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# *N*-(4-(6,7-Disubstituted-quinolin-4-yloxy)-3-fluorophenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides: A novel series of dual c-Met/VEGFR2 receptor tyrosine kinase inhibitors

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ABSTRACT

A series of *N*-(4-(6,7-disubstituted-quinolin-4-yloxy)-3-fluorophenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides targeting c-Met and VEGFR2 tyrosine kinases was designed and synthesized. The compounds were potent against these two enzymes with $IC_{50}$ values in the low nanomolar range in vitro, possessed favorable pharmacokinetic profiles and showed high efficacy in vivo in several human tumor xenograft models in mice.



Receptor tyrosine kinases (RTKs) play crucial roles in signal transduction pathways and cellular processes, and many are implicated in cancer.[1] c-Met [the receptor for hepatocyte growth factor/scatter factor, (HGF/SF)][2] and members of the vascular endothelial growth factor receptor (VEGFR)[3] family1 including VEGFR1 (Flt-1), VEGFR2 (KDR) and VEGFR3 (Flt-4) are among the RTKs under investigation as potential targets for the development of small molecule cancer therapeutics. c-Met activation results in numerous biological responses, including cell migration and invasion, proliferation and survival, morphogenesis, and angiogenesis. While c-Met is involved in normal processes during embryonic development and wound healing, its deregulation is associated with tumorigenesis and correlates with poor prognosis in cancer patients.[2]c-Met has been shown to cooperate synergistically with the VEGFRs, key players in tumor angiogenesis.[3] Molecules that potently inhibit both c-Met[4] and VEGFR[5] may have advantage over VEGFR-selective or c-Met-selective molecules since they can target multiple pathways involved in tumor cell survival, angiogenesis and metastasis. Thus, the combined inhibition of both c-Met and VEGFR signaling represents a promising approach to cancer treatment.[6]

The drug Sunitinib (Sutent™)[7] from Pfizer, recently approved by the FDA for the treatment of both renal cell carcinomas (RCC) and imatinib-resistant gastrointestinal stromal tumors (GIST), is an example of a multi-targeted RTK inhibitor that targets VEGFR but not c-Met. Conversely, PHA-665752 (**2**)[8] is a potent inhibitor of c-Met but a weak inhibitor of VEGFR2. The dual c-Met/VEGFR2 inhibitors (**3**) discovered by Kirin Brewery[9] in 2003 and the related compound described by Exelixis (**4**)[10] inspired our work in this area. We have previously reported a family of dual c-Met/VEGFR2 inhibitors in which the dimethoxyquinoline fragment of **3** was replaced by a 2-substituted thieno[3,2-*b*]pyridine system, exemplified by **5**.[11] While exploring the replacement of the acylthiourea head group of **5** by other functionalities, we discovered that

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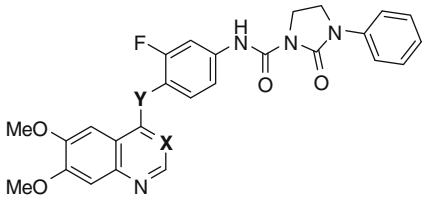
analogs bearing a five-membered cyclic urea headgroup, as in **6**,[12] were similar to the acylthiourea **5** (see Fig. 1). We elected to explore the activity and efficacy of these cyclic ureas when attached to the original dimethoxyquinoline and related fragments.[13]

A typical synthesis of the target compounds is illustrated in Scheme 1, in which 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluoroaniline reacts with 2-oxo-3-phenylimidazolidine-1-carbonyl chloride[14] in the presence of DIPEA. The latter was generated in three steps from triphosgene and 1-phenylimidazolidin-2-one, which was prepared from the corresponding aniline, chloroethyl isocyanate, and a base.[15] The preparation of 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluoroaniline and its analogs has been described elsewhere.[13]

Table 1 illustrates the enzymatic[16] and cellular[17] activities of compounds in which the linker atom or group Y is varied in both the quinoline (X = CH) and quinazoline (X = N) series. In the quinoline series, the oxygen linker (**10**) provided excellent activity against both c-Met and VEGFR2, while the NH (**11**) and NMe (**12**) linkers showed a slight loss of activity against c-Met and a more pronounced loss against VEGFR2. The quinazoline analogs showed a similar pattern, with the oxygen linked compound **7** being very active while the two N-linked molecules showed greatly reduced potency.

