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Novel pyrazolopyrimidines as highly potent B-Raf inhibitors

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ABSTRACT

A novel series of pyrazolo[1,5-*a*]pyrimidines bearing a 3-hydroxyphenyl group at C(3) and substituted tropanes at C(7) have been identified as potent B-Raf inhibitors. Exploration of alternative functional groups as a replacement for the C(3) phenol demonstrated indazole to be an effective isostere. Several compounds possessing substituted indazole residues, such as **4e**, **4p**, and **4r**, potently inhibited cell proliferation at submicromolar concentrations in the A375 and WM266 cell lines, and the latter two compounds also exhibited good therapeutic indices in cells.

The Ras-MAP kinase pathway has been implicated in tumor progression for a variety of human cancers. The Raf kinases, which are components of this cascade, are serine/threonine kinases that activate Mek1/2. Mutant B-Raf containing a V600E substitution causes aberrant constitutive activation of this pathway and has high occurrence in several human cancers.[1] As such, chemotherapeutic inhibition of mutant B-Raf offers a viable means for treating cancer.[2] Recently we disclosed the preliminary characterization of pyrazolo[1,5-*a*]pyrimidine-3-carboxylates (Fig. 1; **1**) as B-Raf inhibitors.[3] Further enhancements to this class of compounds (**2**) were able to boost the in vitro potency of these non-hinge region binders but modest cellular potency remained an issue.[4] Exploration of substituents at the C(2) position provided analogs that could form a hydrogen bond to the hinge region of B-Raf.[5] In an effort to further improve the potency and physical properties of these compounds,[4] we next explored C(2), C(3) disubstituted pyrazolopyrimidines with smaller C(7) substituents to reduce molecular weight. In this paper we describe a novel series of pyrazolopyrimidines incorporating a C(7) tropane moiety (Fig. 1; **3** and **4**) to afford structurally unique compounds with improved potency. Further modification around the core, based on the more highly substituted **5**, led to the preparation of fused tropanone analogs **6**. An important distinction to be noted is that while compounds of series **2** bind the inactive conformation of B-Raf, compounds **3–6** comprise a structural class that targets its active conformation.[6]

The chemistry to prepare these analogs is shown in Scheme 1. Commercially available tropanone **7** was converted in three steps to enaminone **8**.[7] Condensation of this reagent with aminopyrazole **9a**[8] in hot AcOH gave pyrazolopyrimidine **10a**.[9] Selective functionalization with *N*-iodosuccinimide yielded C(3) iodide **10b**, which upon exposure to a variety of boronic acids or esters afforded the arylated products **3** (Table 1; $R^1 = CO_2C_2H_5$; $R^2 = OCH_3$; R^3 = variable). In some instances, these carbamates were further modified to produce anisoles or phenols bearing different R^1 groups on the tropane. For instance phenols **3c–e** (Table 1) were prepared from their corresponding anisoles by exposure to BBr_3. Trimethylsilyl iodide (TMSI) was used to remove the *N*-carboethoxy group from **3a** and **3b** to yield products **3f** and **3g** and subsequent demethylation with BBr_3 gave secondary aminophenols **3h** and **3i**. *N*-Ethyl compound **3j** was synthesized by alkylating **3g** with C_2H_5I in the presence of K_2CO_3. From the appropriate starting materials, phenols **3k–m** were synthesized in like manner followed by deprotection of the methoxy group with BBr_3. Finally, acetamide **3n** and sulfonamide **3o** were prepared from **3b** in three steps: boron tribromide to deprotect the anisole residue, followed by TMSI mediated *N*-carboethoxy group cleavage, and subsequent treatment with acetyl chloride (in the presence of triethylamine as base) to provide **3n**, or methanesulfonyl chloride to provide **3o**.

