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Practical Syntheses of Oxindole Derivatives: Chemical Development towards 2-(5-Chloro-2-oxo-2,3-dihydroindol-1-yl)acetamide and (*S*)-2-(5-Chloro-2-oxo-2,3-dihydroindol-1-yl)propionamide

Fabienne Broeders, Laurent Defrère,* Marie-France Deltent, Frank Driessens, Frédéric Gilson, Luc Grooters, Xavier Ikonomakos, Frédéric Limauge, Emmanuel Sergeef, and Natacha Verstraeten

Chemical Process Research and Early Scale-Up, UCB Pharma, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium

Abstract:

We describe development of scalable syntheses of novel oxindole-type SV2A ligands with improved potency towards seizure suppression.

Introduction

Epilepsy is a chronic, often lifelong, neurological disorder that affects ∼1% of the population worldwide and which is characterized by recurrent involuntary seizures, caused by disturbances in the normal electrical activity of the brain. Epilepsy has a tremendous impact, not only on the individuals afflicted with this disease but also on their families as well as on society in general, because of the resultant personal and financial burden.

Despite the recent introduction of second-generation anticonvulsants, refractory epilepsy is still a significant clinical problem. In a prospective study, Kwan and Brodie[1] show that fewer than 50% of patients with epilepsy become seizure-free after beginning an initial antiepileptic medication. In addition, more than 30% of patients cannot be adequately treated with existing antiepileptic drugs (AED), because of either lack of efficacy or toxicity.

The synaptic vesicle protein SV2A has been identified[2] as the brain-specific binding site for levetiracetam, **1b** (see Figure 1, Keppra, UCB Pharma), a structural analogue of piracetam, **1a** (Nootropil, UCB Pharma). Interaction with SV2A is likely to exert a major role in its antiepileptic properties. Using this novel molecular target, medicinal chemists initiated a thorough drug discovery program[3] targeting the identification of ligands of the so-called acetam family with an improved SV2A affinity. Brivaracetam, **1c**, was selected as the lead compound whose clinical program (phase I and II studies) has been finalized.[4]

In parallel to these studies, another drug discovery program[5] around the relatively unexplored 3-unsubstituted oxindole-*N*-acetamide scaffold **2**,[6] whose structure is similar to that of the acetam family, was undertaken in order to find a new ligand with an improved affinity towards the SV2A protein.

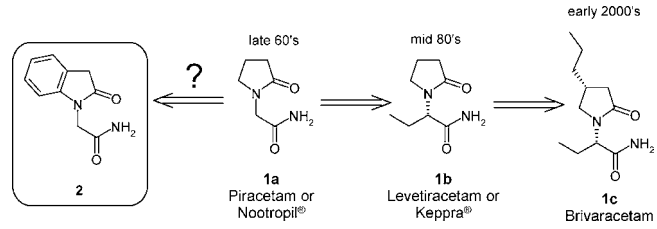

Figure 1. **Progression of the acetam family within UCB.**

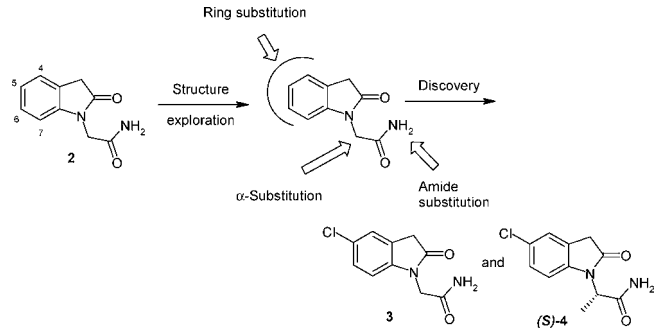

Figure 2. **Discovery of the two oxindole-type lead molecules 3 and (*S*)-4.**

This led to the discovery of two ligands **3** and **(*S*)-4** which were chosen as candidates for development (Figure 2).

In a range of secondary epilepsy models, these two compounds displayed a more complete seizure suppression than levetiracetam, **1b**, itself along with an outstanding safety margin (no marked effects on cardiovascular, respiratory, or CNS functions).

At this stage of the project, we were asked to provide kilograms of both compounds **3** and **(*S*)-4** in order to progress into the preclinical toxicological studies. Ultimately this research work would serve as a framework for future process optimization to allow for larger-scale manufacturing.

Discovery Synthesis

Prior to beginning our chemical development work the total quantity of **3** and **(*S*)-4** was around 5 g. While the synthetic routes were capable of supplying these small amounts (see

* To whom correspondence should be addressed. Telephone: +32 2 386 3315. Fax: +32 2 386 2704. E-mail: laurent.defrere@ucb-group.com.

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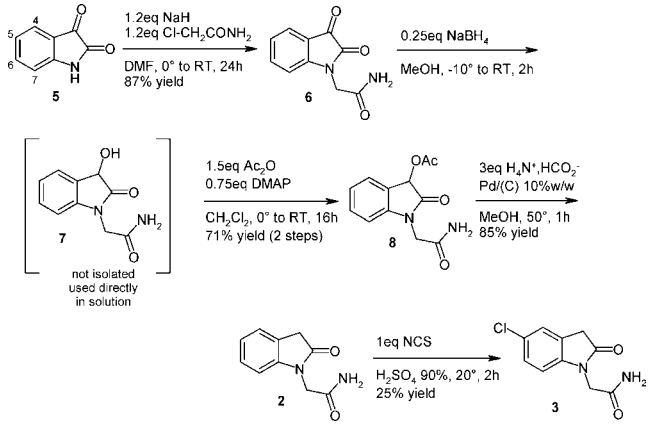
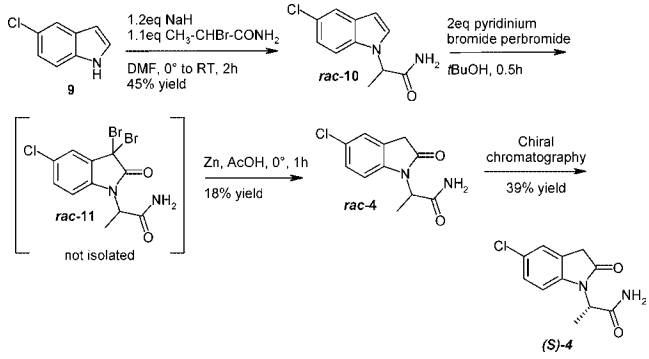
Scheme 1. **Medicinal chemistry route to the acetamide 3**



Scheme 2. **Medicinal chemistry route to the propionamide (*S*)-4**



Schemes 1 and 2), they both suffer from several disadvantages and thus were of limited use for scale-up without extensive modification.

