Bioorganic & Medicinal Chemistry Letters 21 (2011) 4702–4704

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Novel imidazo[1,2-*a*]pyridine based inhibitors of the IGF-1 receptor tyrosine kinase: Optimization of the aniline

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ARTICLE INFO

Article history:
Received 6 May 2011
Revised 15 June 2011
Accepted 19 June 2011
Available online 25 June 2011

Keywords:
IGF1-R
Insulin-like growth factor-1 receptor
Kinase inhibitor

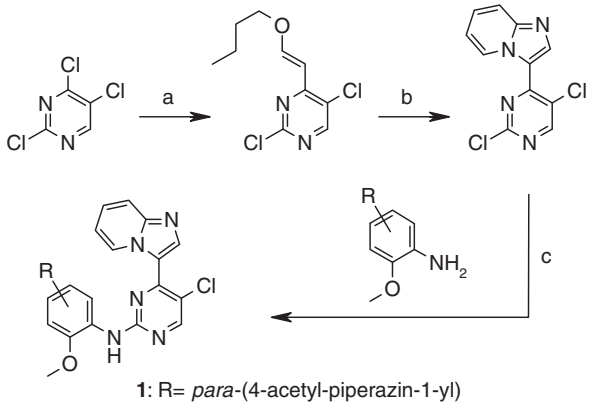
ABSTRACT

Following the discovery of imidazopyridine **1** as a potent IGF-1R tyrosine kinase inhibitor, the aniline part has been modified with the aim to optimize the properties of this series. The structure–activity relationships against IGF-1R kinase activity as well as inhibition of the hERG ion channel are discussed.

Inhibition of the Insulin-like Growth Factor-1 receptor tyrosine kinase has been a growing field of research over the past couple of years.[1] Following up the pioneering clinical studies with antibodies, small molecule kinase inhibitors of IGF-1R are now under evaluation in clinical trials and represent a promising approach in the treatment of a variety of solid cancers.[2] In the first part of this investigation,[3] we disclosed the identification of the imidazo[1,2-*a*]pyridine **1** (Scheme 1) as a potent inhibitor of IGF-1R with suitable pharmacokinetic properties for oral administration. We now wish to report lead optimization work performed through modification of the aniline substitution and the resulting structure–activity relationships with regards to inhibition of the IGF-1R kinase and the ether-a-go-go related gene (hERG) ion channel.

Although compound **1** displays good in vitro activity, as measured by the inhibition of IGF1 stimulated auto-phosphorylation of IGF-1R in cell, and good oral pharmacokinetics in pre-clinical species, the ultimate in vivo efficacy could potentially be limited by the physical properties of this compound. First of all, a relatively high protein binding (98.4% in human plasma) balances the in vitro potency since in vivo efficacy is typically correlated with the concentration of the unbound drug. Furthermore, compound **1** has modest aqueous solubility (1.4 μM in a pH 7.4 phosphate buffer) which is a known cause of limited oral absorption and inter-patient variability. In order to circumvent this risk, replacement of the *N*-acetyl piperazine has been investigated with the aim of either increasing cellular potency over the lead compound, or improving the physical properties while maintaining the activity. Another objective during this work was to retain good selectivity versus hERG since inhibition of this ion channel has the potential to induce cardiac arrhythmia in patients.

The synthesis of compounds **1–36** has been described in the patent literature[4] and will not be detailed herein. The general procedure to obtain such compounds is summarised on Scheme 1. The appropriate aniline was condensed with 3-(2,5-dichloropyrimidin-4-yl)-imidazo[1,2-*a*]pyridine[5] under acidic conditions in 2-pentanol at a typical temperature of 130 °C. In some instances,



1: R= *para*-(4-acetyl-piperazin-1-yl)

Scheme 1. General synthesis of compound **1** and analogues. Reagents and conditions: (a) *n*-butyl-vinyl ether, Et_3N, $Pd(OAc)_2$, PEG-400, 80 °C, 53%; (b) NBS, dioxane-water, rt, then 2-amino-pyridine, 80 °C, 67%; (c) *p*-toluenesulfonic acid, 2-pentanol, 130 °C.

