



## Scaffold oriented synthesis. Part 3: Design, synthesis and biological evaluation of novel 5-substituted indazoles as potent and selective kinase inhibitors employing [2+3] cycloadditions

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### ABSTRACT

We report the synthesis and biological evaluation of 5-substituted indazoles and amino indazoles as kinase inhibitors. The compounds were synthesized in a parallel synthesis fashion from readily available starting materials employing [2+3] cycloaddition reactions and were evaluated against a panel of kinase assays. Potent inhibitors were identified for numerous kinases such as Rock2, Gsk3β, Aurora2 and Jak2.

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As part of our efforts to develop patentable, high quality lead molecules for kinase programs at Abbott,<sup>1</sup> we reported the discovery of underutilized unique heterocycles as hinge binders with potent inhibitory activity against kinase targets.<sup>2</sup> A second part of our strategy has been the implementation of underutilized but robust chemistries to engage known kinase hinge binding elements (Fig. 1). The rationale behind this approach was the ability to rapidly explore the ATP binding site of numerous kinases, utilizing readily

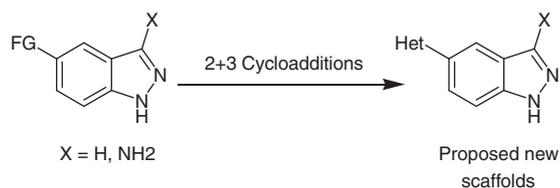
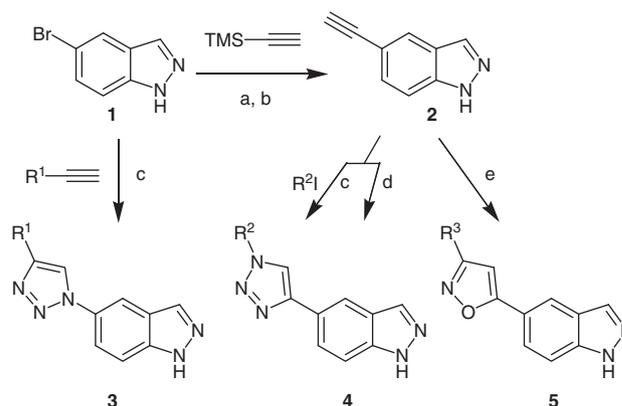


Figure 1. Design of novel molecules based on known kinase hinges.

available starting materials, without compromising the novelty of the final molecules.

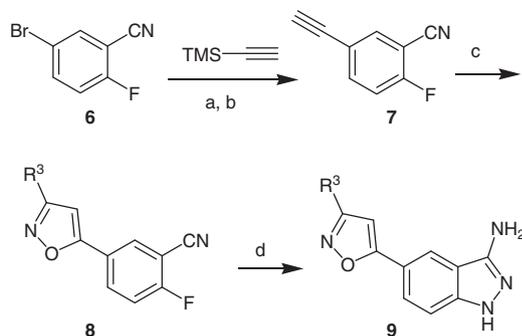


Scheme 1. Reagents and conditions: (a)  $\text{Boc}_2\text{O}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, quant; (b)  $\text{CuI}$ ,  $(\text{Ph}_3)_2\text{Cl}_2\text{Pd}$ , DMF,  $\text{Et}_3\text{N}$ ,  $95^\circ\text{C}$ , 72%, then  $\text{KOH}$ , MeOH, 95%; (c) DMSO,  $\text{NaN}_3$ , L-proline,  $\text{Na}_2\text{CO}_3$ , sodium ascorbate,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ,  $65^\circ\text{C}$ , 6–39%; (d)  $\text{R}^2\text{Cl}$ ,  $\text{NaN}_3$ ,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ,  $\text{Cu}(0)$ , *t*-BuOH,  $\text{H}_2\text{O}$ , CEM microwave, 100 W,  $125^\circ\text{C}$ , 10 min, 3–26%; (e)  $\text{R}^3\text{CHO}$ ,  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , 6 N NaOH, chloramine-T  $\cdot 3\text{H}_2\text{O}$ ,  $\text{CuSO}_4$ , Cu wire, *t*-BuOH,  $\text{H}_2\text{O}$ ,  $50^\circ\text{C}$ , 4–5%.

