Библиотеки ковалентных ингибиторов

Library of Covalent Inhibitors and Fragments

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Consists of three sub-libraries:

- Generic Library of Covalent Inhibitors;
- Smart Library of Covalent Inhibitors;
- Smart Library of Covalent Fragments;
- Library of sp^3-Enriched β-Lactams.

Generic Library of Covalent Inhibitors

Generic library of covalent inhibitors

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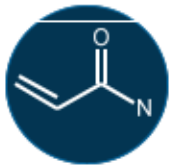
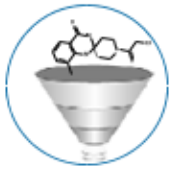
General Strategy



Library members were selected from historical collection. Selection criteria

- *Michael acceptors and dienophiles (acrylamides, acrylonitriles, maleinmides, quinones, vinyl sulfones, aryl(alkyl)idene derivatives of CH-active methylene compounds etc.),*
- *Nucleophil sensitive functionalities (epoxides, acetals/ketals, alky ketones, aldehydes, imines, sulfonate esters, sulfonyl halides, (thio)cyanates, thiones, α-Hal-, RS-, RSO2-azines, other SN_{Ar}-Hal, etc.),*
- *Other reactive compounds (terminal acetylenes, reactive heterocycles, dienes, aliphatic and aromatic thiols, etc .*

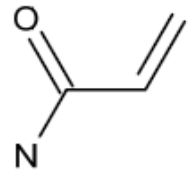


Maximizing drug-likeness: undesired compounds were removed according to Lipinski Ro5.

Chemical diversity: clustering of compounds according to structural features and removal of molecules with low diversity

Generic library of covalent inhibitors

Representative Examples of the Selected Sub-structures



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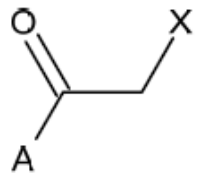

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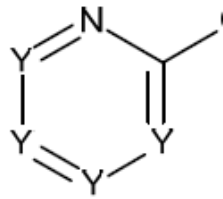
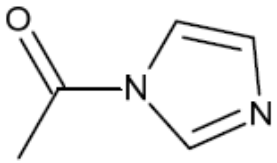


Y = N,C

297



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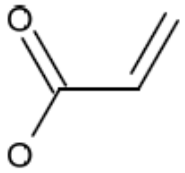

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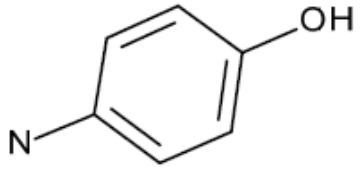

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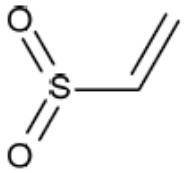

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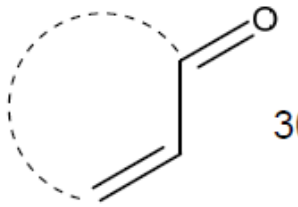

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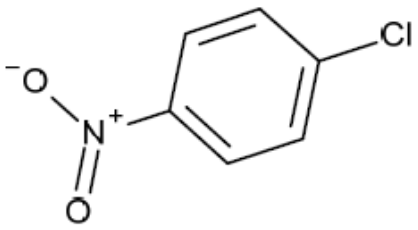
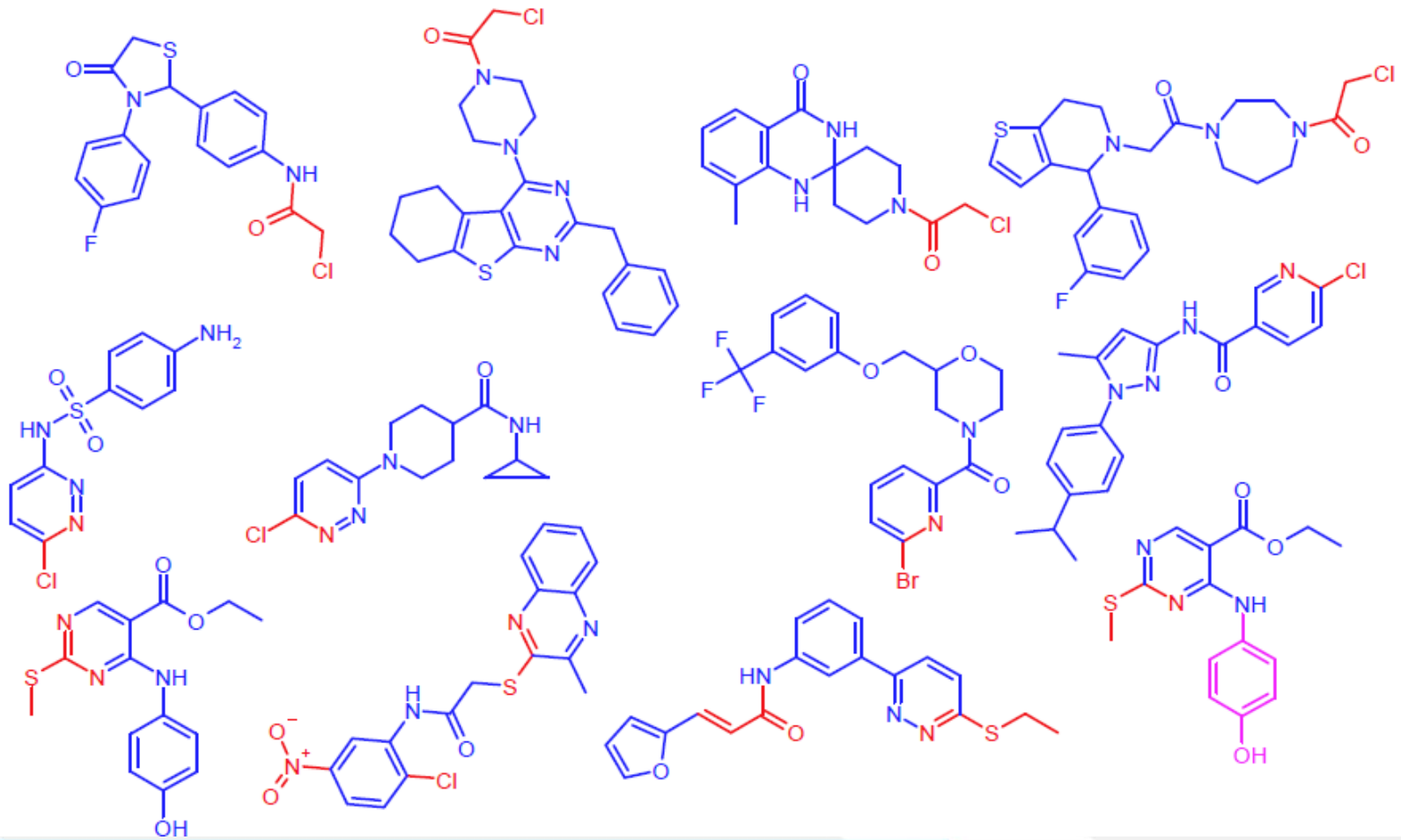


