Organic Process Research & Development **2009,** *13,* 456–462

Development of Scaffold Synthesis for the Preparation of New Insulin-Like Growth Factor 1 Receptor Inhibitors

Ilaria Candiani, Germano D'Arasmo,* Franco Heidempergher, and Attilio Tomasi

Pharmaceutical Science Department, Process Research and Development Group, Nerviano Medical Sciences S.r.l., via Pasteur 10, 20014 Nerviano, Italy

Abstract:

The synthesis of new insulin-like growth factor 1 receptor (IGF-1R) inhibitors is reported. The described molecules have a new sulfonyl-indazole structure. We describe the process research and development for the scaffold synthetic procedure in order to provide the large amount of product required for lead optimization, candidate selection, and preclinical studies.

Introduction

The insulin-like growth factor 1 receptor (IGF-1R) is a member of the insulin receptor subfamily of receptor tyrosine kinases (RTKs) and it is expressed in a wide variety of cell types. IGF-1R mature protein consists of two alpha chains, which are extracellular and contain ligand-binding function, and two beta chains, which span the cell membrane and contain the intracellular kinase domain. Binding of its cognate ligands, IGF-1 and IGF-2, to the extracellular domain of the receptor triggers the activation of the intracellular tyrosine kinase domain and receptor autophosphorylation. The activated receptors have potent mitogenic, motogenic, and anti-apoptotic activity in a wide range of cell types. There is much evidence linking increased IGF-1R signaling to the development and progression of cancer; up-regulated levels of both the receptors and their ligands have been observed in a variety of human tumors, particularly in association with pathological events such as invasion and metastasis.

A research effort within the IGF-1R kinase inhibitor program[1] at Nerviano Medical Sciences resulted in identification of sulfonyl-indazole derivatives showing interesting activity. Chemical expansion led to the identification of IGF-1R kinase inhibitors with potent in vitro, cellular, and in vivo activity. The selected subfamily **3**, see Figure 1, consists of an indazole-like scaffold **1** and a substituted benzoic moiety **2** condensed as a side chain.

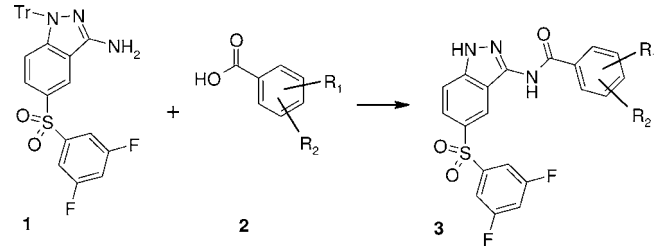


Figure 1. **Subfamily compounds.**

In a typical Medicinal Chemistry approach synthesis consisted of three phases: preparation of the two key intermediates and coupling to assemble the final molecule **3**. This afforded the flexibility of exploring a variety of side chains to optimize pharmacokinetics properties. In view of the need for higher amounts of compound for full preclinical characterization, and possible successive development of the subclass, we undertook evaluation of the synthetic procedure for **1** with the objective of delivering a safe, robust, and reliable process suitable for pilot-plant scale.

The original laboratory-scale procedures involved a number of steps with conditions unsuitable for scale-up (e.g., using concentrated hydrazine, low-yield reactions, etc.), and thus workup and purification steps needed to be highly improved. According to this strategy we initiated investigation of synthetic routes for scaffold preparation.

Results and Discussion

The original synthetic route utilized 5-fluoro-2-nitrobenzoic acid and 3,5-difluorobenzenesulfonylchloride as starting materials as highlighted in Scheme 1. Common reactions had been used to convert the carboxylic acid into a cyano group, while the sulfonylchloride was reduced[2] to a thioderivative.

Economic and practical considerations prompted us to purchase 5-fluoro-2-nitrobenzonitrile **2** and 3,5-difluorothiophenol **3** from suppliers (e.g., the reduction of **13** which occurs via Vilsmeyer iminium salt formation proceeded with very low yield). The starting material **3** must be stored in a nitrogen atmosphere since its thio group is prone to oxidation. We followed the shortest synthetic route, as reported in Scheme 2.

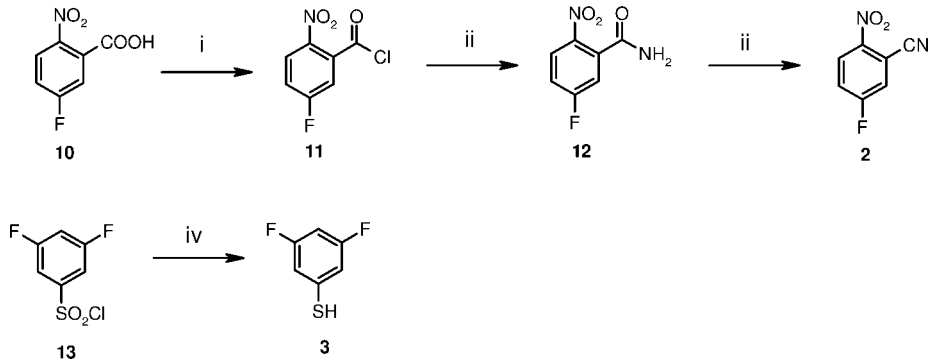
* To whom correspondence should be addressed. E-mail: germano.darasmo@yahoo.it.

