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SAR of PXR transactivation in benzimidazole-based IGF-1R kinase inhibitors

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ABSTRACT

The SAR of PXR transactivation by 3-(benzimidazol-2-yl)-pyridine-2-one based ATP competitive inhibitors of Insulin-like Growth Factor 1 Receptor kinase (IGF-1R) is discussed. Compounds without PXR transactivation, with in vivo antitumor activity, reduced protein binding and improved oral exposure are presented.

The pregnane X receptor (PXR) is a member of the nuclear receptor family of ligand-activated transcription factors. PXR regulates gene expression of several CYP450s and other enzymes involved in phase I and phase II drug metabolism, as well as drug transport.[1–3] PXR transactivation can thereby lead to unwanted drug–drug interactions and is an undesired property of compounds considered for development as a drug. For example, the antibiotic Rifampicin is a strong PXR transactivator and has limited use in humans because of this reason.

The ligand binding site of human PXR is large and flexible. It consists of 20 hydrophobic amino acids, four amino acids with polar side chains (Ser^{208}, Ser^{247}, Cys^{284}, and Gln^{285}) and four that are (potentially) charged (Glu^{321}, His^{327}, His^{407}, and Arg^{410}).[3] A salt bridge between Glu^{321} and Arg^{410} effectively neutralizes their charge leaving the binding cavity relatively hydrophobic. Due to its flexibility the hPXR ligand binding site can accommodate (as an induced fit) molecules that range in size from 300 to 800 Da.[4,5]

Only a few X-ray structures of compounds bound to the ligand binding site of hPXR have been published,[1,6] as well as a small number of publications[7,8] discussing the SAR of PXR transactivation, but the flexibility of the receptor makes it very difficult to extrapolate SAR to structurally different classes of compounds. The common element of all published SAR of hPXR is a H-bond acceptor in the center of the ligand, which according to Ref. 9 binds to Gln^{285} and is indispensible for activation, combined with at least 2 (if aromatic) or 3 (if aliphatic), possibly up to 5, lipophilic features, which are not essential for receptor activation but contribute to ligand affinity.[4,9]

As part of ongoing research[10–15] towards an ATP competitive small molecule inhibitor of IGF-1R kinase[16–20] the PXR transactivation of over 400 compounds within the benzimidazole-pyridone chemotype was measured. The following discussion presents the SAR observations from this effort, which led to the discovery of compounds which inhibit IGF-1R, have in vivo activity and do not transactivate PXR (Fig. 1).

One of the limitations of our first generation IGF-1R inhibitors (e.g., compound **1**) is their strong PXR transactivation.[10,11] In an attempt to reduce PXR transactivation and CYP450 inhibition while

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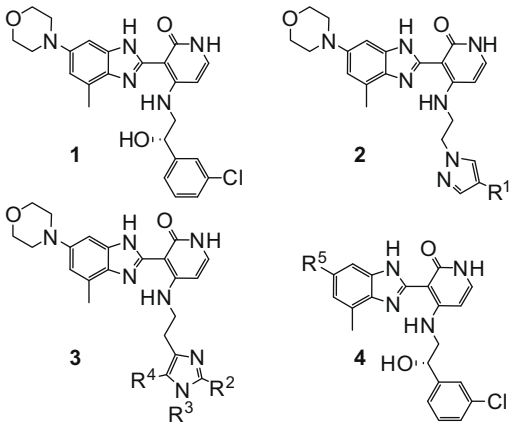


Figure 1. General structure of compounds **1**–**4**.

maintaining potency against IGF-1R kinase and oral exposure the lipophilic *m*-chlorophenyl group of **1** was replaced with heteroaromatic groups. This led to the synthesis of compounds **2a**–**k** and **3a**–**j**.[12] Within the series of C4-substituted pyrazoles **2a**–**k** increasing polarity (decreasing log *D*) correlates with a significant reduction of PXR transactivation (see Table 1 and Fig. 2) log *D* at pH 6.5, log *D* at pH 7.4 and *c*log *P* correlate equally well with PXR data, but polar surface area does not.

The same trend was observed within a series of substituted imidazoles **3a–j**.[12] Increased lipophilicity of the substituents (higher log *D*) led to an increase in PXR transactivation (Table 2 and Fig. 2).

