Bioorganic & Medicinal Chemistry Letters 19 (2009) 1323–1328

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

N-(3-fluoro-4-(2-arylthieno[3,2-*b*]pyridin-7-yloxy)phenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides: A novel series of dual c-Met/VEGFR2 receptor tyrosine kinase inhibitors

Stéphane Raeppel [a,*], Stephen Claridge [a], Oscar Saavedra [a], Frédéric Gaudette [a], Lijie Zhan [a], Michael Mannion [a], Nancy Zhou [a], Franck Raeppel [a], Marie-Claude Granger [a], Ljubomir Isakovic [a], Robert Déziel [a], Hannah Nguyen [b], Normand Beaulieu [b], Carole Beaulieu [b], Isabelle Dupont [b], Marie-France Robert [b], Sylvain Lefebvre [b], Marja Dubay [c], Jubrail Rahil [c], James Wang [d], Hélène Ste-Croix [b], A. Robert Macleod [b,†], Jeffrey Besterman [b], Arkadii Vaisburg [a]

[a] *Department of Medicinal Chemistry, MethylGene Inc., 7220 rue Frederick-Banting, Montréal, QC, Canada H4S 2A1*
[b] *Department of Cell Biology and Pharmacology, MethylGene Inc., 7220 rue Frederick-Banting, Montréal, QC, Canada H4S 2A1*
[c] *Department of Lead Discovery, MethylGene Inc., 7220 rue Frederick-Banting, Montréal, QC, Canada H4S 2A1*
[d] *PK/Analytical Chemistry, MethylGene Inc., 7220 rue Frederick-Banting, Montréal, QC, Canada H4S 2A1*

ARTICLE INFO

Article history:
Received 10 December 2008
Revised 20 January 2009
Accepted 21 January 2009
Available online 27 January 2009

Keywords:
c-Met
VEGFR2
RTK inhibitors
Thieno[3,2-*b*]pyridine scaffold
Oncology

ABSTRACT

A series of *N*-(3-fluoro-4-(2-arylthieno[3,2-*b*]pyridin-7-yloxy)phenyl)-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 numerous signal transduction pathways and cellular processes. Many are implicated in cancer,[1] including the Hepatocyte Growth Factor Receptor c-Met,[2] which is over-expressed and/or mutated in various human tumor types, and the Vascular Endothelial Growth Factor Receptors (VEGFR), which play key roles in tumor angiogenesis.[3] Dysregulation of these RTKs affects cell proliferation, survival and motility, leading to tumor growth, angiogenesis, and metastasis. The combined inhibition of several RTKs is a promising approach for cancer therapy, as it targets multiple pathways involved in angiogenesis and tumor survival.[4]

Figure 1 highlights some of the known inhibitors of c-Met[5] and/or VEGFR[6] enzymes from the patent and scientific literature.

Sutent (**1**),[7] a marketed anticancer drug for patients with advanced renal cancer and gastrointestinal stromal tumors, is a potent inhibitor of VEGFR2 but does not inhibit c-Met. Conversely, PHA-665752 (**2**)[8] is a potent inhibitor of c-Met but a weak inhibitor of VEGFR2. In contrast to both molecules, representative quinoline compounds of Kirin (**3**)[9] and Exelixis (**4**)[10] are effective against both enzymes.

Recently, we reported on a series of 2-substituted thieno[3,2-*b*]pyridine-based c-Met/VEGFR2 inhibitors exemplified by compounds **5**–**10** (Table 1) bearing acyclic structural fragments, such as arylacetyl thioureas, arylacetyl ureas or various arylmalonamides.[11] Of particular interest was compound **8,** which showed the same potency against both c-Met and VEGFR2 as its desmethyl analogue **7**. We hypothesized that connecting the *N*-methyl with the central methylene of the malonamide head group of compound **8** via a CH_2-linker, as illustrated in the *N*-phenylpyrrolidone-type compounds **11** and **12**, could preserve the same kinase inhibitory properties. It turned out that compound **11** was indeed similar to compound **8** (Table 1).[12,13] Moving the carbonyl-group (compound **13**) or creating a quarternary center (compound **14**) resulted in a significant loss of activity against VEGFR2 for both compounds compared to compound **11.** The activities of both

* Corresponding author. Tel.: +1 514 337 3333; fax: +1 514 337 0550.
E-mail address: raeppels@methylgene.com (S. Raeppel).
† Present address: Isis Pharmaceuticals, 1896 Rutherford Road, Carlsbad, CA 92008, USA.