**Table 1**
Enzymatic c-Met and VEGFR2 results for compounds **7**–**12** of general structure



| Compd | X | Y | c-Met $IC_{50}$ (μM) | VEGFR2 $IC_{50}$ (μM) | Phospho-TPR-Met $IC_{50}$ (μM) |
|---|---|---|---|---|---|
| **7** | N | O | 0.04 | 0.03 | >1 |
| **8** | N | NH | 0.6 | >2 | 3.3 |
| **9** | N | NMe | 4.0 | >2 | >10 |
| **10** | CH | O | 0.03 | 0.01 | 0.09 |
| **11** | CH | NH | 0.2 | 1.4 | n.a. |
| **12** | CH | NMe | 0.4 | 5.9 | n.a. |

Unfortunately, compound **7** was inactive in different cell-based assays (data not shown), perhaps due to a lower cross-membrane permeability properties. Subsequent work therefore focused on the O-linked quinoline series.

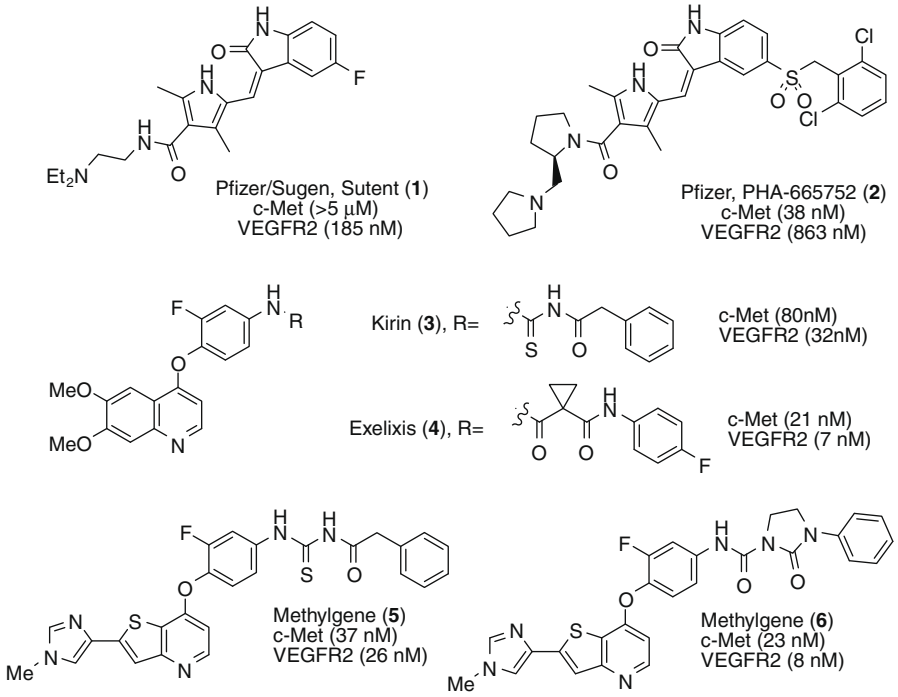
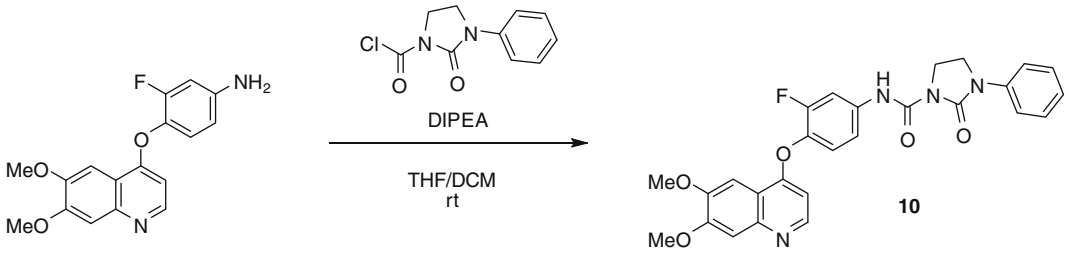



**Figure 1.** c-Met and/or VEGFR inhibitors with their $IC_{50}$ values (generated in house).




**Scheme 1.** Synthesis of compound **10**.

Table 2 shows the effect of varying the substitution of the urea group on enzymatic and cellular activities. Replacing the phenyl in compound **10** with pyridinyl rings (**13** and **14**) resulted in a large decrease of activity against VEGFR2. Cycloalkyl (**19**), allyl (**20**), and *N*-piperidinyl (**21**) also showed reduced activity against VEGFR2 as well as poor activity in the cellular assay. On the other hand, substitution of the phenyl ring seemed to be well tolerated (**15**–**18**) with respect to the enzyme inhibitory activity with the 4-fluorophenyl analog **18** appearing equipotent to **10** in both the enzymatic and the cell-based assays.