Table 1
IGF-1R kinase, log *D* and PXR data of compounds **2a**–**k**

Cmpd	R^1	IGF-1R[a] (nM)	Log *D*[b]	PXR[c] (%)
2a	Cl	120	1.11	147
2b	COOEt	68	1.02	71
2c	CH_3	110	0.97	16
2d	H	330	0.51	16
2e	COOMe	91	0.49	51
2f	CN	680	−0.02	8
2g	CH_2OH	920	−0.67	5
2h	CONHMe	2060	−0.85	2
2i	$CONH_2$	1300	−0.97	4
2j	$CONMe_2$	1550	−1.27	8
2k	COOH	5210	−2.31	6

[a] IGF-1R Kinase IC_{50}.
[b] ACD Log *D* (pH 7.4) values were calculated using ACD/Log *D* Sol Suite 7.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com 2003.
[c] % Transactivation of PXR receptor, compared to Rifampicin at 10 μmol/l concentration. See also Ref. 21.

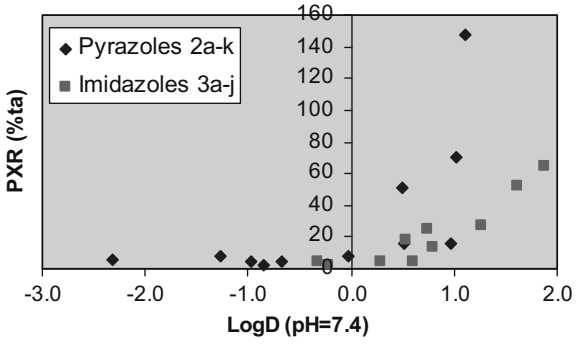


Figure 2. PXR transactivation as a function of log *D* for compounds **2a**–**k** and **3a**–**j**. Graphical representation of data from Tables 1 and 2.

Table 2
IGF-1R kinase, log *D* and PXR data of compounds **3a**–**j**

Cmpd	R^2	R^3	R^4	IGF[a] (nM)	Log *D*[b]	PXR[c] (%)
3a	Cl	Me	Cl	160	1.87	65
3b	H	*i*Pr	Cl	360	1.62	52
3c	H	Et	Cl	83	1.27	27
3d	H	Me	Br	75	0.80	14
3e	H	Me	Cl	38	0.74	25
3f	H	*i*Pr	H	360	0.60	5
3g	H	CH_2CH_2OMe	Cl	290	0.54	18
3h	H	Et	H	480	0.28	5
3i	H	Me	H	190	−0.22	2
3j	H	CH_2CH_2OMe	H	550	−0.33	4

[a] IGF-1R Kinase IC_{50}.
[b] ACD Log *D* (pH 7.4) values were calculated using ACD/Log *D* Sol Suite 7.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com 2003.
[c] % Transactivation of PXR receptor, compared to Rifampicin at 10 μmol/l concentration. See also Ref. 21.

These log *D* versus PXR data within two narrowly defined series **2a–k** and **3a–j** show the same trend as originally described by Gao et al.,[4] in that the introduction of polarity in the periphery of the molecule reduces transactivation of PXR. It is noteworthy that the correlation between log *D* and PXR does not hold true across different chemical series (e.g., compounds **2a** and **3a**).

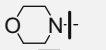
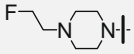
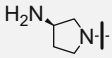
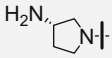
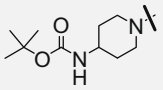
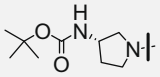
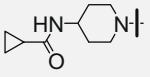
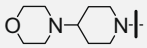
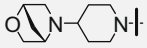
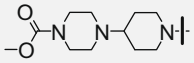
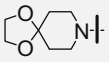
In these two series of compounds, exposed polarity strongly reduces oral exposure. While no compound combines the desired IGF-1R kinase potency with reduced PXR transactivation and sufficient oral exposure, the following observations are noteworthy. The chloropyrazol-compound **2a** has reduced protein binding (compared to **1**) and a remarkably high oral exposure (measured as area-under-the-curve of drug concentration in plasma over time after an oral dose of 20 mg/kg to mice, see Table 4). And among the imidazoles **3a**–**j** the chloro-methyl-imidazol **3e** appears to have the best combination of IGF-1R kinase potency with acceptable oral exposure and low protein binding (see Table 4).[12]

Subsequently, as an alternative approach to address CYP and PXR issues, variation of the left hand side of the molecule was also explored. The morpholine of **1** was replaced with more polar and larger groups, in an attempt to reduce CYP3A4 inhibition and PXR transactivation while maintaining IGF-1R kinase potency and oral exposure.[13,14] Introduction of a polar basic amine functionality in this portion of the molecule resulted in compounds with reduced CYP inhibition but also drastically reduced oral exposure. Polar non-basic groups showed less reduction of CYP3A4 inhibition but maintained better oral exposure.[13,14]

Most dramatically, replacing the morpholine of compound **1** with piperazine (**4a**) resulted in complete loss of PXR transactivation (see Table 3). Burying the polarity by N-methylating the piperazine (**4b**) brings back some PXR transactivation (24%), and the less basic, more sterically hindered fluoroethyl-amine **4c** is as strong a PXR transactivator as the morpholine **1**. Within this limited series lower PXR transactivation correlates with less CYP3A4 inhibition.

