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Bioorganic & Medicinal Chemistry Letters 13 (2003) 1927–1930

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

6,7-Dihydroxyisoquinoline-3-carboxylic Acids are Potent Inhibitors on the Binding of Insulin-Like Growth Factor (IGF) to IGF-Binding Proteins: Optimization of the 1-Position Benzoyl Side Chain

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Received 29 October 2002; accepted 11 February 2003

Abstract—A series of 1-benzoyl isoquinolines, based on compound **1**, was synthesized and evaluated for their ability to displace IGF-I from its complex with IGF–binding protein-3. Successful modifications of **1** included the replacement of the 3,4-dihydroxybenzoyl group with a substituted benzyl group. These alternations culminated in the discovery of compounds such as **7o** which had excellent in vitro potency ($K_i = 9.4$ nM) but with one less of the labile catechol functionality of **1**.

The insulin-like growth factors (IGF-I and II) are small polypeptide hormones regulating cell proliferation, cell differentiation, cell death, and cell metabolic activities.[1] In blood and interstitial fluids, including the cerebrospinal fluid, the concentration of freely circulating IGF is exceedingly low because most of the IGFs are bound to one or more of six high affinity IGF-binding proteins (IGFBPs), which inhibit their interaction with the IGF-I receptor.[2] The major binding protein in circulation is IGFBP-3, which together with an acid labile subunit forms a trimolecular complex with IGF to sequester most of the IGFs in blood.[3]

An orally active compound that can potentiate the action of endogenous IGF-I could be the use of a small molecule ligand that displaces the bound IGF-I from the large pool of IGF/IGFBP complexes in the body fluids. Recently we reported the discovery of isoquinoline-3-carboxylic acids and 3-hydroxy isoquinolines as the first potent non-peptidyl IGF-BP inhibitors (Fig. 1).[4] Notable discoveries within the isoquinoline class included

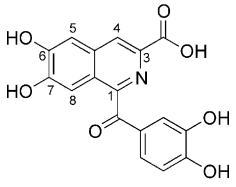

Figure 1. **1**: $K_i = 5.6$ nM.

the potency enhancing 3-carboxylic group and the 1-(3,4-dihydroxybenzoyl) substituents. Methylation of one or more of the four hydroxy groups of compound **1** as a replacement for the metabolically labile catechol group resulted in less active analogues.[5] Isoquinoline **1** was characterized as having excellent in vitro potency in both binding and functional assays.

Despite these favorable characteristics, the in vivo duration of action and blood–brain barrier penetration ability ($< 5\%$) of isoquinoline **1** was low. We attributed this property in part to high polarity caused by the two catechol groups and the carboxylic functionality. To decrease the overall polarity of the molecule, we had already discovered that the 3-carboxylate could be replaced by a less polar hydroxy group with only 5-fold

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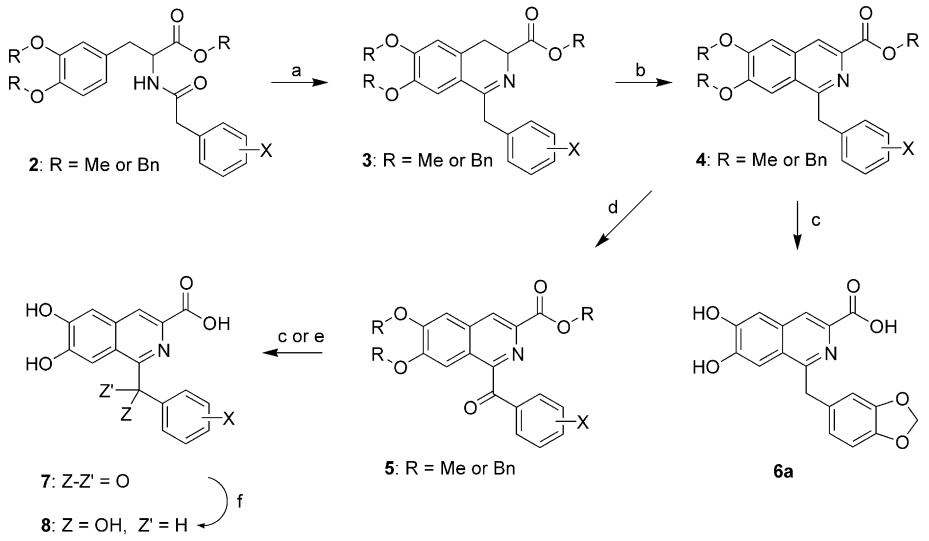
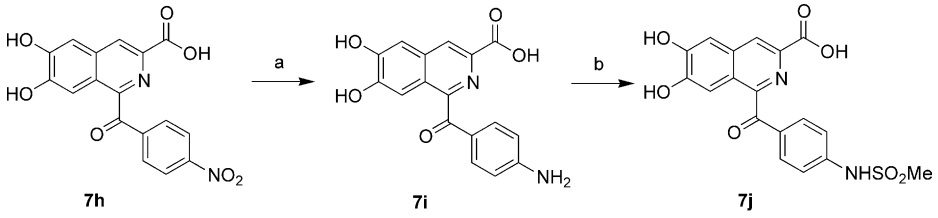
doi:10.1016/S0960-894X(03)00321-4