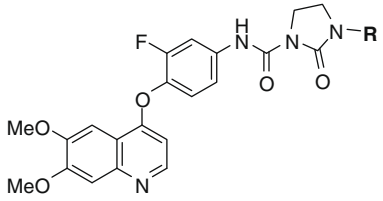
Table 3 indicates the effect of varying the substitution on the central phenyl ring. Replacement of the fluorine with a hydrogen atom (**22** and **23**) is reasonably well tolerated, and the additional replacement of the oxygen with a sulfur linker (**24**) was tolerated as well except for the activity against VEGFR2. Movement of the fluorine from the 3- to 2-position on the phenyl ring (**25**), or replacement of the central 3-fluorophenyl with a pyridinyl ring (**26** and **27**) led to a dramatically reduced cellular potency.[18] Moreover, compound **26** showed a significant decrease in activity against VEGFR2.

Finally, the effect of varying the two methoxy groups on the quinoline was examined with the ultimate goal to introduce water solubilizing groups (Table 4). Aminoalkyl functionalities are well tolerated on both oxygens (**28**–**31**) as well the bis(dimethoxyethyl) tweezer, as in compound **32**.

Rat pharmacokinetic analyses were performed on compound **10**. Compound **10** displayed a long-half life (4.4 h) and decent bioavailability (22%).

Compound **10** was further evaluated in other cell-based assays. First, it was tested for its ability to inhibit two c-Met-specific functional endpoints (Table 5). Compound **10** dramatically impaired HGF-induced epithelial cell migration and scattering, showing that it is able to inhibit c-Met-dependent cell motility events. Second, compound **10** was tested in a variety of VEGF-dependent cellular assays (Table 6). It potently inhibited the VEGF-induced phosphorylation of ERK, a downstream signaling protein of the VEGF pathway, and also impeded the VEGF-dependent proliferation of human umbilical vein endothelial cells (HUVEC). In an in vitro

**Table 2**
Enzymatic c-Met and VEGFR2 and cellular TPR-Met phosphorylation assay results for compounds **13**–**21** of general structure



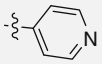
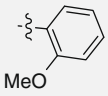
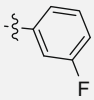
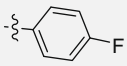
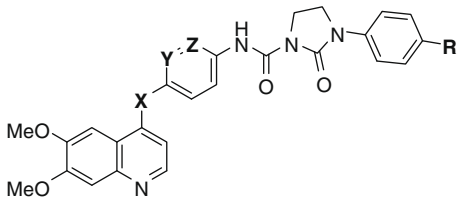
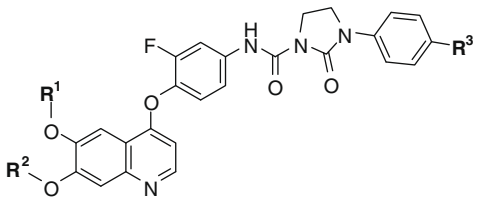
| Compd | R | c-Met $IC_{50}$ (μM) | VEGFR2 $IC_{50}$ (μM) | Phospho-TPR-Met $IC_{50}$ (μM) |
|---|---|---|---|---|
| **10** |  | 0.03 | 0.01 | 0.09 |
| **13** |  | 0.10 | 0.60 | 0.63 |
| **14** |  | 0.04 | 0.23 | n.a. |
| **15** |  | 0.05 | 0.03 | 0.15 |
| **16** |  | 0.06 | 0.02 | 0.37 |
| **17** |  | 0.05 | 0.015 | 0.20 |
| **18** |  | 0.03 | 0.02 | 0.09 |
| **19** |  | 0.11 | 0.21 | 0.86 |
| **20** |  | 0.20 | 0.63 | n.a. |
| **21** |  | 0.06 | 0.37 | 0.64 |

**Table 3**
Enzymatic c-Met and VEGFR2 and cellular TPR-Met phosphorylation assay results for compounds **22**–**27** of general structure



| Compd | X | Y | Z | R | c-Met $IC_{50}$ (μM) | VEGFR2 $IC_{50}$ (μM) | Phospho-TPR-Met $IC_{50}$ (μM) |
|---|---|---|---|---|---|---|---|
| **10** | O | CF | CH | H | 0.03 | 0.01 | 0.09 |
| **22** | O | CH | CH | H | 0.05 | 0.03 | 0.24 |
| **23** | O | CH | CH | F | 0.05 | 0.03 | 0.15 |
| **24** | S | CH | CH | F | 0.04 | 0.10 | 0.08 |
| **25** | O | CH | CF | H | 0.03 | 0.05 | >10 |
| **26** | O | N | CH | H | 0.06 | 1.30 | ~5 |
| **27** | O | CH | N | H | 0.03 | 0.02 | >10 |

