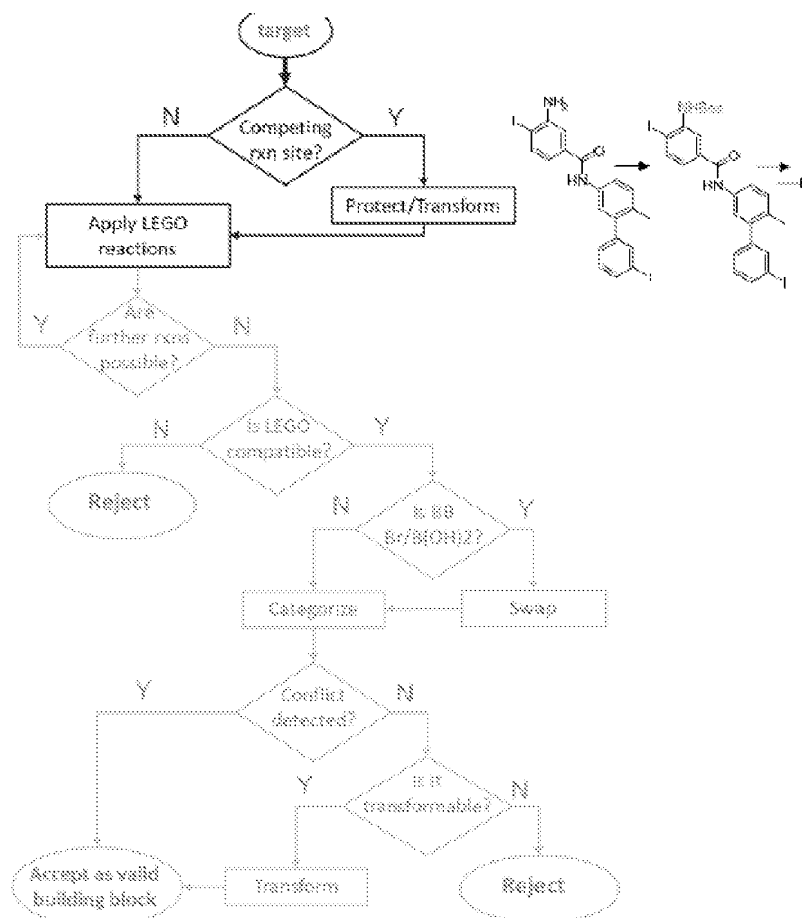


FIG. 6C

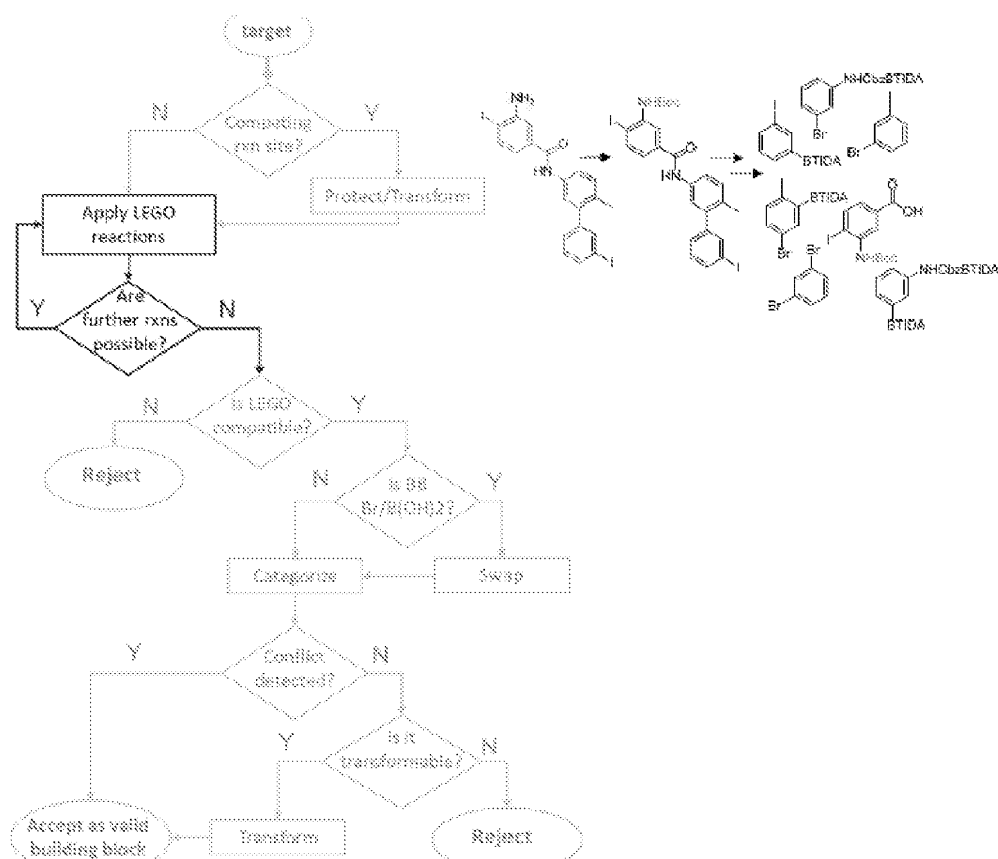


FIG. 6D

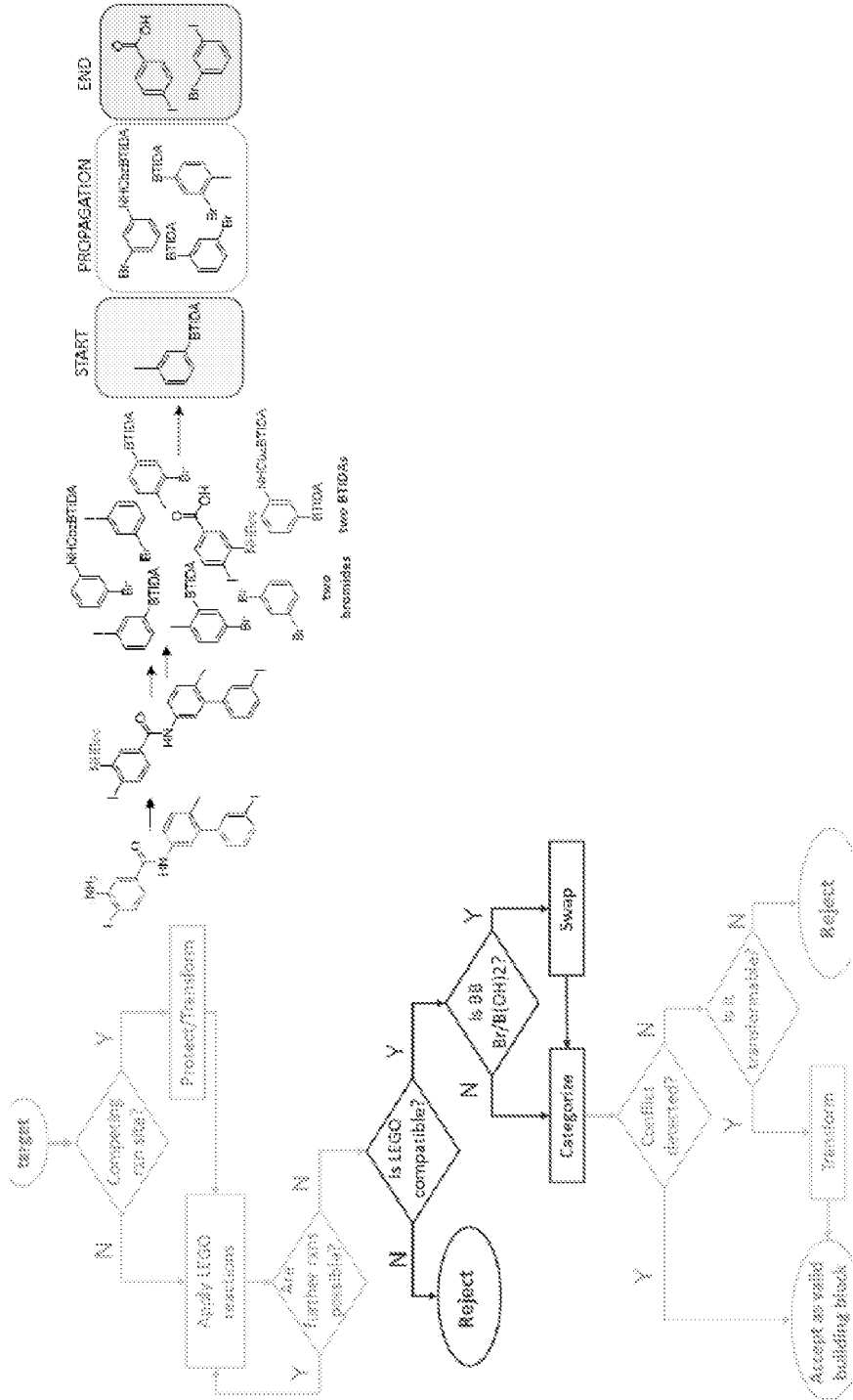


FIG. 6E

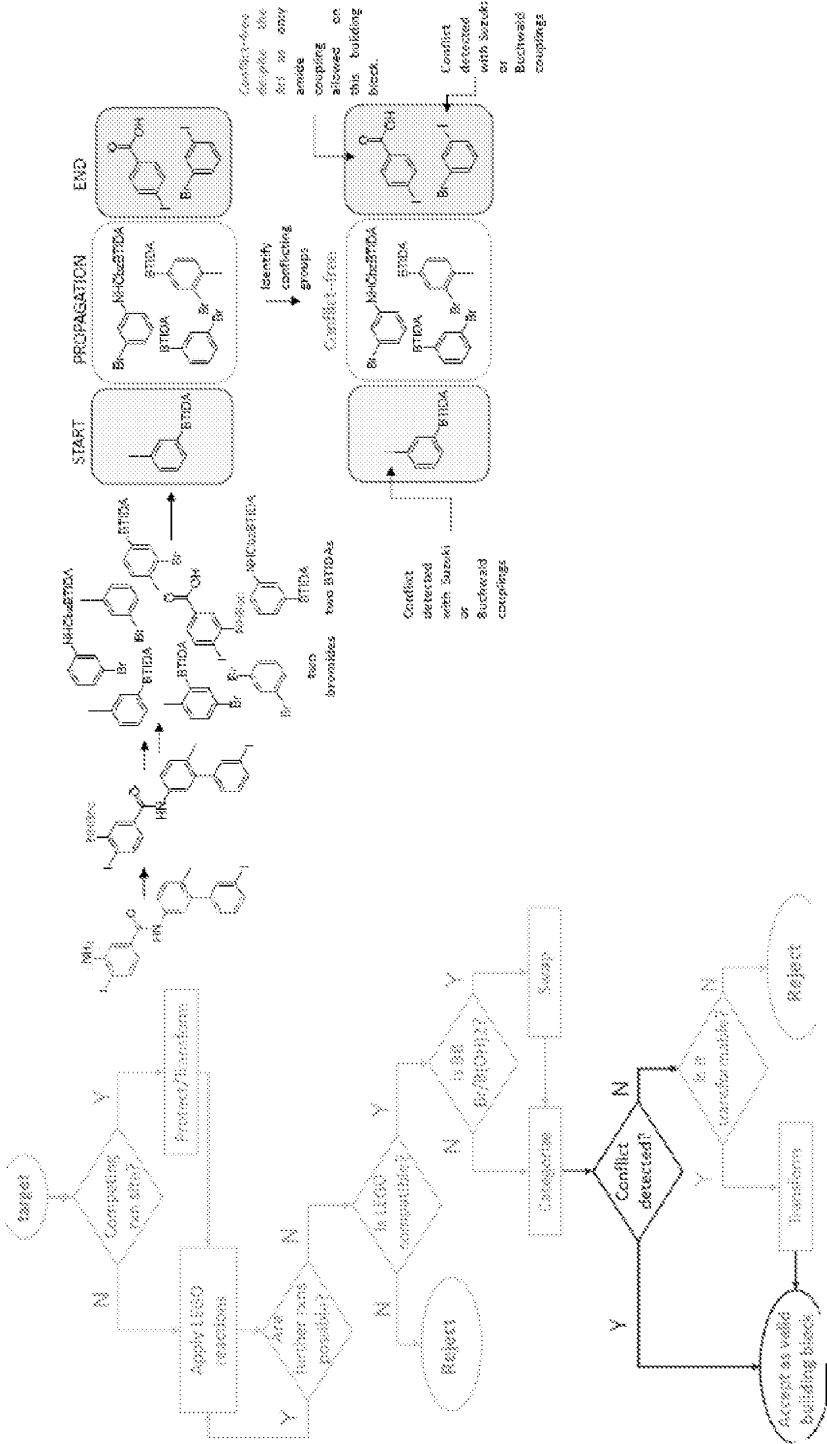


FIG. 7

Transformation of competing and conflicting groups

PROTECTIONS/TRANSFORMATIONS OF COMPETING REACTION SITES



EXAMPLES OF PROTECTIONS/TRANSFORMATIONS OF CONFLICTING GROUPS

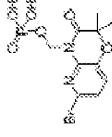
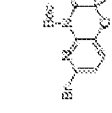
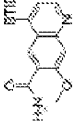
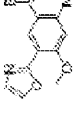
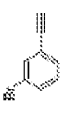
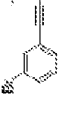
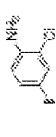
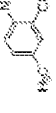
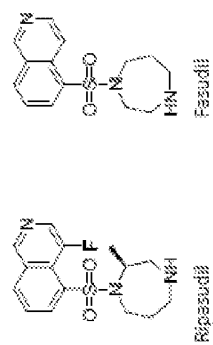
Incompatible group	Incompatibility detected with	Block with conflict	Transformed block	Transformations of conflicting groups are based on bioisosteric replacement.
phosphono hemiaminal	All LEGO reactions			
Primary Amides	BTDA hydrolysis			
Terminal Alkynes	C-N coupling			
Aryl Iodides, Chlorides	C-N coupling, Suzuki coupling			