(1) (a) Bandiera, T.; Lombardi Borgia, A.; Nesi, M.; Perrone, E.; Bossi, R.; Polucci, P. Indazole derivatives as kinase inhibitors for the treatment of cancer. WO/2008/074749 A1, 2008. (b) Fancelli, D. Pulici, M.; Moll, J.; Bandiera, T. Preparation of 1H-furo[3,2-*c*]pyrazole-5-carboxamide derivative as protein kinase inhibitors. WO/2007/138017, 2007. (c) Bandiera, T.; Lombardi Borgia, A.; Polucci, P.; Villa, M.; Nesi, M.; Angiolini, M.; Varasi, M. Substituted pyrazolo[4,3-*c*]pyridine derivatives as tyrosine kinase inhibitors, particularly IGF-1R inhibitors, their preparation, pharmaceutical compositions, and use in therapy. WO/2007/068619, 2007. (d) Bandiera, T.; Lombardi Borgia, A.; Orrenius, S. C.; Perrone, E.; Beria, I.; Fancelli, D.; Galvani, A. Substituted pyrrolopyrazole derivatives as tyrosine kinase inhibitors, their preparation, pharmaceutical compositions, and use in therapy. WO/2007/068637, 2007. (e) Fancelli, D.; Moll, J.; Pulici, M.; Quartieri, F.; Bandiera, T. Preparation of 1H-thieno[2,3-*c*]pyrazoles as kinase, particularly Aurora kinases and IGF-1R inhibitors for treating cancer. WO/2007/009898, 2007.

(2) Hiromi, U.; Susumu, K. *Tetrahedron Lett.* **1999**, *40*, 3179–3182.

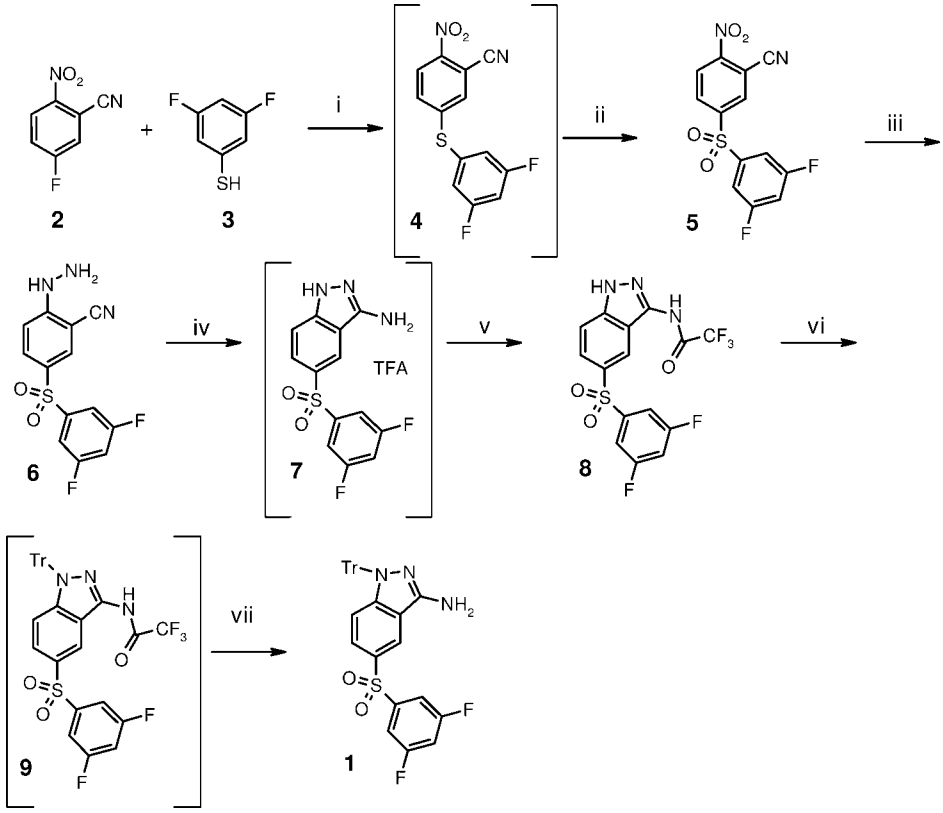
10.1021/op8002536 CCC: $40.75
Published on Web 01/21/2009

Scheme 1. **Original synthetic route**[a]



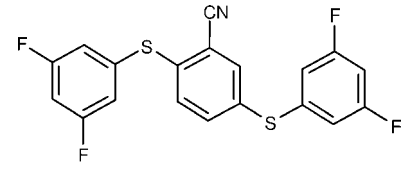
[a] Reagents and conditions: i) $SOCl_2$ (5.0 equiv), $DMF_{cat.}$, 85 °C, 2 h; ii) Dioxane, NH_3 aq 33% (2.0 equiv); iii) $POCl_3$ (4.0 equiv), 60 °C, 18 h; iv) solution of: dimethyldichlorosilane (3.5 equiv), DCM, Zn, plus DMAc (3.0 equiv), reflux 1 h and 50 °C 16 h.

Scheme 2. **New synthetic route**[a]



[a] Reagents and conditions: i) EtOAc, DIPEA (1.05 equiv), 0 °C to rt, 0.5 h; ii) MeCN, water, Oxone (2.5 equiv), 40 °C to rt, 24; iii) THF, N_2H_4 35%, rt; iv) THF, TFA, 5 °C, 15 min; v) DCM, TFAA; vi) DCM, TrCl, TEA, rt, 4 h; vii) MeOH, TEA, refluxed, 5h.