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.01.068

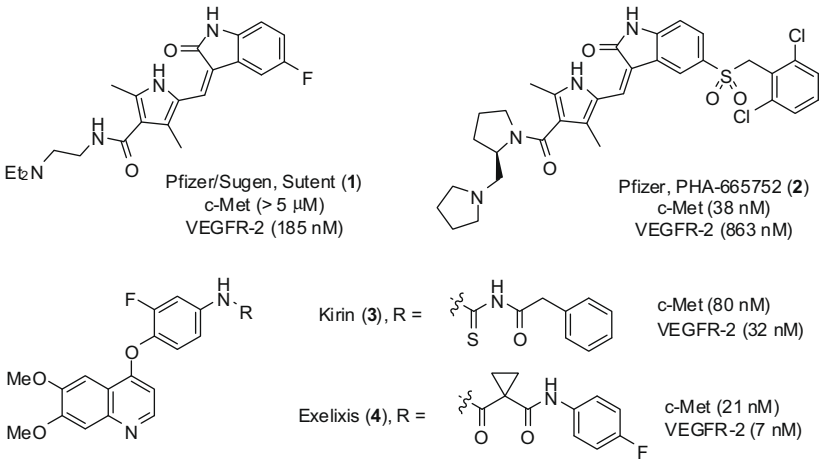
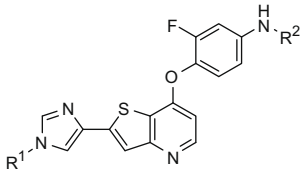
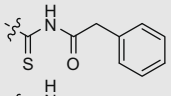
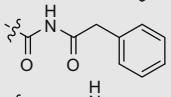
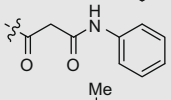
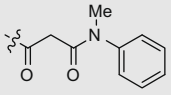
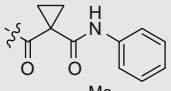
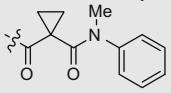
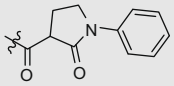
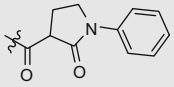
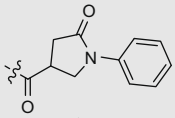
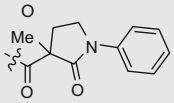
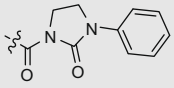
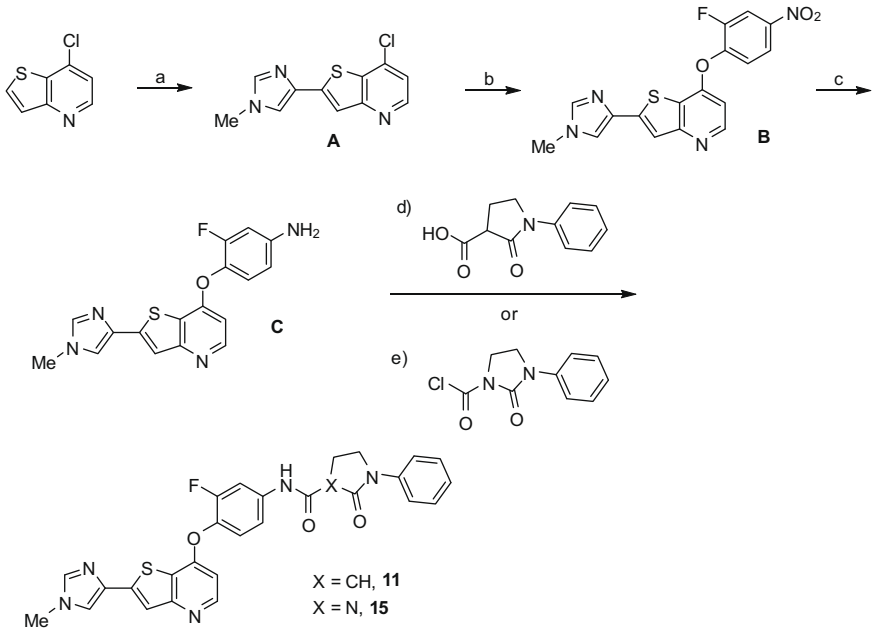


Figure 1. c-Met and/or VEGFR inhibitors with their IC_{50} values (generated in house).

