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Investigation of a novel molecular descriptor for the lead optimization of 4-aminoquinazolines as vascular endothelial growth factor receptor – 2 inhibitors: Application for quantitative structure activity relationship analysis in lead optimization

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Abstract

We investigated the use of infrared vibrational frequency of ligands as a potential novel molecular descriptor in three different molecular target and chemical series. The vibrational energy of a ligand was approximated from the sum of infrared (IR) absorptions of each functional group within a molecule and normalized by its molecular weight (MDIR). Calculations were performed on a set of 4-aminoquinazolines with similar docking scores for the VEGFR2/KDR receptor. 4-Aminoquinazolines with MDIR values ranging 192–196 provided compounds with KDR inhibitory activity. The correlation of KDR inhibitory activity was similarly observed in a separate chemical series, the pyrazolo[1,5-a]pyrimidines. Initial exploration of this molecular descriptor supports a tool for rapid lead optimization in the 4-aminoquinazoline chemical series and a potential method for scaffold hopping in pursuit of new inhibitors.

The lead optimization of a compound for improved binding and/or inhibitory potency remains a time consuming and challenging stage in drug discovery research. Computational chemistry provides a potential solution for rapid quantitative structure to activity relationship (QSAR) analysis to allow the efficient design of next generation analogs with improved biological activity. Molecular descriptors play a pivotal role in computational chemistry for the computational lead optimization of a chemical series. Infrared (IR) vibrations of molecules have received little attention as a molecular descriptor for QSAR analysis. Previous report utilized quantum mechanical IR values for QSAR providing predictive capability comparable to CoMFA.[1] We investigated the vibrational energy of a ligand as a potential intermolecular force contributing to the binding interaction with biomolecules.

The initial QSAR study employed known classical cannabinoids with highly potent and reproducible binding affinities at the cannabinoid receptor 1 (CB1).[2a] A small subset of the compounds within the set was chosen based on uniform distribution of binding affinity. The average IR bond frequencies for each functional group within a molecule were summed and normalized by dividing with a known molecular descriptor (i.e. rotatable bonds, H-bond donors, molecular weight, and heavy atoms). A quadratic type of correlation was observed between the negative log of binding affinities (pKi) and the sum of all average IR bond frequencies divided by the molecular weight of the compound (MDIR). The plot of this molecular descriptor, MDIR, against pKi is shown in figure 1. The binding affinity maximizes with MDIR value of 224 for compound 4. None of the other IR normalized set of values showed an observable correlation other than molecular weight.

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The correlation of MDIR to binding affinities employing alkyl homologation was investigated in a reported SAR of pyrazolo[3,4-*d*]pyrimidines as adenosine deaminase (ADA) inhibitors.[2b] The expected trend of increasing activity upon homologation and maximizing as seen for compounds **8e** and **8f** when n = 7 and 8, respectively (Figure 2), is observed. Based on the homologation SAR, ideal binding affinities are obtained for MDIR values above 250 and lower than 266. Two other compounds (**9a** and **9b**) with additional structural modifications and containing MDIR values in the ideal range were identified and correlated to be active. The correlation of all MDIR values for compounds in figure 2 to ADA binding affinities resemble a parabolic type relationship. However, the abrupt loss of binding affinity in going from MDIR = 261.4 to 265.6 (compounds **8f** and **8g**, respectively) is surprising. The reported study correlated binding modes via docking studies which showed **8g** lacking the ideal binding mode in their docking model. Thus, the use of docking methods coupled with MDIR may prove to be a useful modality for QSAR studies.

We next applied this molecular descriptor within the 4-anilinoquinazoline chemical series, a series known for its inhibitory potency at the vascular endothelial growth factor receptor 2 (VEGFR2/KDR) tyrosine kinase receptor.[3] In order to isolate the contribution of MDIR in QSAR, several 4-anilinoquinazoline compounds were virtually designed and docked at the human KDR receptor. A subset of these compounds was further selected based on similar Flexible Grid Docking score relative to the original ligand present in the Apo crystal structure, 3-(2-aminoquinazolin-6-yl)-4-methyl-1-[3-(trifluoromethyl) phenyl]pyridine-2(1H)-one. MDIR values were then calculated and a final subset of compounds chosen for synthesis and biological evaluation.