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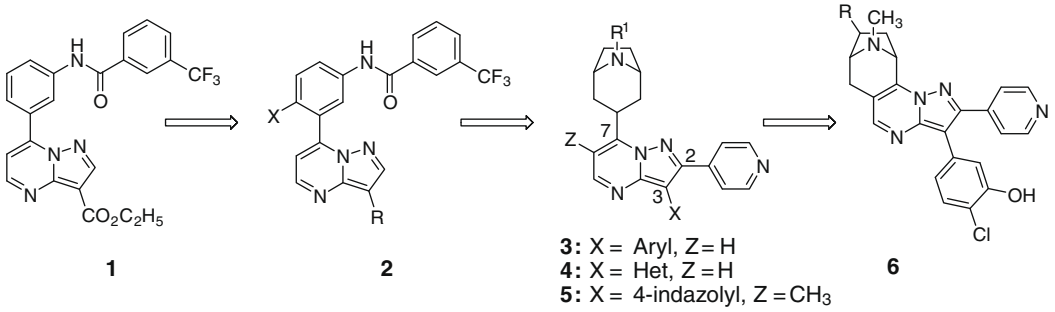
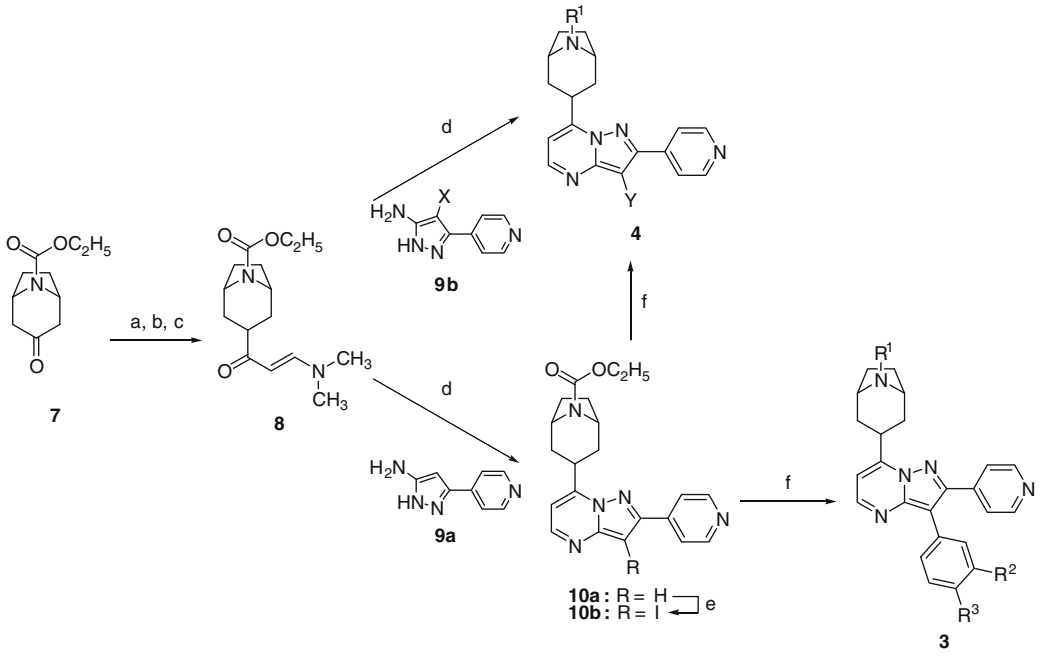


Figure 1. The evolution of B-Raf inhibitors at Wyeth.



Scheme 1. Reagents and conditions: (a) TosMic, KOtBu, −10 °C, 4 h; (b) MeMgBr, 5 °C, 3 h; (c) DMF-DMA, 100 °C, 3 d; (d) AcOH, 80–100 °C; (e) NIS, rt, overnight; (f) $Pd(PPh_3)_4$, $ArB(OR)_2$, aq Na_2CO_3, DME, 80 °C to **3**; $Pd(PPh_3)_4$, $HetB(OR)_2$, aq Na_2CO_3, DME, 80 °C to **4**.

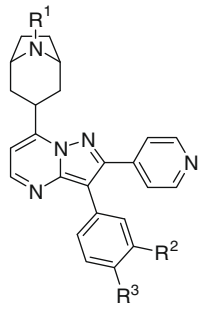
The final products **4** bearing C(3) heterocycles (Tables 2 and 3; $R^1 = CO_2C_2H_5$; Y = heterocycles) were prepared by Suzuki coupling of a heterocyclic boronic acid or ester with iodide **10b** or by direct condensation of **8** with the more elaborate aminopyrazoles **9b** (X = heterocycles).[7,10] Subsequent reaction of these carbamates afforded additional analogs. Thus, compound **4s** (Table 3) was prepared by TMSI induced deprotection of **4r**. Similarly, reaction of **4e**, **4p**, **4t**, or **4v** with TMSI followed addition of the appropriate alkylating reagent in the presence of K_2CO_3 afforded compounds **4k**, **4m**, **4o**, **4q**, **4u**, and **4w**. Compound **4n** was synthesized from the free amine derived from **4e** by reductive amination with acetone in the presence of $NaBH(OAc)_3$. Compounds **4g–j** and **4l** were assembled by acylation of the free amine derived from **4e** with the appropriate reagent and **4f** was derived from **4l** by Boc deprotection with TFA.[7]

