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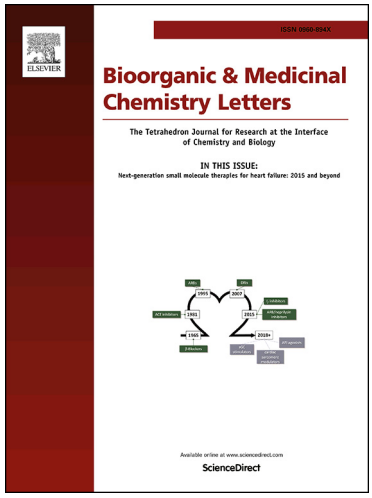

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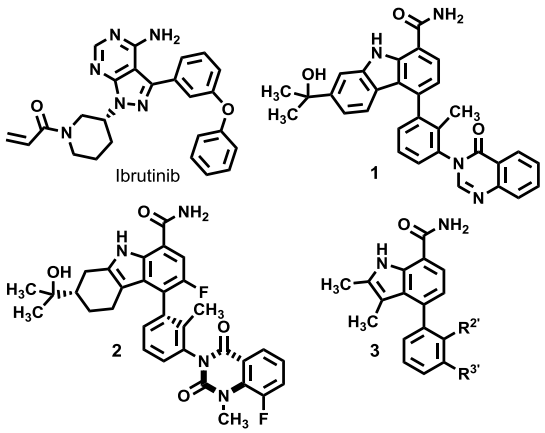
ABSTRACT

Incorporation of a suitably-placed electrophilic group transformed a series of reversible BTK inhibitors based on carbazole-1-carboxamide and tetrahydrocarbazole-1-carboxamide into potent, irreversible inhibitors. Removal of one ring from the core of these compounds provided a potent irreversible series of 2,3-dimethylindole-7-carboxamides having excellent potency and improved selectivity, with the additional advantages of reduced lipophilicity and molecular weight.

Bruton's tyrosine kinase (BTK) is a member of the TEC family of nonreceptor tyrosine kinases which plays an important role in B cell receptor mediated signaling. Because of the involvement of this signaling pathway in the function and proliferation of B lymphocytes, inhibitors of BTK have been actively pursued in the pharmaceutical industry for the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosis, as well as various B cell related cancers.[1] Ibrutinib (Imbruvica®) is the first marketed inhibitor of BTK, approved for the treatment of chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström's macroglobulinemia, marginal zone lymphoma and chronic graft versus host disease.[2]

Since we first described 4,7-disubstituted carbazole-1-carboxamides as reversible BTK inhibitors,[3] two additional reports from our laboratories have detailed further structure-activity relationships in the carbazole and tetrahydrocarbazole series. This work culminated in the discovery of BMS-935177 (**1**)[4] and the single atropisomer BMS-986142 (**2**),[5] two very potent and selective reversible inhibitors of BTK. The latter compound, unlike the former, was a single enantiomer with respect to the 4-substituent, due to severely restricted rotation about the atropisomeric bonds to the linking phenylene moiety. Compound **2** showed significant improvements in potency and selectivity over **1**, and is currently being studied clinically for the treatment of autoimmune diseases.