In the original procedure the nucleophilic attack of **3** to **2** was performed in heterogeneous conditions[3] by using cesium carbonate (Cs_2CO_3). A tetrahydrofuran (THF) solution of **3** was added to a −40 °C solution of **2** and reacted at room temperature overnight. Workup involved replacement of solvent with dichloromethane (DCM), filtration to eliminate possible residual salts, and washing with brine prior to product isolation by evaporation to dryness. The low temperature was recommended for regioselective control, since both fluorine and nitro groups are activated and undergo nucleophilic substitution giving a significant amount of byproduct **14** formation (see Figure 2). The structure was confirmed by ^1H NMR characterization after chromatographic isolation. We investigated the reaction seeking best conditions to achieve minimization of **14**. Temperature,



14

Figure 2. **Byproduct.**

(3) (a) Ruhland, T.; Nielsen, S. D.; Holm, P.; Christensen, C. H. *J. Comb. Chem.* **2007**, *9* (2), 301–305. (b) Arora, V.; Salunkhe, M.; Sinha, N.; Sinha, R. K.; Jain, S. *Bioorg. Med. Chem. Lett.* **2004**, *14* (18), 4647–4650. (c) Beugelmans, R.; Chbani, M. *Bull. Soc. Chim. Fr.* **1995**, *132* (3), 290–305.

Table 1. **Different temperature addition**

entry	int. **2** (equiv)	*T* (°C)	int. **3** (equiv)	yield %	purity A% by HPLC	**14** (A%)
1	1.0	−40	1.00	95.5	98.6	0.24
2	1.0	−3	1.15	98.9	98.1	1.03
3	1.0	0	1.15	100.0	98.4	0.90
4	1.0	0	1.15	94.3	98.1	1.20
5	1.0	25	1.15	90.3	98.0	1.14

solvents, bases, and molar ratios were evaluated by experiments using the HEL parallel synthesis instrument, which allowed us to run four reactions simultaneously.

A set of reactions were made that compared the original procedure at different temperatures, the results of which are reported in the Table 1. We noted that the reaction reaches complete conversion within 2 h and 30 min, with no need to react overnight. Entries 2−5 show that the addition between −3 and 25 °C does not seem to significantly alter the content of **14**, the formation of which is actually more linked to the equivalent (equiv) of thiophenol used within the reaction. In entry 1, where we used 1.0 equiv it was significantly lower; Cs_2CO_3 was used in the ratio of 1.1 equiv for all experiments.

Additional tests were performed for base and solvent screening as reported in Table 2.

In entry 1 the reaction used for byproduct **14** isolation is reported. The use of DCM gave promising results in terms of yield and purity, achieving lower byproduct formation (see entry 3 versus entry 2). The calculated pK_a for 3,5-difluorothiophenol is 5.09 ± 0.11, which means that a strong base was not needed. Upon general consideration usually 4 log units between the acid and the base are sufficient to obtain a complete dissociation of the species. Literature[4] values show: pK_a *t*-BuOK (19), EtONa/MeONa (18), Na_2CO_3 (10), R_3N (10). It is possible to reduce the amount of cesium carbonate, and this represents a significant economic advantage; see entries 4 and 5. We considered the use of more economic carbonate and the switch to a homogeneous reaction in order to achieve a more efficient conversion. As shown in entry 6 the homogeneous reaction obtained using *N*,*N*-diisopropylethylamine (DIPEA) is faster and gives good yield and quality product. The use of cheaper carbonates does not appear to give a real advantage and notably results in a worse impurity profile, possibly due to the higher reaction time, see entries 7 and 8. These carbonates left a certain degree of unreacted starting material, whereas cesium carbonate worked quite well. This might be explained by the low polarity of DCM versus that of the THF used previously, and possibly by the potential impact of the particle size of the bases: Cs_2CO_3 is a very soft powder with very small grain/crystals, while other carbonates have larger particle size. In entry 9 we tested sodium carbonate (Na_2CO_3) with an ethyl acetate (EtOAc)/water solvent mixture in the attempt to speed up the reaction because of better dissolution of the carbonate (bearing in mind, however, that these two solvents are not completely miscible at alkaline pH). The reaction is in fact faster, but unreacted starting material is increased. This may be due to a moderate degradation of 3,5-difluorothiophenol in water (e.g., oxidation effects) limiting reaction completion. In entry 10 we further investigated the use of ethyl acetate as solvent. On a plant scale this solvent would offer at least two main advantages. First, being the top phase in the separation process allows quicker extraction (obviating the need for a second reactor) and also allows the reactor to be kept relatively dry. Second, DCM requires a very efficient condensation plant for recovery. Usually, the recovery ratio does not exceed 35−40% for DCM, while EtOAc could be recycled almost entirely. We focused on the homogeneous phase reaction because of the quicker reaction time. Following the positive results obtained, we decided to apply this synthetic procedure.

The HEL parallel synthesis apparatus also allowed us to obtain preliminary calorimetric data. Although the studies were not expressly designed for this purpose (and thus must be considered as indicative), a small exothermic effect was nonetheless observed when DIPEA was added, increasing with addition of thiophenol. The molar heat was estimated at 159.27 kJ or 38.10 kcal (based on dose of 1.76 g of 3,5-difluorothiophenol).

We moved to the following step for the oxidation of sulfide to sulfone, see Scheme 3. The intermediate **4** does not need to be isolated, and it can be used directly as solution in the oxidation process, with savings in time and resources. According to the original synthetic procedure, it was made by using HIO_4 (cat. Cr_2O_3). For obvious environmental issues and scale-up considerations, this oxidation reactant was abandoned. After having considered other reagents[5] (e.g., urea/H_2O_2,[6] H_2O_2[7]), we focused on investigating the use of Oxone[8] (potassium monopersulfate triple salt technical grade; $KHSO_5$ 47%) as oxidizing agent. Oxone has the main advantage of being an inexpensive reagent easily removed by workup, while it suffers from the drawback of the relatively high amount of product that it is necessary to use in relation to the oxygen content.