The docking was performed with the open source DOCK 6 suite of programs[4] by University of California, San Francisco. The docking score utilized the flexible docking method allowing flexibility to both the ligand and receptor. The docking score presented is an approximation of the binding energies based on van der Waal's interactions and coulombic electrostatic energies. The Apo structure of human KDR receptor was obtained from the Protein Data Bank (PDB No. 3CPC)[5] with an X-ray diffraction resolution of 2.40 AÍ. The receptor and ligand was separately prepared for docking. Branch A of the dimeric receptor was isolated and prepared for docking by the addition of hydrogens and partial charges using Chimera. Structure of designed ligands were drawn with ChemDraw 3D and minimized using Chimera and the dot molecular surface (DMS) write tools. The ligand was saved as a Mol2 format after adding hydrogens and formal charges. The molecular surface and Spheres were generated using DMS and SPHGEN, respectively. A distance of 10 was specified from the location of the original co-crystallized ligand as the binding site. The Grid Box was then generated adding an extra 5 around the sphere. Docking was performed within the Grid Box with the bump filter on and set to 0.75. A flexible docking method was used for both the ligands and receptor and Grid Docking score[6] calculated in kcal/mol.

Compounds **10-19** were synthesized via the chloride displacement of 4-chloro-6,7-dimethoxyquinazolines with the appropriate amine or alcohol. Compound **21** was synthesized from the corresponding (4-Methoxyphenyl)-acetonitrile in a three step fashion. Briefly, the (4-Methoxyphenyl)-acetonitrile is condensed with dimethylforamidedimethylacetal (DMFDMA) to afford the Aldol adduct followed by Michael addition/Cyclization with hydrazine hydrochloride. The 3-amino-4-arylpyrazole formed is then condensed/dehydrated with the corresponding 1,3-dialdehyde to afford Compound **21**.

The KDR ELISA assay was performed using the HTScan®VEGF Receptor 2 Kinase Assay Kit from Cell Signaling Technology but the human N-terminal His6-tagged recombinant enzyme (aa790-end) was purchased from US Biological for a better dynamic range in the

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assay. DELPHIA 200 uL Streptavidin clear coated 96-well plates were purchased from Fisher Scientific Inc. The assay was found to tolerate up to 1% dimethyl sulfoxide (DMSO) to aid solubility of ligands in the kinase buffer. Final concentrations used in the assay was 20 μM ATP, 100 ng human VEGFR2 kinase and 1.5 μM substrate peptide. The absorbance of the wells was read at 450 nm on the xMark™ microplate spectrophotometer by BIO-RAD. Each assay contained a blank, control, DMSO control, and standard (Ki 8751). The average percent inhibitions are calculated from n of 3 data (unless specified otherwise) and assayed on separate days.

The KDR assay from Cell Signaling (HTSscan Kit) provided a highly reproducible assay. It also provided an enzymatic *in vitro* assay with potency similarity to typical cellular potency, where increase ATP concentration in cells often provide much lower potency or high IC_{50} values. The assay was calibrated to an internal standard, a known KDR inhibitor (Ki8751)[7] with a reported IC_{50} value of 0.9 nM (final ATP concentration was 2 μM) and staurosporine. The reported KDR IC_{50} value for Staurosporine using the HTSscan kit from Cell Signalling is 250 nM. The IC_{50} values obtained in our assay for Ki8751 and staurosporine were measured to be 0.8 μM and 250 nM, respectively.

The final subset of compounds was chosen based on a set of MDIR values that uniformly ranged from 170 to 235 and similar grid docking scores (Table 1). These ten compounds were synthesized and evaluated in the KDR ELISA assay as described above.

The most potent of these compounds contain an MDIR value of 192 (compound **14**) while other compounds were either inactive (KDR percent inhibition less than 15%) or marginally active. The IC_{50} evaluation of compound **14** was difficult due to solubility problems at higher concentrations. A five point inhibition curve provided an IC_{50} = 2.5 μM for compound **14**.