The preparation of the C(6) methyl analog **5** commenced with the reaction of enaminone **11** with the aminopyrazole **9b** (X = 4-indazoyl) in hot AcOH to give the desired pyrazolopyrimidine (Scheme 2). The fused analogs **6** (Table 4) required a slight variation of this scheme. Accordingly, tropanones **12a**[11] were treated with dimethylformamide dimethylacetal to give the expected enaminones **12b**, which upon condensation with the fully substituted aminopyrazole **9b** (X = 3-OH-4-Cl–C_6H_3) afforded the desired fused compounds **6**.

With in vitro IC_{50}s <0.1 μM, all compounds presented in Table 1 are effective B-Raf inhibitors[12,13] but typically the phenols were 17- to 87-fold more potent than their methyl ether counterparts (compare **3a**:**3c**; **3b**:**3d**; **3f**:**3h**; **3g**:**3i**; **3j**:**3k**). Additionally, consistent with published data,[6] incorporation of a chlorine atom *ortho* to either the –OH or $–OCH_3$ group generally increased in vitro potency almost 10-fold (for instance, **3f**:**3g**; **3h**:**3i**), presumably due to favorable hydrophobic interaction between this atom and the binding pocket of the enzyme. Though chlorine could be replaced with methyl (**3d**:**3e**) or fluorine (**3k**:**3m**) to give very potent analogs, CN was far less active, apparently being too large (**3k**:**3l**). With respect to the tropane moiety, a diverse set of substituents on nitrogen was tolerated (**3d**, **3i**, **3k**, **3n**, **3o**) and with the exception of the surprisingly potent amine **3g** (compared to analogs **3b**, **3j**), all tropane derivatives with comparable substitution on the C(3) aryl ring were essentially equipotent.

A depiction of **3d** docked into the DFG-in conformation of the active site of B-Raf is shown in Figure 2. The phenolic OH group forms two hydrogen bonds, one to the Glu501 residue, and one to the NH group of Asp594. Additionally, the C(3) pyridine residue

Table 1
In vitro and cell-based IC_{50} data for C(3) *m*-anisoles and phenols[16]



Number	R^1	R^2	R^3	B-Raf (μM)	A375 (μM)	WM266-4 (μM)
3a	$CO_2C_2H_5$	OCH_3	H	0.087	9	8
3b	$CO_2C_2H_5$	OCH_3	Cl	0.0541	nd[a]	>10
3c	$CO_2C_2H_5$	OH	H	0.001	nd	0.24
3d	$CO_2C_2H_5$	OH	Cl	<0.002	nd	0.12
3e	$CO_2C_2H_5$	OH	CH_3	<0.0003	0.57	0.23
3f	H	OCH_3	H	0.0708	6.4	8.4
3g	H	OCH_3	Cl	0.0085	2.6	3.5
3h	H	OH	H	0.004	2.25	0.22
3i	H	OH	Cl	0.0004	0.44	0.09
3j	C_2H_5	OCH_3	Cl	0.0435	2.2	5.6
3k	C_2H_5	OH	Cl	0.0005	0.32	0.23
3l	C_2H_5	OH	CN	0.0579	>10	>10
3m	C_2H_5	OH	F	0.003	0.76	0.45
3n	$COCH_3$	OH	Cl	0.0003	0.9	0.26
3o	SO_2CH_3	OH	Cl	<0.002	0.27	0.09

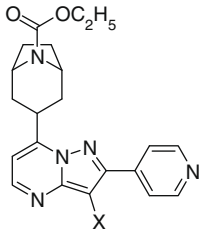
[a] nd = not determined.