Table 1
Enzymatic c-Met and VEGFR2 and cellular TPR-Met phosphorylation assay results for compounds **5**–**15** of general structure



Compound	R^1	R^2	c-Met IC_{50} (μM)	VEGFR2 IC_{50} (μM)	Phospho-TPR-Met IC_{50} (μM)
5	Me		0.037	0.026	0.05
6	Me		0.025	0.037	n.a.
7	Me		0.028	0.015	0.31
8	Me		0.043	0.010	0.16
9	Me		0.028	0.009	0.06
10	Me		1	0.057	1.44
11	Me		0.035	0.039	0.37
12	*i*-Pr		0.039	0.016	0.21
13	*i*-Pr		0.3	0.8	n.a.
14	Me		0.067	0.23	1.00
15	Me		0.023	0.008	0.12



Scheme 1. Synthesis of **11** and **15**. Reagents and conditions: (a) i—*n*-BuLi, THF, −78 °C; ii—$ZnCl_2$, THF, −78 °C to rt; iii—$Pd(PPh_3)_4$, 4-iodo-1-methyl-1*H*-imidazole, THF, reflux. (b) 2-Fluoro-4-nitrophenol, K_2CO_3, Ph_2O, 180 °C. (c) $NiCl_2$, $NaBH_4$, MeOH. (d) HATU reagent, DIPEA, DMF. (e) DIPEA, DCM.

compounds against c-Met changed as well—only slightly for compound **14** but more significantly for compound **13**. We then replaced the stereogenic center in the pyrrolidone fragment of compound **11** with a nitrogen atom to form the corresponding cyclic urea analogue **15.** This compound turned out to be equipotent to compound **8** at both the enzymatic[14] and cellular[15] level. Thus, rigidification of the arylmalonamide fragment into the arylimidazolidine motif is well tolerated, giving rise to a novel class of c-Met/VEGFR2 kinase inhibitors, the *N*-(3-fluoro-4-(2-arylthieno[3,2-*b*]-pyridin-7-yloxy)phenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides (e.g. compound **15**).[12,13]

Synthesis of compounds **11** and **15** is shown in Scheme 1. 7-Chlorothieno[3,2-*b*]pyridine and 4-iodo-1-methyl-1*H*-imidazole underwent a *Negishi* coupling reaction to form a methylimidazolyl substituted thienopyridine **A**.[16] This material was then reacted with 2-fluoro-4-nitrophenol under basic conditions at high temperature to form the nitro compound **B**. The nitro group of **B** was reduced using a mixture of sodium borohydride and nickel chloride in methanol to form the aniline **C**. The intermediate **C** was treated either with 2-oxo-1-phenylpyrrolidine-3-carboxylic acid in the presence of HATU reagent and diisopropylethylamine to form compound **11,** or with 2-oxo-3-phenylimidazolidine-1-carbonyl chloride[17] and diisopropylethylamine to give the cyclic urea **15**.

To study the SAR of compound **15,** we first explored the substituents at position 2 of the thieno[3,2-*b*]pyridine template (Table 2). Elongation of the chain (compound **16**) and/or incorporation of a basic center (compounds **17–19**) were well tolerated and provided potent molecular entities. Changing the orientation of the imidazolyl ring system—proceeding from compound **15** and **16** to compounds **20** and **21**—did not affect potency against c-Met but were slightly less active against VEGFR2. Replacement of the imidazole ring by a *para*-substituted phenyl ring (compounds **22**–**25**) was well tolerated. However, having three basic nitrogens, as in compound **25** resulted in a dramatic decrease in cell-based activity. The *m*-acetophenyl group in compound **26** proved to be detrimental and resulted in reduced enzyme inhibitory activity. A last modification which was explored was the replacement of the heteroaryl or aryl appendages by either an amide (compound **27**) or a tetrahydropyridine (compound **28**). Interestingly, compound **28** was significantly less active against VEGFR2.