265

Generic library of covalent inhibitors

Representative Examples of the Selected Compounds
Alkylators/Arylators



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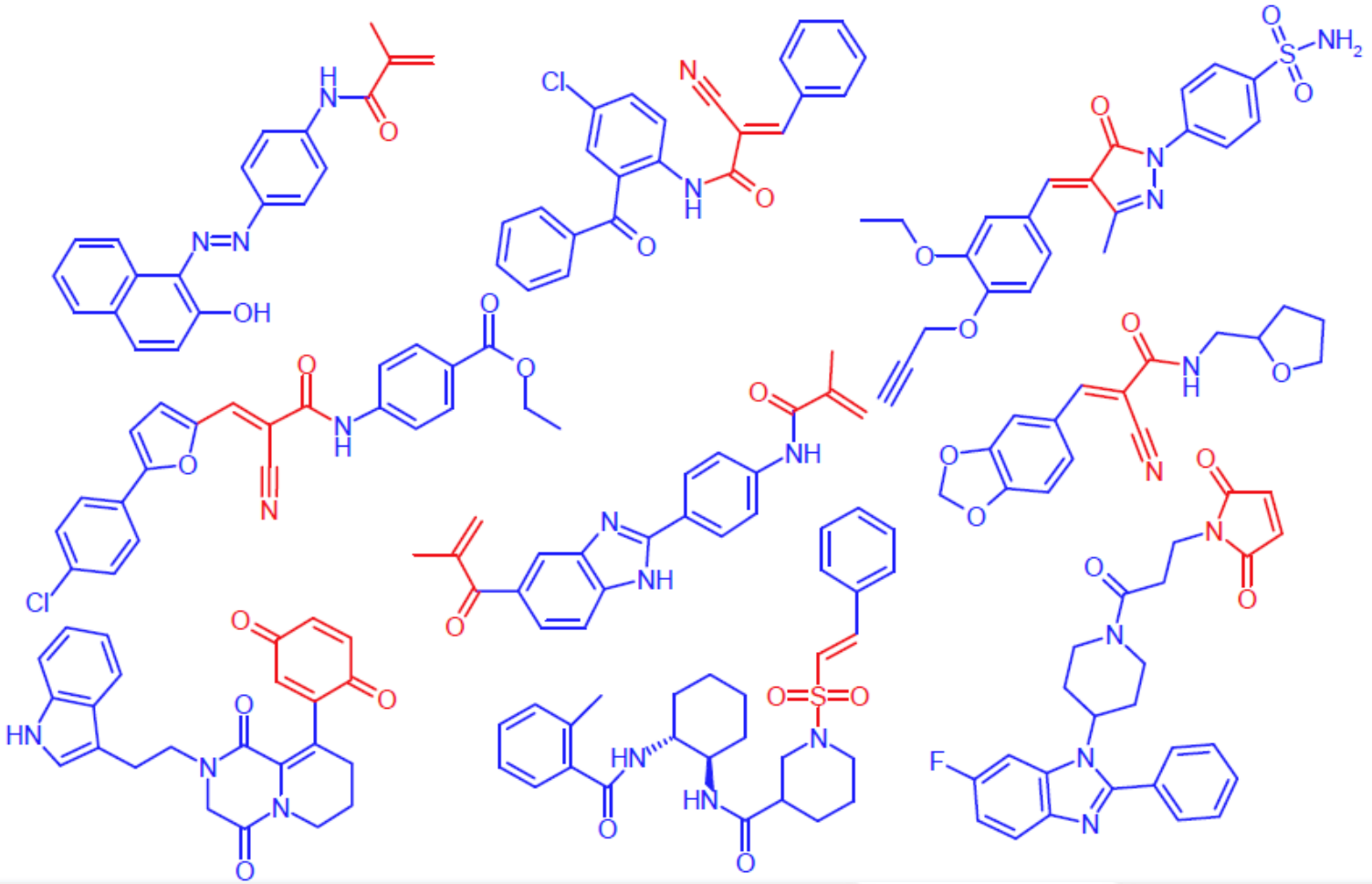
Representative Examples of the Selected Compounds