In the case of Scheme 1, the strategy was based on the *N*-alkylation of the widely available and inexpensive isatin **5** with chloroacetamide, since the same transformation applied to a 3-unsubstituted oxindole as starting product invariably leads to an intractable mixture (*N*- vs *O*- vs *C*-alkylation among other things). Reduction of the ketone function of **6** to the corresponding methylene was achieved in a two-step sequence involving first the reduction to the alcohol **7** and then to the oxindole **2** *via* the acetate **8**. It was already shown that another possibility[7] consisted of preparing a dithioacetal from the isatin and then reducing it to the oxindole with Raney nickel, but this alternative was disfavoured as it involved the need to deal with noxious thiol side products.

It was found that alcohol **7** is somewhat unstable towards molecular oxygen present in air and can easily reoxidize back to the isatin **6** if not trapped quickly as here by acetylation to **8**. We noticed later that this particularly cumbersome behaviour was exacerbated when electron-withdrawing groups were already present on the aromatic ring. This side reaction was the most serious drawback of the preparation presented here, together with the low yield (~25%) of the final aromatic electrophilic substitution with *N*-chlorosuccinimide (NCS). Nevertheless, this strategy has allowed medicinal chemists to introduce diversity at position 5 (and eventually 7) by electrophilic reagents (see ref 5 for more examples) at a late stage without concerning oneself with the structure of the starting isatin.

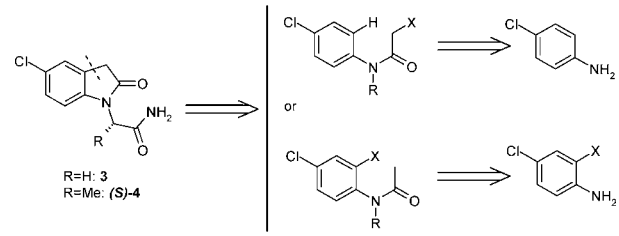


Figure 3. **$C_{arom}-CH_2$ disconnection.**

For the second lead oxindole **(*S*)-4**, whose initial synthesis was depicted in Scheme 2, the main problems encountered were the low overall yield and the reliance upon a chromatographic separation of enantiomers at the final stage. The conversion[8] of indole ***rac*-10** to oxindole ***rac*-4** was particularly troublesome, due to incomplete reaction, a range of impurities, and a tedious workup.

In view of these shortcomings we found it desirable to seek alternative high-yielding and more staightforward routes to the target molecules **3** and **(*S*)-4**. Very clearly the challenge was to identify a safe, robust, and rapid route to the title compounds in order to make them available for the preclinical toxicology studies, rather than identify the commercial synthesis.

We first initiated a literature survey that indicated that many disconnections could possibly lead to the desired 3-unsubstituted oxindoles. Among all the possibilities, we only considered the routes based on readily available aromatic starting materials already possessing the chlorine atom in the position para to the nitrogen atom, thus avoiding the low-yielding NCS-mediated chlorination step.

Given the time constraints to deliver the active materials, it was decided to study the most promising approaches in parallel before testing the viability of the synthesis upon a preliminary scale-up.

Results and Discussion

C−C Bond Formation from Aniline Derivatives. Historically this transformation is best represented as an intramolecular Friedel−Craft alkylation of α-haloacetanilides, but this often requires harsh conditions[9] (excess aluminium trichloride, typically above 150 °C) often incompatible with more sensitive functionalities. Nafion-H- or rhodium (II) salts-mediated cyclizations of α-diazoacetanilides originally reported by Doyle[10] have been used on few occasions,[11] as has the elegant ring contraction of diazoquinolinediones (Wolff rearrangement)[12] induced thermally or by rhodium (II) salts (not shown in Figure 3). However, those two methods suffer from modest yields in many cases, and the diazo precursors are always prepared by diazo transfer from sulfonyl azides that are known to be

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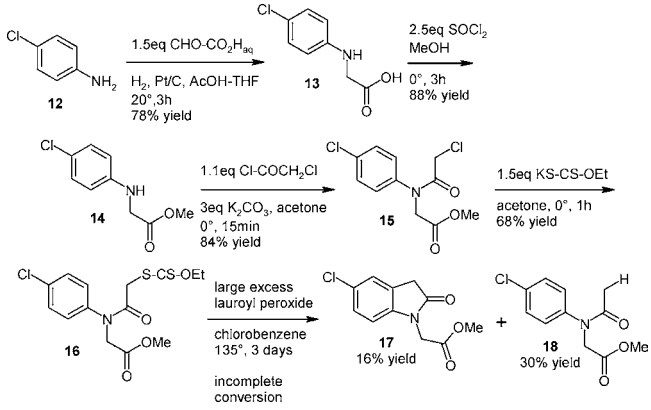
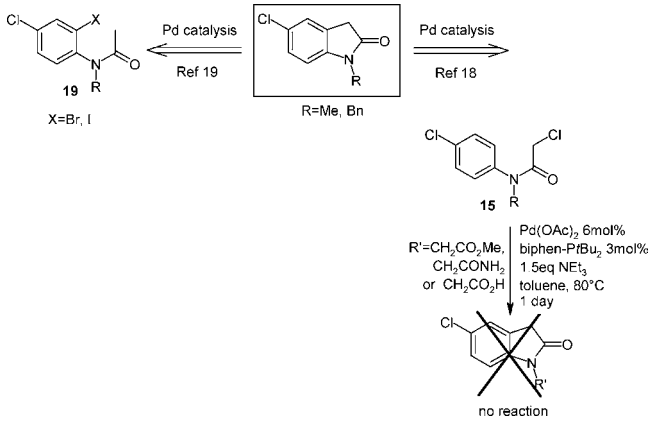
Scheme 3. **Radical-mediated access to oxindoles**



Scheme 4. **Palladium-mediated access to oxindoles**



unstable[13] or not commercially available[14] and thus not amenable to safe large-scale preparations.