FIG. 8

Some targets from the set yield no building blocks:



Modularization

no building blocks

OR

Yield large and complex building blocks (see examples below):

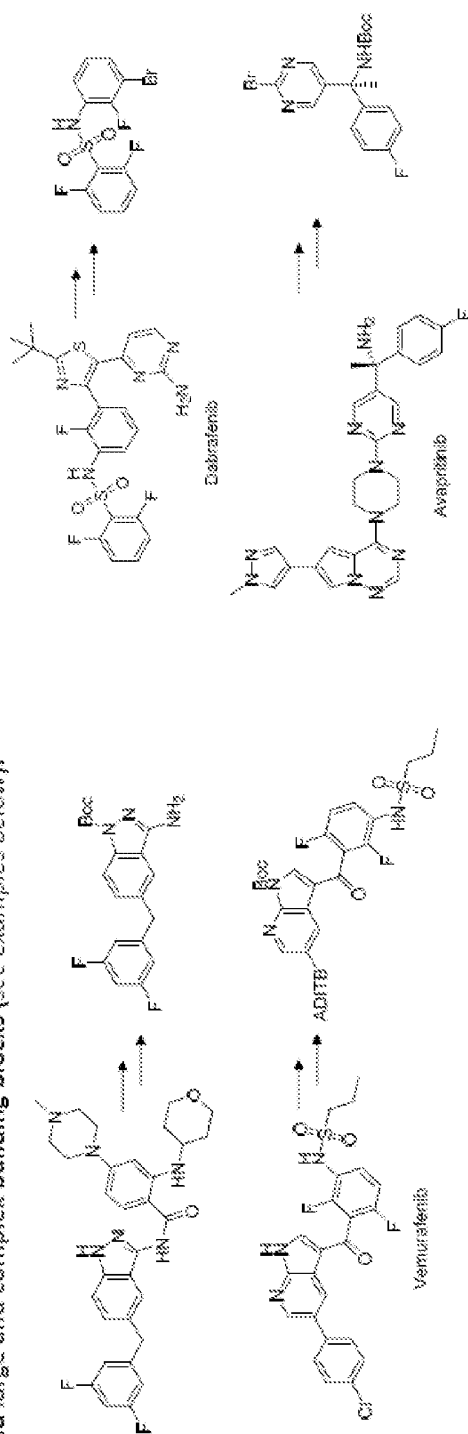


FIG. 10

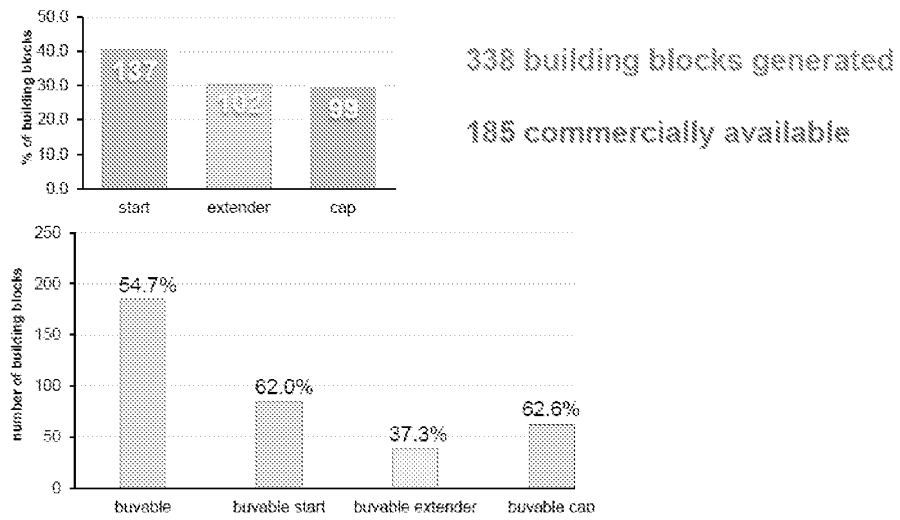
Distribution of building blocks and their commercial availability