The basic terminal nitrogen of compounds **4a–c** is almost fixed in space, does not have the flexibility to seek a favorable interaction with a ligand binding site. Rotation around the bond between C6 of the benzimidazole and the proximal piperazine nitrogen does not alter the position of the distal piperazine nitrogen. In contrast, the basic nitrogen of the closely related amino-pyrrolidines **4d** and **4e** can access different regions of the PXR ligand binding site and both enantiomers are much stronger PXR transactivators then **4a** and **4b**. The same observation is repeated comparing the carbamates **4f** and **4g**. The more flexible, non-linear *N*-BOC-aminopyrrolidine **4g** can find a favorable interaction with the hPXR protein or avoid a steric constraint, and therefore transactivates much stronger (55%) then the straight, less flexible but equally polar *N*-

Table 3
IGF-1R kinase, CYP3A4 and PXR data of compounds **1**, **4a–l**

Cmpd	R^5	IGF[a] (nM)	CYP[b] (μM)	PXR[c] (%)
1		100	0.5	90–123
4a		32	3.0	1
4b		18	3.5	24
4c		32	0.8	120
4d		71	18.0	113
4e		42	>4.4	44
4f		330	16	0
4g		410	>13	55
4h		50	0.7	1
4i		45	1.7	3
4j		29	0.5	2
4k		82	3.5	1
4l		75	0.7	102

[a] IGF-1R Kinase IC_{50}.
[b] CYP3A4 inhibition, 7-benzyloxy-4-trifluoromethylcoumarin was used as probe molecule.
[c] % Transactivation of PXR receptor, compared to Rifampicin at 10 μmol/l concentration. See also Ref. 21.

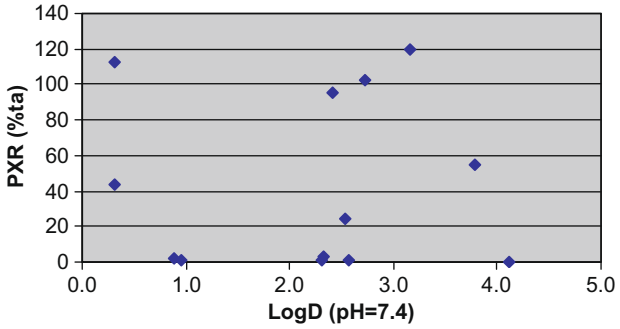


Figure 3. PXR transactivation as a function of log *D* for compounds **1**, **4a–l**.

BOC-aminopiperidine **4f** (0%). The corresponding amides (e.g., **4h**) also do not transactivate hPXR, despite being strong CYP3A4 inhibitors.

In an attempt to balance oral exposure with reduced CYP3A4 inhibition,[13] bicyclic substituents with a moderately basic amine nitrogen were explored (e.g., compounds **4i–k**). None of these compounds have significant PXR transactivation. The less polar, non-basic spiroketal **4l**, with it's two rings orthogonal, is a strong PXR transactivator, confirming that size alone is not the reason why **4f** and **4h–k** do not transactivate hPXR.

These data suggest (in agreement with Ref. 4) that this pocket of the ligand binding site of hPXR prefers lipophilic substituents but can accommodate polar substituents if they have sufficient rotational freedom to find a favorable interaction with one of the eight polar amino acids in the binding site. In contrast, the binding (and the required de-solvation) of polar rigid substituents is energetically unfavorable. [An alternative explanation is that the corresponding PXR + ligand complex forms but does not transactivate.]

PXR transactivation data for the more diverse compounds **1**, **4a–l** in Table 3 (compared to Tables 1 and 2) do not show an obvious correlation with calculated hydrophobicity nor with CYP inhibition data, in agreement with Redinbo's observation that PXR ligands do not cluster in a particular *clog P* region[2] (Fig. 3).