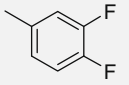
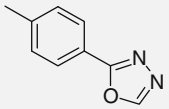
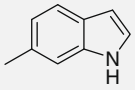
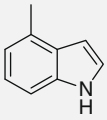
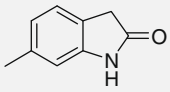
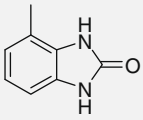
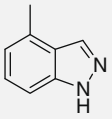
is hydrogen bonded to the hinge region Cys532.[14] Hydrophobic binding interactions of the tropane moiety and the chlorophenol group with the enzyme appear to contribute significantly to the overall binding affinity of this compound.

Subsequent screening against the B-Raf mutant (V600E) human melanoma cell lines A375 and WM266[15] showed the anisoles were only weakly active in both (A375 IC_{50}s >2.2 μM; WM266 IC_{50}s >3.5 μM) and thus were dropped from further consideration. On the other hand, the phenols had IC_{50}s <1 μM against both cell lines (the A375 inhibitory activity of analog **3h** is the sole exception). Most noteworthy were compounds **3c**, **3d**, **3i**, **3k**, and **3o**, which displayed excellent potencies (IC_{50}s <0.24 μM) in the WM266 cell line. While possessing exceptional inhibitory activity in both enzymatic and cell-based assays, the phenol moiety was of concern given the known metabolic liabilities of this functional group. Therefore, attention was focused on the development of an appropriate isostere.

Early attempts to replace the phenol focused on H-bond acceptor groups, such as compounds **3p** and **3q** (Table 2). However these were substantially less active B-Raf inhibitors and therefore we sought to incorporate functional groups that more closely resembled the donor properties of a phenol. The data for indoles **4a** and **4b** clearly indicated a preference by B-Raf for the 6-regioisomer and though **4a** was not as potent as **3c**, this was the first isostere with good enzyme potency. Unfortunately, this activity did not translate in the cell-based assays (IC_{50} >7 μM in both A375 and WM266 cell lines). As these analogs were substantially less active B-Raf inhibitors than phenol **3c**, attention was drawn to a surrogate that could function as both an H-bond donor and acceptor. Phenol replacements 6-indolin-2-one **4c** and 4-imidazolone **4d** were significantly less active. Fortunately, 4-indazole **4e** was comparable in potency to phenol **3c** in the primary assay (IC_{50} = 0.002 μM vs 0.001 μM) and the cell based potency of the original phenol was maintained (0.30 μM in WM266 vs 0.24 μM for **3c**).[17] Surprisingly, the preference for the 6-regioisomer observed in the indole series

Table 2
In vitro and cell-based IC_{50} data for phenol replacements

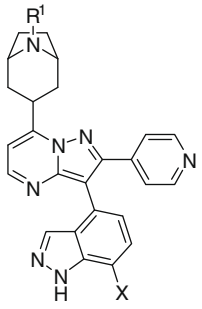


Number	X	B-Raf (μM)	A375 (μM)	WM266-4 (μM)
3p		0.302	nd	nd
3q		0.151	nd	nd
4a		0.036	7.5	>10.0
4b		>1.0	nd	nd
4c		>1.0	nd	nd
4d		>1.0	nd	nd
4e		0.002	0.38	0.3

was reversed for the indazoles as the 4-indazole analog was at least 10-fold more active in vitro and in cells (data not shown). As shown in Figure 3, the C(3) indazole residue of **4e** can form two hydrogen bonds to Glu501 and Asp594 in a similar manner to that proposed for the phenol of **3d** in Figure 2.

Having identified the 4-indazoyl group as a novel replacement for the C(3) phenol, further optimization was pursued (Table 3). A series of C(3) indazoles (**4f**–**o**) was prepared to test the effect of substitution on the tropane N on B-Raf potency. While tolerance to a variety of functional groups at this position was similar to the anisole/phenol series, there was a much greater range of IC_{50} values. For instance, equipotent compounds were observed in the anisole/phenol series regardless of whether R^1 was $CO_2C_2H_5$ or C_2H_5 (vide supra). In the indazole series, the *N*-carboethoxy group was characteristically 10–25 times more potent than the ethyl analog (**4e**:**4m**; **4p**:**4q**; **4t**:**4u**; **4v**:**4w**). Also, unlike the case in the phenol series, methansulfonamide **4g** and acetamide **4j** were several fold less active than the heterocyclic carboethoxy analog **4e**. Other nitrogen substituents such as proline amide **4f** and ureas **4h**, **4i** also afforded effective B-Raf inhibitors but there was a distinct