Scheme 1. Reagents and conditions: (a) $POCl_3$/reflux; (b) S/heat; (c) 48% HBr/reflux; (d) SeO_2/AcOH/reflux; (e) $PdCl_2H_2$/MeOH; (f) $NaBH_4$/MeOH.



Scheme 2. Reagents and conditions: (a) Pd-C/H_2/MeOH; (b) $MeSO_2Cl/Et_3N/CH_2Cl_2$.

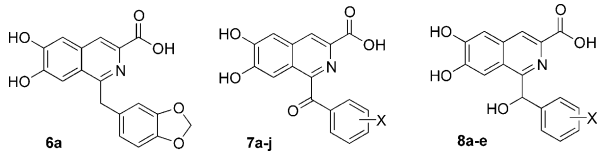
loss in activity. To further improve this lead, we studied the structure–activity relationships of the two catechol sites. In this paper, we present the SAR results from a series of replacement of the 1-(3,4-hydroxybenzoyl) group for optimization of this class of compounds, which were determined in a binding assay using ^{125}I-IGF-I and IGF-BP3.[4]

The isoquinoline core of **7** (Scheme 1) was synthesized by cyclization of *N*-phenethyl amides **2** in the presence of $POCl_3$ at reflux, followed by dehydrogenation with an oxidative procedure to give isoquinolines **4**.[6] When R was a methyl group in **4,** deprotection was accomplished in 48% HBr at reflux to give benzyl compound **6a**. Oxidation of isoquinolines **4** with selenium dioxide in refluxing acetic acid afforded the corresponding ketones **5** which were deprotected to give compounds **7**. When the catechol and acid groups were protected by a benzyl moiety, compounds **5** were subjected to either a palladium chloride catalyzed hydrogenation, or acid catalyzed hydrolysis. Using hydrogenation the alcohol **8** was also isolated in some cases, which could also be obtained from the reduction of compounds **7** with sodium borohydride (Scheme 1).

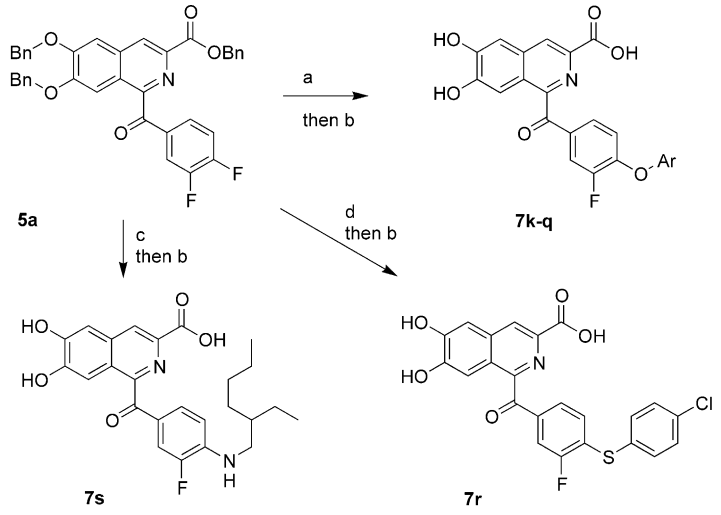
The 4-nitrobenzoyl isoquinoline **7h** was reduced to the corresponding amine **7i** with palladium catalyzed hydrogenation, and mesylation of **7i** afforded the sulphonamide **7j** as showed in Scheme 2. A number of aryloxy derivatives **7k-q** were synthesized by a substitution reaction of 3,4-difluorobenzoyl compound **5a**, as outlined in Scheme 3. The para-fluoride of **5a** was also replaced by thiophenol and alkylamine to give compounds **7r** and **7s**, respectively.