Several of the above compounds have promising pharmacokinetic properties (reduced CYP3A4 inhibition, reduced PXR transactivation or good oral exposure; see Refs. 10–14) but none of them combines all the required properties with the required IGF-1R kinase potency.

The next logical step was to combine the polar and rigid 'left hand pieces' of compounds that do not transactivate PXR (e.g., **4i**, **4k**) with the pyrazolylethyl- and imidazolylethyl-side chains of compounds **2a** and **3e** that had shown reduced protein binding and sufficient oral exposure.

As reported previously for compound **4k**,[13] formally replacing the morpholine group of compounds **2a** and **3e** with the bicyclic carbamate fragment to make compounds **5** and **6** (see Fig. 4 and Table 4) does not negatively impact the kinase or cell potency against the engineered IGF-Sal cell line.[15] The chloro-pyrazole compounds (**2a** and **5**) show lower kinase inhibition (higher IC_{50}'s) and higher protein binding then the corresponding chloro-imidazoles (**3e** and **6**), but significantly better oral exposure. Their potency in the IGF-Sal cell proliferation assay is identical within the accuracy of the assay. The large, hydrophilic and non-flexible piperazino-piperidine substituent (as shown above for **4k**) eliminates hPXR transactivation of **5** and **6**.

One of the limitations of the earlier compounds is their high protein binding (>99% for **1**). Replacing the phenethylamine fragment of compound **1** with heteroarylethylamines significantly increased the free fraction of compounds **2a** and **3e** in human plasma to 1.7% and 5.9%, respectively.[12] Protein binding is generally lower for the piperazino-piperidines **4k, 5, 6** (compared to

Table 4
IGF-1R kinase IC_{50}s of compounds **1**, **2a**, **3e**, **4k**, **5** and **6**, cell potency and selected pharmacokinetic data

Compd	IGF-1R[a] (nM)	IGF-Sal[b] (nM)	CYP 3A4[c] (μM)	PXR%TA[d]	AUC[e] (μM h)	%PB[f]
1	100	110	0.5	90–123	51	99.6
2a	120	376	2.1	147	90	98.3
3e	38	336	1.9	25	8.2	94.1
4k	82	77	3.5	1	11	>98
5	86	279	1.0	1	52	96.7
6	19	222	0.7	1	48	89.0

[a] IGF-1R Kinase IC_{50}.
[b] Cellular IC_{50}, measured via thymidine incorporation.
[c] CYP3A4 inhibition, 7-benzyloxy-4-trifluoromethylcoumarin was used as probe molecule.
[d] % Transactivation of PXR receptor, compared to Rifampicin at 10 μmol/l concentration. See also Ref. 21.
[e] Area under the curve for plasma concentration of compound versus time, interval 0–4 h, after oral administration of 20 mg/kg to mice.
[f] % Protein binding in human plasma.

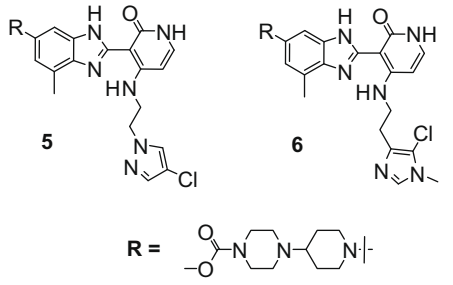
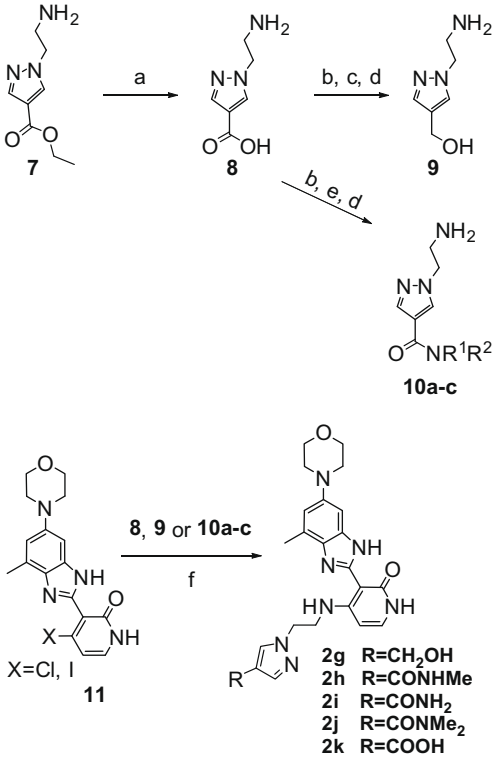


Figure 4. Structures of compounds **5** and **6**.

