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Scaffold oriented synthesis part 4: Design, synthesis and biological evaluation of novel 5-substituted indazoles as potent and selective kinase inhibitors employing heterocycle forming and multicomponent reactions

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ABSTRACT

We report the synthesis and biological evaluation of 5-substituted indazoles as kinase inhibitors. The compounds were synthesized in a parallel synthesis fashion from readily available starting materials employing heterocycle forming and multicomponent reactions and were evaluated against a panel of kinase assays. Potent inhibitors were identified for Gsk3β, Rock2, and Egfr.

As part of our efforts to enhance the Abbott compound collection with kinase inhibitors[1] we disclosed previously the implementation of [2+3] cycloaddition reactions to prepare novel and potent indazole and aminoindazole kinase inhibitors.[2] The rationale behind this approach was the ability to rapidly explore the ATP binding site of numerous kinases, utilizing readily available starting materials, without compromising the novelty of the final molecules. In this report we describe our efforts in applying the same strategy employing heterocycle forming and multicomponent reactions to suitably substituted indazoles (Fig. 1).

The majority of the reaction sequences utilized shared common starting materials and intermediates and were highly divergent. Starting with 5-bromoindazole **1** (Scheme 1), aryl acetyl ketone intermediate **6** could be obtained via Stille coupling of **3** with Boc protected indazole **2**. Alternatively, substituted ketones of generic structure **6** could be obtained from the 5-carboxylic acid indazole **4** via Weinreb amide **5**. Bromination of ketones **6** provided intermediates **7** which were poised for heterocycle forming reactions with aminopyrimidines and thioamides to yield imidazopyrimidine and thiazole substituted indazoles **8** and **9**, respectively.

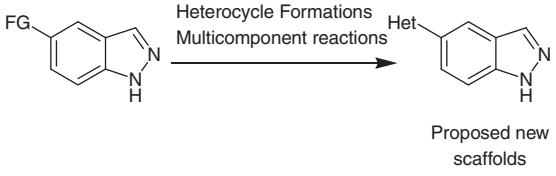

Figure 1. Design of novel molecules based on known kinase hinges.

Amino-substituted fused imidazo-pyridines, -pyrimidines, -pyrazines and -thiazoles **11** and **12** (Scheme 2) could be obtained in one step by applying multicomponent reactions[3] to commercially available aldehyde **10**. Aldehyde **10** could also be used as an input in Van Leusen reactions[4] to afford imidazolyl-indazoles **14**. It should be noted that although the above-mentioned procedures were synthetically facile the resulting final molecules were highly complex and to our knowledge had never been made before.

Having secured numerous analogs in a highly efficient manner we proceeded to evaluate them in a panel of kinase assays.[2] We again identified highly potent kinase inhibitors that exhibited a

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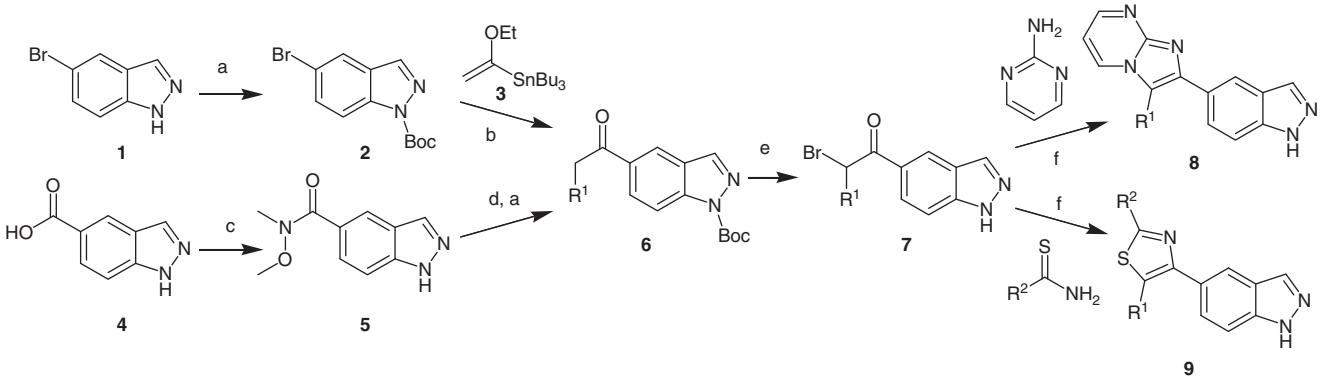
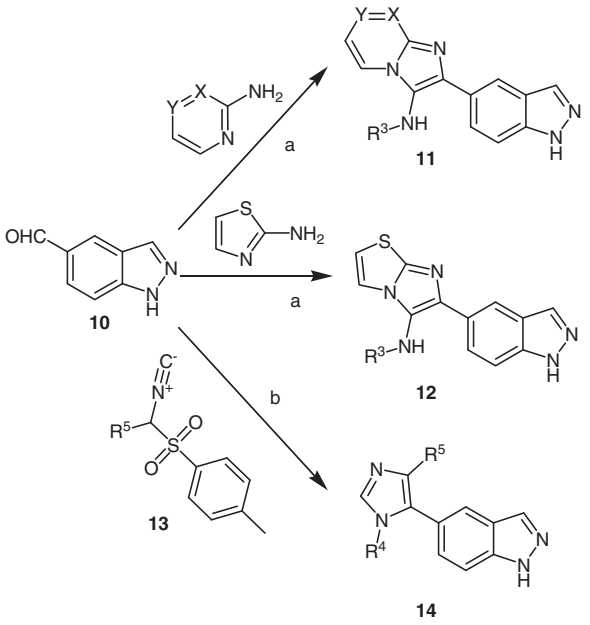