The synthesis of 6-amino-7-hydroxyisoquinolines **14–16** is described in Scheme 4. Attempt to cyclize *N*-3-nitro-

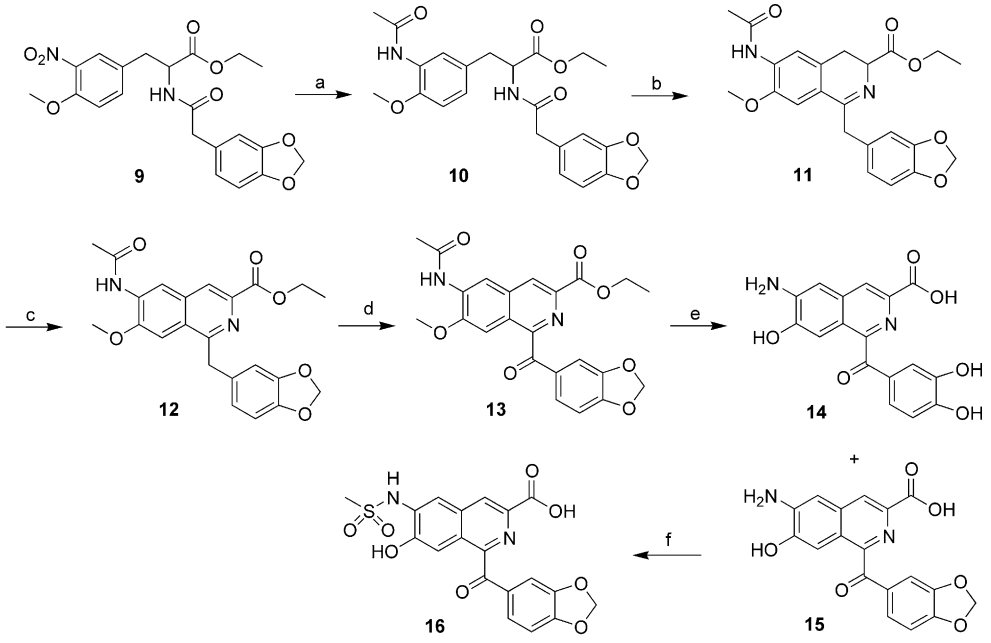
Table 1. SAR at the 1-position of quinolines **6**, **7** and **8**



Compd	X	hIGFBP-3 K_i (nM)
1	3,4-$(OH)_2$	5.6±0.5
6a	3,4-OCH_2O–	72±10
7a	3,4-OCH_2O–	70±24
7b	2,4,6-Me_3	100±100
7c	2-Cl	110±34
7d	3-F	110±18
7e	4-CF_3	38±8
7f	3,4-F_2	51±18
7g	3,4-Cl_2	29±5
7h	4-NO_2	32±1
7i	4-NH_2	130±59
7j	4-$NHSO_2Me$	110±77
8a	4-PhO	32±22
8b	2,4,6-Me_3	11±6
8c	2-Cl	25±20
8d	3-F	24±7
8e	4-CF_3	18±3



Scheme 3. Reagents and conditions: (a) ArOH/*t*BuOK/THF; (b) 48% HBr/reflux; (c) ArSH/ACN/Δ; (d) $Me(CH_2)_3CH(Et)CH_2NH/\Delta$.

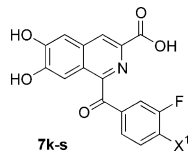


Scheme 4. Reagents and conditions: (a) Pd/C-H_2/MeOH; (ii) Ac_2O/heat; (b) $POCl_3$/reflux; (c) S/heat; (d) SeO_2/AcOH/reflux; (e) 48% HBr/reflux; (f) $MeSO_2Cl/Et_3N/CH_2Cl_2$.

4-methoxylphenethylamide **9** was unsuccessful, so compound **9** was first converted to the acetylamino analogue **10**, which was then subjected to an acid catalyzed cyclization, followed by oxidation to give compound **13**. Hydrolysis of **13** in 48% HBr at reflux gave the desired amino compound **14** and a partially hydrolyzed by-product **15**. The later was converted to the corresponding sulphonamide **16**.

In our efforts to improve physicochemical properties of this class of compounds for potential in vivo biological activities we have prepared a series of substituted benzoyl isoquinolines (**7a–s**) without one of the labile catechol groups of **1**. In our initial series, compound **7a**, which has the catechol masked by a methylene group, showed good activity ($K_i = 70$ nM). The corresponding benzyl analogue **6a** had the same potency ($K_i = 72$ nM), indicating the carbonyl group played a limited role in binding. While the 2,4,6-trimethyl-, 2-chloro- and 3-fluorobenzoyl analogues had no improvement in potency (**7b**, **7c** and **7d**, $K_i = 100$, 110 and 110 nM, respectively), a strong electron-withdrawing group, such as trifluoromethyl and nitro, at the *para*-position of the benzoyl group increased activity 3-fold (**7e** and **7h**, $K_i = 38$ and 32 nM, respectively). When the 4-nitro group of **7h** was reduced to the electron-donating amine the potency of compound **7i** decreased about 4-fold to 130 nM. Mesylation of compound **7i** gave the corresponding sulfonamide **7j**, which did not increase activity ($K_i = 110$ nM). This result suggests that an acidic proton, such as phenol in **1**, at this position may not be needed for high potency (Table 1).