Different conditions of solvent, temperature, time, and molar ratio were investigated for Oxone; the results are reported in Table 3. Entry 1 shows that in *N*,*N*-dimethylformamide (DMF) the reaction is relatively fast, being virtually completed after 6 h. Moving to a mixture of water/ethyl acetate, entry 2, the sulfide is transformed relatively rapidly into the sulfoxide **4a**, but oxidation to sulfone **5** does not go to completion, as the reaction runs in heterogeneous phase. The addition of a phase transfer catalyst (i.e., Bu_4NBr) and an extra amount of fresh Oxone does not significantly improve the conversion. We needed to improve the workup because, when water is added, the product tends to crash out in lumps, trapping unreacted Oxone salts, see entry 3. Dissolution in organic solvent was

(4) Comer, J. *Chem. Br.* **1994**, 983–986.

(5) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Brown Ripin, D. H. *Chem. Rev.* **2006**, *106*, 2943–2989.

(6) Cooper, M.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533–535.

(7) (a) Shokrolahi, A.; Zali, A.; Pouretedal, H. R.; Mahdavi, M. *Catal. Commun.* **2008**, *9* (5), 859–863. (b) Bahrami, K. In *Regio- and stereocontrolled oxidations and reductions*; Roberts, S. M., Whitall, J., Eds.; Catalysts for Fine Chemical Synthesis, Vol. 5; Wiley: Chichester, England; Hoboken, NJ, 2007; pp 283−287. (c) Shaabani, A.; Rezayan, A. H. *Catal. Commun.* **2007**, *8* (7), 1112–1116. (d) Velusamy, S.; Kumar, A.; Saini, R.; Punniyamurthy, T. *Tetrahedron Lett.* **2005**, *46* (22), 3819–3822.

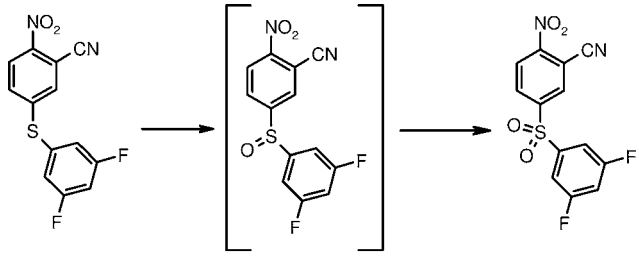
(8) (a) Ward, R. S.; Roberts, D. W.; Diaper, R. L.; Richard, L. *Sulfur Lett.* **2000**, *23* (3), 139–144. (b) Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. *J. Am. Chem. Soc.* **2000**, *122* (18), 4280–4285. (c) Llauger, L.; He, H.; Chiosis, G. *Tetrahedron Lett.* **2004**, *45* (52), 9549–9552.

Table 2. **Base and solvent screening**

entry	int. **2** (equiv)	int. **3** (equiv)	base (equiv)	yield %	purity A% HPLC	RRT[c]1.57 impurity	**14** (A% HPLC)	time (h)	not reacted int. **2**	solvent
1	1.0	2.0	Cs_2CO_3 (2.0)	–	20.0	–	80.0	4	–	THF
2	1.0	1.03	Cs_2CO_3 (1.05)	91.0	93.7	0.5	3.7	2	1.4	THF
3	1.0	1.03	Cs_2CO_3 (1.05)	94.3	98.9	0.12	0.7	2	0.2	DCM
4	1.0	1.0	Cs_2CO_3 (1.0)	92.6	98.5	–	0.4	2	1.0	DCM
5	1.0	1.0	Cs_2CO_3 (0.5)	93.2	97.4	0.3	0.7	2	1.5	DCM
6	1.0	1.0	DIPEA (1.0)	95.7	99.2	–	0.4	0[a]	0.3	DCM
7	1.0	1.0	K_2CO_3 (1.0)	94.6	94.6	2.32	0.6	23	2.3	DCM
8[b]	1.0	1.0	Na_2CO_3 (1.0)	51.1	74.8	5.0	–	28	19.7	DCM
9	1.0	1.0	Na_2CO_3 (0.5)	96.6	95.2	0.91	1.3	2	2.4	AcOEt/H_2O
10	1.0	1.0	DIPEA (1.0)	100.0	95.9	–	2.3	0[a]	1.6	AcOEt

[a] The reaction was instantaneous. [b] Stirring problem experienced. [c] Related to instability of thiophenol derivate (e.g., oxidation process), HPLC method no.1.

Scheme 3. **Oxidation to sulfone**



required in order to efficiently wash the product with a reducing agent (e.g., $Na_2S_2O_5$ or Na_2SO_3) for neutralization of remaining oxidant.

Unfortunately, when using methanol/water (entry 4) again the reaction was incomplete; the ratio between **4a** and **5** was 30:65, possibly due to poor solubility or heterogeneous conditions. In entries 5 and 6 the effect of different reaction temperatures using acetone/water are compared. Despite the fact that both reactions were incomplete (a significant amount of sulfoxide remained), we observed during HPLC monitoring that at 40 °C the reaction was very fast in the early stage and probably stopped because Oxone started to decompose. The main impurity in this step is the one reported as RRT 1.24 min. By HPLC study we saw that this is related to the synthesis of **4** because of the formation in this step of the double nucleophilic substitution byproduct **14**. When sulfide with a high level of **14** is used, a high level of the impurity RRT 1.24 min is obtained (e.g., see entries 4 and 5). In fact, not surprisingly it can go through the process generating oxidized compounds such as the disulfoxide **15**, see Figure 3, or sulfide-sulfoxide, etc. As yet, we have not isolated this impurity, but in entry 7 we applied the same conditions as for entry 5 using a cleaner intermediate **4**, and we obtained confirmation of our hypothesis.

We achieved a breakthrough in the oxidation step when using a mixture of acetonitrile/water as solvent. Running the reaction at 40 °C we obtained virtually complete conversion, see entries 8, 9, and 10, with a good yield and impurity profile. In this set of reactions we optimized the amount of Oxone to 2.5 equiv and the workup procedure throughout ethyl acetate extraction and deep washing to neutralize and eliminate residual salts.