It was therefore decided to explore the possibility of carrying out the ring closure by radical cyclization from xanthate derivatives, which is generally a very powerful carbon−carbon bond-forming process.[15] The α-xanthyl-acetanilide precursor **16** was easily and efficiently prepared without any optimization as depicted in Scheme 3, but despite a promising precedent in the literature,[16] cyclization onto the electron-poor aromatic ring remained very sluggish. The conversion was incomplete after 3 days at 135 °C even though fresh lauroyl peroxide was added portionwise every few hours (∼5 equiv in all). Moreover, the final product **17** was always accompanied by the reduction product **18** as already pointed out earlier for a similar radical-mediated oxindole formation,[17] and even in a separate reaction conducted at higher dilution.

We also considered the possibility of preparing our oxindoles by a palladium-catalyzed process (see Scheme 4), such as cylization of an α-chloro-acetanilide **15** using Buchwald methodology[18] or by α-arylation[19] of the appropriate 2-halo-*N*-acetylaniline **19** although both of these methods suffer from

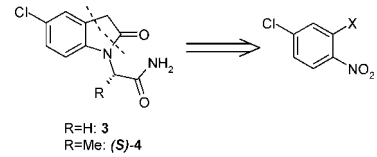
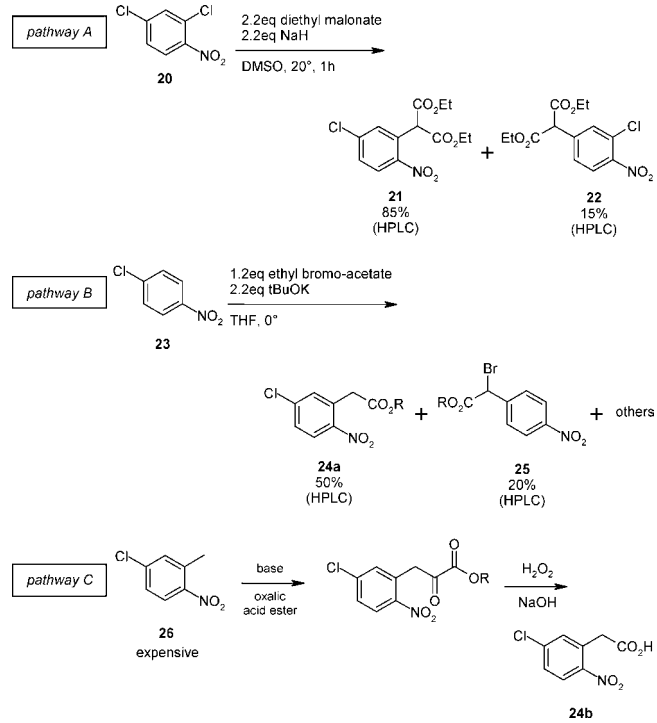


Figure 4. **Synthesis from nitroaromatics.**

Scheme 5. **Nucleophilic substitution approaches**



the disadvantage of using moisture- and/or air-sensitive catalytic systems. However, in our hands, compounds **15** (R = CH_2CO_2Me, CH_2CONH_2, or CH_2CO_2H) did not show any conversion to the expected oxindoles.

These poor results and other unfavorable consideration led us to set this disconnection aside to explore others.

C−C Bond Formation from Nitroaromatic Derivatives. In this approach (see Figure 4) the key compound is the 2-(5-chloro-2-nitrophenyl)acetic acid **24b** which can be accessed by different methods (Scheme 5). It was obvious to first study the incorporation of the acetic acid side chain *via* malonate chemistry facilitated by the presence of an ortho nitro function on the aromatic ring starting from the cheap 2,4-dichloronitrobenzene **20** (aromatic nucleophilic substitution/*pathway A*)[20] or from even cheaper 4-chloronitrobenzene **23** (vicarious nucleophilic substitution of hydrogen or VNS/*pathway B*)[21] (see Scheme 5).

Unfortunately, the reactions between the nitro derivatives **20** and **23** and the anions of a malonate ester and a bromoacetate, respectively, failed to be totally regioselective, with partial displacement of the chlorine atom in the para position always accompanying the formation of the desired product (this has already been reported by a group[20a] from Pfizer). These routes were therefore discarded.

The classical two-step sequence (see *pathway C*)[22] involved the condensation of the deprotonated nitrotoluene with an oxalic acid ester[23] followed by oxidative cleavage to the corresponding phenylacetic acid by hydrogen peroxide in the presence of a

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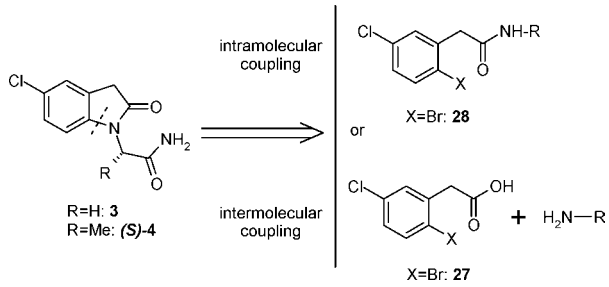


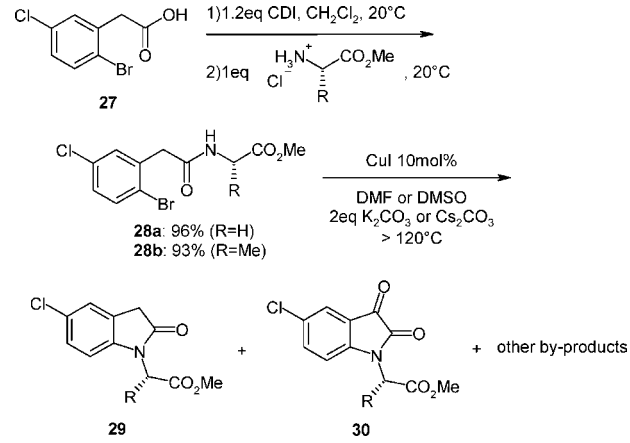
Figure 5. **Disconnection *via* a C−N coupling reaction.**

base (typically sodium hydroxide). This approach was not followed up as a viable option given the expense of the starting 2-nitro-5-chlorotoluene **26**.