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**Scheme 2.** Reagents and conditions: (a) CuI,  $(\text{Ph}_3)_2\text{Cl}_2\text{Pd}$ , DMF,  $\text{Et}_3\text{N}$ ,  $95^\circ\text{C}$ , 24 h, 93%; (b) TBAF, THF, 55%; (c)  $\text{R}^3\text{CHO}$ ,  $\text{NH}_2\text{OH}\cdot\text{HCl}$ , 6 N NaOH, chloramine-T- $3\text{H}_2\text{O}$ ,  $\text{CuSO}_4$ , Cu wire, *t*-BuOH,  $\text{H}_2\text{O}$ ,  $50^\circ\text{C}$ , 33–69%; (d)  $\text{NH}_2\text{NH}_2$ , EtOH,  $70^\circ\text{C}$ , 24 h, 53–78%.

In this report, we describe our efforts in applying the above strategy to indazoles and aminoindazoles, which are well known kinase hinge binding motifs.<sup>3</sup> We were pleased to discover that application of [2+3] cycloaddition reactions to suitably substituted indazoles rendered the compounds novel.

Starting with 5-bromo indazole **1** (Scheme 1), 5-(4-substituted-1,2,3-triazol-1-yl)-indazoles **3** could be obtained directly by cycloaddition reactions of in situ generated 5-azido-indazole with commercially available acetylenes following literature procedures.<sup>4</sup>

Alternatively, Sonogashira coupling of Boc protected **1** with trimethylsilylacetylene and subsequent base induced desilylation and Boc deprotection provided 5-ethynyl-indazole **2** which upon cycloaddition reactions with azides<sup>4,5</sup> yielded 5-(1-substituted-1,2,3-triazol-4-yl)-indazoles **4**. Intermediate **2** could also be utilized for the synthesis of isoxazoles **5** via the in situ formation of nitrile

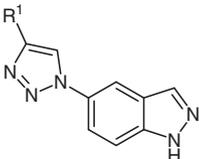
oxides.<sup>6</sup> Similarly, 5-substituted-3-amino indazoles could be prepared by Sonogashira coupling of trimethylsilylacetylene with commercially available 2-fluoro-5-iodobenzonitrile **6** (Scheme 2). Deprotected intermediate **7** was subjected to cycloaddition reactions, followed by treatment with hydrazine to afford the final products **9**.

Following these procedures numerous analogs were prepared in a short period of time in a parallel synthesis fashion. The compounds were tested in a panel of kinase assays<sup>7</sup> covering all of the branches of the kinome tree.<sup>8</sup>

We were pleased to find that the majority of the compounds showed inhibitory activity in at least one of the kinase assays. In the case of triazoloindazoles **3** (Table 1) most of the compounds were potent inhibitors of Rock2 but they also inhibited Gsk3 $\beta$ , Aurora2 and Jak2. Depending on the substitution pattern the activity against the various kinases could be modulated. For example, although compounds **3g** and **3h** had similar potencies against Rock2, **3h** was more potent than **3g** against Aurora2 and Jak2. Furthermore, a cyclohexylmethyl substituent in compound **3f** greatly improved the Jak2 activity, while tethered phenyl groups in compounds **3g–3i** improved Gsk3 $\beta$  activity.

In the case of triazoloindazoles **4** (Table 2) we observed a different potency profile. A direct comparison of **3g** to **4b** showed that in contrast to **3g**, **4b** was more potent against Gsk3 $\beta$  and Aurora2 than Rock2 while the 3-amino indazole **4c** lost some of its Aurora2 and Gsk3 $\beta$  potency and gained Rock2 and Jak2 activity. Simple substitutions on the benzyl ring also have a dramatic effect on the potency and selectivity of the analogs. For example, although *meta* substituted benzyl ring derivatives improved potency against Aurora2, Gsk3 $\beta$  and Rock2 the methyl group appears to be the best substituent for Aurora2 activity, the fluoro for Gsk3 $\beta$  and the chloro for Rock2. For the dichloro analogs **4l**, **4m** and **4n** the