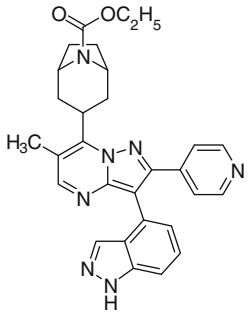
Table 3
In vitro and cell-based IC_{50} data for indazoles **4**



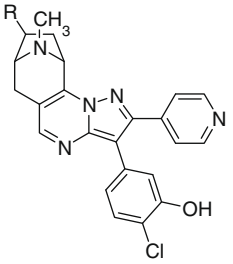
Number	R^1	X	B-Raf IC_{50} (μM)	A375 IC_{50} (μM)	WM266-4 IC_{50} (μM)
4e	$CO_2C_2H_5$	H	0.002	0.38	0.30
4f	H-Pro-CO	H	0.0021	5.94	1.86
4g	SO_2CH_3	H	0.0049	0.95	0.57
4h	$CON(CH_3)_2$	H	0.0064	3.00	2.14
4i	$CONHC_2H_5$	H	0.0067	2.81	1.52
4j	$COCH_3$	H	0.0091	2.54	1.80
4k	CH_2CH_2OH	H	0.0228	3.44	1.37
4l	Boc-Pro-CO	H	0.0394	3.40	6.17
4m	C_2H_5	H	0.0466	2.90	2.40
4n	$HC(CH_3)_2$	H	0.0670	1.96	1.75
4o	CH_2COCH_3	H	0.0759	nd	nd
4p	$CO_2C_2H_5$	Cl	0.0004	0.58	0.28
4q	C_2H_5	Cl	0.0044	1.09	0.86
4r	$CO_2C_2H_5$	F	0.0004	0.62	0.30
4s	H	F	0.0038	nd	nd
4t	$CO_2C_2H_5$	CF_3	0.0044	2.50	2.30
4u	C_2H_5	CF_3	0.0450	1.70	2.90
4v	$CO_2C_2H_5$	CH_3	0.0007	1.00	0.67
4w	C_2H_5	CH_3	0.0170	1.60	0.84

drop in potency for amide **4l** and basic amines **4m**–**o**. Nonetheless, despite excellent in vitro potency, for this series of indazoles with differentially substituted tropanes (**4e**–**o**), only compounds **4e** and **4g** were appreciably active in cells (IC_{50} <1 μM).

Table 4
In vitro and cell-based IC_{50} data for **5** and **6**



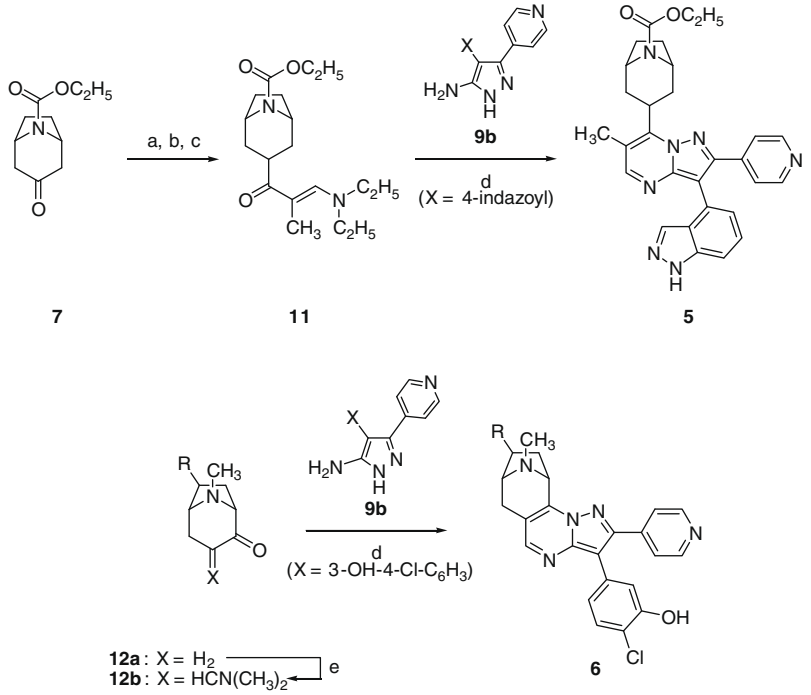
5



6

Number	R	B-Raf IC50 (μM)	A375 IC50 (μM)	WM266-4 IC50 (μM)
5	–	0.0084	1.22	1.87
6a	CO_2CH_3	0.0016	2.30	1.10
6b	CH_2OH	0.0006	1.70	0.75
6c	$SO_2C_6H_5$	0.0008	1.00	0.60