FIG. 11

Some examples of building blocks

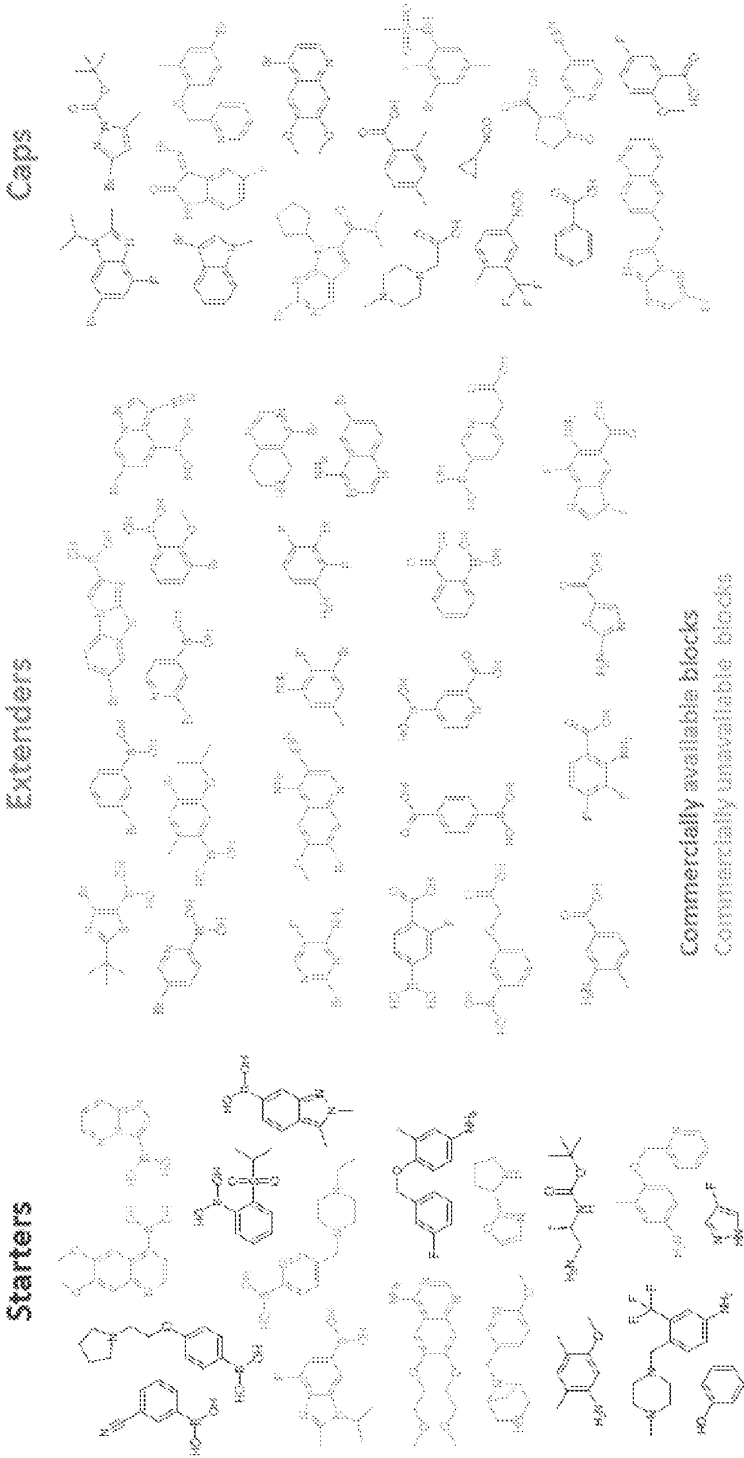


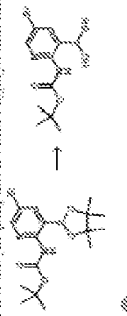
FIG. 12

SYNTHESIZABLE IN 3 GENERATIONS

80 molecules out of 153

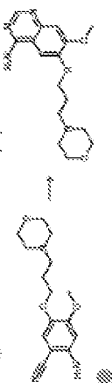
1.

Reaction name: Pinacolborane hydrolisis
Reaction conditions: NaIO₄
Solvent: acetone+water
Literature reference: 10.3390/molecules27192850 and 10.1021/acs.chem.2c01015 and 10.1016/j.jmech.2018.11.007



2.

Reaction name: Pyrimidine synthesis
Reaction conditions: formamide, reflux
Solvent: neat
Literature reference: 10.1016/j.jmech.2017.07.003 and 10.1021/mo30787 and 10.1016/j.jmech.2017.03.007



Reaction name: Sandmeyer reaction
Reaction conditions: HBr, NaNO₂, CuBr
Solvent: THF or MeCN
Literature reference: 10.1021/acs.chem.2c01015 and 10.1016/j.jmech.2017.07.003 and 10.1016/j.jmech.2017.03.007

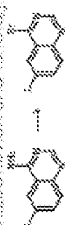


SYNTHESIZABLE IN 5 GENERATIONS

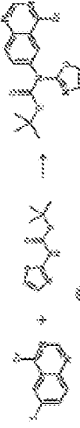
93 molecules out of 153

3.

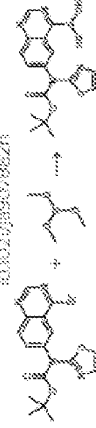
Reaction name: Sandmeyer reaction
Reaction conditions: HBr, NaNO₂, CuBr
Solvent: THF or MeCN
Literature reference: 10.1021/acs.chem.2c01015 and 10.1016/j.jmech.2017.07.003 and 10.1016/j.jmech.2017.03.007



Reaction name: Sandmeyer reaction
Reaction conditions: HBr, NaNO₂, CuBr
Solvent: THF or MeCN
Literature reference: 10.1021/acs.chem.2c01015 and 10.1016/j.jmech.2017.07.003 and 10.1016/j.jmech.2017.03.007



Reaction name: Boronic acid synthesis
Reaction conditions: nBuLi, trimethyl borate then H+
Solvent: THF
Literature reference: 10.1016/j.jmech.2017.07.003 and 10.1016/j.jmech.2017.03.007



Reaction name: N-Boc deprotection
Reaction conditions: TFA
Solvent: DCM or dioxane or AcOEt
Literature reference: 10.1016/j.jmech.2017.07.003 and 10.1016/j.jmech.2017.03.007