Additional compounds with reported KDR inhibitory activity, similar Flexible grid dock scores, and MDIR values in close proximity to 192 were identified and evaluated (Table 2). Of these four compounds, all are known inhibitors of KDR except for Compound **14**. In spite of good docking scores, Compound **10** with a non-ideal MDIR value (172) is a known KDR inhibitor but with weak activity[8] and relatively inactive in our assays. Compound **20**[8] represent a fairly large structural modification towards enhanced water solubility relative to the 4-aminoquinazolines studied herein. In spite of these major structural modifications, the ideal dock score (−27 to −34 kcal/mol) and MDIR value (192) correlated with a potent KDR inhibition. Within the pyrazolo[1,5-a]pyrimidine series, we identified one compound with a dock score and MDIR value within our desired range. Compound **21**[9] was active in our KDR assay and also a reported potent KDR inhibitor. The latter example illustrates MDIR as a potential molecular descriptor tool for scaffold hopping (design of a different chemotype). Ki 8751 was not included in our exploration of MDIR as related to KDR inhibitory activity due to its failure to dock within our designated binding pocket.

In summary, the preliminary study of MDIR as a molecular descriptor in QSAR is supportive. Thus, further studies are warranted for the validation of MDIR as a molecular descriptor using the method employed by Matter.[11] The utility of MDIR coupled with docking methods seems to be amenable for scaffold hopping. Further examples of scaffold hopping to afford novel and active chemical series as KDR inhibitors will be required for validation studies.

Acknowledgments

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12. Calculation of MDIR for Compound **2** as a representative example:

Compound 2			
FunctionalGroup	**Qty**	**IR**	**Sub Total**
-C-H	23	1480	34040
=C-C-	8	1680	13440
-C=C-	4	1680	6720
-C=N-	0	1810	0
=N-H	0	1600	0
-C=N-	0	1810	0
=C-H	3	1000	3000
-C-C-	9	1680	15120
C-O-Alcohol	1	1150	1150
-O-H	1	3600	3600
-C=O	0	1820	0
-N-H	0	1600	0
-C-O-Ether	2	1300	2600
-C-N-Alkyl	0	1360	0
c-Cl	0	800	0

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Compound 2			
FunctionalGroup	**Qty**	**IR**	**Sub Total**
C-F	0	1400	0
-CN	0	2260	0
=C-N-	0	1360	0
-C-Br	1	600	600
	Sum of IR Absorptions		80270
Molecular Weight	379.33	**MDIR**	**211.6099**