C−N Coupling Approach. When ideas were put down on paper, it was obvious that a carbon−nitrogen coupling reaction between an amino acid derivative and the appropriate halo-aromatic would be a considerable improvement of the discovery synthesis (see Figure 5). This was particularly true for the chiral structure **(*S*)-4** since coupling of an L-alanine derivative would allow a straightforward access to the expected structures and most notably with the right absolute configuration therefore avoiding any chiral separation, resolution or asymmetric synthesis. It was then discovered that 2-bromo-5-chloro-phenylacetic acid **27** was commercially available and was an ideal halogenated substrate to study this particular C−N coupling reaction.

The transition metal-catalyzed C−N bond formation of aromatic compounds has made tremendous advances in the past decade. The palladium version of this reaction has been reviewed a couple of times these last years.[24] In this field most of the papers disclose the preparation of oxindoles by the intramolecular coupling of the corresponding amide, but this transformation seems to be restricted to *N*-alkyl-phenylacetamide derivatives.[25] Moreover, palladium catalysis is limited in many cases due to the air and moisture sensitivity as well as the higher cost of palladium and the associated ligands. For this reason we decided to first investigate the use of copper

Scheme 6. **Study of the intramolecular coupling**



catalysis.[26] At the outset of our work, only a few methods were available for the clean and efficient copper-mediated *N*-arylation of amino acids.[27] In this area a major breakthrough was made in 1998 by Ma's group[27b] followed by numerous variants, and his work served as a starting point for our investigations.

We first chose to study the intramolecular version of this coupling reaction. The starting 2-bromo-5-chlorophenylacetamides **28** were efficiently prepared as depicted in Scheme 6. Activation of the starting phenylacetic acid **27** was performed with carbonyl diimidazole (CDI) under standard conditions (1.2 equiv CDI, dichloromethane, 20 °C), and the activated ester was then reacted with the hydrochloride salt of glycine- or L-alanine methyl ester (1 equiv) at the same temperature. The corresponding phenyl acetylamino-acetic and -propionic acid compounds **28** were isolated in 96% and 93% yields, respectively.

A quick screening of conditions (copper source, solvent, base, and temperature) revealed that significant *N*-arylation took place with copper (I) iodide in dimethylsulfoxide or *N*,*N*-dimethylformamide (>120 °C) in the presence of cesium- or potassium carbonate with no additional ligands. However, oxindoles **29** formed under these conditions are partly consumed and oxidized to the corresponding isatins **30** which can further condense with oxindoles **29** still present in the medium to form indigoïd derivatives[28] as detected by mass spectroscopy. Degradation of oxindoles under similar conditions has already been reported,[29] while it has been pointed out that copper salts[30a] or molecular oxygen[30b] can catalyze oxidation of oxindoles to isatins.

On the other side, the intermolecular version of the C−N coupling reaction would furnish the 2-aminophenylacetic acid derivatives **31** which logically should be less oxidation prone. Results are shown in Scheme 7are and listed in Table 1.

The coupling of L-alanine was first studied, and after a quick screen it was found that again polar aprotic solvents were markedly better for this transformation. No reactions occurred in toluene (entries 1 and 2), while reactions in dioxane, *tert*-

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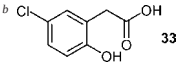
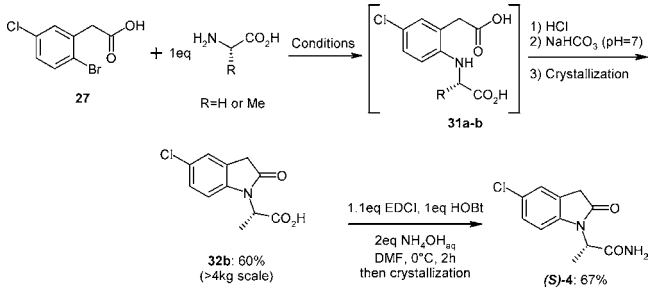
Table 1. **Screening of conditions for the intermolecular C−N coupling reaction**

entry	R	conditions	oxindole **32**[a] (%)	comments
1	Me	toluene, CuI 10 mol %, 1.5 equiv K_2CO_3, 100 °C, 15 h	0	no reaction
2	Me	toluene, CuI 10 mol %, 1.5 equiv K_3PO_4, 100 °C, 15 h	0	no reaction
3	Me	dioxane, CuI 10 mol %, 1.5 equiv K_2CO_3, 100 °C, 15 h	20	very slow, many impurities
4	Me	*t*BuOH, CuI 10 mol %, 1.5 equiv K_2CO_3, 80 °C, 15 h	19	very slow
5	Me	H_2O, CuI 10 mol %, 1.5 equiv K_2CO_3, 100 °C, 15 h	29	57% of phenol **33**[b]
6	Me	DMF, CuI 10 mol %, 1.5 equiv K_2CO_3, 90 °C, 15 h	73	9% starting material, ee = 82%[c]
7	Me	DMF, CuI 10 mol %, 1.5 equiv K_2CO_3, 110 °C, 1.5 h	89	ee = 80%[c]
8	Me	DMF, CuI 10 mol %, 2.2 equiv K_2CO_3, 110 °C, 1.5 h	77	ee = 64%[c]
9	Me	DMF, CuI 10 mol %, 1.5 equiv $NaHCO_3$, 110 °C, 10 h	13	reaction stalled
10	Me	DMF, CuI 10 mol %, 1.5 equiv K_2CO_3, 140 °C, 1 h	88	ee = 76%[c]
11	Me	DMF, CuI 5 mol %, 1.5 equiv K_2CO_3, 140 °C, 0.7 h	91	ee = 87.4%[c]
12	Me	DMF, CuI 1 mol %, 1.5 equiv K_2CO_3, 140 °C, 1 h	61	incomplete conversion and formation of an unidentified impurity (17%)
13	Me	DMF, CuI 3 mol %, 1.5 equiv K_2CO_3, 140 °C, 0.7 h	68	5% of the same unidentified impurity
14	Me	DMF, CuI 5 mol %, 1.5 equiv K_2CO_3, 140 °C, 3 h	84	>4 kg scale[d], ee = 80%[c], 60% yield after crystallization (ee unchanged)
15	H	DMF, CuI 10 mol %, 1.5 equiv K_2CO_3, 140 °C, 10 h	0	no reaction
16	H	DMF, CuI 10 mol %, 2 equiv K_3PO_4, 140 °C, 10 h	0	no reaction
17	H	DMF, CuI 10 mol %, 2 equiv Cs_2CO_3, 140 °C, 10 h	0	no reaction