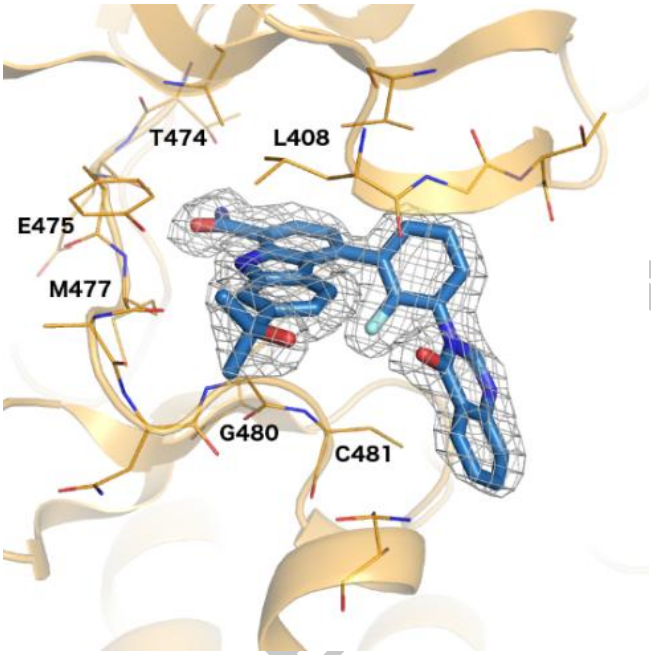
Due to the potential for exceptional potency and selectivity, there has been widespread interest in recent years in irreversible kinase inhibitors, although there are obvious concerns about the potential for off-target or idiopathic toxicity.[6] Ibrutinib is an irreversible inhibitor of BTK, and many recent publications of experimental BTK inhibitors in the peer-reviewed and patent literature also disclose irreversible inhibitors.[1] These compounds contain electrophiles, generally acrylamide or related Michael acceptors, designed to alkylate cysteine 481 which is located in the ATP binding site of BTK. A cysteine at this location is relatively rare in the kinome, occurring in only 10 other kinases, so selectivity is generally accepted to be a manageable concern.



We now report the conversion of our carbazole- and tetrahydrocarbazole-based series of BTK inhibitors into irreversible inhibitors by incorporation of a suitably-placed electrophilic group. These compounds further improved the potency and selectivity of our previous series. Also, dissection of the tetrahydro ring of the latter series led to a new series of 2,3-dimethylindole-7-carboxamide inhibitors (**3**), which provides a promising lead series for the development of additional irreversible inhibitors having excellent potency and selectivity combined with physicochemical properties better than those of the carbazoles.

Examination of a previously reported[4] X-ray structure of **4**, a close analog of **1**, bound to BTK showed that the quinazolinone moiety of this compound was positioned very close to Cys481 (Figure 1). Indeed, the thiol of Cys481 appears to be ideally oriented to react with an electrophilic center near the space occupied by C-5 of the quinazolinone, immediately suggesting replacement of that ring system by an acrylamide.

A.



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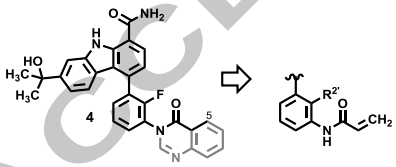


Figure 1. (A) X-ray crystal structure of compound **4** bound to the BTK kinase domain. (PDB code 5JRS).[4] (B) Structure of **4** and replacement of the quinazolinone by acrylamide.

The resulting analog (**5**) was readily prepared, and comparison with **1** supported this hypothesis. As shown in Table 1, **5** gave a nearly 6-fold increase in potency over **1** against recombinant human BTK, and an almost 4-fold improvement in potency in a Ramos cell-based assay measuring inhibition of BTK-induced calcium flux.[7] Although selectivity for BTK over other TEC family kinases, which also have Cys481, was not significantly changed or even reduced, selectivities over LCK and JAK2, two other kinases involved in immune cell function which lack Cys481, were increased by 4.6- and 4-fold, respectively, relative to **1**. (Data not shown.)

Additional analogs, also shown in Table 1, were prepared to briefly explore the SAR of the electrophilic moiety. Mono- (**6**) or di-substitution (**7**) at the β-position of the acrylamide reduced potency against the enzyme, in the case of **7** back to the same level as **1**. In both compounds, cell potency was reduced even further. This is consistent with conjugate addition of the thiol of Cys481 to the acrylamide, since steric hindrance from the methyl substituents would be expected to impede this process. These changes also returned selectivities against other kinases to levels similar to those seen with **1**. *N*-Methylation of the acrylamide moiety, accompanied by removal of the methyl substituent at the $R^{2'}$ position (compound **8**), improved potency even further, although cell potency was reduced. Replacement of the acrylamide with the nearly isosteric and non-electrophilic propionamide (**9**) gave a compound with even less potency than **1**.

It should be noted that the potency of a compound having a BTK IC_{50} value significantly less than 1 nM may, in fact, be underestimated, since this approaches the lower limit of the enzyme assay.[7] Therefore, such a compound may also be even more selective relative to other kinases than the values indicated.