**Table 4**
Enzymatic c-Met and VEGFR2 and cellular TPR-Met phosphorylation assay results for compounds **28**–**32** of general structure



| Compd | $R^1$ | $R^2$ | $R^3$ | c-Met $IC_{50}$ (μM) | VEGFR2 $IC_{50}$ (μM) | Phospho-TPR-Met $IC_{50}$ (μM) |
|---|---|---|---|---|---|---|
| **10** | Methyl | Methyl | H | 0.03 | 0.01 | 0.09 |
| **28** | Methyl | Piperidin-4-ylmethyl | H | 0.04 | 0.02 | 0.08 |
| **29** | Methyl | 1-Methyl-piperidin-4-ylmethyl | H | 0.05 | 0.02 | 0.13 |
| **30** | Methyl | 3-Morpholino-propyl | H | 0.05 | 0.03 | 0.05 |
| **31** | 3-Morpholino-propyl | Methyl | F | 0.04 | 0.12 | 0.03 |
| **32** | 2-Methoxy-ethyl | 2-Methoxy-ethyl | H | 0.06 | 0.04 | 0.02 |

**Table 5**
Effect of compound **10** on c-Met and VEGF-mediated cellular endpoints

| Compd | A549 wound healing inh. $IC_{50}$ (μM) | DU145 scattering inh. $IC_{50}$ (μM) | VEGF-dept phospho-ERK $IC_{50}$ (μM) | VEGF- dept HUVEC proliferation $IC_{50}$ (μM) | Angiokit, tubule length $IC_{50}$ (μM) | Angiokit, tubule length with VEGF (% inh.) |
|---|---|---|---|---|---|---|
| **10** | 0.08 | 0.08 | <0.001 | 0.002 | 0.008 | 99.4 |

angiogenesis assay, which measures the formation of tubules generated by a co-culture of endothelial and fibroblast cells (Angiokit™; TCS Cellworks), compound **10** significantly affected tubule growth and was also able to almost completely inhibit tubule formation at the 100 nM dose where cells were purposely supplemented with VEGF (Table 6). These results show that compound **10** has a significant effect on VEGF-dependent angiogenic activity in cells.

Third, compound **10** was also profiled against a small set of kinases using Millipore's Kinaseprofiler™ assay services (Table 6). In addition to targeting c-Met and VEGFR2, it also showed specificity for VEGFR1, VEGFR3, Ron, Ret and TrkA, moderately inhibited Flt3 and was not significantly active against 19 other kinases.

Compound **10** was evaluated for its ability to inhibit the proliferation of several human cancer cell lines, using a 72 h MTT assay. Consistent with its inhibitory activity against c-Met, it was very potent against MKN-45 gastric carcinoma cells, whose growth is driven by c-Met. Compound **10** was also effective in inhibiting the growth of the HCT116 colon carcinoma cells, but not of primary human mammary epithelial cells (HMEC) (Table 7).

Finally, compound **10** was tested in a mouse xenograft model bearing tumors derived from the c-Met–driven MNNG-Hos cells (Fig. 2). Interestingly, oral administration of a 40 mg/kg dose once daily for 12 days caused complete regression of tumor.

In conclusion, a series of *N*-(4-(6,7-disubstituted-quinolin-4-yloxy)-3-fluorophenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides was designed and synthesized. The compounds show low nanomolar inhibitory activity against both c-Met and VEGFR2 enzymes. Compound **10,** the lead molecule of the series, shows an excellent in vitro profile and favorable pharmacokinetic characteristics and exhibits significant in vivo efficacy in the MNNG-Hos human tumor xenograft mouse model. These results represent an important step toward the development of multi-targeted RTK inhibitors with favorable drug-like characteristics in the fight against human cancers.

**Table 6**
% Human enzyme inhibition at 100 nM of compound **10**

| Kinase | % Inh. at 100 nM | Kinase | % Inh. at 100 nM | Kinase | % Inh. at 100 nM |
|---|---|---|---|---|---|
| ALK | 0 | FGFR1 | 11 | PDGFRβ | 6 |
| Aurora A | 0 | Flt3 | 72 | PKBα | 0 |
| CDK2/Cyclin E | 0 | GSK3β | 0 | Ret | 96 |
| CHK1 | 0 | IKKβ | 0 | Ron | 92 |
| CHK2 | 1 | JAK2 | 4 | Tie-2 | 23 |
| c-Kit | 12 | JAK3 | 6 | TrkA | 94 |
| c-Raf | 42 | MEK1 | 0 | VEGFR1 | 100 |
| c-SRC | 7 | Met | 100 | VEGFR2 | 92 |
| EGFR | 0 | PDGFRα | 26 | VEGFR3 | 93 |