Based on the anisole/phenol series precedent, a new set of functionalized C(7) indazoles (**4p**–**w**) was prepared in the tropane series.[7] As expected, the 7-Cl (**4p**), 7-F (**4r**), and 7-CH_3 (**4v**) ethyl carbamates were sub-nanomolar enzyme inhibitors and each was more potent than the parent **4e**. Substitution with CF_3 at C(7) of the indazole also gave a very potent compound (**4t**) but it was several fold less active than the other C(7) substituted indazoles examined. In contrast to the potency of phenol **3k** (IC_{50} = 0.0005 μM), the similarly substituted *N*-ethyl tropane **4q** (IC_{50} = 0.0044 μM) was only modestly potent in the enzyme assay. Based on the observed trend in the phenol series (vide supra) that demonstrated analogs with in vitro IC_{50}s <0.001 μM possessed submicromolar cellular potency, the observed efficacy of **4q** in cells (IC_{50}s >1 μM) was not surprising. For substituted indazoles, the aforementioned trend with respect to A375 and WM266 activity



Scheme 2. Reagents and conditions: (a) TosMic, KOtBu, −10 °C, 4 h; (b) EtMgBr, 5 °C, 3 h; (c) diethylformamide dimethylacetal, reflux, 48 h; (d) AcOH, 80–100 °C; (e) DMF-DMA, 100 °C, overnight.

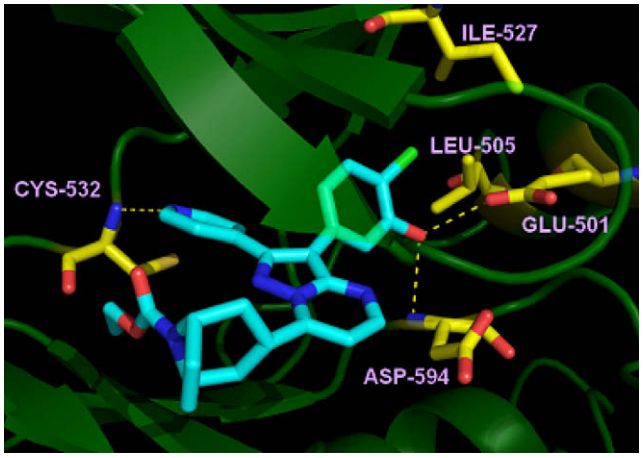


Figure 2. Docking model of **3d** bound to the active conformation of B-Raf.

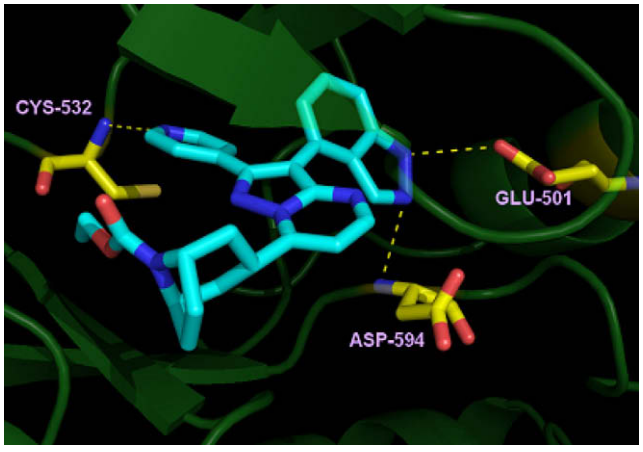


Figure 3. Compound **4e** docked in the active conformation of B-Raf, showing the network of H-bonds made by the indazole group.

generally held true. Thus, both the 7-Cl (**4p**) and 7-F (**4r**) analogs were potent in both cell lines (IC_{50}s $\leqslant$0.3 μM in WM266 for both analogs) but the methyl **4v** analog was only nominally active (IC_{50} ~1 μM in A375). Not surprisingly, the less active analogs **4t**, **4u**, and **4w** had modest cell potency.