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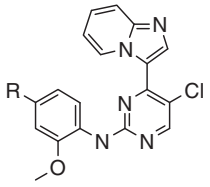
doi:10.1016/j.bmcl.2011.06.090

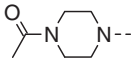
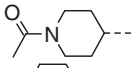
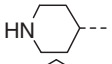
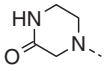
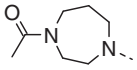
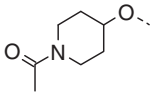
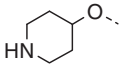
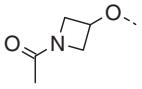
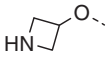
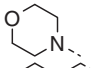
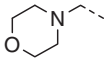
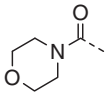
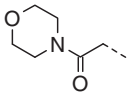
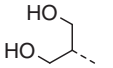
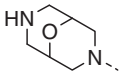
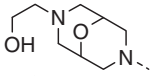
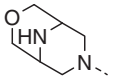
the resulting product was further derivatized to provide the desired compound.

The inhibitory activities of compounds **1–17** against IGF-1R in our enzymatic and cellular assays as well as the inhibition of the hERG ion channel in an electrophysiology assay are compiled in Table 1.[6] Replacement of the piperazine ring with a piperidine (**2** and de-acetyl analogue **3**) led to a similar IGF-1R activity but also to a moderate hERG inhibition (our objective was to have no significant hERG inhibition at 33 μM). The piperazinone **4** and the 1-acetyl-1,4-diazepane **5** were less potent, the latter being also active in the hERG assay. Introduction of an ether linkage in the form of a 4-oxy-piperidine or a 3-oxy-azetidine (**6–9**) was also disappointing as it led to some hERG inhibition, with the exception of compound **8** which unfortunately had a reduced IGF-1R potency. Morpholine **10** displayed a reduced IGF-1R activity in addition to some hERG inhibition. Homologation of **10** into the benzylamine **11**, the benzamide **12** or the phenylacetamide **13** led to a further reduction of IGF-1R activity with no clear beneficial effect on hERG compared to **10**. The 1,3-propanediol derivative **14** had a reasonable activity against IGF-1R, given the log *D* reduction induced by the hydroxyl groups (measured log *D* 3.1, compared to 3.6 for **1**), and showed no hERG inhibition. However, this compound did not offer any advantage over **1** as it showed a higher plasma clearance and a lower oral bioavailability in the rat (data not shown).

The first improvement in cellular activity was achieved with compounds **15** and **16** which incorporate a 9-oxa-3,7-diazabicyclo[3.3.1]nonane ring, also called oxa-bispidine in reference to the related bispidine skeleton (3,7-diazabicyclo[3.3.1]nonane) found in the alkaloids Sparteine and Cytisine.[7] The exquisite potency against IGF-1R of **16** (2 nM in the cellular assay) and its higher fraction unbound in human plasma compared to **1** (5% versus 1.6%) represented a significant improvement over our lead compound. However, this was balanced by its ability to inhibit hERG with an IC_{50} of 1.5 μM. The basicity of **16** is much higher than would be anticipated based on the inductive effect of the hydroxylethyl group. Indeed, the measured pK_a of **16** (8.4, see Table 2) is much higher than the value of 6.8 for 4-(hydroxyethyl)-morpholine.[8] This observation can be rationalised by the ability of such a bicycle to adopt a 'chair-chair' conformation in which the lone pair of the phenyl-linked nitrogen stabilizes the ammonium ion (Fig. 1). This hypothesis is consistent with a similar effect reported for the parent bispidine ring.[9] In order to find a related bicycle with a reduced hERG activity, we prepared compound **17** in which the oxa-bispidine moiety is replaced by a 3-oxa-7,9-diazabicyclo[3.3.1]nonane.[10] Although this derivative is significantly less basic than its isomer **15** (ΔpK_a = 2.0), this modification only had a minor impact on hERG