Michael Acceptors/Dienophiles



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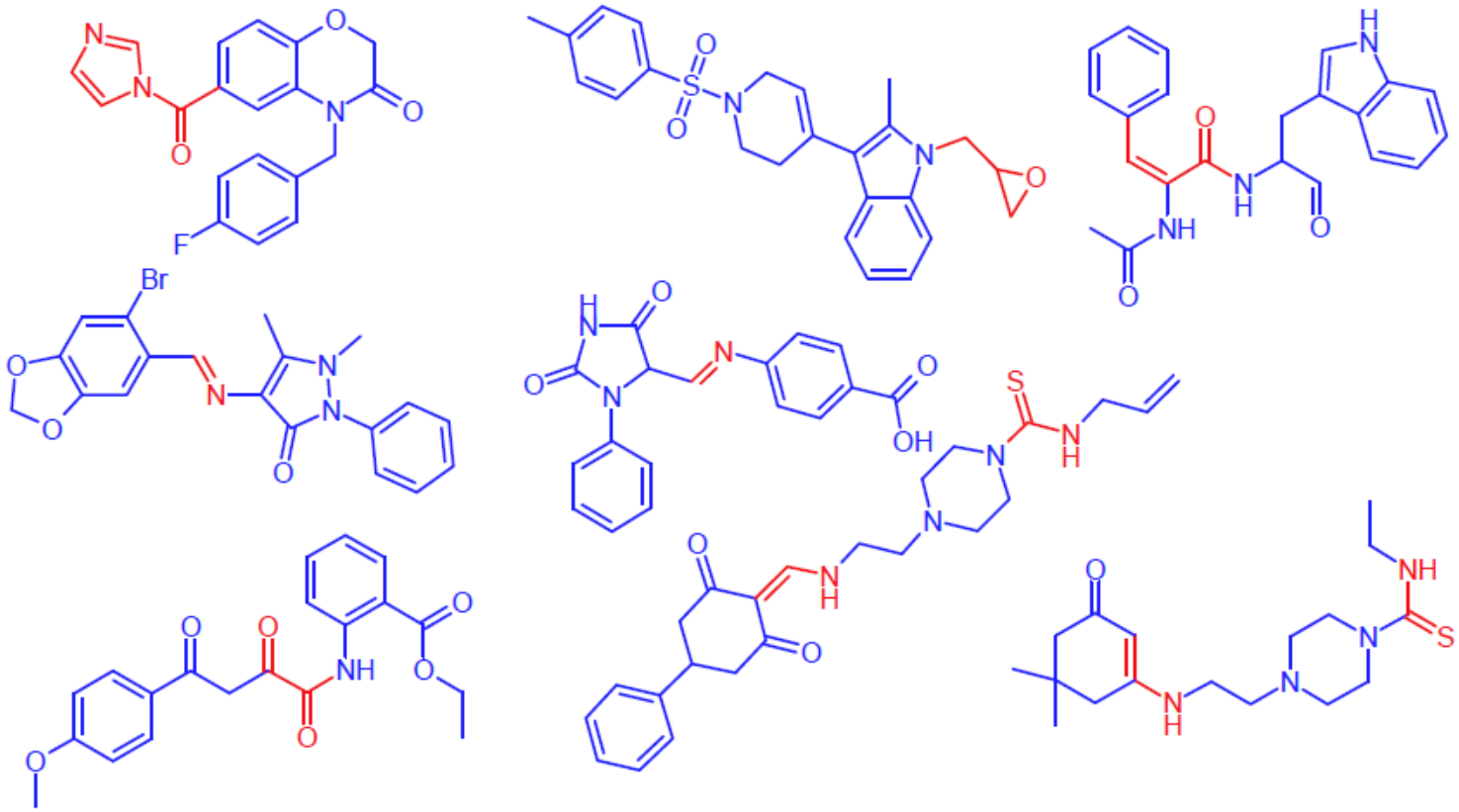
Representative Examples of the Selected Compounds

Other nucleophile-sensitive structures



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Smart Libraries of Covalent Inhibitors and Covalent Fragments

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Smart library of covalent inhibitors

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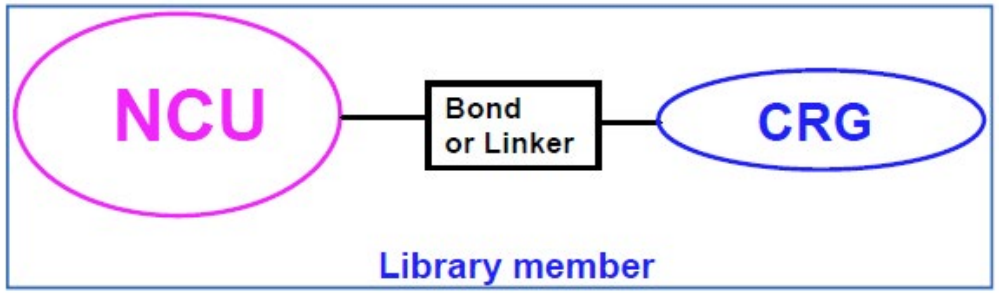
General Strategy