FIG. 13

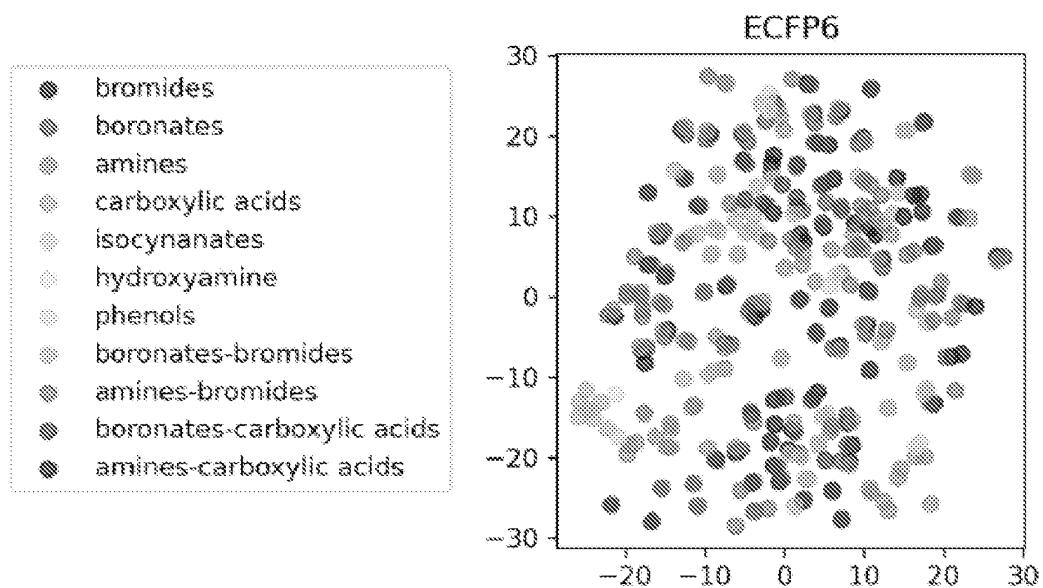


FIG. 14

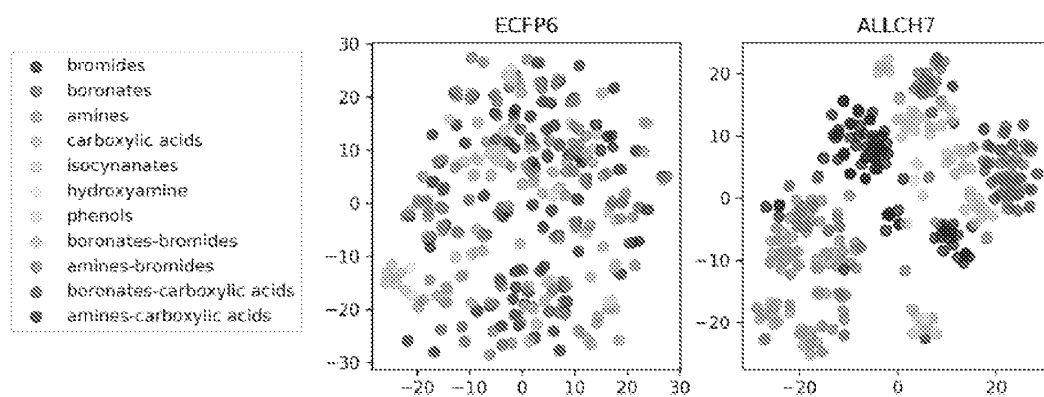


FIG. 15

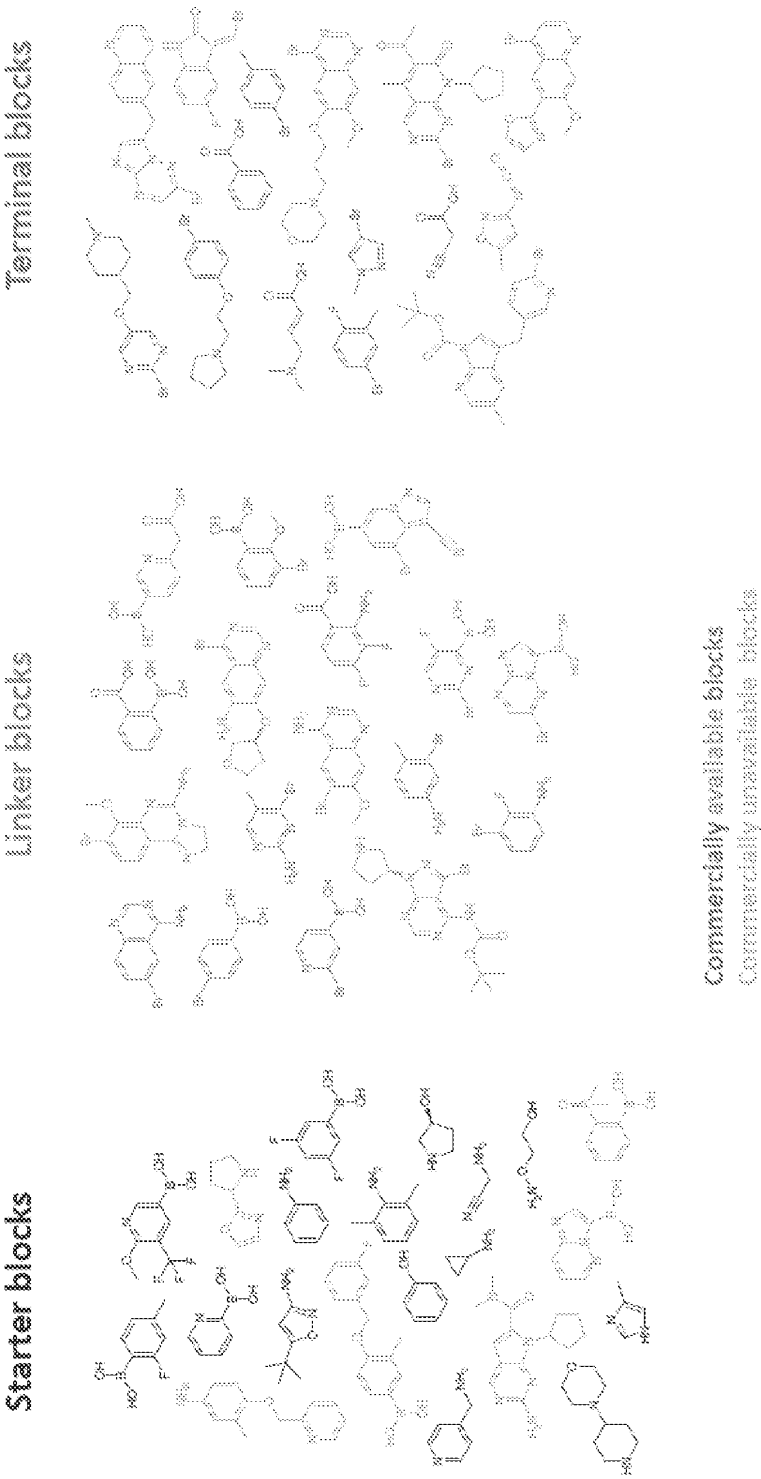
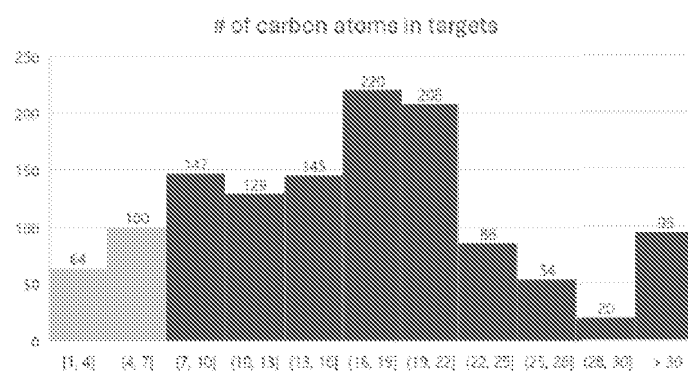