Table 2. SAR of substituted 1-(3-fluorobenzoyl) isoquinolines and related compounds **7k–s**



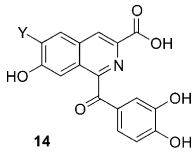
7k-s

Compd	X^1	hIGFBP-3 K_i (nM)
7k	3-ClPhO	11±9
7l	4-ClPhO	20±0.4
7m	3,4-Cl_2PhO	12±6.6
7n	3,5-Cl_2PhO	9.0±5.6
7o	4-MePhO	9.4±8.0
7p	4-CF_3PhO	32±24
7q	4-PhPhO	32±8
7r	4-ClPhS	31±10
7s	$Me(CH_2)_3CH(Et)CH_2NH$	62±21

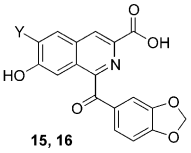
Unexpectedly, the alcohol compounds **8** obtained from reduction of the corresponding ketone (**7b–e**) showed much improved activities. For example, compound **8b** (K_i = 11 nM) had 10-fold increase in activity over **7b** (K_i = 110 nM). Compounds **8c–d** all showed good activities. Encouraged by these initial results we further expanded the SAR to investigate more lipophilic substituents. Thus chlorine substituted phenoxyphenyl derivatives **7k–7n** had K_i values between 9 and 20 nM (Table 2). The 4-methylphenoxy analogue **7o** also showed very good activity (K_i = 9.4 nM), while the 4-trifluoromethyl and 4-pheny compound **7p** and **7q** were about 3-fold less potent (both had K_i values of 32 nM). Finally, Replacement of the aryloxy group with phenylthio (compound **7r**) or alkylamino (compound **7s**) also resulted in active compounds (K_i = 31 and 62 nM, respectively). All these results demonstrated that a lipophilic group at the 1-position of the isoquinoline core is favored for high potency (Table 3).

Based on the successful modifications of the 3,4-dihydroxybenzoyl group of **1**, we next initiated the investigation on the possibility of replacing the catechol moiety on the isoquinoline ring. Compound **14**, where the 6-hydroxyl group of compound **1** was replaced by an amino group, showed promising activity (K_i = 60 nM), while the methylenedioxy derivative **15** was 10-fold less active in comparison with **7a** (K_i = 70 nM). Further sulfonylation of **15** resulted in an inactive compound **16**, which certainly was unexpected since we designed the sulfonamide to mimic the hydroxy group. One explanation for this result is that the sulfonamide might be too bulky to mimic a much smaller hydroxy group.

Table 3. SAR of 6-aminoisoquinoline derivatives **14–16**



14



15, 16

Compd	Y	hIGFBP-3 K_i (nM)
14	NH_2	60±29
15	NH_2	850±790
16	$NHSO_2Me$	>10,000

In conclusion, we have demonstrated that the catechol moiety at 1-position of the isoquinoline core **1** can be replaced with a series of lipophilic benzoyl, benzyl and α-hydroxybenzyl group while maintaining IGF-BP inhibitory activity. In addition, an attempt to mimic the 6-hydroxy isoquinoline with sulfonamide was not successful. In this study, 3,5-dichlorophenoxybenzoyl isoquinoline **7n** was a potent IGF-BP inhibitor with much less polar characteristics (clog$P$ = 6.0) than compound **1** (clog$P$ = 1.7).[7] Further investigation on the optimization of this series toward blood–brain barrier penetration will be reported in due course.

References and Notes

1. (a) For recent reviews, see: Roith, D. L.; Bondy, C.; Yakar, S.; Liu, J.; Butler, A. *Endocr. Rev.* **2001**, *22*, 53. (b) Jones, J. I.; Clemmons, D. R. *Endocr. Rev.* **1995**, *16*, 3.
2. (a) Shimasaki, S.; Ling, N. *Progress in Growth Factor Res.* **1992**, *3*, 243. (b) Shimasaki, S.; Shimonaka, M.; Zhang, H.; Ling, N. *J. Biol. Chem.* **1991**, *266*, 10646.
3. Leong, S. R.; Baxter, R. C.; Camerato, T.; Dai, J.; Wood, W. I. *Mol. Endocr.* **1992**, *6*, 870.
4. Liu, X.-J.; Xie, Q.; Zhu, Y.-F.; Chen, C.; Ling, N. *J. Biol. Chem.* **2001**, *276*, 32419.
5. Chen, C.; Zhu, Y.-F.; Liu, X.-J.; Lu, Z.-X.; Xie, Q.; Ling, N. *J. Med. Chem.* **2001**, *44*, 4001.
6. Redel, J.; Bouteville, A. *Bull. Soc. Chim. Fr.* **1949**, 443.
7. The program Pallas from CompuDrug Ltd was used to calculate the log$P$ value.