As in the previous step we made a gross calorimetric evaluation (entry 10) by using HEL parallel synthesis. By adding Oxone in water an endothermal response was detected. Next, addition of a solution of **4** in acetonitrile was performed. The exothermal effect of the oxidation process seemed to be balanced and compensated for by the endothermal response to the water/acetonitrile mixing. Overall this reaction showed an endothermic behaviour. Although values must be considered as only indicative, the molar heat was estimated at −93.34 kJ or −22.33 kcal (based on 1.0 g of **4**).

With intermediate **5** in hand we moved to formation of the indazole ring. The synthesis went through a nucleophilic substitution of the nitro group by hydrazine[9] followed by ring-closure[10] involving the cyano group as reported in Scheme 4.

The preparation of **6** was pursued by employing the safer 35% hydrazine (N_2H_4) in water at room temperature instead of the N_2H_4 1.0 M in THF as in the original procedure. Following the quench in water the hydrazine derivative precipitated and was isolated by simple filtration. Although the nitro group, being doubly activated by cyano and sulfonyl groups, was readily displaced, the evolving nitrite salt was deleterious to the 2-hydrazino intermediate. The reaction run in methanol or butanol gave the indazole in moderate yield (no more than 60%) and in low-purity grade. The nature of the solvent is crucial; in alcohols the reaction is extremely slow at room temperature (rt) (and dirty upon heating), while in DMF complete degradation occurs from even −78° to rt. We found THF to be a good compromise: addition of hydrazine hydrate to diluted THF solutions of **5** usually brought complete conversion to **6** accompanied by variable amounts of the final indazole (cyclization is catalyzed by acids, even by silica upon TLC). Eliminating any nitrite salt before acidification is of crucial importance, since nitrous acid rapidly converts the intermediate 2-hydrazinonitrile to the corresponding 2-azidonitrile. The cake of **6** on the filter must be washed thoroughly with water. THF is the same solvent used in the next step. In comparison with the original procedure we also modified the order of addition of the starting material **5** solution. It was dropped into the solution of N_2H_4 to avoid the risk of producing the dimer **6a** (see Figure 4). The crude, typically obtained with a 96% yield,

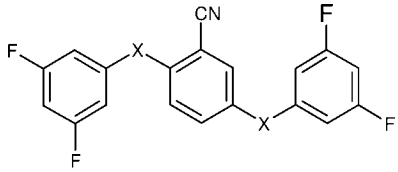
(9) (a) Lokhande, P. D.; Raheem, A.; Sabale, S. T.; Chabukswar, A. R.; Jagdale, S. C. *Tetrahedron Lett.* **2007**, *48* (39), 6890–6892. (b) Suryakiran, N.; Prabhakar, P.; Venkateswarlu, Y. *Chem. Lett.* **2007**, *36* (11), 1370–1371.

(10) (a) Shirtcliff, L. D.; Hayes, A. G.; Haley, M. M.; Köhler, F.; Hess, K.; Herges, R. *J. Am. Chem. Soc.* **2006**, *128* (30), 9711–9721. (b) Yakaiah, T.; Lingaiah, B. P. V.; Narsaiah, B.; Shireesha, B.; Ashok, K. B.; Gururaj, S.; Parthasarathy, t.; Sridhar, B. *Bioorg. Med. Chem. Lett.* **2007**, *17* (12), 3445–3453. (c) Lukin, K.; Hsu, M. C.; Fernando, D.; Leanna, M. R. *J. Org. Chem.* **2006**, *71* (21), 8166–8172.

Table 3. **Oxidation screening conditions**

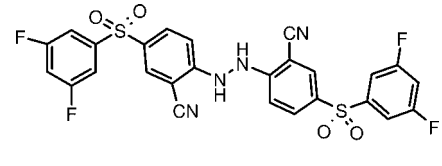
entry	**4** (equiv)	Oxone (equiv)	yield %	purity % by HPLC	**4a**	**15** (RRT 1.24)[d]	reaction time (h)	*T* (°C)	solvent
1	1.0	2.0	92.8	95.4	–	0.8	23[a]	25	DMF
2	1.0	5.05	92.0	81.5	10.6	4.3	143	25	AcOEt/water
3	1.0	2.0	121.8	92.8	0.3	2.2	15.5	25	DMF
4	1.0	2.5	92.0	87.7	6.5	4.4	96	25	MeOH/water
5	1.0	2.0	91.0	91.5	2.4	4.5	23 h[b]	40[b]	acetone/water
6	1.0	4.0	100.0	93.1	5.5	0.4	28 h[c]	25[c]	acetone/water
7	1.0	3.0	111.6	91.6	7.3	0.28	24 h[b]	40[b]	acetone/water
8	1.0	3.0	87.3	98.4	0.2	0.27	24 h[a,b]	40[b]	MeCN/water
9	1.0	2.5	110.0	95.2	0.3	2.4	24 h[a,b]	40[b]	MeCN/water
10	1.0	2.5	92.0	98.4	0.5	0.24	24 h[a,b]	40[b]	MeCN/water

[a] After 8 h the reaction was substantially complete. [b] 8 h at 40 °C and left at rt overnight. [c] 25 h at rt and 3 h at 40 °. [d] HPLC method no.1 (see Supporting Information).