FIG. 16

Modularization of 1792 FDA, Canada & EU approved drugs

Mass distribution over the target set



Note: Quite a few drugs (yellow bars) are already very small

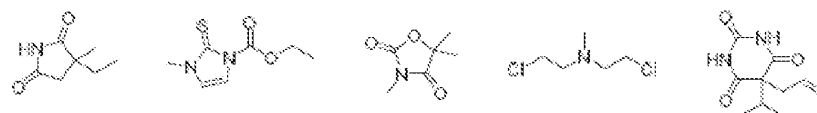


FIG. 17

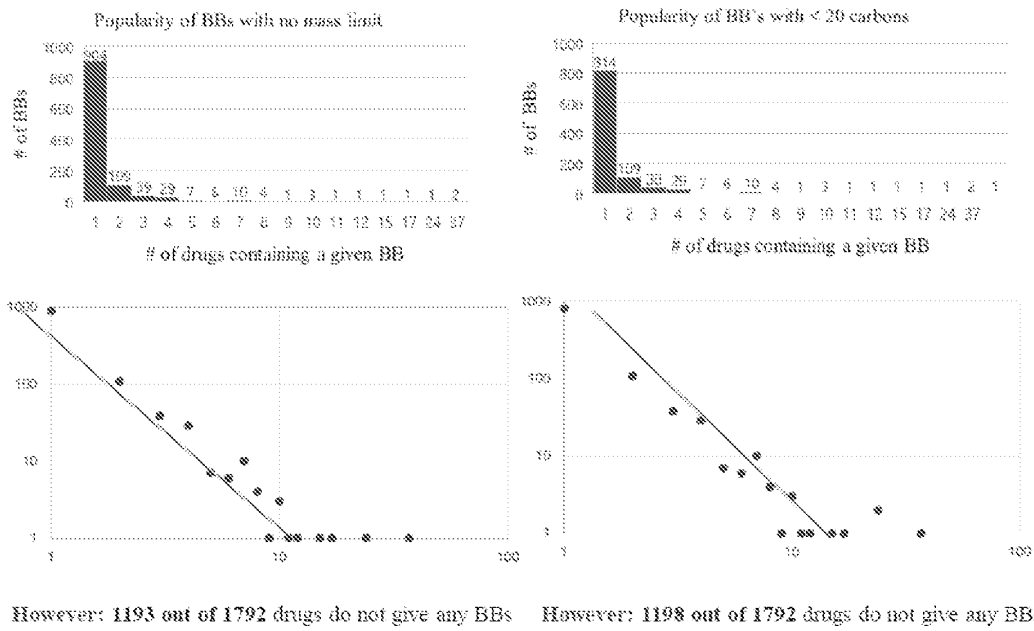


FIG. 18

Size distribution of the BBs
(measured in C atoms)

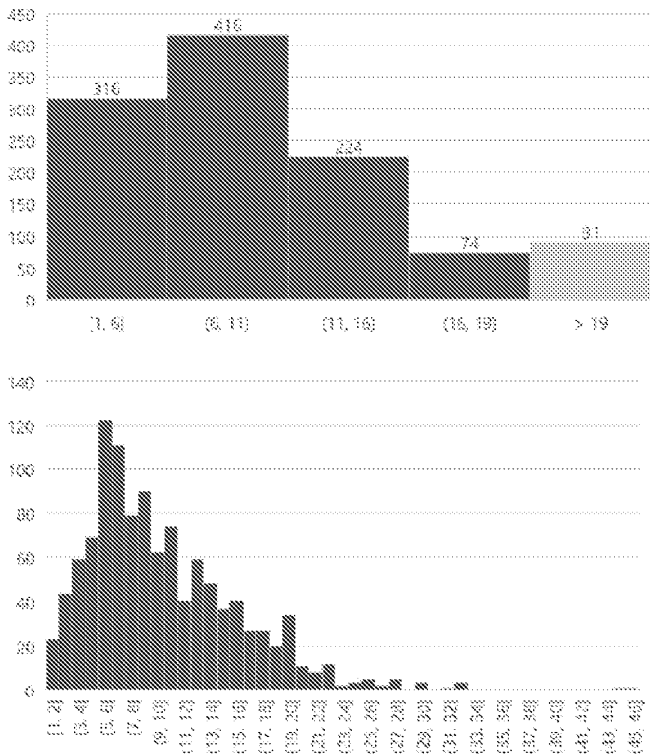


FIG. 19A

Examples of BBs and their “parent drugs”
(numbers give the number of drugs in which a block is found)

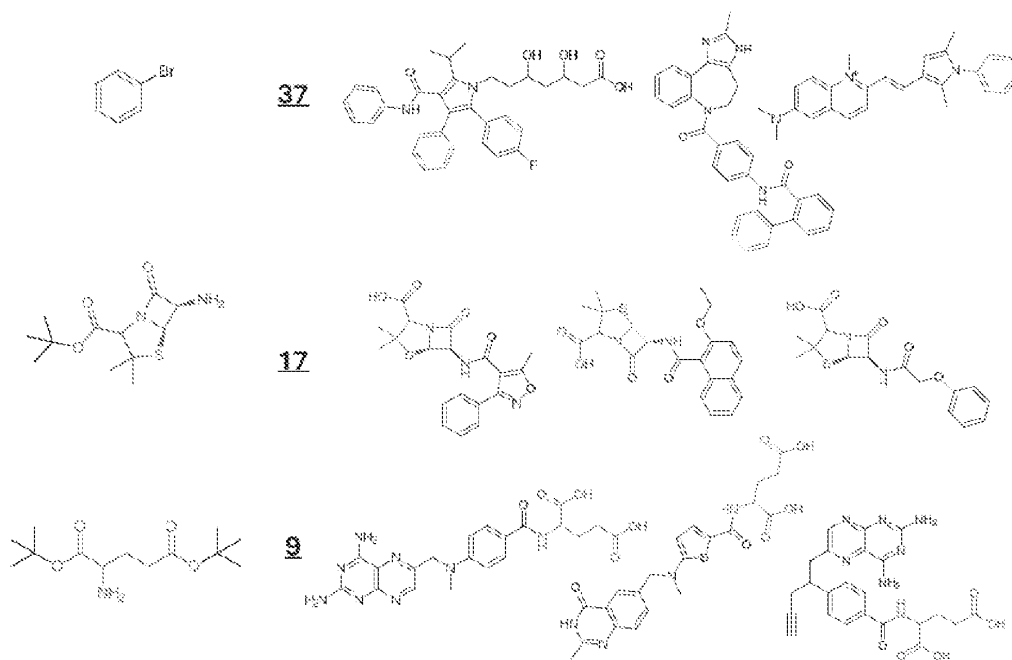


FIG. 19B

Examples of BBs and their “parent drugs”
(numbers give the number of drugs in which a block is found)