[a] HPLC area in the crude reaction mixture.
[b]  **33**
[c] Measured after cyclization to oxindole **32b** in HCl.
[d] See Experimental Section for more details.

Scheme 7. **Study of the intermolecular coupling**



butanol, or water were sluggish (20−30% yield on average after 15 h) and accompanied by the formation of many different impurities (mainly phenol **33** in water, entry 5). On one hand, 73% (HPLC area %) of 2-aminophenylacetic acid derivative **31b** was obtained in *N*,*N*-dimethylformamide at 90 °C (entry 6). Cyclization to the oxindole **32b** was not observed under these conditions, while significant racemization took place (but did not intensify upon prolonged reaction time). On the other hand racemization was found to be more significant when more base was added (entry 8), while a temperature rise up to 140 °C completed the reaction in 30−40 min on a 0.5 g scale and improved the yield and quality of the final product (entry 10). The quantity of copper (I) iodide was also reduced successfully down to 5 mol % (entry 11), but a drop to 1% (entry 12) extended the reaction time, and reduced the yield while an unidentified impurity was generated (17 HPLC area %). It was therefore decided to stick to the best conditions found to scale the C−N coupling reaction up to 4−5 kg of starting material (entry 14, see Experimental Section for more details).

Unfortunately we were very disappointed to see that under similar conditions, *N*-arylation of glycine did not work at all (entries 15−17). This has already been disclosed in the literature[27b] although efficient methods have been developed since.[31] We thus had to revise our work to find an alternative route to **3** (see next part and Figure 6).

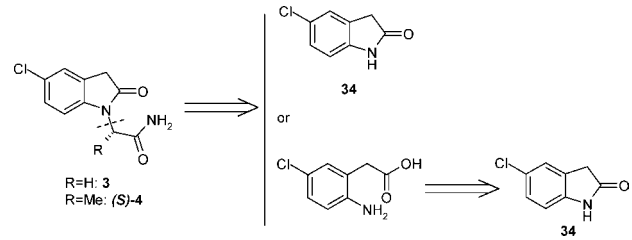


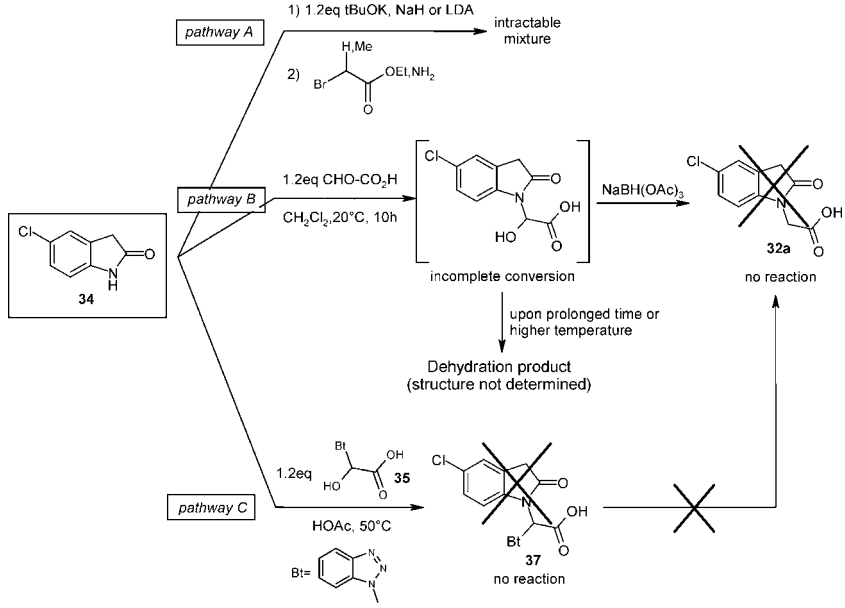
Figure 6. **Disconnection with 5-chlorooxindole 34 as starting material.**

Aqueous hydrochloric acid was added to cyclize the 2-aminophenylacetic acid **31b** to the oxindole **32b**. At that stage the acidic pH is brought back to 7.0 with sodium bicarbonate to break an oxindole−copper complex (first detected by the signals broadening in the ^{1}H NMR spectrum caused by paramagnetic copper species), then the final uncomplexed oxindole **32b** was extracted and crystallized from methanol/water (2/1 v/v) in 60% yield. This crystallization did not alter the enantiomeric excess of the crude coupling reaction mixture.