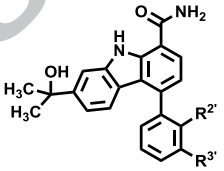


Table 1. Analogs of **1** bearing electrophilic groups

Compd	$R^{2'}$	$R^{3'}$	BTK[a]	Ramos[a]
1	CH_3	3-quinazolin-4-one	2.6	26
5	CH_3	-NHCOCH=CH_2	0.46	7.1
6	CH_3	-NHCOCH=CH-CH_3[b]	1.2	68
7	CH_3	-NHCOCH=$C(CH_3)_2$	2.4	75
8	H	-$N(CH_3)$COCH=CH_2	0.16	23
9	CH_3	-NHCOCH_2-CH_3	7.3	59

[a] IC_{50}, nM.[7] [b] *trans* stereochemistry.

In light of the known SAR for this series,[3,4] the increase in potency for compounds bearing smaller, electrophilic groups over the optimized quinazolinone is suggestive of, but does not prove, irreversible inhibition. Therefore, a dialysis assay was used to compare the rate of dissociation from BTK of **8** with that of the sterically similar **9**.[8] After incubation of **9** (at a concentration 25-fold higher than the IC_{50}) with BTK for 90 minutes, followed by two 6-hour periods of dialysis against assay buffer, all of the original BTK activity was recovered, while the same treatment with **8** at the same relative concentration yielded essentially inactive BTK (101% activity and 3.5% activity recovered for **9** and **8**, respectively). This demonstrated that **8** does indeed bind essentially irreversibly with BTK, supporting this as the basis for the increased potency.

The tetrahydrocarbazole series (represented by **2**) was previously shown to improve potency and selectivity over the fully aromatic series, and also provided improved oral exposure.[5] This is in line with current thought that reductions in aromatic ring count and planarity are desirable tactics in drug discovery.[9] We therefore prepared irreversible analogs (in racemic form) in this partially saturated series as well, with results shown in Table 2.

As in the carbazole series, replacing the quinazolinone of **10** with acrylamide (**11**) increased the potency significantly both in the enzyme and cell assays to an even greater extent than was seen in the fully aromatic series (44- and 26-fold, respectively). Likewise, dramatic increases in selectivity with respect to LCK

(from 98-fold to >2000-fold) and JAK2 (from 610-fold to 15,000-fold) were observed, although again the selectivity differences in the other TEC family kinases were relatively small (see below). Both β-methylation (**12**) and α-methylation (**13**) of the olefin reduced potency and selectivity back to the levels of the quinazolinone, the former possibly through steric hindrance to conjugate addition and the latter perhaps through a conformational effect. Interestingly, substitution of **12** with a dimethylamino group (**14**), designed to activate the thiol of Cys481 by deprotonation,[2] regained much of the enzyme potency. However, cell potency was reduced, presumably due to poorer cell penetration by this charged species. Removal of the methyl $R^{2'}$ substituent (**15**) had little effect, nor did moving the methyl onto the acrylamide nitrogen (**16**), although this compound did show reduced cell potency. The *N*, 2'-dimethylated compound **17** also lost some potency, both against the enzyme and in the cell assay.

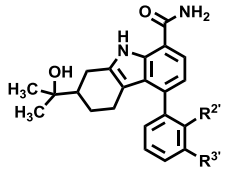


Table 2. Tetrahydrocarbazoles bearing electrophilic groups

Compd	$R^{2'}$	$R^{3'}$	BTK[a]	Ramos[a]
10	CH_3	3-quinazolin-4-one	9.3	120
11	CH_3	-NHCOCH=CH_2	0.21	4.6
12	CH_3	-NHCOCH=CH-CH_3[a]	12	370
13	CH_3	-NHCOC(CH_3)=CH_2	9.1	290
14	CH_3	-NHCOCH=CH-$CH_2N(CH_3)_2$	0.82	1000
15	H	-NHCOCH=CH_2	0.17	5.1
16	H	-N(CH_3)COCH=CH_2	0.24	28
17	CH_3	-N(CH_3)COCH=CH_2	1.1	15
18	CH_3	-$NHSO_2$CH=CH_2	0.079	nt[c]
19	H	-N(CH_3)SO_2CH=CH_2	0.18	8.8
20	H	-CH_2-NHCOCH=CH_2	3.5	200
21	H	-C(CH_3)$_2$-NHCOCH=CH_2	36	2000

[a] IC_{50}, nM.[7] [b] *trans* stereochemistry. [c] Not tested.

