Novel Approach towards the Synthesis of 3,3a,4,5-Tetrahydroquinolino-[4,3-*c*]isoxazole Derivatives: Application to the Preparation of Previously Unattainable 3a,4-Dihydroazabenzopyrano[4,3-*c*]isoxazole Scaffolds

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Abstract: A novel synthetic approach towards the preparation of 3-substituted-7,8-dimethoxy-3,3a,4,5-tetrahydroquinolino[4,3-*c*]isoxazole derivatives is reported. Further application of this methodology to the preparation of previously unattainable 3a,4-dihydroazabenzopyrano[4,3-*c*]isoxazole derivatives is also described.

Key words: isoxazolines, fused-ring systems, ring closure, heterocycles, antidepressants

The potential antidepressant activity of 3-piperazinylmethyl-3a,4-dihydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole derivatives represented by compound **1** (Figure 1) was recently described by our group.[1–3] This class of compounds presents an interesting combination of activities acting as dual α_2-adrenoceptor antagonists and 5-HT reuptake inhibitors. Several research programs around these structures have been initiated at Johnson & Johnson Pharmaceutical Research and Development to fully explore the SAR of this family of compounds. From this exploration, 3-substituted-7,8-dimethoxy-3,3a,4,5-tetrahydroquinolino[4,3-*c*]isoxazole derivatives emerged as potential additional promising leads for further pharmacological evaluation (Figure 1, compound **2**).[3]

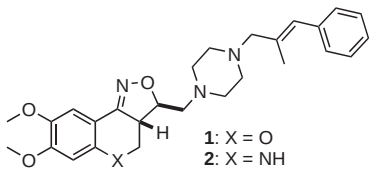
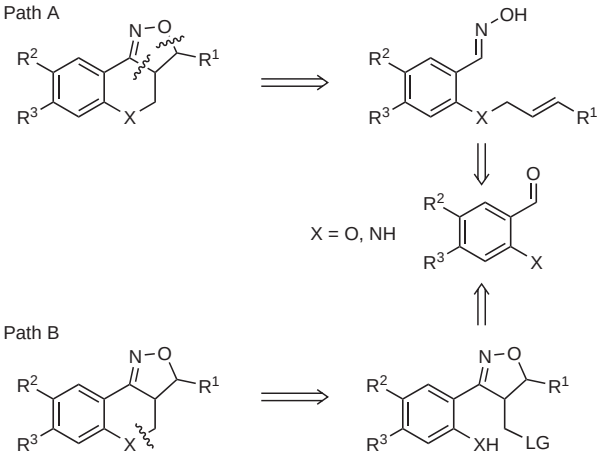


Figure 1 Lead tricyclic isoxazoline derivatives with potential antidepressant activity.

The preparation of these analogues was firstly achieved following the original procedure described by Baraldi et al. (Scheme 1).[4] This procedure involves the generation of the tricyclic system by intramolecular 1,3-dipolar cycloaddition, via nitrile oxides, of the appropriate intermediates (Scheme 1, path A). Unfortunately, when this approach was applied to the preparation of 7,8-dimethoxy-3,3a,4,5-tetrahydroquinolino[4,3-*c*]isoxazole derivatives, the desired compounds were only obtained in very low yields (<5%), making further exploration around this core difficult.[3] Furthermore, the application of this approach to the synthesis of some analogues of prototype **1** presenting a pyridine moiety replacing the phenyl ring proved to be unsuccessful.

In order to circumvent those issues, novel approaches towards the preparation of these analogues were envisaged. After prospecting several alternatives, the construction of the tricyclic core by intramolecular cyclization of the appropriate isoxazoline intermediates (Scheme 1, path B) emerged as the best option. Herein we report an improved method for the synthesis of 7,8-dimethoxy-3,3a,4,5-tetrahydroquinolino[4,3-*c*]isoxazole derivatives and also the application of this novel strategy to the synthesis of 3a,4-dihydroazabenzopyrano[4,3-*c*]isoxazole derivatives previously unattainable via the former procedure.



Scheme 1 Retrosynthetic analyses towards the synthesis of tricyclic isoxazoline cores.