13. (4-Chloro-phenyl)-(6,7-dimethoxy-quinazolin-4-yl)-amine (**10**): 4-Aminoquinazo- lines were prepared according to literature methods[10] with a slight procedural modification. A typical procedure utilized is demonstrated for compound **10** as a representative example. In a 25 mL seal-tube reaction vessel equipped with a magnetic stirrer, 100.0 mg (0.445 mmol) of 4-chloro-6,7-dimethoxy-quinazoline was added followed by 2.0 mL of acetonitrile and 62.5 mg (0.490 mmol) of 4-chloroaniline. The vessel was sealed and heated to 100°C. After stirring at said temperature for a period of one day, the reaction was cooled, solvent evaporated via speed-vac, and tritiated three times with cold acetonitrile. Any remaining solvent was evaporated *in vacuo* to afford 140 mg (quantitative yield) of **10** as a white crystalline solid. LCMS: m/z = 316.0 (M+1, 100% intensity) and 318.0 (M+1, 33% intensity). ^{1}H-NMR (300 MHz, d6-DMSO): δ 11.4 (1H, br s), 8.83 (1H, s), 8.33 (1H, s), 7.77 (2H, br d, J = 9.3 Hz), 7.55 (2H, br d, J = 9.0 Hz), 7.35 (1H, s), 4.02 (3H, s), 4.00 (3H, s).
14. (3,4-Difluoro-phenyl)-(6,7-dimethoxy-quinazolin-4-yl)-amine (**11**): Following a similar reaction procedure to **10**, 81 mg (57% yield) of **11** was isolated as a white crystalline solid. LCMS: m/z = 318.0 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, d6-DMSO): δ 11.3 (1H, br s), 8.85 (1H, s), 8.25 (1H, s), 7.96–7.89 (1H, m), 7.60–7.55 (2H, m), 7.32 (1H, s), 4.01 (3H, s), 4.00 (3H, s).
15. (3-Chloro-4-methyl-phenyl)-(6,7-dimethoxy-quinazolin-4-yl)-amine(**12**): Following a similar reaction procedure to **10**, 125 mg (85% yield) of **12** was isolated as a white crystalline solid. LCMS: m/z = 330.1 (M+1, 100% intensity) and 332.1 (M+1, 37% intensity). ^{1}H-NMR (300 MHz, d6-DMSO): δ 11.3 (1H, br s), 8.85 (1H, s), 8.28 (1H, s), 7.86 (1H, d, J = 1.8 Hz), 7.61 (1H, dd, J = 8.1, 2.4 Hz), 7.46 (1H, d, J = 8.7 Hz), 7.33 (1H, s), 4.02 (3H, s), 4.00 (3H, s), 2.37 (3H, s).
16. (6,7-Dimethoxy-quinazolin-4-yl)-(4-fluoro-phenyl)-amine (**13**): Following a similar reaction procedure to **10**, 141 mg (quantitative yield) of 13 was isolated as a white crystalline solid. LCMS: m/z = 300.0 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, d6-DMSO): δ 11.3 (1H, br s), 8.80 (1H, s), 8.27 (1H, s), 7.71 (2H, br dd, J = 9.3, 5.4 Hz), 7.34 (2H, br t, J = 8.7 Hz), 7.33 (1H, s), 4.01 (3H, s), 4.00 (3H, s).
17. (6,7-Dimethoxy-quinazolin-4-yl)-(3-fluoro-4-methyl-phenyl)-amine (**14**): Following a similar reaction procedure to **10**, 131 mg (94% yield) of **14** was isolated as a white crystalline solid. LCMS: m/z = 314.1 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, d6-DMSO): δ 11.4 (1H, s), 8.85 (1H, s), 8.32 (1H, s), 7.64 (1H, dd, J = 11.4, 2.1 Hz), 7.47 (1H, dd, J = 8.4, 1.8 Hz), 7.38 (1H, t, J = 8.7 Hz), 7.34 (1H, s), 4.02 (3H, s), 3.99 (3H, s), 2.27 (3H, d, J = 1.8 Hz).
18. (6,7-Dimethoxy-quinazolin-4-yl)-phenyl-amine (**15**): Following a similar reaction procedure to **10**, 131 mg (quantitative yield) of **15** was isolated as a white crystalline solid. LCMS: m/z = 282.0 (M +1, 100% intensity). ^{1}H-NMR (300 MHz, d6-DMSO): δ 11.4 (1H, br s), 8.80 (1H, s), 8.34 (1H, br d, J = 3.9 Hz), 7.69 (2H, br d, J = 7.2 Hz), 7.50 (1H, br d, J = 7.8 Hz), 7.48 (1H, br d, J = 8.4 Hz), 7.36 (1H, br d, J = 4.8 Hz), 7.32 (1H, br t, J = 7.8 Hz), 4.02 (3H, s), 3.99 (3H, s.).
19. 4-Ethoxy-6,7-dimethoxy-quinazoline (**16**): Following a similar reaction procedure to **10**, 129 mg (58% yield) of **16** was isolated as a white crystalline solid. LCMS: m/z = 235.0 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.85 (1H, s), 7.97 (1H, s), 7.41 (1H, s), 4.83 (2H, q, J = 6.9 Hz), 4.14 (3H, s), 4.07 (3H, s), 1.59 (3H, t, J = 6.9 Hz).
20. 4-Isopropoxy-6,7-dimethoxy-quinazoline (**17**): Following a similar reaction procedure to **10**, 221 mg (61% yield) of **17** was isolated as a white crystalline solid. LCMS: m/z = 249.1 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (1H, s), 7.62 (1H, s), 7.16 (1H, s), 4.07 (1H, heptet, J = 6.9 Hz), 4.02 (3H, s), 4.02 (3H, s), 1.22 (7H, d, J = 6.9 Hz).