Replacement of the acrylamide with vinyl sulfonamide, as an alternative electrophilic group, gave **18** which showed an even greater increase in potency against BTK relative to **10**. However, this and other vinyl sulfonamides prepared (see below) appeared to be somewhat unstable, showing significant decomposition on storage for several days at room temperature. *N*-Methylation to give **19** provided a compound comparable to the *N*-unsubstituted acrylamide.

Two compounds were prepared with a one carbon spacer between the aromatic ring and the acrylamide moiety (**20** and **21**), but both caused loss of potency, dramatically in the gem-dimethyl substituted case. The ideal placement of the electrophile for reaction with Cys481 thus appeared to be that of **11** or **15**.

In addition to improving selectivity as well as potency (by 45-fold for **11** compared to **10**), replacing the quinazolinone substituent by acrylamide also reduced the molecular weight and heavy atom count by about 15%, and lowered the calculated log P by 0.7 units. Many literature reports have promoted the desirability of reducing these characteristics of drug candidates to improve solubility and oral bioavailability.[10] Since the tetrahydro ring of that series extends toward solvent,[5] we explored the possibility of further reducing the size and lipophilicity of these molecules by excising the ring completely to give indole-7-carboxamides, relying on the added potency offered by irreversibility to offset any lost binding interactions.

We first prepared examples bearing the quinazolinone moiety (Table 3), to establish baseline potency relative to an unsubstituted carbazole (**22**), itself significantly less potent than **1** due to removal of the tertiary carbinol moiety. The unsubstituted indole **23** lost over 30-fold in potency, while adding one methyl substituent at either R^2 (**24**) or R^3 (**25**) regained some potency (only 5- to 6-fold reduced from **22**). Gratifyingly, the 2,3-dimethyl analog **26** regained the enzyme potency of the carbazole, and showed a 2-fold increase in cell potency over **22**.

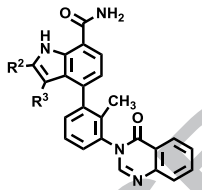


Table 3. Reversible indole inhibitors of BTK: 2- and 3-substituent variation

Compd	R^2	R^3	BTK[a]	Ramos[a]
22	-CH=CH-CH=CH-		16	1700
23	H	H	550	nt[b]
24	CH_3	H	81	>2000
25	H	CH_3	92	>2000
26	CH_3	CH_3	12	890

[a] IC_{50}, nM.[7] [b] Not tested.

As shown in Table 4, replacing the quinazolinone of **26** with acrylamide (**27**) provided an expected boost in potency (32-fold), in line with the results seen in the tetrahydrocarbazole series. Although removal of both indole methyl substituents, or of the 2-methyl, did reduce potency, the loss was much less severe than in the case of the quinazolinones shown in Table 3. The 2-methyl analog **29** was as potent as the dimethyl analog against the enzyme, although cell potency dropped by 3- to 4-fold. While the 3-methyl analog **30** was similar to the unsubstituted analog **28** against the enzyme, it was similar to **27** in cells. All four compounds showed excellent selectivity against JAK2, LCK (>1500-fold) and ITK (>200-fold).

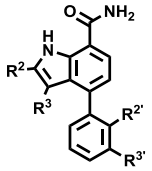


Table 4 Irreversible indole inhibitors of BTK

Compd	R^2, R^3	$R^{2'}$	$R^{3'}$	BTK[a]	Ramos[a]
27	CH_3, CH_3	CH_3	-NHCOCH=CH_2	0.38	9.2
28	H, H	CH_3	-NHCOCH=CH_2	1.1	57
29	CH_3, H	CH_3	-NHCOCH=CH_2	0.32	34
30	H, CH_3	CH_3	-NHCOCH=CH_2	1.2	15
31	CH_3, CH_3	CH_3	-$NHSO_2$CH=CH_2	0.14	23
32	CH_3, CH_3	CH_3	-N(CH_3)COCH=CH_2	0.59	61
33	CH_3, CH_3	CH_3	-N(CH_3)SO_2CH=CH_2	0.11	26
34	CH_3, CH_3	H	-NHCOCH=CH_2	0.21	16
35	CH_3, CH_3	H	-$NHSO_2$CH=CH_2	0.077	6.4
36	CH_3, CH_3	H	-N(CH_3)COCH=CH_2	0.23	170
37	CH_3, CH_3	H	-N(CH_3)SO_2CH=CH_2	0.068	63