Thus, commercially available 6-nitroveratraldehyde **3** was chosen as starting material for the application of this new procedure (Scheme 2). Conversion of **3** into the corresponding oxime, using standard procedures, followed by oxidation to the corresponding nitrile oxide and in situ 1,3-dipolar cycloaddition with dimethyl fumarate afforded the isoxazoline intermediate **4**. The relative *trans* disposition of substituents at positions 3 and 4 of the

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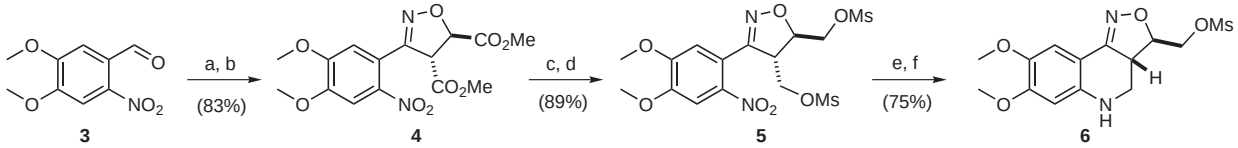
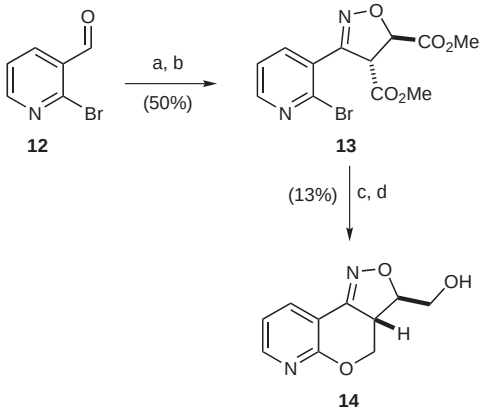


Scheme 2 ***Reagents and conditions***: (a) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, r.t., 1 h; (b) dimethyl fumarate, NaClO, Et_3N, CH_2Cl_2, r.t., 2 h; (c) $NaBH_4$, MeOH–THF, 0 °C, 2 h; (d) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 30 min; (e) H_2, Pd/C, THF–H_2O, r.t., 24 h; (f) Et_3N, THF, reflux, 24 h.

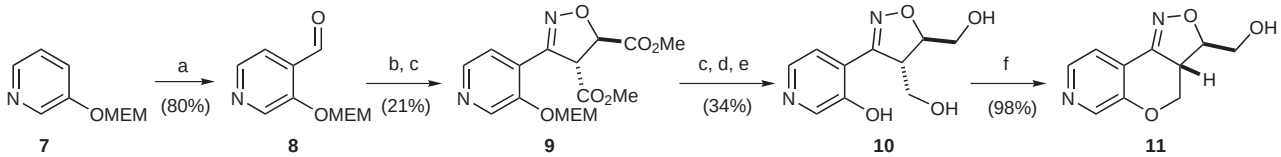
isoxazoline ring was predetermined by the *trans* stereochemistry of the alkene fragment and was unequivocally assigned by NMR analysis. Simultaneous reduction of both ester groups with sodium borohydride in a mixture of tetrahydrofuran–methanol[5] followed by reaction of the dihydroxy derivative obtained with methanesulfonyl chloride furnished compound **5**. Further reduction of the nitro group and subsequent cyclization by intramolecular N-alkylation reaction of the amino group with the adjacent methanesulfonyl group afforded compound **6**.[6] This intermediate additionally bears a second methanesulfonyl group ready for further derivatization. For instance, preparation of compound **2** could be easily performed by simple reaction of intermediate **6** with *trans*-1-(2-methyl-3-phenylpropenyl)piperazine with an overall yield of 26%, what clearly improved the result obtained with the previous procedure (2%).[3] Moreover, the excellent overall yield obtained in the synthesis of scaffold **6** offered clear advantages for further exploration around this heterocyclic system.