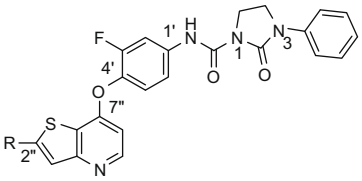
We next investigated the presence of a small substituent on the phenyl ring of the phenylimidazolidine fragment of the ethyl substituted analogues of compound **16**. (Table 3). The ortho- and para-substituted fluoride atom allowed us to slightly improve VEGFR2 inhibitory activity (compounds **29** and **30,** compared to compound **16**). On the other hand, the presence of an *ortho*-fluoro group (compound **30**) had a slightly negative impact on cell-based activity. Finally, although compound **31** with an *ortho*-methoxy group was equipotent to compound **16**, it showed reduced activity in our c-Met-driven cellular assays (data not shown).

We also examined the replacement of the oxygen atoms by sulfur atoms in the dicarbonyl framework of compound **15** (Table 4). Compound **32** (an analogue of compound **5**) was as potent as compound **15**, while compound **33** was inactive against c-Met and VEGFR2.

Rat pharmacokinetic analyses were performed on a small set of compounds (Table 5). Compounds with *N*-methylimidazole fragments (e.g. compounds **11** and **15**) showed a short to medium half-life and poor bioavailability. Results were encouraging, particularly for compound **29** as it displayed a long half-life and decent bioavailability, an appreciable improvement when compared to compound **5**. Compounds that had basic substituents generally had a shorter half-life and lower bioavailability (data not shown).

Compound **29** was further evaluated in other cell-based assays. First, it was tested for its ability to inhibit two c-Met-specific functional endpoints (Table 6). Compound **29** dramatically impaired HGF-induced epithelial cell migration and scattering, showing that it is able to inhibit c-Met-dependent cell motility events. Second, compound **29** was tested in a variety of VEGF-dependent cellular assays (Table 6). It potently inhibited the VEGF-induced phosphorylation of ERK, a downstream effector of the VEGF pathway, and also impeded the VEGF-dependent proliferation of human umbilical vein endothelial cells (HUVEC). In an *in vitro* angiogenesis assay, which measures the formation of tubules generated by a co-culture of endothelial and fibroblast cells (Angiokit™, TCS Cellworks), compound **29** potently inhibited tubule growth and was also able to almost completely inhibit tubule formation at the 100 nM dose

Table 2
Enzymatic c-Met and VEGFR2 and cellular TPR-Met phosphorylation assay results for compounds **16**–**28** of general structure



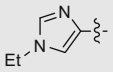
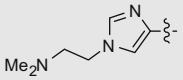
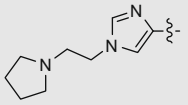
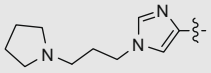
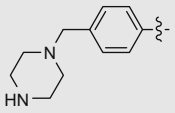
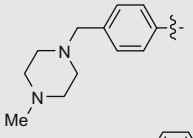
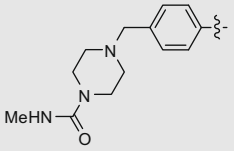
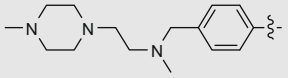
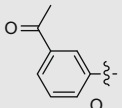
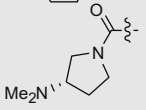
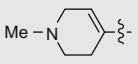
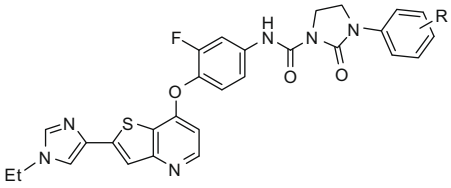
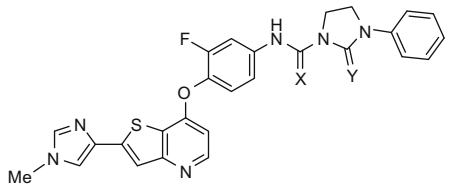
Compound	R	c-Met IC_{50} (μM)	VEGFR2 IC_{50} (μM)	Phospho-TPR-Met IC_{50} (μM)
16		0.025	0.012	0.04
17		0.034	0.014	0.06
18		0.035	0.02	0.32
19		0.021	0.008	0.30
20		0.026	0.031	0.12
21		0.024	0.026	0.14
22		0.022	0.011	0.42
23		0.029	0.012	0.25
24		0.016	0.008	0.08
25		0.028	0.003	0.83
26		0.2	0.88	0.27
27		0.042	0.023	0.23
28		0.033	0.17	0.30