Scheme 1. (a) Boc_2O, DMAP, CH_2Cl_2, rt, quant; (b) $PdCl_2(PPh_3)_2$, toluene, 100 °C, ON, 36%; (c) CH_3ONHCH_3, CH_2Cl_2, DMF, Et_3N, EDC, rt, 24 h, 44%; (d) R^1CH_2MgCl, THF, 0 °C to rt, 58 %; (e) py·HBr_3, THF, 40 °C, 42%; (f) EtOH, 80 °C, 24 h, 25–71%.



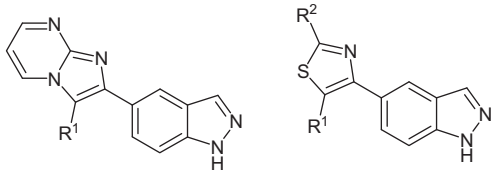
Scheme 2. (a) $Sc(OTf)_3$, MeOH, $R^3N^+{\equiv}C^-$, rt, 10–74%; (b) R^4NH_2, DMF, 60 °C, 4 h, then K_2CO_3, tosmic **13**, 60 °C, ON, 4–23%.

variety of selectivity patterns depending on the heterocycle and its substituents in the 5-position of the indazole ring.

Imidazopyrimidine ring attachments provided potent inhibitors for Rock2 and Gsk3β (Table 1) with a phenyl substituted heterocycle being much more potent than the parent (**8b** vs. **8a**). Compound **8b** also exhibited some Pim1 activity although it was much more potent against Rock2 and Gsk3β. Thiazolyl-indazoles **9** were, in general, more selective for Rock2 over Gsk3β but not as potent as **8b**. Benzylamino and phenethylamino substitutions at the 2 position of the thiazole ring improved Rock2 potency, however the compounds were also potent against Aurora2 (compounds **9e** and **9f**). Interestingly, anilino substituted compound **9d**, while equipotent for Rock2 and Aurora2 was about threefold more selective for Gsk3β. The additional substitution of a phenyl ring in the 5-position of the thiazole ring diminished the Gsk3β activity (compound **9g** vs. **9d**).

A reverse trend was observed with amino-substituted imidazo-fused heterocyclic attachments to the indazole ring (compound **11**, Table 2). In this case the compounds were more selective for Gsk3β over Rock2. The highest inhibitory activity against Gsk3β was observed with imidazopyrimidines which were much more potent than imidazopyridines (**11c** vs. **11a**). Depending on the substituents on the amino group of the 3 position of the imidazole ring the Rock2 activity could also be attenuated. A cyclohexyl or a phenyl substituent (compounds **11c** and **11f**, respectively)

Table 1
Kinase inhibitory activity of 2-(indazol-5-yl)-3-substituted imidazopyrimidines **8** and 4-(indazol-5-yl)-2,5-substituted thiazoles **9**[a]

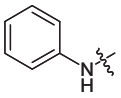
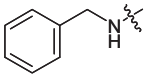
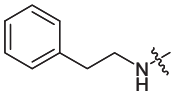
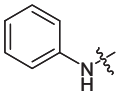
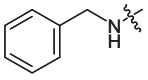


8 **9**

Compound	R^1	R^2	Aurora2 K_i (μM)	Egfr K_i (μM)	Gsk3β K_i (μM)	Jak2 K_i (μM)	Kdr K_i (μM)	Pak4 K_i (μM)	Pim1 K_i (μM)	Rock2 K_i (μM)
8a	H		>4.900	>1.800	0.141	ND	>8.880	>3.750	1.664	0.226
8b			>4.900	ND	0.010	ND	>8.880	>3.750	0.339	0.006
9a	H		4.45	ND	2.861	ND	>8.880	>3.750	4.156	0.513
9b	H		2.125	ND	4.472	ND	>8.880	>3.750	2.899	0.909

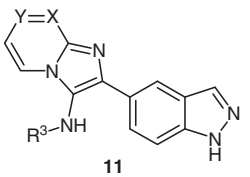
(*continued on next page*)

Table 1 (*continued*)