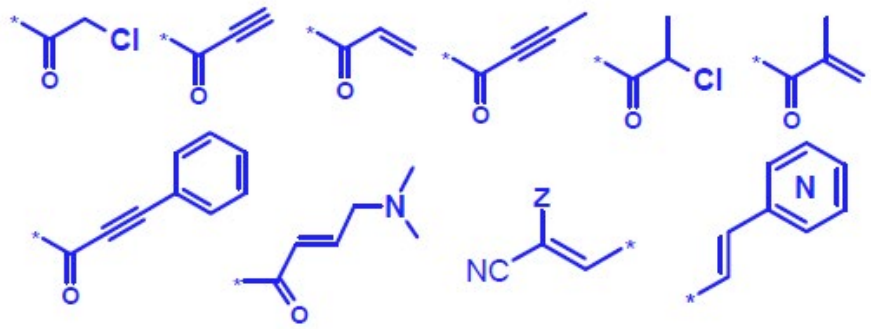
Non-covalent Unit (NCU)

Criteria:

- ***2D- and 3D-Diversity;***
- ***Physico-Chemical Parameters;***
- ***Stock/Synthetic feasibility;***
- ***Unique or rare structure. ****

**** Commercially available cores also have been used for covalent fragment library design and synthesis.***

The most widely used warheads (Covalent Reactive Groups, CRG):



Which one to choose?

Smart library of covalent inhibitors

Anti-cancer drugs on the market

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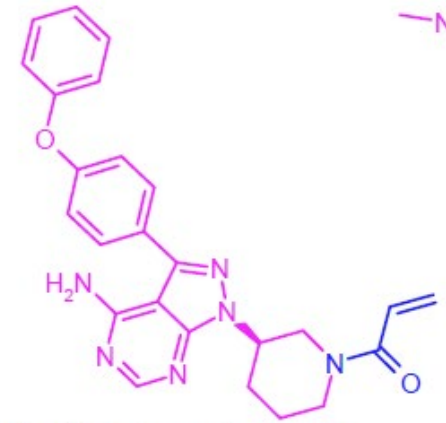
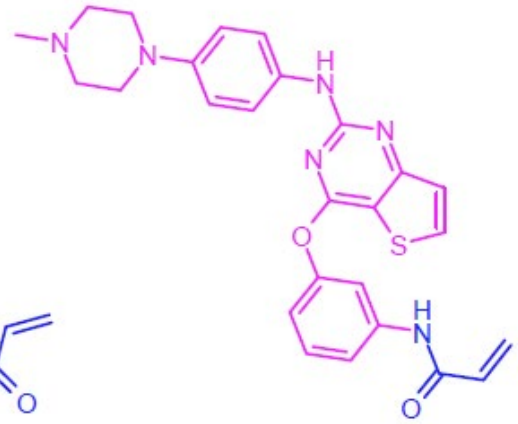
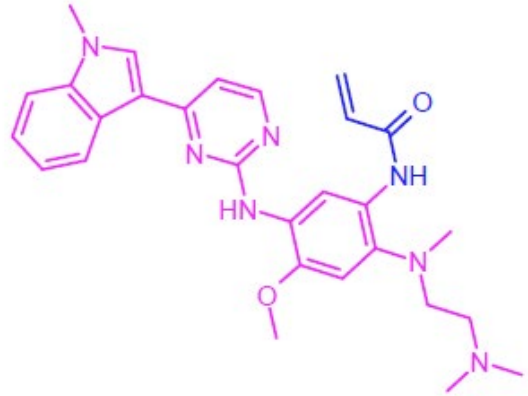


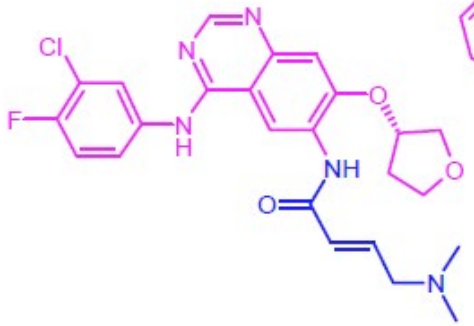
Ibrutinib (Launched-2013)



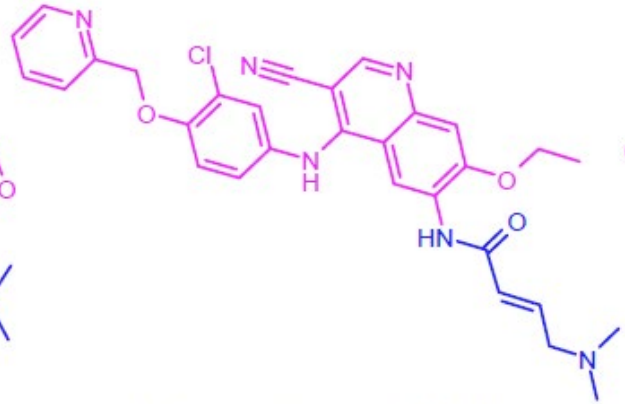
Olmutinib (Launched-2016)