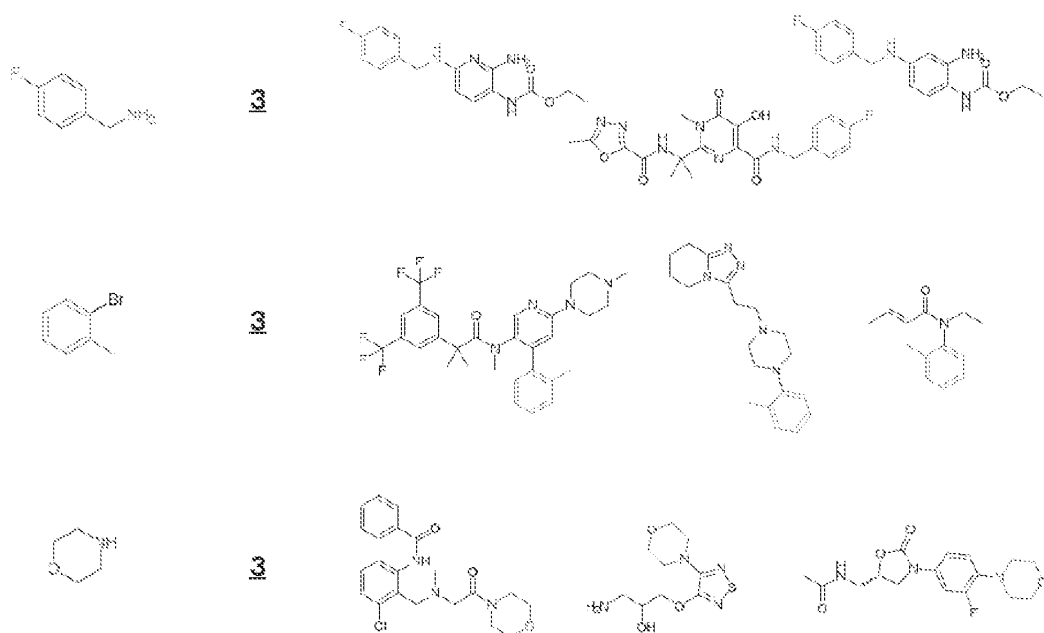


FIG. 19C

Examples of BBs and their “parent drugs”
(numbers give the number of drugs in which a block is found)

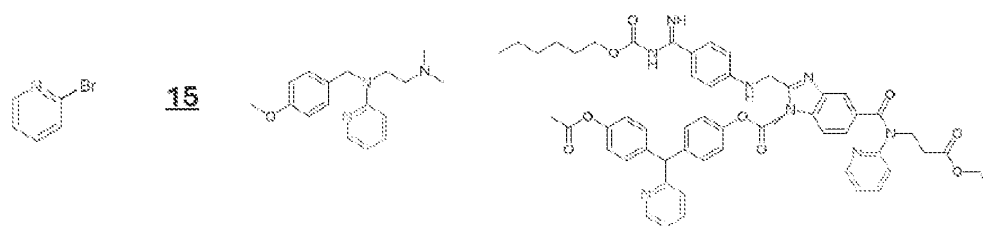
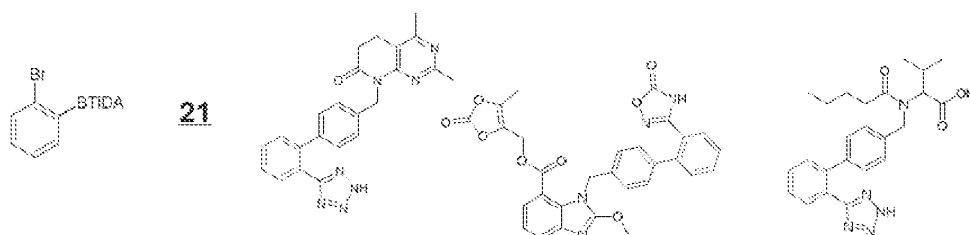
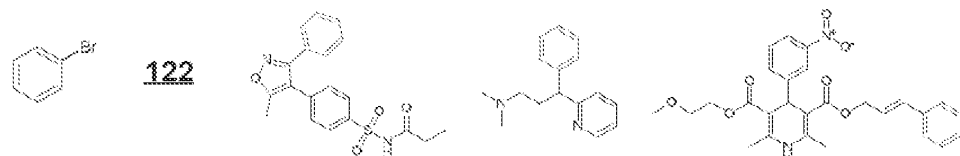


FIG. 19D

Examples of BBs and their “parent drugs”
(numbers give the number of drugs in which a block is found)