Table 3
Enzymatic c-Met and VEGFR2 and cellular TPR-Met phosphorylation assay results for compounds **29**–**31** of general structure



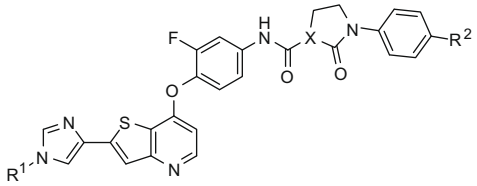
Compound	R	c-Met IC_{50} (μM)	VEGFR2 IC_{50} (μM)	Phospho- TPR-Met IC_{50} (μM)
16	H	0.025	0.012	0.04
29	*p*-F	0.027	0.007	0.05
30	*o*-F	0.021	0.003	0.10
31	*o*-OMe	0.026	0.014	0.06

Table 4
Enzymatic c-Met and VEGFR2 and cellular TPR-Met phosphorylation assay results for compounds **32** and **33** of general structure



Compound	X	Y	c-Met IC_{50} (μM)	VEGFR2 IC_{50} (μM)	Phospho-TPR-Met IC_{50} (μM)
15	O	O	0.023	0.008	0.12
32	S	O	0.024	0.012	0.08
33	O	S	2	1.8	>10

Table 5
Rat PK analysis: iv half-life and bioavailability (F%) for select compounds with general structure



Compound	R^1	X	R^2	$t_{1/2}$ iv (h)[a]	*F* (%)[b]
5	Me			1.2	12
11	Me	CH	H	1.1	14
15	Me	N	H	2.3	13
29	Et	N	F	6.3	37

[a] iv doses 2.17–2.86 mg/kg.
[b] po doses 4.28–4.98 mg/kg.

where cells were purposely supplemented with VEGF (Table 6). These results show that compound **29** can potently inhibit VEGF-dependent functional activity in cells.

Table 7
Effect of compound **29** on human cancer cell proliferation

Compound	MKN-45 IC_{50} (μM)	MNNG-HOS IC_{50} (μM)	HCT 116 IC_{50} (μM)	MDA MB-231 IC_{50} (μM)
29	0.01	0.033	13	20

Third, compound **29** was evaluated for its ability to inhibit the proliferation of a variety of human cancer cell lines, using a 72 h MTT assay. It displayed nanomolar IC_{50}s in tumor lines whose growth is known to be sensitive to c-Met inhibition, namely the MKN-45 gastric carcinoma and the TPR-Met-expressing MNNG-HOS cell lines. In contrast, significantly higher concentrations of compound **29** were required to inhibit the growth of c-Met-independent HCT116 colon carcinoma and MDA-MB-231 breast adenocarcinoma cells (Table 7). These results show that compound **29** specifically targets c-Met-driven cancer cell proliferation in culture.

Lastly, compound **29** was also profiled against a small set of kinases [using Millipore's Kinaseprofiler™ assay services] (Table 8). It strongly inhibited VEGFR1, VEGFR3, Ron and Tie-2, moderately inhibited Flt-3 and was not active against Aurora A.

Finally, compound **29** was tested in a mouse xenograft model bearing tumors derived from the c-Met-driven MKN-45 cells (Fig. 2). Interestingly, oral administration of a 40 mg/kg dose once daily for 12 days caused significant regression of MKN-45 tumor growth.

In conclusion, a series of 2-oxo-3-aryl-*N*-(4-(thieno[3,2-*b*]pyridin-7-yloxy)phenyl)imidazolidine-1-carboxamides was designed and synthesized. The compounds show low nanomolar inhibitory activity of both c-Met and VEGFR2 enzymes.