[a] IC_{50}, nM.[7]

Replacement of the acrylamide by a vinyl sulfone (**31**) gave a slight increase in enzyme potency, as was seen in the

tetrahydrocarbazole series, but this was accompanied by a slight decrease in cell potency. *N*-Methylation (**32**, **33**) gave very little change in potency, although a significant drop in cell potency was seen in the case of the acrylamide. Removal of the methyl at C-2' (**34** – **37**) caused two-fold increase in enzyme potency, but a two- to three-fold decrease in cell potency except in the case of the vinyl sulfone **35**. The loss of cell potency for **34**, **36** and **37** relative to the methylated analogs may reflect poorer cell penetration, perhaps due to decreased shielding of the polarity and hydrogen-bonding ability of the amide moiety.

Selectivity for BTK over other kinases is summarized in Table 5 for three irreversible compounds (**11**, a tetrahydrocarbazole, and two indoles, **27** and **31**), along with the tetrahydrocarbazole quinazolinone **10** for comparison. Selectivity over LCK, which is involved in leukocyte function, is greatly increased for all three compounds relative to **10**, dramatically so for the indole vinyl sulfone. Compound **10** is already very selective with respect to JAK2, but this selectivity is greatly improved (5000- to 16,000-fold) for the three irreversible compounds. ITK is also involved in leukocyte function and, like BTK, is a member of the TEC family. Despite also having a cysteine homologous to Cys481 in the ATP binding site, selectivity over ITK is improved in the irreversible compounds relative to that seen with **2**, especially for the indole acrylamide **27**. Differences in selectivity are less profound and more varied for the remaining TEC family kinases (BMX, TEC and TXK). Selectivities for two other kinases having homologous cysteines are also shown. Compound **10** was already very selective for JAK3; the irreversible compounds were still selective but less so. Against HER4, the acrylamides showed good selectivity, while the vinyl sulfonamide was about 10-fold less selective.

Table 5. Kinase selectivity for three irreversible BTK inhibitors compared to reversible inhibitor **10**[a,b]

Kinase	**10** (THC, reversible)	**11** (THC, irreversible)	**27** (indole, irreversible)	**31** (indole, irreversible)
BTK	9.3	0.21	0.38	0.14
LCK	910 (98)	420 (2000)	>2000 (>5300)	>2000 (>14000)
JAK2	5700 (610)	3300 (16,000)	>2000 (>5300)	1100 (7900)
ITK	290 (31)	23 (110)	88 (230)	8.3 (59)
BMX	200 (22)	5.2 (25)	13 (34)	3.3 (24)
TEC	56 (6.0)	2.3 (11)	6.4 (17)	0.9 (6.4)
TXK	nt	15 (71)	26 (68)	2.3 (16)
JAK3	15,000 (1600)	41 (200)	28 (74)	11 (79)
HER4	nt	150 (710)	240 (630)	10 (71)

[a] IC_{50} (nM). Numbers in parentheses are selectivities for BTK over the indicated kinase. nt = not tested. [b] THC = tetrahydrocarbazole