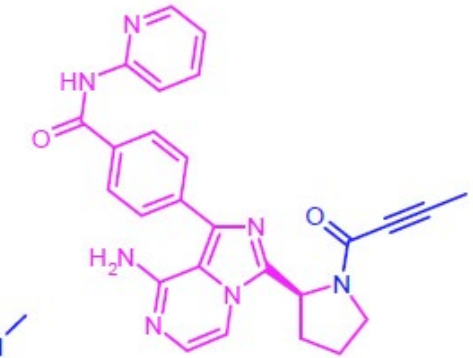
Osimertinib (Launched-2015)



Afatinib (Launched-2013)



Neratinib (Launched-2017)



Acalabrutinib (Launched-2017)

All of them are still under active development

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Appearance in covalent drugs

(Integrity database search results)

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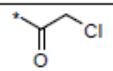
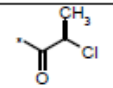
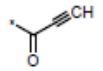
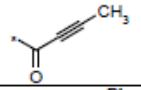
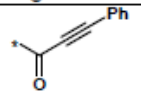
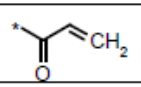
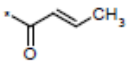
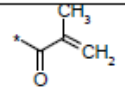
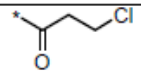
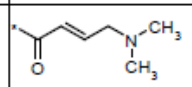
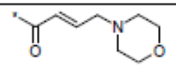
CRG	Structure	# of hits	Launched	Phase 1 - 3	Preclinical	Under active development
CRG-1a		252	0	1	18	0
CRG-1b		7	0	0	1	0
CRG-2a		30	0	0	2	0
CRG-2b		126	1	2	2	3
CRG-2c		210	1	0	21	0
CRG-3a		1842	3	11	95	19
CRG-3b		25	0	0	2	0
CRG-3c		21	0	0	2	0
CRG-4		10	0	0	1	0
CRG-5a		223	2	4	21	6
CRG-5b		18	0	0	2	0

Smart library of covalent inhibitors

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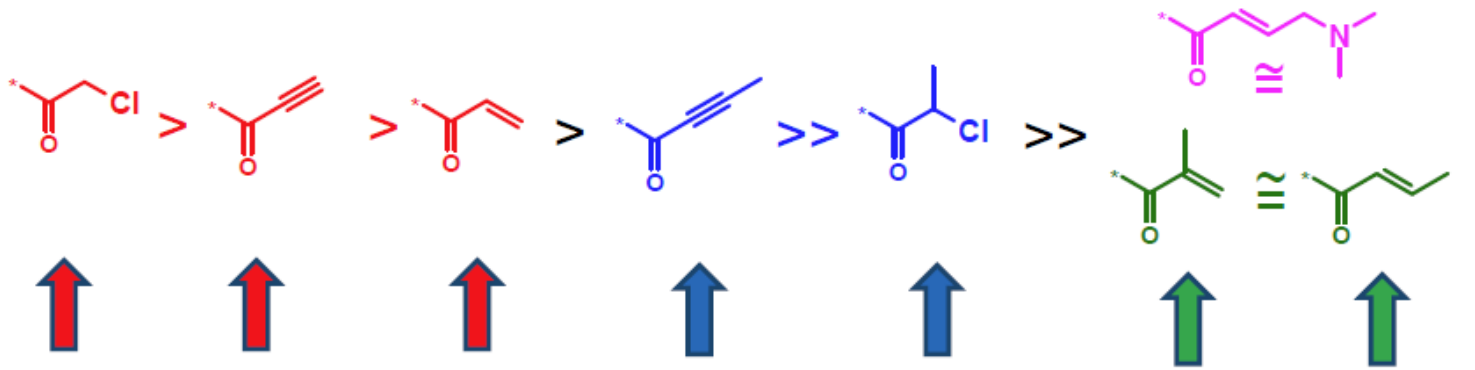
Warhead to choose

Related Reactivity of Covalent Reactive Groups (CRG, warheads) on Glutathione Model *