Table 1
Inhibition of IGF-1R kinase activity and inhibition of receptor autophosphorylation in cell of compounds **3–10**



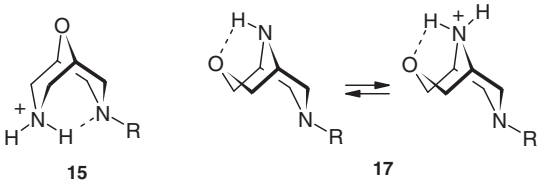
Compd	R	IGF-1R IC_{50}[a] (μM)	Cell IC_{50}[a] (μM)	hERG IC_{50}, μM
1		0.009	0.017	>33
2		0.006	0.013	12
3		0.005	0.009	9.1
4		0.032	0.039	>33
5		0.023	0.046	11
6		0.016	0.017	10
7		0.012	0.046	4.8
8		0.060	0.070	>33
9		0.057	0.026	5.9
10		0.013	0.042	3.2
11		0.041	0.093	9.9
12		0.060	0.157	2.7
13		0.039	0.112	8.8
14		0.018	0.080	>33
15		0.004	0.007	5.3
16		0.004	0.002	1.5
17		0.045	0.082	10

[a] IC_{50} values are means of at least two experiments, standard deviation is less than 2.

Table 2
Measured pK_a and log *D* for compounds **15**, **16** and **17**

Compd	Measured pK_a [a]	Measured log *D* [b]	Log *P* [c]
15	8.7	2.3	3.6
16	8.4	2.5	3.5
17	6.7	3.0	3.1

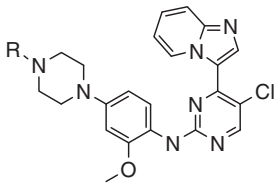
[a] Measured by UV spectrophotometric titration on a Sirius GLpK_a/D-PAS instrument.
[b] Measured in duplicate using a shake-flask method.
[c] Log *P* = Log *D* + Log(1+$10^{pKa-7.4}$).



15 **17**

Figure 1. Proposed conformations of the oxa-diaza-bicyclononane rings in compounds **15** and **17**. At physiological pH (7.4), **15** is essentially protonated, whereas **17** is present mostly as a free base and its protonated form is likely to adopt the same conformation.

Table 3
Inhibition of IGF-1R kinase activity and inhibition of receptor autophosphorylation in cell of compounds **3–10**



Compd	R	IGF-1R IC_{50}[a] (μM)	Cell IC_{50}[a] (μM)	hERG IC_{50} (μM)
18	H	0.020	0.020	4.6
19	CH_2CH_2OH	0.015	0.017	3.7
20	CH_2CONMe_2	0.012	0.040	12
21	$CH_2CH_2SO_2Me$	0.017	0.035	9.4
22	SO_2Me	0.009	0.019	>33
23	CO_2Me	0.027	0.033	>33
24	$CONH_2$	0.008	0.249	>33
25	$CONMe_2$	0.011	0.018	16
26	$COCH_2OH$	0.008	0.027	14
27	(S)-COCH(Me)OH	0.009	0.047	8.1
28	(R)-COCH(Me)OH	0.013	0.016	15
29	$COCH_2NH_2$	0.005	0.011	16
30	$COCH_2NHMe$	0.004	0.009	9.5
31	(S)-$COCH(Me)NH_2$	0.005	0.009	9.4
32	(R)-$COCH(Me)NH_2$	0.006	0.013	14

[a] IC_{50} values are means of at least two experiments, standard deviation is less than 2.