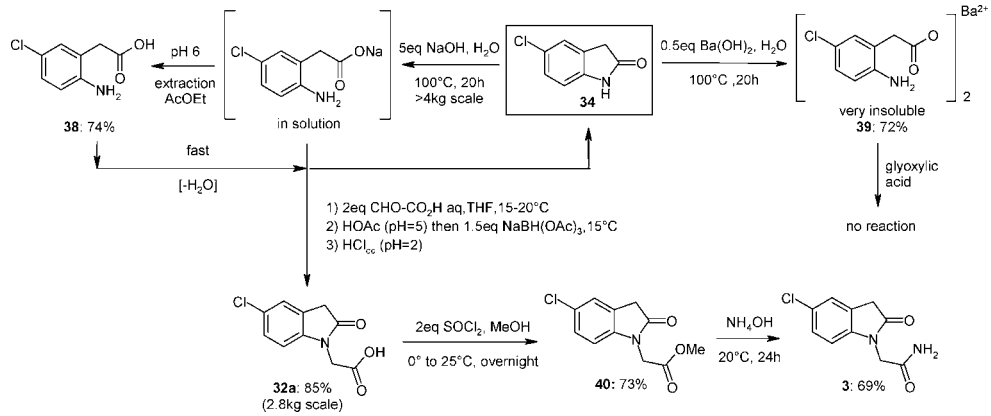
The acid **32b** obtained in this way was transformed to the final primary amide **(*S*)-4** using EDCI (1.1 equiv), HOBt (1 equiv), and NH_4OH_{aq} (2 equiv) in *N*,*N*-dimethylformamide (5 vol) at 0 °C for 2 h. This allowed us to isolate a crude material by extraction with an unchanged ee of 80%. In parallel to this, we found that the racemate amide ***rac*-4** belongs to the class of racemic compounds[32] with a eutectic composition of 99.5/0.5. The solubility of this eutectic composition has been evaluated in ethyl acetate to be close to 20 mg/mL. We therefore decided

(30) (a) Rossiter, S. *Tetrahedron Lett.* **2002**, *43*, 4671. (b) Bonanomi, M.; Baiocchi, L. *Gazz. Chim. Ital.* **1989**, *119*, 445.
(31) Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997.
(32) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Krieger: Malabar, FL, U.S.A., 1994; pp 88 and 192.

Scheme 8. ***N*-Alkylation attempts from 5-chlorooxindole 34**



Scheme 9. **Reductive amination from (5-chloro-2-aminophenyl)acetic acid (sodium salt) in aqueous solution**



to capitalize on this situation and to use the minimum amount of ethyl acetate to dissolve a 99.5/0.5 composition (eutectic) from the crude 90/10, thus leaving a chemically pure solid with a nearly racemic composition (55/45 as measured by chiral HPLC, see Experimental Section). The solution containing the expected amide **(*S*)-4** was then stripped under vacuum and the residue slurried in isopropanol (6 vol) to lead to **(*S*)-4** in 67% isolated yield (99% ee).

***N*-Alkylation Route.** In parallel to this, the disconnection involving the readily available 5-chlorooxindole **34** as advanced starting material was also explored. However, it had been shown previously that deprotonation of such substrates followed by alkylation does not proceed cleanly (see Scheme 8/*pathway A*).

For these reasons we investigated the possibility of making the C−N bond of **3** by reductive amination with glyoxylic acid. However Scheme 8(*pathway B*) shows that even if amidation of glyoxylic acid is possible (though always incomplete), reduction of the iminium species after addition of sodium triacetoxyborohydride to lead to the acetic acid compound **32a** was never observed. Instead of that the intermediate hemiaminal smoothly loses a molecule of water to lead to dehydration products.

In a similar manner the "benzotriazole" methodology developed by Katritzky[33] was briefly investigated, but the reaction of 5-chlorooxindole **34** with benzotriazol-1-yl-hydroxyacetic acid **35**[34] (*pathway C*) led to the same disappointing results.

A paper in the literature reporting the preparation of tenidap[35] (structure based on the 5-chlorooxindole moiety) mentions the possibility of carrying out the ring opening of the oxindole **34** with aqueous sodium hydroxide and then further functionalizing the resulting aniline with an electrophile. This prompted us to explore the possibility of incorporating the amino acid residue *via* a reductive amination protocol after the ring opening of oxindole **34** (Scheme 9). The cleavage of the amide bond of the oxindole **34** was reproduced with sodium hydroxide 4 M (5 equiv) at 100 °C overnight followed by neutralization to pH 6, and extraction into ethyl acetate allowed us to isolate the phenylacetic acid **38** in 74% yield. Unfortunately the latter

(33) Katritsky, A. R.; Yao, G.; Lan, X.; Zhao, X. *J. Org. Chem.* **1993**, *58*, 2086.
(34) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc. Perkin Trans. I* **1987**, 791.
(35) Kumar, P. R.; Goud, P. S.; Raju, S.; Sailaja, M.; Sarma, M. R.; Reddy, G. O. *Org. Process Res. Dev.* **2001**, *5*, 61.

recyclizes in solution to the oxindole **34** too quickly to be considered as an isolable and viable intermediate.

We also looked at the possibility to isolate a carboxylate salt of this amino acid as intermediate. All attempts to isolate the sodium or potassium salt failed, but following a previous experience in another related transformation we discovered that oxindole **34** is slowly cleaved in aqueous barium hydroxide (0.5 equiv, 100 °C, 20 h), while the barium carboxylate **39** precipitates spontaneously from the reaction mixture in 72% isolated yield. Unfortunately salt **39** turned out to be too poorly soluble to further react significantly in a reductive amination process.

It was then discovered that the reductive amination protocol from the sodium salt could be performed in the original basic aqueous solution. The previously obtained solution of 2-aminophenylacetate was cooled to 20 °C, and aqueous glyoxylic acid (2 equiv) was added in tetrahydrofuran. Glacial acetic acid was added until pH adjusted to 5, followed by the portionwise addition of 1.5 equiv of solid sodium triacetoxyborohydride while the reaction mixture was kept at 15 °C. The temperature was maintained below 20 °C in order to avoid the ring-closure of the unreacted 2-aminophenylacetate to the oxindole **34**.

After 17 h at this temperature, the complete conversion to the expected aniline was observed. Concentrated hydrochloric acid was then added to adjust the pH to 2 which allowed the cyclization and the precipitation of the acetic acid derivative **32a** in 85% yield (98% purity HPLC). Ultimately this method proved very efficient and successful upon scaling-up (>2.5 kg scale, see Experimental Section).