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21. (6,7-Dimethoxy-quinazolin-4-yl)-isopropyl-amine (**18**): Following a similar reaction procedure to **10**, 73 mg (66% yield) of **18** was isolated as a white crystalline solid. LCMS: m/z = 248.0 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.88 (1H, s), 8.16 (1H, s), 7.44 (1H, s), 4.76 (1H, heptet, *J* = 6.9 Hz), 4.17 (3H, s), 4.08 (3H, s), 1.47 (6H, d, *J* = 6.9 Hz).
22. Cyclohexyl-(6,7-dimethoxy-quinazolin-4-yl)-amine (**19**): Following a similar reaction procedure to **10**, 45 mg (35% yield) of **19** was isolated as a white crystalline solid. LCMS: m/z = 288.0 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.39 (1H, s), 7.44 (1H, s), 7.28 (1H, s), 4.32 – 4.28 (1H, m), 4.11 (3H, s), 3.98 (3H, s), 3.14 (1H, tt, *J* = 11.0, 3.9 Hz), 2.14 – 2.10 (2H, m), 1.85 – 1.81 (2H, m), 1.63 – 1.25 (5H, m).
23. Compound **20** (ZM 323881) and Ki8751 were both purchased from Tocris Bioscience and used as received.
24. Compound **21** was prepared following a three step reaction from the corresponding (4-Methoxyphenyl)-acetonitrile based on a previously reported method.[9] 6-(4-Methoxy-phenyl)-3-thiophen-3-yl-pyrazolo[1,5-a]pyrimidine (**21**): LCMS: m/z = 308.0 (M+1, 100% intensity). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.79 (1H, d, J = 2.4 Hz), 8.77 (1H, d, J = 2.4 Hz), 8.37 (1H, s), 7.90 (1H, dd, J = 3.0, 1.2 Hz), 7.70 (1H, dd, J = 5.1, 1.2 Hz), 7.54 (2H, d, J = 9.0 Hz), 7.43 (1H, dd, J = 5.1, 3.0 Hz), 7.06 (2H, d, J = 8.7 Hz), 3.89 (s, 3H).

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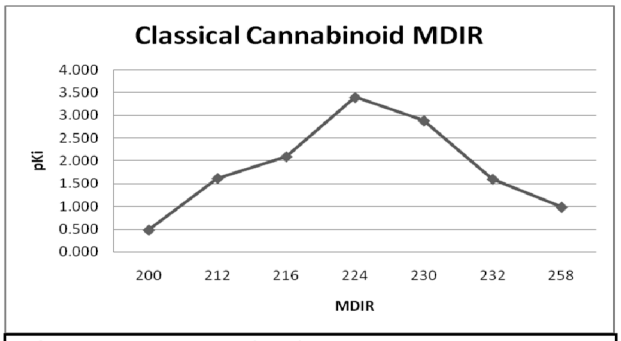

Compound	Ki(uM)	MDIR	pKi
1	0.328	200	0.484
2	0.024	212	1.620
3	0.008	216	2.097
4	0.0004	224	3.398
5	0.0013	230	2.886
6	0.025	232	1.602
7	0.103	258	0.987

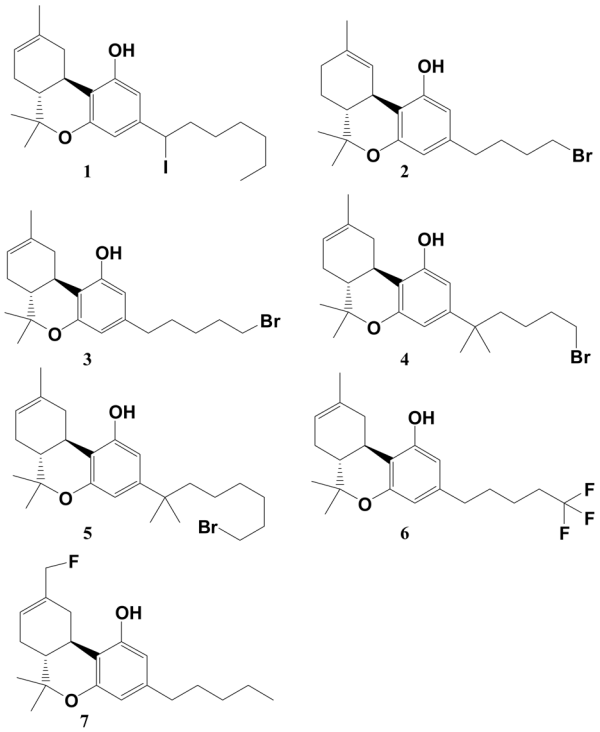

Figure 1.
MDIR as a molecular descriptor for QSAR of classical cannabinoids.