**Table 7**
Effect of compound **10** on human cancer cell proliferation

| Compd | MKN-45 $IC_{50}$ (μM) | HCT 116 $IC_{50}$ (μM) | HMEC $IC_{50}$ (μM) |
|---|---|---|---|
| 10 | 0.008 | 0.3 | >2.5 |

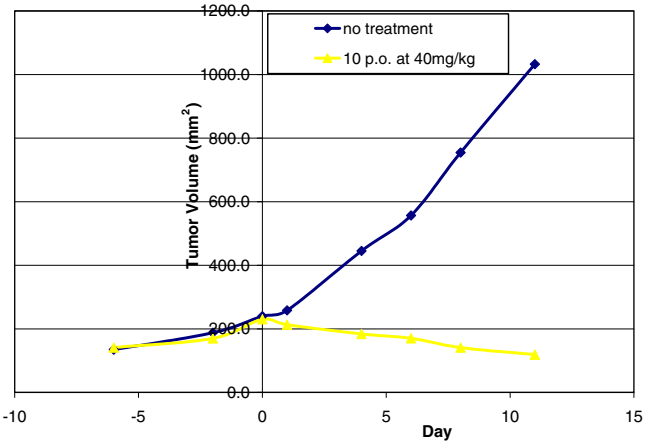



**Figure 2.** Oral anti-tumor activity of compound **10** in the MNNG-Hos tumor xenograft model. Compound **10** was dosed p.o., once daily, at 40 mg/kg (6 mice per group). Vehicle: 40/60 PEG 400/0.1 N HCl in saline.