Another structural modification that was explored was based on the observation that *N*-carboethoxy tropane **5** was identified as a potent B-Raf inhibitor. Though approximately fourfold less potent than **4e**, the presence of the C(6) methyl group raised the possibility of fusing the tropane to the pyrimidine ring of the core. The three analogs shown (**6a**–**c**) in Table 4 were more potent than B-Raf inhibitor **5**. However, the cellular activity of these analogs was modest.

In conclusion, a novel series of pyrazolo[1,5-*a*]pyrimidines bearing a 3-hydroxyphenyl group at C(3) and substituted tropanes at C(7) has been identified as potent B-Raf inhibitors. However, the potential metabolic soft spot posed by the phenol led to the identification of indazole as an effective isostere. Several compounds possessing substituted indazoles, such as **4e**, **4p**, and **4r**, potently inhibited cell proliferation at submicromolar concentrations in the A375 and WM266 cell lines, and the latter two compounds also exhibited good therapeutic indices in cells.[18] Fusing the tropane moiety to C(6)–C(7) of the pyrimidine core led to novel, potent B-Raf inhibitors that unfortunately lacked good efficacy in cells. A detailed description of our efforts to further improve the potency and properties of this series of B-Raf inhibitors will be reported in due course.

Acknowledgments

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8. Prepared in two steps from methyl isonicotinate: (1) KOtBu, CH_3CN; (2) H_2NNH_2; see Ref. 7a.
9. This reaction yielded a mixture of regioisomers (typically 4:1) of which **10a** was isolated as the major component.
10. For Het = 4-indazoyl, the aminopyrazole was prepared in several steps from the known methyl 1*H*-indazole-4-carboxylate; see: Batt, D. G.; Petraitis, J. J.; Houghton, G. C.; Modi, D. P.; Cain, G. A.; Corjay, M. H.; Mousa, S. A.; Bouchard, P. J.; Forsythe, M. S.; Harlow, P. P.; Barbera, F. A.; Spitz, S. M.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 41. and Ref. 7 for details.
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12. For a description of the assays used in this Letter, see Ref. 3.
13. As a preliminary measure of selectivity, compounds were screened for IC_{50}s in a 22-kinase panel and the most potent analogs (IC_{50} <0.01 μM) described herein demonstrated good to excellent selectivity. For instance, the very potent B-Raf inhibitor **4r** was more than 200-fold selective against all the kinases screened except one (p38α), where it exhibited 19-fold selectivity.
14. A model built from 2FB8(PDB) was used; see: King, A. J.; Patrick, D. R.; Batorsky, R. S.; Ho, M. L.; Do, H. T.; Zhang, S. Y.; Kumar, R.; Rusnak, D. W.; Takle, A. K.; Wilson, D. M.; Hugger, E.; Wang, L.; Karreth, F.; Lougheed, J. C.; Lee, J.; Chau, D.; Stout, T. J.; May, E. W.; Contractor, R. G.; Smalley, K. S. M.; Herlyn, M.; Morrissey, M. M.; Tuveson, D. A.; Huang, P. *Cancer Res.* **2006**, *66*, 11100.
15. Caco-2 (WT) cells were used as a control. All described compounds with an IC_{50} <1 μM in either A375 or WM266 cells had IC_{50}s >3.6 μM in Caco-2 cells and therapeutic indices (control/functional activity) ranging from 5.8 to 37 for A375 cells and 9.7 to 110 for WM266 cells (data not shown). The lone exception to this was compound **4e**, which had a Caco-2 IC_{50} = 0.8 μM and a therapeutic index of 2.1 and 2.7 for A375 and WM266 cells, respectively.
16. All IC_{50} values reported in this Letter are a mean of at least two separate determinations with typical variation <30% between replicate runs.
17. For a report that discloses the use of an indazole as a phenol isostere, see: Bamborough, P.; Angell, R. M.; Bhamra, I.; Brown, D.; Bull, J.; Christopher, J. A.; Cooper, A. W. J.; Fazal, L. H.; Giordano, I.; Hind, L.; Patel, V. K.; Ranshaw, L. E.; Sims, M. J.; Skone, P. A.; Smith, K. J.; Vickerstaff, E.; Washington, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4363.
18. Compound **4p** had a therapeutic index of 9.4 and 19.3 for A375 and WM266 cells, respectively, and compound **4r** had indices of 5.8 and 12, respectively; see Ref. 15.