**Table 1**  
Kinase inhibitory activity of 5-(4-substituted-1,2,3-triazol-1-yl)-indazoles **3**<sup>a</sup>

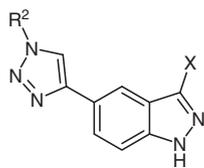


Compound	R <sup>1</sup>	Aurora2 K <sub>i</sub> (μM)	Egfr K <sub>i</sub> (μM)	Gsk3 $\beta$ K <sub>i</sub> (μM)	Jak2 K <sub>i</sub> (μM)	Kdr K <sub>i</sub> (μM)	Pak4 K <sub>i</sub> (μM)	Pim1 K <sub>i</sub> (μM)	Rock2 K <sub>i</sub> (μM)
<b>3a</b>		>4.900	>1.800	2.026	0.756	>8.880	>3.750	8.359	0.108
<b>3b</b>		>4.900	>1.800	>5.450	>1.450	>8.880	>3.750	>8.570	0.635
<b>3c</b>		>4.900	>1.800	5.216	1.453	>8.880	>3.750	>8.570	0.230
<b>3d</b>		>4.900	>1.800	3.466	1.453	>8.880	>3.750	>8.570	0.356
<b>3e</b>		>4.900	>1.800	1.298	0.791	>8.880	>3.750	>8.570	0.044
<b>3f</b>		>4.900	>1.800	0.891	0.281	>8.880	>3.750	>8.570	0.100
<b>3g</b>		1.577	>1.800	0.542	1.282 <sup>b</sup>	>8.880	>3.750	>8.570	0.018
<b>3h</b>		0.524	>1.800	0.446	0.898	>8.880	>3.750	>8.570	0.019
<b>3i</b>		1.930	>1.800	0.528	0.644	>8.880	>3.750	>8.570	0.062

<sup>a</sup> K<sub>i</sub> values are based on six point curves unless otherwise noted.

<sup>b</sup> K<sub>i</sub> value is based on an eleven point curve done in triplicate.

**Table 2**  
Kinase inhibitory activity of 5-(1-substituted-1,2,3-triazol-4-yl)indazoles **4**<sup>a</sup>



Compound	R <sup>2</sup>	X	Aurora2 K <sub>i</sub> (μM)	Egfr K <sub>i</sub> (μM)	Gsk3β K <sub>i</sub> (μM)	Jak2 K <sub>i</sub> (μM)	Kdr K <sub>i</sub> (μM)	Pak4 K <sub>i</sub> (μM)	Pim1 K <sub>i</sub> (μM)	Rock2 K <sub>i</sub> (μM)
<b>4a</b>	H	H	0.493	ND	0.448	1.453 <sup>b</sup>	3.554	69.911	2.219	0.209
<b>4b</b>		H	0.073	>1.800	0.039	0.284 <sup>b</sup>	>8.880 <sup>c</sup>	>5.450	0.923	0.097
<b>4c</b>		NH <sub>2</sub>	0.252	>1.800	0.265	0.091 <sup>b</sup>	3.978	>3.750	>8.570	0.064
<b>4d</b>		H	0.553	ND	0.045	>1.453 <sup>b</sup>	ND	ND	4.153	0.097
<b>4e</b>		H	0.160	ND	0.023	1.450	13.142	ND	ND	0.039
<b>4f</b>		H	0.186	ND	0.197	ND	2.710	ND	37.846	0.068
<b>4g</b>		H	0.016	ND	0.091	ND	>0.915 <sup>b</sup>	13.090	10.153	0.285
<b>4h</b>		H	0.042	ND	0.026	ND	ND	ND	12.000	0.180
<b>4j</b>		H	ND	ND	0.070	ND	ND	ND	165.230	0.285
<b>4k</b>		H	0.015	ND	0.070	ND	>0.915 <sup>b</sup>	ND	ND	0.375
<b>4l</b>		H	0.066	ND	0.048	ND	ND	67.636	20.307	0.015
<b>4m</b>		H	ND	ND	0.016	ND	126.500	ND	36.000	0.018
<b>4n</b>		H	0.240	ND	0.028	ND	>0.915 <sup>b</sup>	ND	41.538	0.041

<sup>a</sup> K<sub>i</sub> values are based on six point curves unless otherwise noted.

<sup>b</sup> K<sub>i</sub> value is based on an eleven point curve done in triplicate.

position of the second chloro group modulates the Gsk3β and Rock2 activity with **4l** being more potent in Rock2, **4m** being equi-potent against Gsk3β and Rock2 and **4n** being more potent against Gsk3β.

When the heterocyclic ring at the 5-position of the indazole ring is an isoxazole (Table 3) the compound **5a** maintained its Rock2 and Gsk3β potency but it was also more potent against Aurora2 and Jak2 as compared to **3g**. Addition of an amino group at the 3-position of the indazole improved significantly its Aurora2 and

Jak2 activity. Aliphatic substituents on the isoxazole ring maintained moderate Rock2 activities.

In conclusion, we have discovered multiple series of easily accessible 5-substituted indazoles as potent kinase inhibitors. Although the compounds showed high potency against multiple kinases we have already observed selectivity trends based on substitution patterns of very close analogs. In addition to the panel of kinase assays reported here, numerous compounds were also tested in a large panel of more than 100 kinases. Many interesting