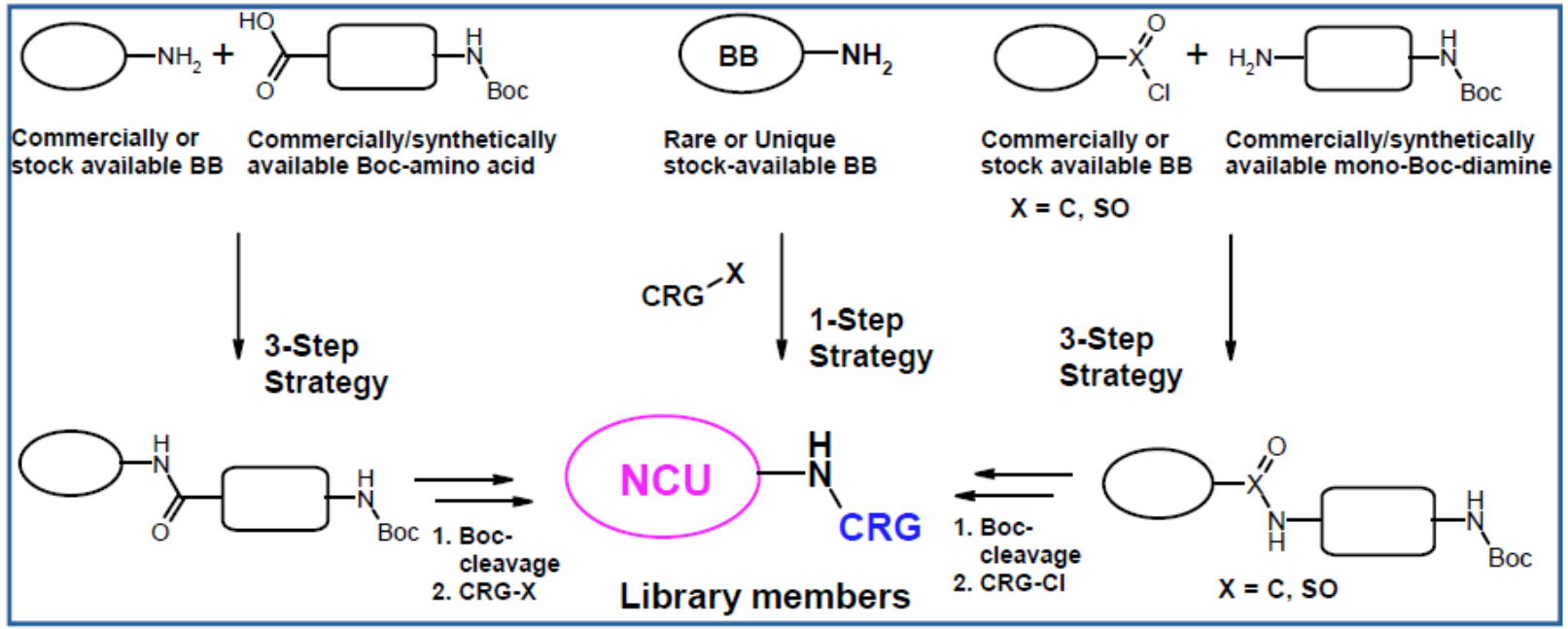


Over reactive *Low selectivity* *High toxicity* *Long term stability issue*	*Intermediate reactivity* *Moderate selectivity* *and toxicity* *Seem to be stable*	*Low reactivity* *High selectivity* *Low toxicity* *Seem to be stable*

** J. Med. Chem. 2014, 57, 10072–10079.*

Smart library of covalent inhibitors

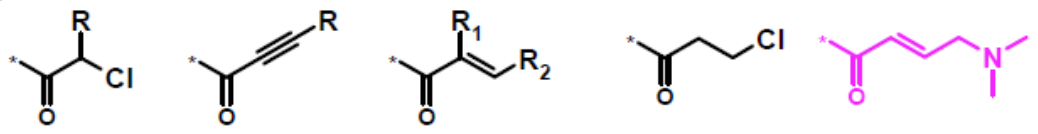
Synthesis



Smart library of covalent inhibitors

Variable in a wide range of reactivity warheads have been used for library members synthesis:

CRG =



CRG-1:	CRG-2:	CRG-3:	CRG-4	CRG-5
R=H (a)	R=H (a)	R1=R2=H (a)		
R=Me (b)	R=Me (b)	R1=H, R2=Me (b)		
	R=Ph (c)	R1=Me, R2=H (c)		

Smart library of covalent inhibitors

Representative examples of library members :

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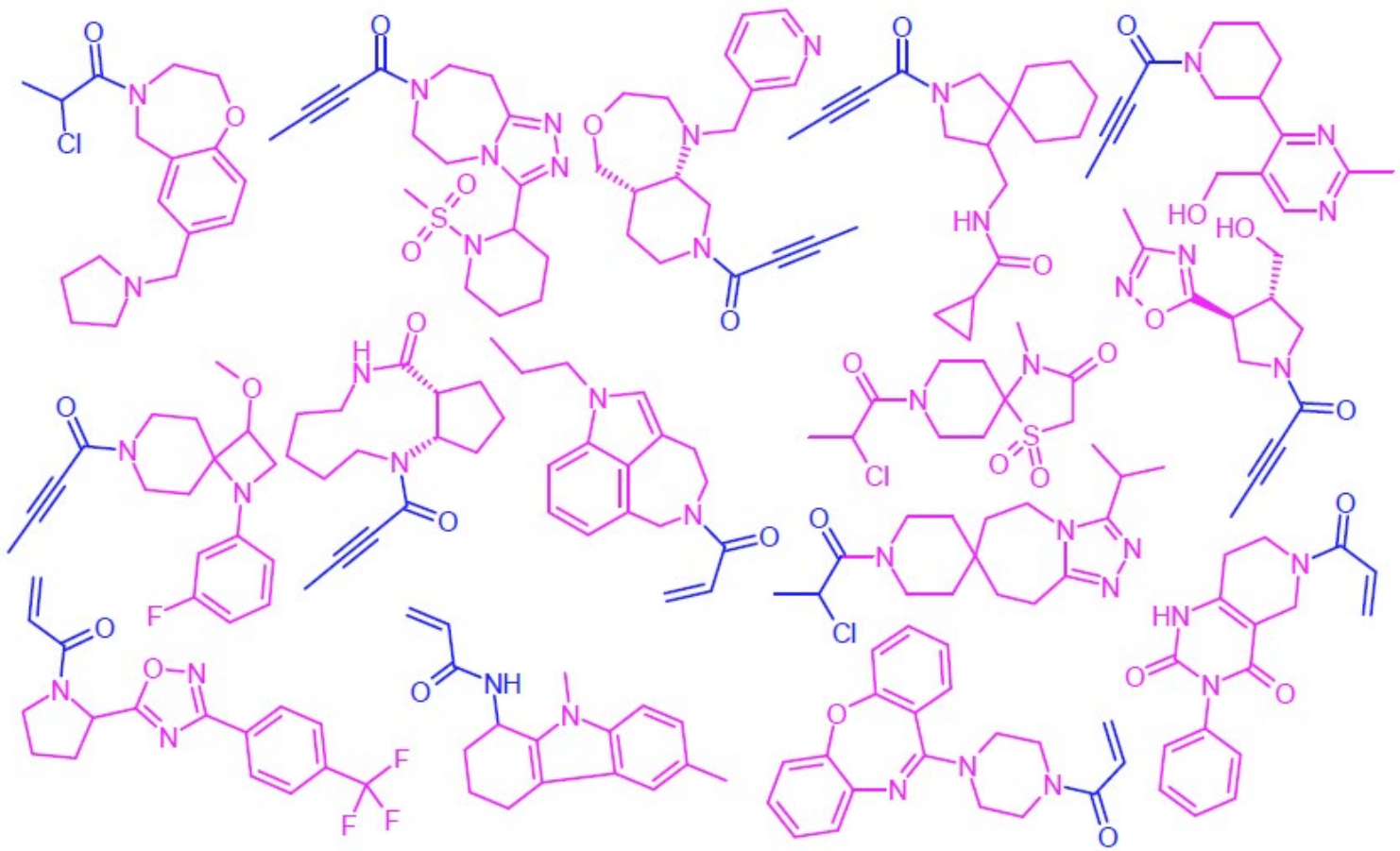