Application of this strategy to the synthesis of 3a,4-dihydro-7-aza-3*H*-[1]benzopyrano[4,3-*c*]isoxazole derivative **11** is shown in Scheme 3. Thus, MEM-protected 3-hydroxypyridine **7**[7] was first lithiated at position 4 and then the anion was reacted with methyl formate furnishing 4-carboxaldehyde pyridine derivative **8**. Then, the sequence of oxime formation, oxidation and 1,3-dipolar cycloaddition reactions yielded diester **9**. The relative stereochemistry of both stereocenters was again predetermined by the *trans* configuration of the alkene and remained unaltered during the rest of the synthesis procedure. Subsequent reduction of both ester groups followed by MEM-deprotection in acidic media afforded trihydroxy derivative **10**. Finally, the 3a,4-dihydro-7-aza-3*H*-[1]benzopyrano[4,3-*c*]isoxazole core **11** could be prepared via intramolecular Mitsunobu reaction between the aromatic OH group and the closest hydroxyalkyl moiety.[8] This novel tricyclic system[9] presented a primary hydroxy group suitable for further derivatization.

For the synthesis of the 3-substituted 3a,4-dihydro-6-aza-3*H*-[1]benzopyrano[4,3-*c*]isoxazole derivative **14**, nucleophilic aromatic substitution reaction was chosen as final cyclization step. O-Alkylation or Mitsunobu reactions were tried unsuccessfully as 2-hydroxypyridines mainly exist in the pyridone form.[10] Thus, 5-[2-bromopyridyl-3-yl]isoxazoline derivative **13** was prepared from commercially available 2-bromopyridine-3-carboxaldehyde **12** following the same sequence of reactions already described (Scheme 4). In this case the oxidizing system NCS/pyridine was found to be optimal for the 1,3-dipolar cycloaddition reaction. Then, reduction of both esters of **13** to the corresponding hydroxy groups followed by intramolecular nucleophilic aromatic substitution reaction promoted by basic media afforded desired scaffold **14**[11] in low yield but easily isolated after purification by standard flash chromatography. In this case, again the stereochemistry of both stereocenters was not affected by the cyclization step.



Scheme 4 *Reagents and conditions*: (a) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, r.t., 16 h; (b) dimethyl fumarate, NCS, pyridine, Et_3N, $CHCl_3$, reflux, 2 h; (c) $NaBH_4$, THF–H_2O, 0 °C, 1.5 h; (d) K_2CO_3, methyl isobutyl ketone, reflux, 16 h.



Scheme 3 *Reagents and conditions*: (a) BuLi, TMEDA, methyl formate, Et_2O, 0 °C to r.t., 16 h; (b) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, r.t., 16 h; (c) dimethyl fumarate, NaClO, Et_3N, CH_2Cl_2, r.t., 16 h; (d) $LiAlH_4$, THF, 0 °C, 2 h; (e) TFA, CH_2Cl_2, r.t., 16 h; (f) polymer-supported PPh_3, Et_3N, DEAD, THF, reflux, 16 h.

In conclusion, the synthesis of 3-substituted 7,8-dimethoxy-3,3a,4,5-tetrahydroquinolino[4,3-*c*]isoxazole derivatives has been clearly improved applying a new synthetic approach. This strategy has been successfully applied to the preparation of previously unattainable 3-substituted 3a,4-dihydroazabenzopyrano[4,3-*c*]isoxazole analogues as well. Additionally, three different approaches for the final cyclization step, intramolecular N-alkylation, Mitsunobu and aromatic nucleophilic substitution reactions, have been used, what clearly highlight the versatility of this new procedure. Further applications of these intermediates to the preparation of biologically active compounds will be matter of future publications.

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(5) The absence of water during the reduction step is crucial in order to keep the stereochemistry of both stereocenters, otherwise a mixture of both diastereoisomers is obtained.

(6) **Synthesis of Compound 6 from 5.**
A solution of compound **5** (5.3 mmol, 2.5 g) in THF–H_2O (7.5/1, 85 mL) was hydrogenated at 40 psi of hydrogen in the presence of 10% Pd/C (0.25 g) at r.t. for 24 h. Then the catalyst was removed by filtration over Celite® and the filtrate was concentrated and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated. The residue obtained (2.36 g, 5.3 mmol, 100%) was dissolved in THF (50 mL) and Et_3N (13.25 mmol, 1.85 mL) was added. The resulting solution was stirred at reflux for 24 h and then sat. $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 and the organic layer was separated, dried (Na_2SO_4), filtered and evaporated. The residue was purified by short open-column chromatography on silica gel (CH_2Cl_2–EtOAc, 4:1 and EtOAc) yielding compound **6** as a colorless syrup (4 mmol, 1.36 g, 75%).
Representative analytical data for compound **6**: foam. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 6.90 (s, 1 H, H-9), 6.30 (s, 1 H, H-6), 6.12 (s, 1 H, NH), 4.62 (m, 1 H, CH_2OMs), 4.50 (m, 2 H, H-3 and CH_2OMs), 3.72 (s, 3 H, CH_3O), 3.68 (s, 3 H, CH_3O), 3.45–3.65 (m, 2 H, H-4), 3.23 (s, 3 H, CH_3SO_2O), 3.15 (m, 1 H, H-3a). ESI-HRMS: *m/z* calcd for $C_{14}H_{18}N_2O_6S$ $[MH]^+$: 343.0958; found: 343.0963.