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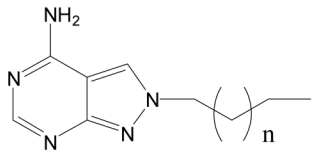
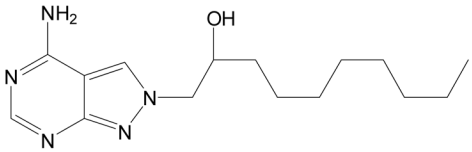
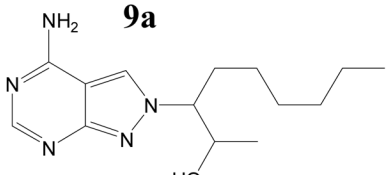
Compound	n	MDIR	Ki (nM)
8a	3	239.1	> 1,000
8b	4	244.7	818
8c	5	249.5	530
8d	6	253.9	8
8e	7	257.8	0.13
8f	8	261.4	0.47
8g	9	265.6	> 1,000
9a	na	254.9	0.28
9b	na	251.0	53



8a - g, n = 3 - 9



9a



9b

Figure 2.
MDIR and Binding affinities of adenosine deaminase inhibitors

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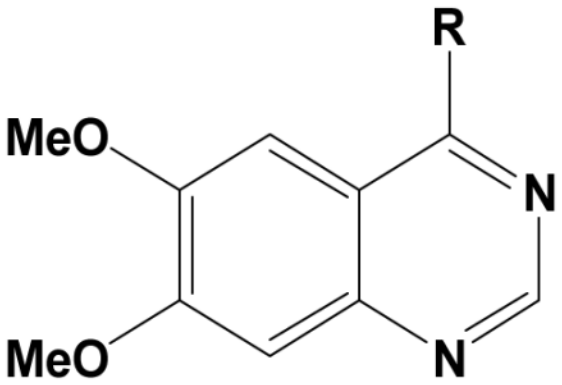
Table 1

Grid Docking score and MDIR correlation to KDR inhibitory activity of 4-Aminoquinazolines



Cmpd	R	Dock Score[a]	MDIR[b]	KDR Inhibition[c]
10	4′-Chloro-anilino	−27.8	172	4%
11	3′,4′-Difluoro-anilino	−24.9	178	5%
12	3′-Chloro-4′-methyl-anilino	−25.0	180	9%
13	4′-Fluoro-anilino	−24.8	184	6%
14	3′-fluoro-4′-methyl-anilino	−27.3	192	66%
15	Anilino	−25.1	194	19%
16	Ethoxyl	−25.7	200	0%
17	Isopropoxyl	−25.5	207	2%
18	Isopropyl amine	−26.3	215	13%
19	Cyclohexyl amine	−26.0	234	17%

[a]Grid Scoring from Flexible Docking (kcal/mol).

[b]amu/cm.

[c]Percent inhibition (average taken from n of 3 performed on separate days) KDR ELISA assay (20 μM ATP) at 10 μM final compound concentration.

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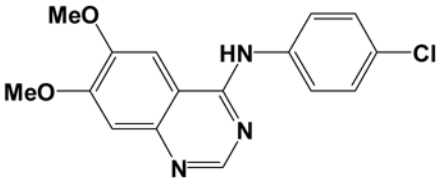
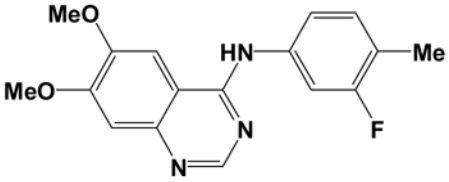
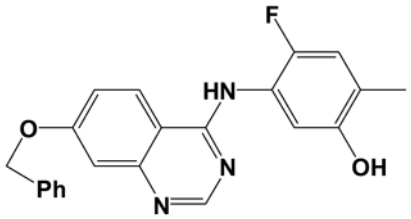
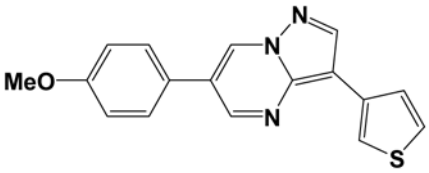
Table 2

Grid Docking score and MDIR correlation to KDR inhibitory activity.

	Dock Score[a]	MDIR[b]	Reported KDR Inhibition[10]	Measured[c] KDR Inhibition
 10	−27.8	172	IC_{50} = 800 nM	4% @ 10 μM (n=2)
 14	−27.3	192	NR	66% @ 10 μM (n=2)
 20	−33.9	192	IC_{50} = 2 nM	37% @ 20 μM (n=2)
 21	−29.6	199	IC_{50} = 19 nM	46% @ 25 μM (n=2)

[a]Grid Scoring from Flexible Docking (kcal/mol).

[b]amu/cm.

[c]Percent inhibition KDR ELISA assay (20 μM ATP) with HTSscan.