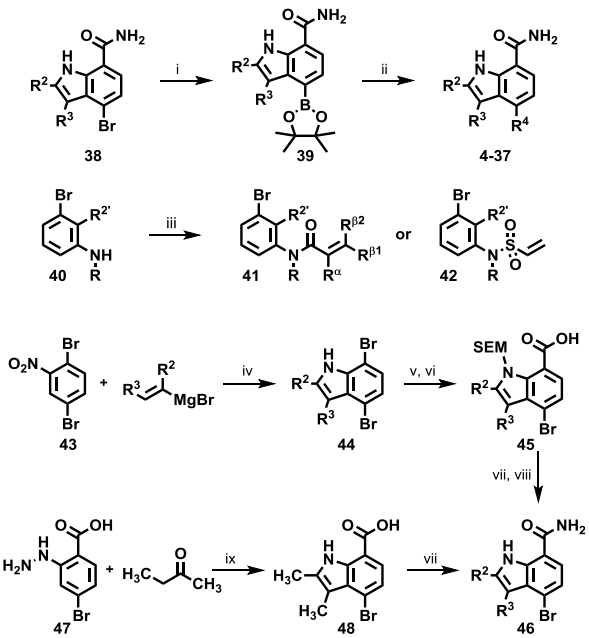
Some physicochemical properties for the same four compounds are compared in Table 6. As mentioned previously, replacement of the quinazolinone of **10** with the acrylamide of **11** decreases molecular weight, heavy atom count, polar surface area and calculated log P, clearly improving these parameters of "drug-likeness".[10] The trend obviously continues in moving from **11** to the dimethylindole **27**, along with further improvement in hydrogen bond donor/acceptor count and polar surface area through removal of the tertiary carbinol. The smaller sizes of these molecules, particularly in the indole series, combines with the increased potency (seen despite the loss of the tertiary carbinol in **27** and **31**) to give significant increases in ligand efficiency.

Unfortunately, compared to the quinazolinone-based reversible inhibitors, the dimethylindole acrylamides and vinyl sulfones showed reduced metabolic stability on incubation with microsomes from human and (especially) mouse hepatocytes. Because of this, although *in vivo* studies were not performed on the irreversible compounds described here, their pharmacokinetic profiles are expected to be poor. It should be noted, though, that irreversible inhibitors are expected to require less prolonged and elevated plasma levels than reversible inhibitors, since any inhibitor bound to BTK would equilibrate only very slowly, if at all, with plasma, leading to a favorable disconnect between pharmacokinetics and pharmacodynamics. Further SAR, as well as study and optimization of the ADME properties and efficacy of this new class of inhibitors, will be reported elsewhere.

Table 6. Physicochemical properties and metabolic stability for three irreversible BTK inhibitors compared to reversible inhibitor **10**

Property	**10**	**11**	**27**	**31**
MW[a]	506.60	431.53	347.42	383.47
HAC[b]	38	32	26	27
HBD/A[c]	3/4	4/3	3/2	3/3
PSA[d]	111.78	108.21	87.98	105.05
clogP[e]	4.61	3.91	3.76	2.85
LE[f]	0.19	0.29	0.35	0.36
hLM[g]	84	90	71	71
mLM[g]	86	100	1.6	12

[a]molecular weight. [b]heavy atom count. [c]H-bond donors/acceptors. [d]Polar surface area. [e]Calculated log P. [f]Ligand efficiency. [G]Percent remaining after 15 min incubation with human or mouse liver microsomes.



Scheme 1. Reagents and conditions: (i) bis-pinacol diborane, KOAc, $PdCl_2(dppf)_2$, dioxane, 110 °C, 16 h (50-70%). (ii) $Pd(PPh_3)_4$, R^4Br, Na_2CO_3 or K_2CO_3, toluene/EtOH, 90 °C, 16 h (19-65%). (iii) $ClC(=O)C(R^{\alpha})=C(R^{\beta 2})R^{\beta 1}$ or $ClSO_2CH_2CH_2Cl$, Hünig's base, CH_2Cl_2, rt, 16 h (17-94%). (iv) -78 °C to rt, THF, 4 h (37-45%). (v) SEM-Cl, NaH, THF, 0 °C to rt, 3 h (82-95% crude). (vi) n-BuLi, THF, -78 °C, 10 min; then CO_2, -78 °C to rt, 4 h (93-95% crude). (vii) NH_4OH, HOBT, EDC, THF/DCM, rt, 16 h (36-83%). (viii) TBAF, ethylenediamine, THF, 50 °C, 1-3 days (49-74%). (ix) HOAc, 110 °C, 16 h (50-80%).