15 X= SO or SO_2

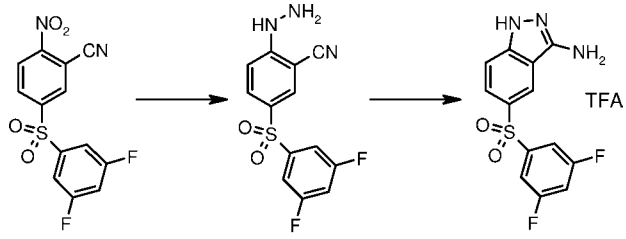
Figure 3. **Possible byproducts.**



6a

Figure 4. **Dimer formation.**

Scheme 4. **Indazole ring formation**



was employed without further purification for the cyclization process to obtain **7**. This workup avoids the need to evaporate the solvent, bearing in mind the problems associated with the presence of N_2H_4. The conversion of **6** to **7** was pursued in THF at 5 °C, employing 1.0 equiv of trifluoroacetic acid (TFA) for 15 min. Alternatively, the hydrochloride salt could also be obtained by using HCl in organic solvent.

Intermediate **7** was not isolated since the reaction mixture was utilized for the following step. The preparation was carried out with the procedure described above, giving a product with 86.8% A% HPLC purity. The following reactions were ordinary protection and deprotection of amino groups[11] needed to reach the target molecule **1**, and they were pursued in standard conditions, Scheme 2. To discriminate between the primary amino group and the indazole nitrogen, TFAc and tritylchloride (TrCl) groups were chosen as protections. The trifluoroacetylation[11,12] on the amino group of **7** to obtain intermediate **8** was made by switching the THF with DCM and using 2 equiv of trifluoroacetic anhydride (TFAA). In theory, 2 equiv of TFAA are required, because of concomitant acylation at ring nitrogens. Addition of TFAA had the immediate effect of dissolving the starting material, initially as a suspension. Soon after, precipitation of the product took place. The organic solution was washed by water twice in order to cleave any residual TFAA and then cooled at 4 °C overnight. The crystallized solid was collected by filtration; overall yield from intermediate **6** to **8** was usually around 63%.

The trityl group[11,13] had the best results during the original screening. It was prepared by dissolving **8** in DCM and adding 1.0 equiv of TrCl and 3.0 equiv of triethylamine (TEA) followed by stirring at room temperature for 4 h. The reacting solution was quenched by washing with ammonium chloride (NH_4Cl) and was carried over to the last step without product isolation. Finally, the cleavage of the trifluoroacetamido group[11] to get the target molecule **1** was made by switching the DCM with MeOH and using 4.0 equiv of TEA. The reaction was gently refluxed 5 h to complete the conversion. Previously, sodium hydroxide (NaOH) was used, but this gave a 10% byproduct due to a monofluoro substitution with a hydroxyl group. This byproduct was very difficult to eliminate even with chromatographic purification. After workup the compound was obtained as a pure solid, 98.21% by HPLC. The overall yield for intermediate **8** to **1** is usually 85%. With a robust synthesis in hand to provide a large amount of the scaffold **1**, it was possible to proceed in further development of these IGF-1R inhibitors.

Conclusion

We have synthesized **1** formally in seven linear steps starting from readily available starting materials. Three of the intermediates do not need to be isolated, the synthesis is short and efficient and has been scaled up to multigram preparations. It represents a substantial simplification and safer protocol compared to the original medicinal chemistry process, which had very low-yield steps and required chromatographic purifications. Environmentally unsuitable and hazardous reagents have been changed; for example, concentrated hydrazine has been replaced with the

(11) Greene, T. W. Wuts, P. G. M. *Protective Groups in Organic Synthesis* 2nd ed.;Wiley: New York, 1991.

(12) (a) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Chem. Pharm. Bull.* **2000**, *48* (10), 1586–1592. (b) Engqvist, R.; Stensland, B.; Bergman, J. *Tetrahedron* **2005**, *61* (18), 4495–4500.

(13) Claramunt, R. M.; Elguero, J.; Fruchier, A. *Bull. Soc. Chim. Belg.* **1985**, *94* (6), 421–424.

safer 35% hydrazine in water; we introduced the safer and environmentally friendly Oxone as the oxidizing agent. Overall, we fulfilled our objective in order to provide a process able to deliver the requested amount of product for development work.

Experimental Section

General. 5-Fluoro-2-nitrobenzonitrile 98% (batch F03937AD) was purchased from ABCR; 3,5-difluorothiophenol 97% (batch Y051) was from Fluorchem. All the other chemicals and reagents were purchased from Sigma-Aldrich and Riede-de Haen. The ^{1}H NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer. The high performance liquid chromatography (HPLC) analyses were carried out using an Agilent series 1100 system and Waters series Millennium according to methods and columns reported in the Supporting Information. The LC/MS system used is a Waters Alliance HT 2795 separation module with a UV-VID detector Waters 996 PDA and a MS detector Waters ZQ^{TM} (single quadrupole). Two methods were applied, one with acid eluent and one with basic eluent, as reported in the Supporting Information. The melting points were obtained through a DSC analysis made with a Mettler Toledo Star system DSC 822. The parallel reactions trials were performed using a Hazard Evaluation Laboratory (HEL) parallel synthesis chem-SCAN and auto-MATE system equipped with syringe pumps (Supporting Information).

5-(3,5-Difluorophenylsulfonyl)-2-nitrobenzonitrile (4). In a 1.0 L jacketed reactor, equipped with an overhead stirrer, were charged 15.16 g (0.091 mol) of 5-fluoro-2-nitrobenzonitrile and 195 mL of ethyl acetate at room temperature. The yellow solution was cooled to 0 °C, and 16.64 mL (0.096 mol) of DIPEA was added while stirring. In the meantime in a second round-bottom flask were charged 13.34 g (0.091 mol) of 3,5-difluorothiophenol and 150 mL of ethyl acetate while stirring at room temperature. This solution was transferred into a dropping funnel and added to the main reactor. The addition was made over ∼45 min. The mixture was left to react for 30 min after the end of the addition.