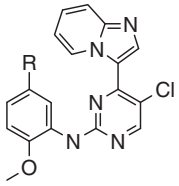
activity (2 fold decrease). This result, in addition to the small difference in hERG inhibition between compounds **2** and **6** and their basic analogues **3** and **7**, shows the lack of correlation between hERG inhibition and basicity in this series.

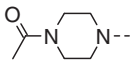
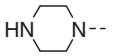
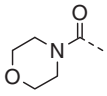
Compound **17** was a less potent IGF-1R inhibitor than **15** (10 fold reduction in enzyme and cellular assays). This is possibly a consequence of the different shapes of the bicycles as the 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane is likely to be in a 'chair-boat' conformation stabilised by an internal hydrogen bond, as opposed to the 'chair-chair' conformation of the oxa-bispidine (Fig. 1). In addition, the calculated log *P* values from the measured pK_a and log *D* (pH 7.4) show a higher intrinsic lipophilicity for **15** compared to **17**. This reflects a higher solvation state for the 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane moiety in water, presumably detrimental to the ligand affinity for the ATP binding site of the kinase.

The replacement of the piperazine ring in compound **1** having proved unsuccessful, we pursued our investigation by modifying the acetyl group (Table 3). The unsubstituted piperazine derivative **18** was as potent as compound **1** but displayed some hERG affinity. Reducing the piperazine basicity using a nitrogen substituent with a strong inductive effect (compd **19–21**) did not remove hERG activity. Sulfonamide derivative **22**, carbamate **23** and urea **24** were inactive against hERG but only **22** was as potent as **1**, while showing a lower aqueous solubility (<0.6 μM compared to 1.4 μM for **1**). Dimethylurea **25** and glycolic or lactic acid derivatives **26–28** had some hERG affinity without any IGF-1R activity improvement over **1**. Likewise, compounds derived from glycine, sarcosine and alanine (**29–32**) displayed good potency against IGF-1R but were moderately active in the hERG assay.

Finally, moving the aniline substituent from the *para* to the *meta*-position only provided compounds with inferior properties (Table 4). Compound **33** was less active than **1** in the IGF-1R assays and displayed some affinity for the hERG channel. The unsubstituted piperazine **34** had a profile similar to its analogue **18** and compounds **35**

Table 4
Inhibition of IGF-1R kinase activity and inhibition of receptor autophosphorylation in cell of compounds



Compd	R	IGF-1R IC_{50}[a] (μM)	Cell IC_{50}[a] (μM)	hERG IC_{50} (μM)
33		0.051	0.141	4.3
34		0.06	0.031	4.8
35		0.083	0.160	5.1
36		0.12	1.06	1.3

[a] IC_{50} values are means of at least two experiments, standard deviation is less than 2.

and **36** were less active against IGF-1R than their *para*-counterparts (**10** and **12** respectively) but had a similar hERG IC_{50}.

In summary, we have explored the structure–activity relationship around our lead compound **1**. We have identified compound **16** having a superior IGF-1R inhibitory activity in a cellular assay and a higher free fraction in human plasma. However this compound showed a higher affinity for the hERG channel, which precluded its selection as a possible candidate drug.

Acknowledgments

We would like to thank the following people for their contribution to the synthesis of the compounds described: Myriam Didelot, Hervé Germain, Maryannick Lamorlette, Mickael Maudet and Morgan Ménard.

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4. Detailed experimental procedures and ^1H NMR characterizations can be found in the patent application WO-2010/049731.
5. For the preparation of 3-(2,5-dichloropyrimidin-4-yl)-imidazo[1,2-*a*]pyridine see: Ducray, R.; Boutron, P.; Didelot, M.; Germain, H.; Lach, F.; Lamorlette, M.; Legriffon, A.; Maudet, M.; Ménard, M.; Pasquet, G.; Renaud, F.; Simpson, I.; Young, G. L. *Tetrahedron Lett.* **2010**, *51*, 4755.
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