The last goal, quite trivial at first sight, was to prepare the primary amide **3** from the freshly prepared acid **32a**. This one-step transformation turned out to be much more difficult than expected. Indeed, the use of classical coupling agents (carbonyl diimidazole CDI, carbodiimide EDCI/HOBt, uronium salts TBTU/HOBt), and different ammonia equivalents (ammonium-hydroxide, -chloride, or -bicarbonate) led only to partial conversions together with the formation of a dimeric compound (often as major product) whose structure was not determined.

Finally it was decided to perform this transformation in two steps as explained below. Indeed acid **32a** is cleanly transformed to the corresponding methyl ester **40** under standard conditions (2 equiv thionyl chloride in methanol, 0° to 25 °C overnight) which is subsequently crystallized from dichloromethane/methanol in 73% isolated yield. This ester **40** is then smoothly converted to the expected amide **3** in aqueous ammonia (NH_4OH 28% w/w, 6 mL/g of ester **40**, 24 h, 20 °C). Under these conditions, conversion of the ester **40** is always greater than 98% although the reaction is accompanied by a reproducible ~5% quantity of hydrolysis product **32a**. The final product **3** is easily purified and isolated by crystallization from acetone/water (3:1) at 60 °C in 70% yield (43% overall from **34**).

Summary and Conclusions

During the development of two new ligands for the SV2A protein, the requirement for bulk (multikilogram) drug supplies within a strict time frame were met using two distinct routes. The first relied on a copper-mediated C−N coupling reaction of L-alanine to indroduce the chiral (*S*)-propionamide side chain but proved to be uneffective with glycine as aminoacid. Thus, another strategy involving a one-pot "oxindole ring opening/reductive amination/ring closure" was chosen for the second lead oxindole.

Overall the processes were safe, reproducible, reliable, robust, and high yielding. Isolation of final products was very convenient, and the purity and impurity profiles were strictly controlled and reproducible.

Experimental Section

Unless specified otherwise, all reagents and solvents were used as supplied by the manufacturer. All reactions were conducted under an inert nitrogen atmosphere. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 with TMS as internal standard using a Bruker AV 400 spectrometer at 400 and 100 MHz respectively. HPLC was performed on a Waters Alliance 2695 mounted with a X-Terra C18, 5 μm, 150 mm × 4.6 mm column, using a water/acetonitrile/NH_4CO_3/NH_4OH gradient method at a 2.5 mL/min at 215 nm or with an Inertsil ODS3, 5 μm, 150 mm × 4.6 mm column, using a water/acetonitrile/TFA gradient at a 2.5 mL/min at 215 nm. Chiral purity was determined by HPLC using a Prontosil Chiral AX-QN 1, 150 mm × 4 mm column, methanol/formic acid: 99/1 at 1 mL/min *(Conditions A)* or a Chiralcel OD-H, 250 mm × 4.6 mm column, ethanol/isohexane/diethylamine: 50/50/0.1 at 1 mL/min *(Conditions B)*. LC/MS analysis was performed on a ZQ Waters single quadrupole spectrometer equipped with a ESI source and HPLC Waters 2795 quaternary pump with diode array. Data were acquired in a full MS scan from *m/z* 90 to 1000 in positive mode with an acidic elution and in both positive and negative modes with a basic elution. Specific rotation was recorded on a Perkin-Elmer MC341 polarimeter. DSC were recorded on a Perkin-Elmer DSC 7 with a heating ramp of 10 °C/min.

(5-Chloro-2-oxo-2,3-dihydroindol-1-yl)acetic acid, 32a. A 70 L vessel, charged with aqueous 4 M NaOH (20.59 L, 82.36 mol), was heated to 60 °C, and 5-chlorooxindole **34** (2.817 kg, 16.81 mol) was added. The reaction mixture was heated at 100 °C for 19 h. Upon completion of the hydrolysis, the mixture was cooled down to 15 °C, aqueous 50 wt % glyoxylic acid (4.878 kg, 32.94 mol) diluted with 5.6 L of THF was charged, and the pH of the reaction mixture was adjusted to 5 by addition of acetic acid (3.5 L). Solid sodium triacetoxyborohydride (5.398 kg, 25.47 mol) was added portionwise, maintaining mass temperature below 20 °C, and the mixture was stirred for 17 h at 15 °C. After addition of HCl, 37%, until the pH = 2 (7.5 L), the solid was filtered, washed with water (2 × 8.5 L), and dried under vacuum at 70 °C for 48 h. Yield: 3.224 kg (85%), HPLC purity: 98.3% (area %); ^1H NMR (DMSO-d_6) δ 7.34 (s, 1 H), 7.30 (d, J = 8.3 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 4.44 (s, 2 H), 3.66 (s, 2 H); MS *m/z*: 226/228 (MH^+).

(5-Chloro-2-oxo-2,3-dihydroindol-1-yl)acetic acid methyl ester, 42. A 40 L vessel was charged with (5-chloro-2-oxo-2,3-dihydro-indol-1-yl)acetic acid **32a** (3.220 kg, 14.27 mol) and 25 L of methanol, and the mixture was cooled to 0 °C. Thionyl chloride (3.47 kg, 29.17 mol) was then added dropwise, maintaining mass temperature below 10 °C, and the reaction mixture was stirred for 19 h at 25 °C. The suspension was

cooled to 0 °C and stirred for 1 h. The solid was filtered, washed with 12.5 L of methanol at 0 °C, and dried under vacuum at 60 °C for 18 h to afford 3.256 kg of crude **42** as a yellow solid. The crude material was dissolved in dichloromethane (12.6 L) and stirred with 320 g of activated charcoal at 25 °C for 1 h. The suspension was filtered on a Celite pad (Hyflo Super Cel) and concentrated to dryness, and the residue was taken up with methanol (29.3 L). The mixture was stirred at 0 °C for 1 h, and the solid was filtered, washed with cold methanol (0 °C) (6.4 L), and dried under vacuum at 60 °C for 18 h to afford **42** as a white solid. Yield: 2.520 kg (73%), HPLC purity: 99.7% (area %); ^{1}H NMR (DMSO-d_6) δ 7.35 (s, 1 H), 7.31 (d, J = 8.3 Hz, 1 H), 7.01 (d, J = 8.3 Hz, 1 H), 4.56 (s, 2 H), 3.68 (2 × s, 2 H + 3 H); MS m/z: 240/242 (MH^+).