Workup. The mixture was cooled at 0 °C, and then a solution of 150 mL brine was added. The quenched mixture was warmed to 25 °C, and 50 mL of additional water was added. The two layers were separated, and the organic phase was washed again with a solution of 150 mL of brine and 50 mL of water. The solution was concentrated to a small volume (100 mL) by evaporation on reduced pressure. [Ethylacetate (100 mL) was added, and the resulting mixture was concentrated to reduced volume for product isolation and characterization. This was dried at 50 °C for at least 6 h, and a pale-yellow solid was obtained in a 95.0% yield.]

In the synthetic protocol the isolation process could be avoided by operating as follows: after the first concentration to 100 mL, 100 mL of acetonitrile was added, and the volume was reduced again by evaporation to 100 mL. Finally 400 mL of acetonitrile was added, and the solution went to the following step without isolation: DSC mp = 139.84 °C (steel crucible), mp = 134.81 °C (aluminium crucible); HPLC (method no.1) R_t = 13.1 min., purity >96.0%; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J = 8.60 Hz, 1H), 7.48 (d, J = 1.96 Hz, 1H), 7.42 (dd, J = 8.80, 2.15 Hz, 1H), 7.02 (dd, J = 6.45, 2.15 Hz, 2H), 6.87−6.95 (m, 1H); LC/MS: R_t = 6.25 min, 99%; ES^+, ES^- not responding.

5-(3,5-Difluorobenzenesulfonyl)-2-nitrobenzonitrile (5). In a 1.0 L jacketed reactor, equipped with an overhead stirrer, was charged 138 g (0.228 mol) of Oxone and 500 mL of water. The mixture ws stirred vigorously to complete dissolution with the temperature maintained at 25 °C. The solution of **4** obtained in the preparation described above was then added. For the 400 mL acetonitrile solution a quantitative yield was assumed, corresponding to 26.4 g (0.091 mol) of **4**. The mixture was heated to 40 °C for 7 h 30 min; the heating system was switched off and left to react overnight at room temperature. After an overall 24 h, the mixture was concentrated by evaporation of acetonitrile at reduced pressure. To the resulting mixture was added 400 mL of ethyl acetate and 100 mL of water. After separation, the organic phase was washed once with NaCl 30% (4 × 300 mL), Na_2SO_3 15% (1 × 150 mL), and then again with NaCl 30% (1 × 300 mL). In the final wash the acqueous phase pH ≈ 7. The organic phase was concentrated for product isolation and characterization. After drying at 60 °C overnight, 27.91 g of yellow solid was obtained with 94.3% yield: DSC mp = 120.07 °C (steel crucible) mp = 118.02 °C (aluminium crucible); HPLC (method no.1) R_t = 10.3 min. purity 95.3%; ^{1}H NMR ($CDCl_3$) δ 8.41 (d, J = 8.60 Hz, 1H), 8.36 (d, J = 1.96 Hz, 1H), 8.28 (dd, J = 8.60, 1.95 Hz, 1H), 7.41−7.50 (m, 1H), 7.04−7.12 (m, 2H); LC/MS: R_t = 5.45 min, 100%; ES^+, ES^- not responding.

2,5-Bis-(3,5-difluorophenylsulfonyl)benzonitrile (14). Into a 25 mL three-necked round-bottomed flask was charged 0.5 g (3.0 mmol) of 5-fluoro-2-nitrobenzonitrile, and this was dissolved in 10 mL of THF. Cs_2CO_3 [2.06 g (6.0 mmol)] was added and cooled to 0 °C while stirring. A solution of 0.88 g (6.0 mmol) of 3,5-difluorothiophenol in 5 mL of THF was added over 5 min.

Workup. The reaction was monitored by HPLC after 4 h and concentrated to low volume with a rotary evaporator. DCM (60 mL) was added; the mixture was washed with brine (2 × 30 mL), and the organic phase was treated with Na_2SO_4 prior to filtration on Gooch. After evaporation to dryness a gross yellow solid was obtained as a mixture with **4** and the byproduct **14** as main products. The target compound was isolated and purified by flash chromatography on Silica-gel 60 Å; eluent hexane/ethyl acetate, 10:1, followed by hexane/ethyl acetate, 10:3. TLC was checked by Pancaldi's reagent, R_f in hexane/ethyl acetate, 10:1, results are as follows: (**4**) 0.09, (**2**) 0.18, (**14**) 0.33, (**3**) 0.70. After drying at 40 °C for at least 4 h, 0.78 g of **14** was obtained in a yield of 67.0% as a white solid: HPLC (method no. 1) R_t = 21.4 min; purity 99.3%; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 1.96, 1H), 7.38 (dd, J = 8.41, 2.15 Hz, 1H), 7.25 (d, 1H), 6.78−6.86 (m, 4H), 6.68−6.76 (m, 2H).

5-(3,5-Difluorobenzenesulfonyl)-2-hydrazinobenzonitrile (6). Ten grams (30.84 mmol) of 5-(3,5-difluorobenzenesulfonyl)-2-nitrobenzonitrile dissolved in 70 mL of THF was dropped at 4 °C over 15 min into a solution of 5.6 mL of 35% N_2H_4 (61.6 mmol) in 30 mL of THF. The reaction was stirred at ambient temperature for 4 h. HPLC analysis revealed complete disappearance of the staring material. At 4.0 °C 430

mL of cold water was added, and the mixture was stirred for 15 min. The solid product was collected by filtration and washed with 30 mL of cold water. After drying at 45 °C for at least 12 h 9.23 g of a crude (96.8% yield, strength not determined, HPLC A% (at 254 nm) = 90.5%) was obtained and employed for the next step without further purification. A small aliquot was isolated for NMR and MS characterization: HPLC (method no. 2) R_t = 1.91 min; purity 90.5%; ^{1}H NMR (DMSO-d_6) δ 8.57 (s, 1H), 8.09 (d, J = 2.35 Hz, 1H), 7.86 (dd, J = 9.19, 2.15 Hz, 1H), 7.75−7.66 (m, 2H), 7.64−7.56 (m, 1H), 4.56 (s, 2H); MS m/z (M^+) 310, (M^-) 308.