## References and notes


1. Blume-Jensen, P.; Hunter, T. *Nature* **2001**, *411*, 355.
2. (a) Ma, P. C.; Maulik, G.; Christensen, J.; Salgia, R. *Cancer Metastasis Rev.* **2003**, *22*, 309; (b) Birchmeier, C.; Birchmeier, W.; Gherardi, E.; Vande Woude, G. F. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 915; (c) Christensen, J. G.; Burrows, J.; Salgia, R. *Cancer Lett.* **2005**, *225*, 1; (d) Corso, S.; Comoglio, P. M.; Giordano, S. *Trends Mol. Med.* **2005**, *11*, 284; (e) Boccaccio, C.; Comoglio, P. M. *Nat. Rev. Cancer* **2006**, *6*, 637; (f) Peruzzi, B.; Bottaro, D. P. *Clin. Cancer Res.* **2006**, *12*, 3657; (g) Knudsen, B. S.; Vande Woude, G. *Curr. Opin. Gen. Dev.* **2008**, *18*, 87; (h) Toschi, L.; Jänne, P. A. *Clin. Cancer Res.* **2008**, *14*, 5941; (i) Dussault, I.; Bellon, S. F. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 221; (j) Cipriani, N. A.; Abidoye, O. O.; Vokes, E.; Salgia, R. *Lung Cancer* **2009**, *63*, 169.
3. (a) Ferrara, N.; Gerber, H. P.; LeCouter, J. *Nat. Med.* **2003**, *9*, 669; (b) Paz, K.; Zhu, Z. *Front. Biosci.* **2005**, *10*, 1415.
4. (a) Cui, J. *Expert Opin. Ther. Patents* **2006**, *16*, 713; (b) Cui, J. J. *Expert Opin. Ther. Patents* **2007**, *17*, 1035; (c) Abidoye, O.; Murukurthy, N.; Salgia, R. *Rev. Recent Clin. Trials* **2007**, *2*, 143; (d) Zou, H. Y.; Li, Q.; Lee, J. H.; Arango, M. E.; McDonnell, S. R.; Yamazaki, S.; Koudriakova, T. B.; Alton, G.; Cui, J. J.; Kung, P.-P.; Nambu, M. D.; Los, G.; Bender, S. L.; Mroczkowski, B.; Christensen, J. G. *Cancer Res.* **2007**, *67*, 4408; (e) Kung, P.-P.; Funk, L.; Meng, J.; Alton, G.; Padrique, E.; Mroczkowski, B. *Eur. J. Med. Chem.* **2008**, *43*, 1321; (f) Bellon, S. F.; Kaplan-Lefko, P.; Yang, Y.; Zhang, Y.; Moriguchi, J.; Rex, K.; Johnson, C. W.; Rose, P. E.; Long, A. M.; O'Connor, A. B.; Gu, Y.; Coxon, A.; Kim, T.-S.; Tasker, A.; Burgess, T. L.; Dussault, I. *J. Biol. Chem.* **2008**, *283*, 2675; (g) Schroeder, G. M.; Chen, X.-T.; Williams, D. K.; Nirschl, D. S.; Cai, Z.-W.; Wei, D.; Tokarski, J. S.; An, Y.; Sack, J.; Chen, Z.; Huynh, T.; Vaccaro, W.; Poss, M.; Wautlet, B.; Gullo-Brown, J.; Kellar, K.; Manne, V.; Hunt, J. T.; Wong, T. W.; Lombardo, L. J.; Fargnoli, J.; Borzilleri, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1945; (h) Cai, Z.-W.; Wei, D.; Schroeder, G. M.; Cornelius, L. A. M.; Kim, K.; Chen, X.-T.; Schmidt, R. J.; Williams, D. K.; Tokarski, J. S.; An, Y.; Sack, J.; Manne, V.; Kamath, A.; Zhang, Y.; Marathe, P.; Hunt, J. T.; Lombardo, L. J.; Fargnoli, J.; Borzilleri, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3224; (i) Albrecht, B. K.; Harmange, J.-C.; Bauer, D.; Berry, L.; Bode, C.; Boezio, A. A.; Chen, A.; Choquette, D.; Dussault, I.; Fridrich, C.; Hirai, S.; Hoffman, D.; Larrow, J. F.; Kaplan-Lefko, P.; Lin, J.; Lohman, J.; Long, A. M.; Moriguchi, J.; O'Connor, A.; Potashman, M. H.; Reese, M.; Rex, K.; Siegmund, A.; Shah, K.; Shimanovich, R.; Springer, S. K.; Teffera, Y.; Yang, Y.; Zhang, Y.; Bellon, S. F. *J. Med. Chem.* **2008**, *51*, 2879; (j) Comoglio, P. M.; Giordano, S.; Trusolino, L. *Nat. Rev. Drug Disc.* **2008**, *7*, 504; (k) Liu, L.; Siegmund, A.; Xi, N.; Kaplan-Lefko, P.; Rex, K.; Chen, A.; Lin, J.; Moriguchi, J.; Berry, L.; Huang, L.; Teffera, Y.; Yang, Y.; Zhang, Y.; Bellon, S. F.; Lee, M.; Shimanovich, R.; Bak, A.; Dominguez, C.; Norman, M. H.; Harmange, J.-C.; Dussault, I.; Kim, T.-S. *J. Med. Chem.* **2008**, *51*, 3688; (l) Kim, K. S.; Zhang, L.; Schmidt, R.; Cai, Z.-W.; Wei, D.; Williams, D. K.; Lombardo, L. J.; Trainor, G. L.; Xie, D.; Zhang, Y.; An, Y.; Sack, J. S.; Tokarski, J. S.; Darienzo, C.; Kamath, A.; Marathe, P.; Zhang, Y.; Lippy, J.; Jeyaseelan, R., Sr.; Wautlet, B.; Henley, B.; Gullo-Brown, J.; Manne, V.; Hunt, J. T.; Fargnoli, J.; Borzilleri, R. M. *J. Med. Chem.* **2008**, *51*, 5330; (m) D'Angelo, N. D.; Bellon, S. F.; Booker, S. K.; Cheng, Y.; Coxon, A.; Dominguez, C.; Fellows, I.; Hoffman, D.; Hungate, R.; Kaplan-Lefko, P.; Lee, M. R.; Li, C.; Liu, L.; Rainbeau, E.; Reider, P. J.; Rex, K.; Siegmund, A.; Sun, Y.; Tasker, A. S.; Xi, N.; Xu, S.; Yang, Y.; Zhang, Y.; Burgess, T. L.; Dussault, I.; Kim, T.-S. *J. Med. Chem.* **2008**, *51*, 5766; (n) Schroeder,

G. M.; An, Y.; Cai, Z.-W.; Chen, X.-T.; Clark, C.; Cornelius, L. A. M.; Dai, J.; Gullo-Brown, J.; Gupta, A.; Henley, B.; Hunt, J. T.; Jeyaseelan, R.; Kamath, A.; Kim, K.; Lippy, J.; Lombardo, L. J.; Manne, V.; Oppenheimer, S.; Sack, J.; Schmidt, R. J.; Shen, G.; Stefanski, K.; Tokarski, J. S.; Trainor, G. L.; Wautlet, B. S.; Wei, D.; Williams, D. K.; Zhang, Y.; Zhang, Y.; Fargnoli, J.; Borzilleri, R. *J. Med. Chem.* **2009**, *52*, 1251; (o) Porter, J.; Lumb, S.; Lecomte, F.; Reuberson, J.; Foley, A.; Calmiano, M.; Le Riche, K.; Edwards, H.; Delgado, J.; Franklin, R. J.; Gascon-Simorte, J. M.; Maloney, A.; Meier, C.; Batchelor, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 397; (p) Koolman, H.; Heinrich, T.; Böttcher, H.; Rautenberg, W.; Reggelin, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1879; (q) Porter, J.; Lumb, S.; Franklin, R. J.; Gascon-Simorte, J. M.; Calmiano, M.; Riche, L. K.; Lallemand, B.; Keyaerts, J.; Edwards, H.; Maloney, A.; Delgado, J.; King, L.; Foley, A.; Lecomte, F.; Reuberson, J.; Meier, C.; Batchelor, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2780.