Table 8
% enzyme inhibition at 100 nM of **29**

VEGFR-1	VEGFR-3	Ron	Tie-2	FLT-3	Aurora A
99	99	100	99	80	9

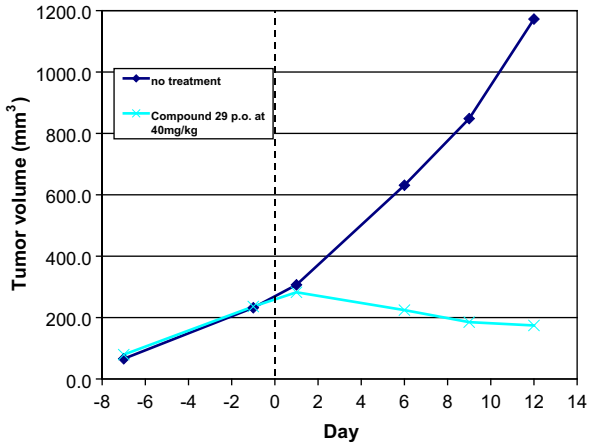


Figure 2. Oral anti-tumor activity of compound **29** in the MKN-45 tumor xenograft model. Compound **29** was dosed po, once daily, at 40 mg/kg (6 mice per group) starting on Day 0.

Table 6
Effect of compound **29** on c-Met and VEGF-mediated cellular endpoints

Compound	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.)
29	0.24	0.08	0.001	0.006	0.006	98

Compound **29,** the lead molecule, shows an excellent in vitro profile and favorable pharmacokinetic characteristics and exhibits significant in vivo efficacy in the MKN-45 human xenograft mouse model. Efforts to further optimize pharmacokinetic characteristics and physicochemical properties of *N*-(3-fluoro-4-(2-arylthieno[3,2-*b*]pyridin-7-yloxy)phenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides as well as attempts to expand this series of compounds towards chemical entities with a different kinase inhibitory profile is in progress.

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 Metast. 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. *Cur. Opin. Gen. Dev.* **2008**, *18*, 87; (h) Toschi, L.; Jänne, P. A. *Clin. Cancer Res.* **2008**, *14*, 5941.
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. Bilanges, B.; Torbett, N.; Vanhaesebroeck, B. *Nat. Chem. Biol.* **2008**, *4*, 648.
5. (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.
6. (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. *The Oncologist* **2007**, *11*, 753; (e) Kiselyov, A. S.; Balakin, K.; Tkachenko, S. E. *Expert Opin. Investig. Drugs* **2007**, *16*, 83; (f) Cabebe, E.; Fisher, G. A. *Expert Opin. Investig. Drugs* **2007**, *16*, 467; (g) Zhong, H.; Bowen, J. P. *Curr. Top. Med. Chem.* **2007**, *7*, 1379; (h) Schenone, S.; Bondavalli, F.; Botta, M. *Cur. Med. Chem.* **2007**, *14*, 2495.
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 Discov.* **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. (a) WO 2006/010264 A1.; (b) US 2006/0287343 A1.; (c) US 2007/0004675 A1.; (d) 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. The details for the synthesis and the characterization of all the new compounds are described in US 2007/0004675 A1 and WO 2007/107005 A1.
13. The present work was first presented (poster session) at the International Conference on Medicinal Chemistry. Drug Discovery and Selection. 43èmes Rencontres internationales de Chimie Thérapeutique. July 4–6, 2007, Faculté de Pharmacie, Lille, France.
14. 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 VEGFR-2/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 uM 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. (VEGFR-2/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 (%).
15. A cellular clone of 293T 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-well 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 treatment points were used to prepare IC_{50} curves using a 4-parameter fit model. These curves were calculated using GraFit 5.0 software.
16. Ragan, J. A.; Raggon, J. W.; Hill, P. D.; Jones, B. P.; Mcdermott, R. E.; Munchhof, M. J.; Marx, M. A.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Lu, Y. *Org. Process Res. Dev.* **2003**, *7*, 676.
17. (a) Bayer, A. G. *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.