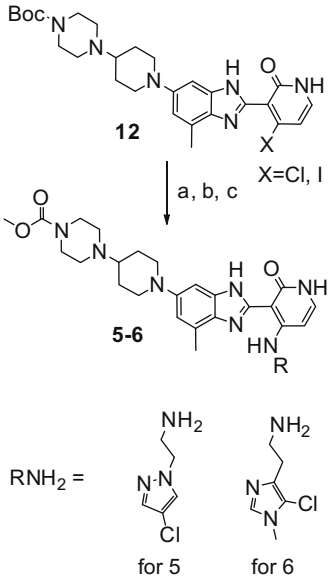
morpholine-analogs **1**, **2a**, and **3e**) and within this series, the same trend can be seen as described above. The phenethylamine **4k** has a free (unbound) fraction of ~1–2%, whereas the heteroaryl analogs **5** and **6** have unbound fractions of 3.3% and 11%, respectively (see Table 4). This significant improvement in protein binding warranted further in vivo studies.

Drug concentration in plasma (measured as area-under-the-curve of drug concentration in plasma over time after an oral dose of 20 mg/kg to mice) was found to be moderate for compound **4k** (see Table 4) and high for compounds **5** and **6**, despite the high molecular weight of these compounds (620, 594, and 608 Da, respectively).

Finally, compounds **5** and **6** were evaluated in different mouse tumor xenograft models. While both compounds **5** and **6** showed ~100% tumor growth inhibition[23] (TGI) at 100 mg/kg dosed once a day for 14 days in the constitutively activated IGF-Sal tumor model,[15] only compound **6** inhibited tumor growth at 50 mg/kg (65% TGI), whereas **5** (30% TGI) was not efficacious at this lower dose.



Scheme 1. Synthesis of compounds **2g**–**k**. Reagents and conditions: (a) 1 M aq HCl, 12 h, 90 °C; (b) BOC_2O, Et_3N, CH_2Cl_2, 1 h, 20 °C; (c) BH_3, THF, 1.5 h, 20 °C; (d) 4 M HCl/dioxane, 1 h, 20 °C; (e) EDC, HOBt, NR^1R^2H, 18 h, 20 °C; (f) amine **8**, **9** or **10**, Huenig's base, DMSO, 80 °C 16 h.



Scheme 2. Synthesis of compounds **5** and **6**. Reagents and conditions: (a) $\mathbf{RNH_2}$, Huenig's base, CH_3CN, 80 °C 16 h, 75%; (b) CF_3COOH, CH_2Cl_2, 20 °C; (c) CH_3OCOCl, Huenig's base, MeOH, 0–20 °C, ~80%.

Efficacy was also observed in the Colo205 human colon carcinoma model. Compounds **5** and **6** are both active at 100 mg/kg qd dosing, compound **6** is also active at 50 mg/kg. The less sensitive GEO human colon carcinoma model showed a moderate response (~60% TGI) for both compounds **5** and **6** at 100 mg/kg on a QD × 14 day dose schedule, whereas 200 mg/kg doses of both compounds are toxic.

Conclusions: In summary, we report two in vivo active IGF-1R inhibitors (compounds **5** and **6**) and discuss a successful SAR optimization strategy away from PXR transactivation, which we expect to be of general interest to many medicinal chemists.

Further studies of compounds **5** and **6** led to the discovery that both compounds, despite not showing significant PXR transactivation still induce CYP3A4 mRNA in human hepatocytes. Further studies into the mechanism of this non-PXR induction are underway and will be published soon.

Chemistry: The syntheses of compounds **1**,[10] **2a**–**f**,[12] **3a**–**j**,[12] **4a**–**c**,[14] **4f**,[13] and **4h**–**l**[13] have been described in our previous publications. Compounds **2g**–**k** are available from **7**[12] via borane reduction (for **2g**) or ester saponification (for **2k**) and amide bond formation (for **2h**–**j**), followed by S_NAr reaction with **11** (Scheme 1).[12]

Compounds **4d, 4e**, and **4g** were easily accessed following the synthetic route as described for **4f**,[13] using commercially available 3-BOC-aminopyrrolidine. The synthesis of compounds **5** and **6** followed the route shown in Scheme 2. Intermediate **12**[13] was reacted with the heteroarylethylamine components[12] in acetonitrile at 80 °C. Cleavage of the BOC protecting group and methyl carbamate formation following standard methods gave access to the target compounds in high yields.

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