5. (a) Underiner, T. L.; Ruggeri, B.; Gingrich, D. E. *Curr. Med. Chem.* **2004**, *11*, 731; (b) Dumas, J.; Dixon, J. A. *Expert Opin. Ther. Patents* **2005**, *15*, 647; (c) Loriot, Y.; Massard, C.; Armand, J.-P. *Oncologie* **2006**, *8*, 815; (d) Morabito, A.; De Maio, E.; Di Maio, M.; Normanno, N.; Perrone, F. *Oncologist* **2007**, *11*, 753; (e) Kiselyov, A. S.; Balakin, K.; Tkachenko, S. E. *Expert Opin. Invest. Drugs* **2007**, *16*, 83; (f) Cabebe, E.; Fisher, G. A. *Expert Opin. Invest. Drugs* **2007**, *16*, 467; (g) Zhong, H.; Bowen, J. P. *Curr. Top. Med. Chem.* **2007**, *7*, 1379; (h) Schenone, S.; Bondavalli, F.; Botta, M. *Curr. Med. Chem.* **2007**, *14*, 2495.
6. Bilanges, B.; Torbett, N.; Vanhaesebroeck, B. *Nat. Chem. Biol.* **2008**, *4*, 648.
7. (a) WO 2001/60814 A2.; (b) WO 2002/096361 A2.; (c) Faivre, S.; Delbaldo, C.; Vera, K.; Robert, C.; Lozahic, S.; Lassau, N.; Bello, C.; Deprimo, S.; Brega, N.; Massimini, G.; Armand, J. P.; Scigalla, P.; Raymond, E. *J. Clin. Oncol.* **2006**, *24*, 25; (d) Faivre, S.; Demetri, G.; Sargent, W.; Raymond, E. *Nat. Rev. Drug Disc.* **2007**, *6*, 734.
8. (a) Christensen, J. G.; Schreck, R.; Burrows, J.; Kuruganti, P.; Chan, E.; Le, P.; Chen, J.; Wang, X.; Ruslim, L.; Blake, R.; Lipson, K. E.; Ramphal, J.; Do, S.; Cui, J. J.; Cherrington, J. M.; Mendel, D. B. *Cancer Res.* **2003**, *63*, 7345; (b) Ma, P. C.; Schaefer, E.; Christensen, J. G.; Salgia, R. *Clin. Cancer Res.* **2005**, *11*, 2312; (c) Smolen, G. A.; Sordella, R.; Muir, B.; Mohapatra, G.; Barmettler, A.; Archibald, H.; Kim, W. J.; Okimoto, R. A.; Bell, D. W.; Sgroi, D. C.; Christensen, J. G.; Settleman, J.; Haber, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 2316.
9. WO 2003/000660 A1.
10. WO 2005/030140 A2.
11. Claridge, S.; Raeppel, F.; Granger, M.-C.; Bernstein, N.; Saavedra, O.; Zhan, L.; Llewellyn, D.; Wahhab, A.; Deziel, R.; Rahil, J.; Beaulieu, N.; Nguyen, H.; Dupont, I.; Barsalou, A.; Beaulieu, C.; Chute, I.; Gravel, S.; Robert, M.-F.; Lefebvre, S.; Dubay, M.; Pascal, R.; Gillespie, J.; Jin, Z.; Wang, J.; Besterman, J.; Macleod, A. R.; Vaisburg, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2793.
12. Raeppel, S.; Claridge, S.; Saavedra, O.; Gaudette, F.; Zhan, L.; Mannion, M.; Zhou, N.; Raeppel, F.; Granger, M.-C.; Isakovic, L.; Déziel, R.; Nguyen, H.; Beaulieu, N.; Beaulieu, C.; Dupont, I.; Robert, M.-F.; Lefebvre, S.; Dubay, M.; Rahil, J.; Wang, J.; Ste-Croix, H.; Macleod, A. R.; Besterman, J.; Vaisburg, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1323.
13. The details for the synthesis and the characterization of all the new compounds are described in U.S. 2008/0004273 A1.
14. (a) Patent application from Bayer AG, *Chem. Abstr.* **1975**, *84*, 4975.; (b) Maclaren, J. A. *Aust. J. Chem.* **1977**, *30*, 455; (c) Su, W.; Zhang, Y. *J. Chem. Res. Synop.* **2000**, *9*, 440.
15. Mayer, P.; Brunel, P.; Chaplain, C.; Piedecoq, C.; Calmel, F.; Schambel, P.; Chopin, P.; Wurch, T.; Pauwels, P. J.; Marien, M.; Vidaluc, J.-L.; Imbert, T. *J. Med. Chem.* **2000**, *43*, 3653.