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(8) Several attempts to convert the alkyl hydroxy groups into leaving groups suitable for further intramolecular O-alkylation failed.

(9) **Synthesis of Compound 11 from 10.**
To a solution of **10** (2.72 mmol, 0.61 g) in THF (10 mL), in a sealed tube under N_2, Et_3N (2.72 mmol, 0.38 mL), polymer supported PPh_3 (5.44 mmol, 1.81 g) and diethyl azodicarboxylate (3.41 mmol, 0.67 mL) were added. The reaction mixture was stirred at reflux for 16 h and then filtered through Celite®. The Celite® pad was washed with MeOH and the combined filtrates were evaporated. The residue was re-dissolved in CH_2Cl_2 and washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash-column chromatography on silica gel (EtOAc) yielding compound **11** as a white foam (2.66 mmol, 0.55 g, 98%).
Representative analytical data for compound **11**: syrup. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.41 (s, 1 H, H-6), 8.27 (d, *J* = 5.1 Hz, 1 H, H-8), 7.59 (d, *J* = 5.0 Hz, 1 H, H-9), 4.72 (dd, *J* = 10.5 and 5.7 Hz, 1 H, H-4), 4.50 (dt, *J* = 11.8 and, 3.5 Hz, 1 H, H-3), 4.11–4.22 (m, 2 H, CH_2OH and H-4), 3.98 (td, *J* = 12.2 and 5.7 Hz, 1 H, H-3a), 3.89 (d, *J* = 12.2 Hz, 1 H, CH_2OH), 2.15 (s, 1 H, OH). ESI-HRMS: *m/z* calcd for $C_{10}H_{10}N_2O_3$ $[MH]^+$: 207.0764; found: 207.0759.

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(11) **Synthesis of Compound 14 from 13.**
To a solution of **13** (16.4 mmol, 5.64 g) in THF–MeOH (8:1, 90 mL) at 0 °C $NaBH_4$ (4.1 mmol, 1.55 g) was added portionwise. The mixture was stirred at 0 °C for further 4 h and then an aq sat. NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and evaporated. The crude was purified by short open-column chromatography on silica gel (heptane–EtOAc, 1:1). The residue obtained (0.52 mmol, 1.5 g, 32%) was dissolved in methyl isobutyl ketone (50 mL) and K_2CO_3 (11.7 mmol, 1.62 g) was added. The mixture was stirred at reflux for 4 d and then the solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude was purified by short open-column chromatography on silica gel (CH_2Cl_2–NH_3 sat. MeOH 19:1) yielding compound **14** as a colorless syrup (2.13 mmol, 0.44 g, 41%).
Representative analytical data for **14**: syrup. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.29 (dd, *J* = 4.9, 2.0 Hz, 1 H, H-7), 8.12 (dd, *J* = 7.7, 2.1 Hz, 1 H, H-9), 7.07 (dd, *J* = 7.7 and 4.9 Hz, 1 H, H-8), 4.79 (dd, *J* = 10.7 and 5.9 Hz, 1 H, H-4), 4.47 (dt, *J* = 11.8 and 4.1 Hz, 1 H, H-3), 4.28 (dd, *J* = 12.5 and 10.7 Hz, 1 H, H-4), 3.85–4.03 (m, 3 H, CH_2OH and H-3a), 3.26 (s, 1 H, OH). ESI-HRMS: *m/z* calcd for $C_{10}H_{10}N_2O_3$ $[MH]^+$: 207.0764; found: 207.0769.