5-(3,5-Difluorobenzenesulfonyl)-1H-indazol-3-ylamine, Trifluoroacetic Salt (7). 5-(3,5-Difluorobenzenesulfonyl)-2-hydrazinobenzonitrile [6.16 g (19.9 mmol, theoretical value)] was dissolved in 120 mL of THF. The solution was cooled to 4 °C, and 1.48 mL (19.9 mmol) of TFA was added dropwise over 3 min. HPLC control after 30 min of stirring revealed a complete cyclization process (A% at 254 nm = 97.3%). The solvent was rotaevaporated to 1/20 of the initial volume. A small aliquot was isolated for characterization, obtaining a pale-cream powder: HPLC (method no. 2) R_t = 1.51 min; purity 97.3%; free base ^{1}H NMR (DMSO-d_6) δ 12.05 (s, 1H, NH), 8.59 (s, 1H), 7.77 (dd, J = 8.99, 1.96 Hz, 1H), 7.68−7.57 (m, 3H), 7.40 (d, J = 8.99 Hz, 1H), 5.81 (s, 2H, NH_2); LC/MS: R_t = 3.84 min, 95%; MS m/z (M^+) 310, (M^-) 308.

5-(3,5-Difluorophenyl)sulfonyl-3-trifluoro-acetamidoindazole (8). The solution obtained above was diluted with 120 mL of DCM, and 5.6 mL (39.8 mmol) of TFAA was added dropwise over 1 h to the stirred solution maintained at 4 °C. After 1 h of stirring the reaction was monitored by HPLC analysis. Examination revealed the complete disappearance of the starting material. The reaction mixture was washed twice with water (2 × 150 mL). The organic phase was stored at 4 °C overnight. The whitish crystallized solid was collected by filtration, yielding 5 g of target as whitish powder, HPLC A% at 254 nm = 97.59%. The overall yield is calculated over the two reactions (from intermediate **6**) and results to be 62.5%: HPLC (method no. 2) R_t = 1.97 min; purity 99.5%; ^{1}H NMR (DMSO-d_6) δ 13.63 (s, 1H, NH-indazole), 12.22 (s, 1H, NH-$COCF_3$), 8.63 (dt, J = 1.50, 0.70, 0.65 Hz, 1H), 7.94 (dd, J = 8.60, 1.52 Hz, 1H), 7.76−7.70 (m, 3H), 7.64 (sc, J = 9.02, 2.80, 1H); LC/MS: R_t = 4.82 min; m/z (M^+) 405, ($M - H_2O^-$) 386.

5-(3,5-Difluorophenyl)sulfonyl-3-trifluoroacetamido-1-tritylindazole (9). 5-(3,5-Difluorophenyl)sulfonyl-3-trifluoro-acetamido-indazole [3.0 g (7.4 mmol)] was dissolved in 18 mL of DCM. The solution was cooled to 4.0 °C, and 1.67 mL (22.2 mmol) of TEA was added. At 4 °C and over 5 min was added dropwise triphenylmethyl chloride [2.06 g (7.4 mmol)] dissolved in 3.5 mL of DCM. HPLC monitoring after 1 h of stirring revealed complete conversion (HPLC at 254 nm = 97.8%). The solvent was rotaevapotated to 1/10 of the initial volume, and this solution was processed further in the following step without isolation. A small aliquot was isolated for characterization: HPLC (method no. 2) R_t = 15.5 min; ^{1}H NMR (DMSO-d_6) δ 8.46 (dd, J = 1.52, 0.65 Hz, 1H), 7.77 (dd, J = 8.60, 1.52 Hz, 1H), 7.57−7.47 (m, 2H), 7.35−7.18 (m, 10H), 6.97−6.90 (m, 7H); LC/MS: R_t= 8.07 min, 100%, (M^+) 648 weak, (M^-) 646.

3-Amino-[5-(3,5-difluorobenzenesulfonyl)-1-tritylindazole (1). The solution obtained above was diluted with 20 mL of MeOH, and 2.8 mL (37 mmol) of TEA was added. The remaining DCM was eliminated by evaporation, and the reaction was gently refluxed for 5 h. HPLC control revealed the complete removal of the trifluoroacetamido group (A% at 254 nm = 97.0%). The reaction was left at ambient temperature overnight, and the solid thus obtained was collected by filtration, affording 3.46 g (84.7%; overall yield of two reactions, from intermediate **8**) of target as off-white powder: HPLC (method no. 2) R_t = 9.5 min. purity 94.33%; ^{1}H NMR (DMSO-d_6) δ 8.54 (dd, J = 1.52, 0.65 Hz, 1H), 7.67−7.60 (m, 3H), 7.54 (dd, J = 8.60, 1.52 Hz, 1H), 7.33−7.20 (m, 15H), 6.34 (dd, J = 8.60, 0.65 Hz, 1H), 6.04 (sb, 1H, NH_2); LC/MS: R_t = 7.66 min, 100%; (M^+) 552 very weak, (M^-) 550 very weak, 610 (M^+ + HOAc).

Acknowledgment

We thank Dr. Marco Cattaneo and Mr. Mario Ungari for their support in the DSC analysis.

Supporting Information Available

Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review October 6, 2008.

OP8002536