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Smart library of covalent fragments

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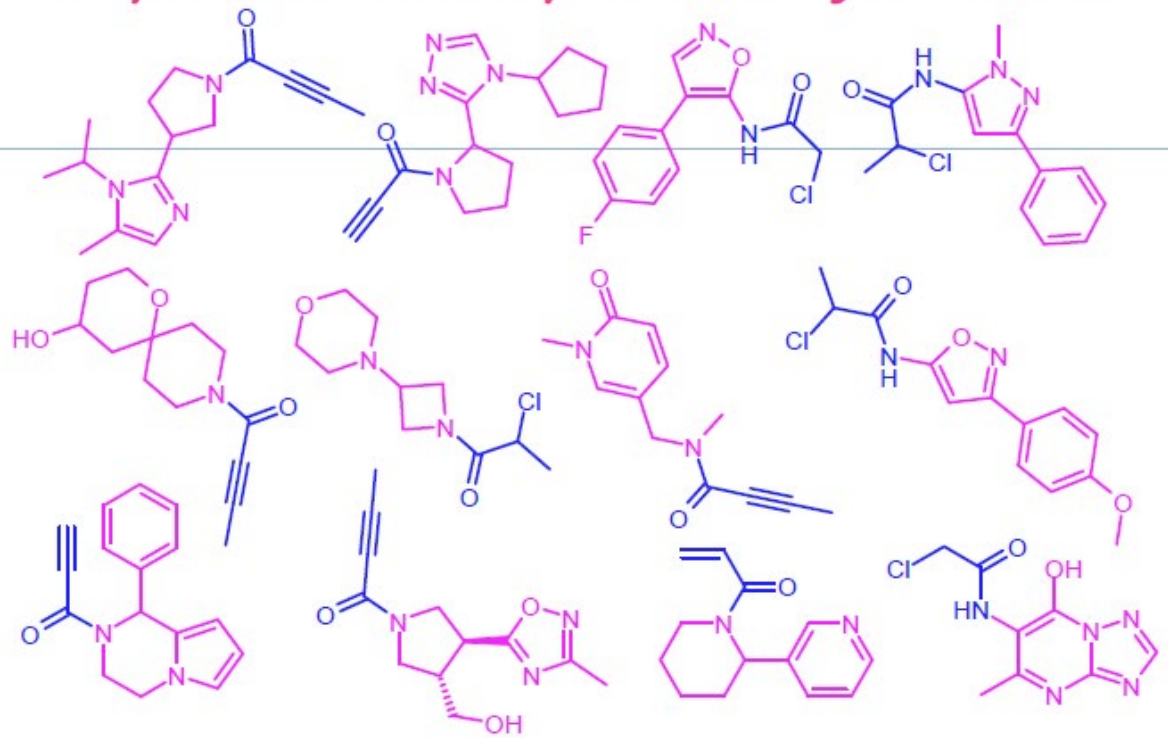
Criteria for library members selection:

- ***Should be rationally designed as members of Smart LCI;***
- ***Core structures (excluding warhead) should meet criteria applied for general fragment library.***

Representative examples of library members :



Smart libraries statistics by warheads:

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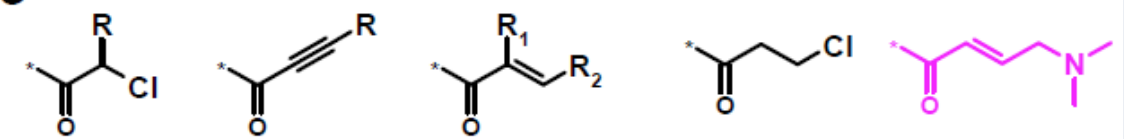
CRG Type	Smart Covalent Inhibitors	Smart Covalent Fragments
CRG-1a	676	127
CRG-1b	151	133
CRG-2a	104	81
CRG-2b	670	339
CRG-3a	342	249
CRG-4	10	0
CRG-5*	0	0
Total	1953	929

** Custom design and fast-track synthesis of the library members with warhead CRG-5 and/or other warheads specified by customer is available on demand.*

CRG =



CRG-1: R=H (a) R=Me (b)

CRG-2: R=H (a) R=Me (b)

CRG-3: R1=R2=H (a) R1=H, R2=Me (b)

CRG-4

CRG-5

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Library of sp^3-Enriched β-Lactams

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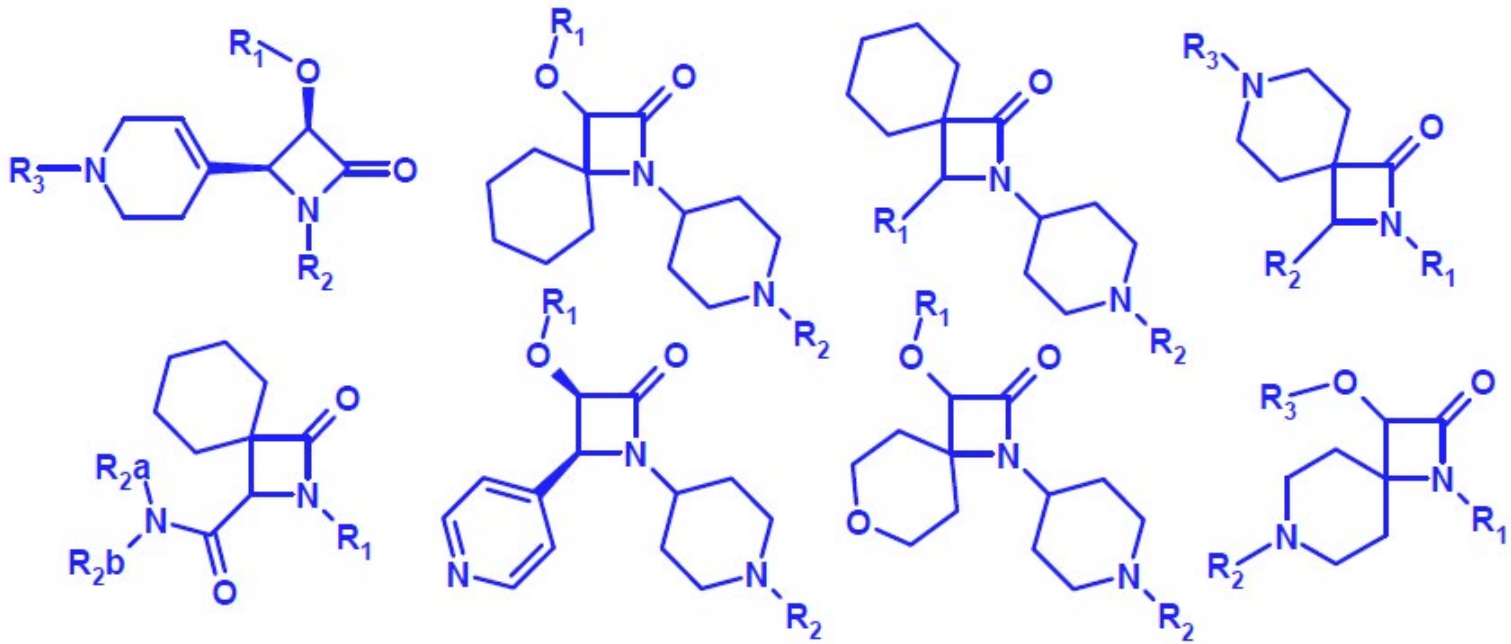
Library of β-Lactams

2K Members library has been designed around β-lactam core decorated with sp^3-enriched substituents.

Representative examples of β-lactam scaffolds:



Summary

Library of Covalent Inhibitors consists of four sub- libraries, namely:

- **Generic Library of Covalent Inhibitors includes compounds bearing nucleophile-sensitive functional groups selected from historical collection, 9K members;**
- **Smart Library of Covalent Inhibitors includes rationally designed and purposefully synthesized compounds with installed selected warheads, 1.95K members;**
- **Smart Library of Covalent Fragments includes those members of Smart LCI that meet "fragment" criteria for their non-covalent units, 0.9K members;**
- **Library of sp^3-Enriched β-Lactams, 2K members.**

Both Smart Libraries are constantly growing.

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Благодарим за внимание

Инструкция по заказу соединений из библиотеки «ХимРар»:

Наш сайт: https://chemrar.ru/library-full-list/

Направьте список интересующих соединений на email: vvk@chemrar.ru

В соответствии с вашим запросом менеджер выполнит подборку соединений и направит информацию о наличии. Имеется возможность сделать поиск по структуре/буквенному идентификатору (ID, CAS, MFCD), а также импортировать файл в различных форматах: SMILE, sdf, txt.