16. In vitro kinase assays (c-Met and VEGFR-2/KDR): Preparation of GST fusion proteins: recombinant baculovirus containing the catalytic domain of c-Met and of the VEGFR-2/KDR receptor fused to glutathione *S*-transferase (GST) fusion genes were used to infect High five (c-Met) or Sf9 (VEGFR-2/KDR) cells at a multiplicity of infection of 1 or 0.1, respectively. Cell lysates were prepared after ~72 h of infection in 1% Triton X-100, 2 μg of leupeptin/mL, and 2 μg of aprotinin/mL after ~72 h of infection in phosphate-buffered saline, and the fusion proteins were purified over glutathione agarose (Sigma) according to the manufacturer's instructions. Biochemical kinase assays for $IC_{50}$ determination and kinetic studies: Inhibition of c-Met and VEGFR2/KDR was measured in a DELFIA$^{TM}$ assay (Perkin Elmer). The substrate poly($Glu_4$,Tyr) was immobilized onto black high-binding polystyrene 96-well plates (Nunc Maxisorp). The c-Met kinase reaction was conducted in 25 mM Hepes pH 7.5 containing 20 mM NaCl, 10 mM $MgCl_2$, 5 mM β-Mercaptoethanol, 0.1 mg/mL bovine serum albumin (BSA) and 20 μM vanadate, while the VEGFR-2/KDR reaction was conducted in 60 mM Hepes pH 7.5 containing 3 mM $MgCl_2$, 3 mM $MnCl_2$, 1.2 mM β-Mercaptoethanol, 0.1 mg/mL BSA and 3 μM vanadate. ATP concentrations in the assay were 10 μM for c-Met (5× the $K_m$) and 0.6 μM for VEGFR-2/KDR (2× the $K_m$). Enzyme concentration was 25 nM (c-Met) or 5 nM (VEGFR-2/KDR).The recombinant enzymes were pre-incubated with inhibitor and Mg-ATP on ice in polypropylene 96-well plates for 4 min, and then transferred to the substrate coated plates. The subsequent kinase reaction took place at 30 °C for 30 min. (c-Met) or 10 min. (VEGFR2/KDR). After incubation, the kinase reactions were quenched with EDTA and the plates were washed. Phosphorylated product was detected by incubation with Europium-labeled anti-phosphotyrosine MoAb. After washing the plates, bound MoAb was detected by time-resolved fluorescence in a Gemini SpectraMax reader (Molecular Devices). Inhibitors were tested at seven different concentrations each in triplicate. $IC_{50}$s were calculated in a four parameters equation curve plotting inhibition (%).
17. A cellular clone of 293T kidney epithelial cells stably expressing TPR-Met (Park, M.; Dean, M.; Cooper, C. S.; Schmidt, M.; O'Brien, S. J.; Blair, D. G.; Vande Woude, G. F. *Cell* **1986**, *45*, 895), the activated mutated form of the receptor Met, under a CMV promoter was derived. Cells were treated with compounds dilutions for 150 min and lysate samples from treatment wells were transferred to high-binding white polysterene 96-wells plates (Corning). TPR-Met autophosphorylated levels were detected by ELISA using the primary antibodies anti-phospho-Tyrosine (Millipore, 4G10) and a reporter antibody, anti-mouse -horseradish peroxidase (Sigma). Plates were washed on a plate washer (SkanWasher, Molecular Devises) and subsequently incubated with chemiluminescent substrate solution (ECL, Roche). Luminescence signal was captured on a Polar Star Optima apparatus (BMG LabTech). Average values of triplicate streatment points were used to prepare $IC_{50}$ curves using a four-parameter fit model. These curves were calculated using GraFit 5.0 software.
18. Compounds **25**–**27** caused cell vacuolation and precipitated during the Phospho-TPR-Met and the HGF-induced epithelial cell migration and scattering cell-based assays.