Synthesis of the compounds described generally followed chemistry disclosed previously.[4,5,8,11] (Scheme 1). Carbazole, tetrahydrocarbazole or indole derivatives **38** bearing a bromide *para* to the primary carboxamide were converted to boronate esters **39**, which underwent Suzuki coupling with an appropriate bromobenzene derivative bearing the desired electrophilic moiety to give the desired compounds. (Alternatively, the boronate and bromide coupling partners could be exchanged: a 4-bromoindole or 4-bromocarbazole derivative could be reacted with a phenylboronate substituted with the desired electrophilic moiety, prepared from the corresponding bromobenzene derivative.) Bromides **41** and **42** were simply prepared by acylation of the appropriate bromoaniline **40** with acryloyl chloride or a substituted derivative, or in the case of vinyl sulfonamides **42** with 2-chloroethylsulfonyl chloride. In the latter case, elimination of HCl during the sulfonylation reaction gave the vinyl sulfonamide directly. 4-Bromoindole carboxamides **46** were prepared by two different routes. In the cases where one or both indole substituents was H, 2,5-dibromonitrobenzene **43** was treated with an appropriate vinylic Grignard reagent (the Bartoli indole synthesis) to give the dibromoindole **44**.[12] After protection as the SEM derivative, lithium-halogen exchange occurred selectively at the 7-position,[13] and treatment with carbon dioxide gave the corresponding acid **45**. Conversion to the primary carboxamide followed by deprotection provided **46**. Alternatively, in the case of the 2,3-dimethylindole core, the known carboxyhydrazine **47** underwent condensation with 2-butanone (the Fischer indole synthesis[14]) to provide the acid **48**, which was then converted to the carboxamide **46**.

In summary, two series of potent reversible BTK inhibitors based on carbazole-1-carboxamide or tetrahydrocarbazole-1-carboxamide were converted to even more potent and selective irreversible inhibitors by replacing the previously optimized substituents at C-3' of the pendent 4-phenyl group with an electrophile designed to alkylate Cys481 of the enzyme. Acrylamides and vinyl sulfonamides displayed sub-nanomolar potency against isolated BTK enzyme, and were also very potent in a cell-based calcium flux assay. A further significant reduction in molecular weight and lipophilicity, achieved by removing one ring of the carbazole core to provide the corresponding indole, retained the excellent potency and increased selectivity against some kinases, particularly LCK and ITK. The compounds reported here provide good starting points for further SAR study as well as optimization of potency, selectivity, and oral bioavailability and efficacy.

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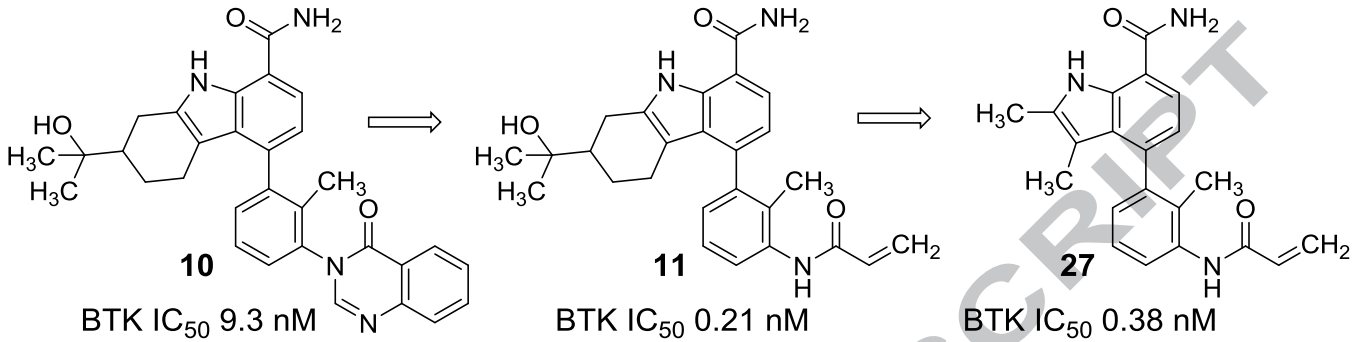
Graphical Abstract:



Highlights:

Electrophilic groups increased potency and selectivity of carbazole BTK inhibitors.

Related indole analogs retained this potency and further increased selectivity.

Irreversible inhibition was demonstrated using a dialysis assay.

Better physicochemical characteristics accompanied the improved biochemical profile.