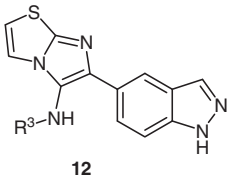
Compound	R^1	R^2	Aurora2 K_i (μM)	Egfr K_i (μM)	Gsk3β K_i (μM)	Jak2 K_i (μM)	Kdr K_i (μM)	Pak4 K_i (μM)	Pim1 K_i (μM)	Rock2 K_i (μM)
9c	H		3.406	ND	3.925	ND	>8.880	>3.750	1.952	0.888
9d	H		0.834	>1.800	0.289	ND	>8.880	>3.750	2.656	0.864
9e	H		0.588	>1.800	>5.450	>1.450	>8.880	>3.750	>8.570	0.136
9f	H		0.810	ND	>5.450	ND	>8.880	>3.750	>8.570	0.364
9g			>4.900	ND	>5.450	ND	>8.880	>3.750	>8.570	1.413
9h			>4.900	ND	3.402	ND	>8.880	>3.750	>8.570	0.822

[a] K_i values are based on six point curves.

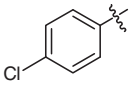
Table 2
Kinase inhibitory activity of 6-(indazol-5-yl)-3-substituted fused imidazoles **11** and 6-(indazol-5-yl)-5-substituted imidazothiazoles **12**[a]



11



12

Compound	Y	X	R^3	Aurora2 K_i (μM)	Egfr K_i (μM)	Gsk3β K_i (μM)	Jak2 K_i (μM)	Kdr K_i (μM)	Pak4 K_i (μM)	Pim1 K_i (μM)	Rock2 K_i (μM)
11a	C	C		8.666	ND	2.611	ND	ND	ND	2.307	2.475
11b	N	C		2.066	ND	ND	ND	ND	ND	1.846	ND
11c	C	N		5.333	>1.800	0.010	ND	ND	ND	0.307	0.245
11d	C	N		4.340	>1.800	0.017	ND	>8.880	>3.750	0.242	0.065
11e	C	N		>4.900	ND	0.019	ND	>8.880	>3.750	0.114	0.116
11f	C	N		2.805	ND	0.121	ND	>8.880	>3.750	>8.570	1.565
12				1800	ND	0.642	ND	5.339	ND	1.292	0.622

[a] K_i values are based on six point curves.

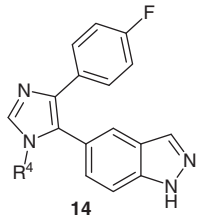
imparted the highest selectivity for Gsk3β over Rock2. Small aliphatic group substitutions maintained similar Gsk3β potencies, however they also exhibited potent Rock2 inhibition (compounds **11d** and **11e**). Imidazo thiazole **12** was equipotent for Gsk3b and Rock2 but much less potent than its imidazo pyrimidine counterpart **11c**.

A completely different activity profile was obtained with imidazoloindazoles **14**. These compounds were potent Egfr inhibitors but did not inhibit any of the other kinases of our panel (Table 3). By preparing a diverse library of analogs **14** single digit nanomolar Egfr inhibitors were identified.

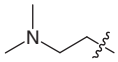
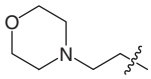
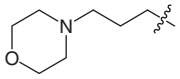
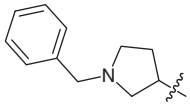
In conclusion, we have demonstrated that by applying heterocycle ring forming and multicomponent reactions to the suitably functionalized 5-position of the indazole ring we could obtain potent kinase inhibitors.

In the past, it has often been debated whether one could achieve selectivity with kinase inhibitors targeting the ATP binding site. Subsequently it was shown that kinases can be classified in a

Table 3
Kinase inhibitory activity of 5-(indazol-5-yl)-1,4-substituted imidazoles **14**[a]



14

Compound	R^4	Aurora2 K_i (μM)	Egfr K_i (μM)	Gsk3β K_i (μM)	Jak2 K_i (μM)	Kdr K_i (μM)	Pak4 K_i (μM)	Pim1 K_i (μM)	Rock2 K_i (μM)
14a		>4.900	0.067	>5.450	>1.450	>8.880	>3.750	>8.570	>6
14b		>4.900	0.017	>5.450	>1.450	>8.880	>3.750	>8.570	>6
14c		>4.900	0.027	>5.450	>1.450	>8.880	>3.750	>8.570	>6
14d		>4.900	0.008	>5.450	>1.450	>8.880	>3.750	>8.570	>6

[a] K_i values are based on six point curves.

different manner based on small molecule selectivity data[5] rather than genetic sequencing.[6] Furthermore once thought selective molecules were found to inhibit additional kinases upon further testing.[7] Extensive profiling of numerous kinase chemotypes and the availability of crystal structures of inhibitor/kinase complexes resulted in a wealth of information that has been used in a variety of ways to explain and/or predict kinase selectivity.[8]

The data presented in the present and previous communications suggests that although there are general trends governing the activity of various chemotypes, each compound possessed its own unique activity print thus allowing for manipulation of selectivity. We have been exploring this concept with extensive analoging and testing against large panels of kinases and the results of these efforts will be reported in due course.

Acknowledgments

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