2-(5-Chloro-2-oxo-2,3-dihydroindol-1-yl)acetamide, 3. A 40 L vessel was charged with (5-chloro-2-oxo-2,3-dihydroindol-1-yl)acetic acid methyl ester **42** (2.518 kg, 10.50 mol) and 15.1 L of aqueous ammonia 28% w/w. After stirring at 20 °C for 21 h, the solid was filtered, washed with water (3 × 5 L), and dried under vacuum at 60 °C for 48 h to afford 2.160 kg of crude **3**. The crude material was suspended in a 3/1 mixture of acetone/water (44 L) and heated at 60 °C for 1 h. The mixture was cooled down to 0 °C and stirred for 30 min; the crystals were filtered, washed with cold acetone (0 °C) (3 × 3.6 L), and dried under vacuum at 60 °C for 18 h to afford pure **3** as an off-white solid. Yield: 1.628 kg (69%), HPLC purity: 100% (area %); ^{1}H NMR (DMSO-d_6) δ 7.59 (s, 1 H), 7.33 (s, 1 H), 7.29 (d, J = 8.3 Hz, 1 H), 7.22 (s, 1 H), 6.85 (d, J = 8.3 Hz, 1 H), 4.24 (s, 2 H), 3.60 (s, 2 H); MS m/z: 225/227 (MH^+); DSC (onset): 236.18 °C.

(*S*)-2-(5-Chloro-2-oxo-2,3-dihydroindol-1-yl)propionic acid, 32b. A 70 L vessel was charged with (2-bromo-5-chlorophenyl)acetic acid **27** (4.247 kg, 17.02 mol), (*S*)-alanine (1.518 kg, 17.04 mol), potassium carbonate (3.531 kg, 25.55 mol), CuI (0.162 kg, 0.85 mol), and DMF (20 L). The mixture was then heated to 140 °C and stirred for 45 min. After cooling down at 20 °C, 2 N HCl (22 L) was added, and the mixture was stirred for 1 h and extracted with ethyl acetate (2 × 30 L). The combined organic layers were then washed with water (2 × 16 L), and after addition of water (22 L), the pH was adjusted to 7 with 1 N NaOH (15 L). The two layers were separated, ethyl acetate (46 L) was added to the aqueous layer, and the pH was adjusted to 2 by addition of 2 N HCl (8 L). After decantation, the organic layer was washed with water (10 L) and evaporated to dryness to afford 3.98 kg of crude **32b** as a brownish solid. HPLC purity: 95% (area %); ee: 80%. This crude material was dissolved in methanol (9.33 L) at 60 °C, and water (4.67 L) was added dropwise. The suspension was then stirred at 20 °C for 16 h and the solid was filtered, washed with a 2:1 mixture of methanol/water (1.5 L), and dried under vacuum at 45 °C for 18 h to afford chemically pure **32b**. Yield: 2.472 kg (60%), HPLC purity: 99.2% (area %); ee = 80% determined by chiral HPLC upon *Conditions A*: 7.1 min (90.1%, *S*-isomer) and 8.5 min (9.9%, *R*-isomer); ^{1}H NMR (DMSO-d_6) δ 13.01 (broad, 1 H), 7.35 (s, 1 H), 7.30 (d, J = 8.3 Hz, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 5.04 (q, J = 7.3 Hz, 1 H), 3.63 (s, 2 H), 1.47 (d, J = 7.3 Hz, 3 H); MS m/z: 240/242 (MH^+).

(*S*)-2-(5-Chloro-2-oxo-2,3-dihydroindol-1-yl)propionamide, (*S*)-4. A 40 L vessel was charged with (*S*)-2-(5-chloro-2-oxo-2,3-dihydroindol-1-yl)propionic acid **32b** (2.465 kg, 10.28 mol, ee = 80%) and DMF (12.3 L). The solution was cooled down at 0 °C, EDCI (2.170 kg, 11.32 mol) and HOBT monohydrate (1.575 kg, 10.28 mol) were added, and the mixture was stirred at 0 °C for 2 h. Aqueous ammonia 28% (1.6 L) was added over a period of 15 min, maintaining mass temperature below 5 °C. After stirring at 0 °C for 1 h and addition of water (12.5 L), the mixture was extracted with dichloromethane (2 × 12.5 L). Dichloromethane was stripped off, and the residue was taken up with enough ethyl acetate (26 L) to dissolve the entire eutectic mixture. The resulting solid (55/45 mixture of **(*S*)-4** and its enantiomer) was filtered, and the filtrate was washed with water (3 × 10 L) and concentrated under vacuum to afford crude **(*S*)-4** as a brownish solid (1.802 kg). This solid was then suspended in isopropanol (11 L), stirred at 40 °C for 1 h, filtered, washed with isopropanol (2 × 0.6 L), and dried under vacuum at 40 °C for 18 h to afford pure **(*S*)-4**. Yield: 1.645 kg (67%), HPLC purity: 99.0% (area %); ee = 99% determined by chiral HPLC upon *Conditions B*: 6.6 min (0.7%, *R*-isomer) and 9.4 min (99.3%, *S*-isomer); $[\alpha]^{25}_D = -59.5°$ (c = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.51 (s, 1 H), 7.35 (s, 1 H), 7.29 (d, J = 8.6 Hz, 1 H), 7.24 (s, 1 H), 6.84 (d, J = 8.6 Hz, 1 H), 4.97 (q, J = 7.3 Hz, 1 H), 3.59 (s, 2 H), 1.43 (d, J = 7.3 Hz, 3 H). MS m/z: 239/241 (MH^+).

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