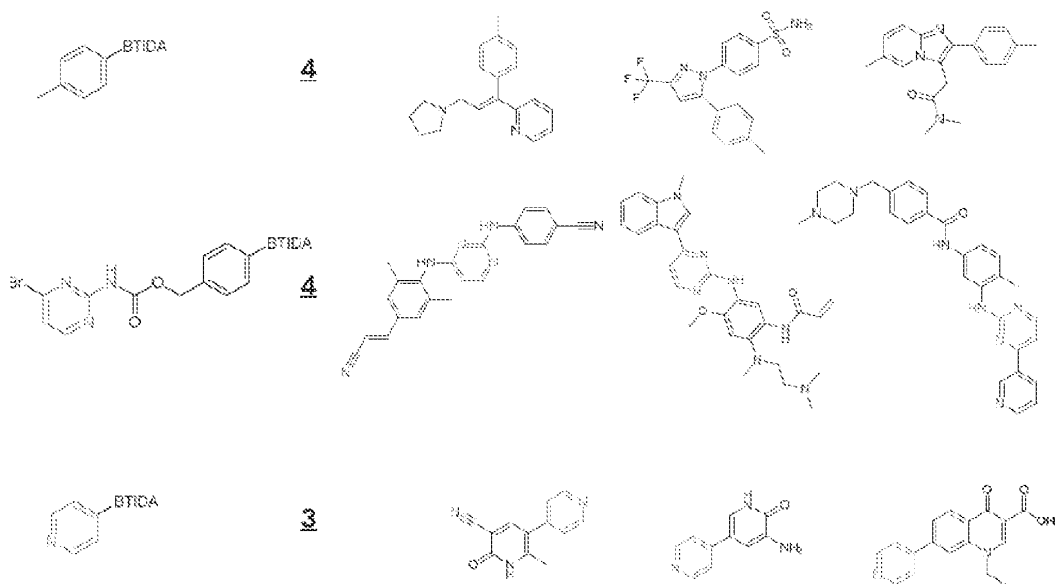


FIG. 20

Modularization allowing for sp3 Suzuki

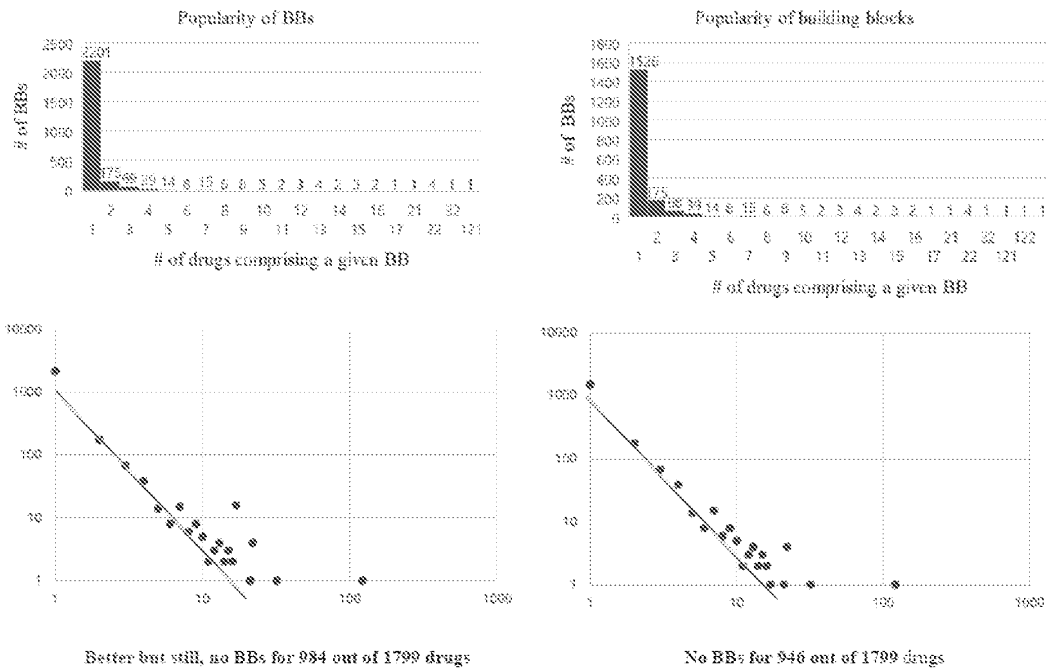


FIG. 21

We can fully modularize 348 FDA drugs using ~750 BBs

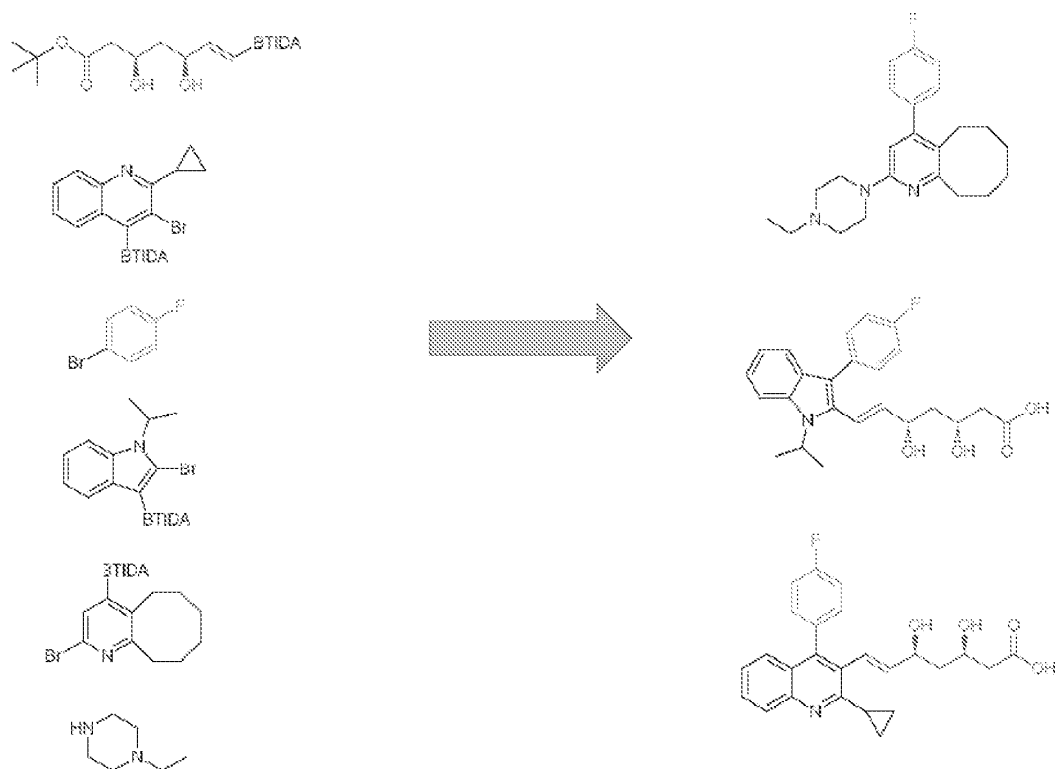


FIG. 22

We can fully modularize 348 FDA drugs using ~750 BBs

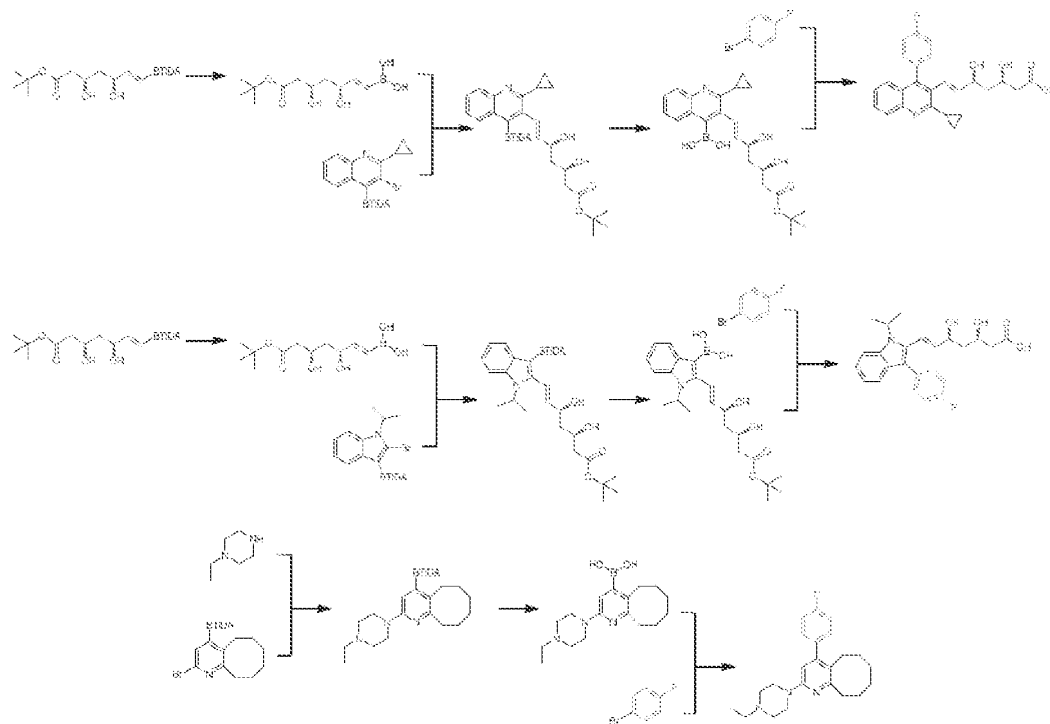


FIG. 24

