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Novel analogues of 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines: modifications in the dioxane ring

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Abstract—The synthesis of a series of novel analogues of the 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine core, modified in the non-aromatic ring, is described. Due to the presence of a versatile hydroxymethyl group in their structure, these novel scaffolds are attractive intermediates for the preparation of potential new therapeutic agents.

Bioisosteric replacement of benzene by pyridine in compounds containing the 2-substituted-2,3-dihydro-1,4-benzodioxin core[1] has yielded derivatives of biological interest in diverse therapeutic areas such as CNS (5-HT_{1A} receptor agonists **1**[2] and **2**[3]) and cardiovascular diseases (calcium antagonist **3**[4]) (Fig. 1). These promising results have prompted interest in the area of 1,4-dioxino-[2,3-*b*]pyridine analogues although described modifications have been mainly focused on the pyridine ring. Thus the synthetic routes to 1,4-dioxinopyridines **4**,[2,5] **5**,[5,6] **6**,[7] **7**[7] and to the 1,4-dioxino[2,3-*d*]pyrimidine **8**,[7] bearing a group on the non-aromatic ring amenable to derivatization (FG), have been reported by Guillaumet and co-workers and by our group (Fig. 1).

In spite of these interesting preliminary findings, to our knowledge, the only potentially derivatizable analogues of the 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine core modified in the 1,4-dioxane ring reported in the literature are systems **9**[8] and **10**[9] (Fig. 2).

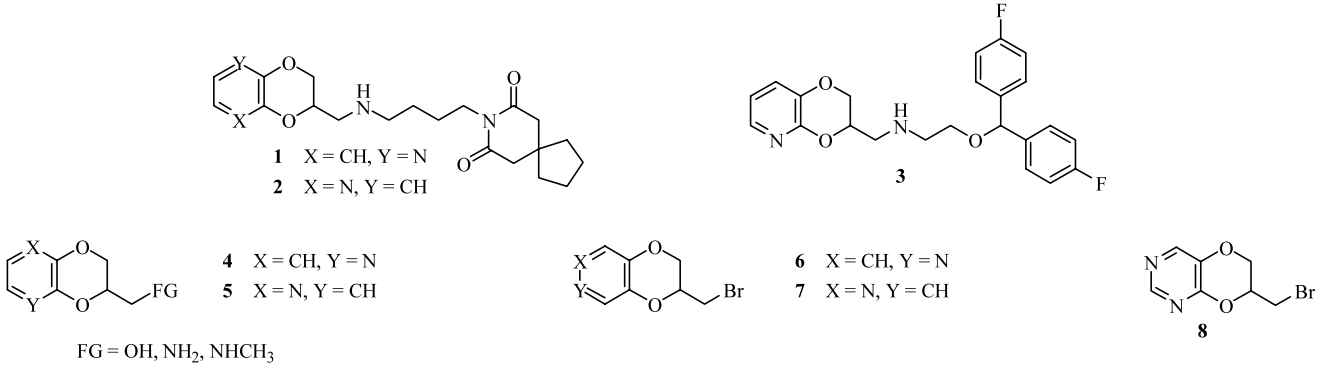

Figure 1.

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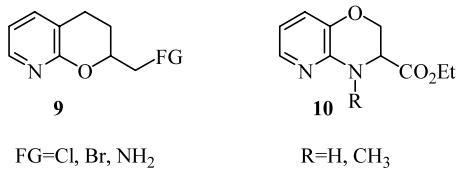


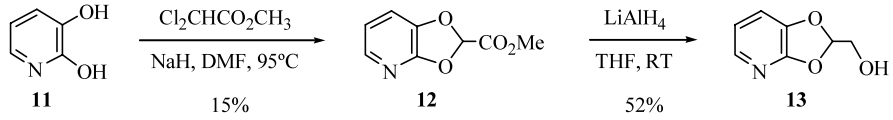
Figure 2.

Herein we report on the most relevant results of our work in this area included in the development of one of our Drug Discovery Programs. Synthetic routes to four novel analogues of the 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine nucleus modified in the oxygenated ring are described. The versatile hydroxymethyl group present in the structure of these scaffolds makes them attractive intermediates for the synthesis of novel potential bioactive compounds.

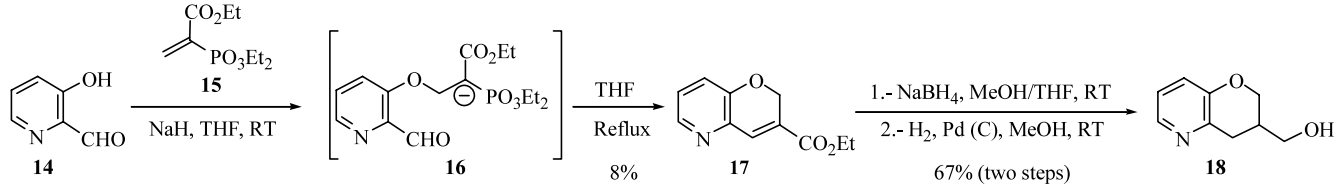
The first targeted modification was the constraint of the 1,4-dioxane ring to a five-membered 1,3-dioxolane ring. The synthesis was initiated using commercially available 2,3-dihydroxypyridine **11** as starting material (Scheme 1). Thus, reaction of **11** with methyl dichloroacetate in DMF in the presence of 2.5 equivalents of NaH as base afforded, in low yield,[10] the 1,3-dioxolo[4,5-*b*]pyridine **12**.[11] Reduction of the ester group of **12** using $LiAlH_4$ yielded, after 1 h of reaction,[12] the expected 2-hydroxymethyl-1,3-dioxolo[4,5-*b*]-pyridine **13** as confirmed by its ^1H NMR and LC/MS data.[13]

The procedure followed to replace the oxygen atom at position 4 of the 1,4-dioxane ring by a carbon is shown in Scheme 2. Key intermediate **17** was prepared from 3-hydroxypyridine-2-carboxaldehyde **14**[14] following a one-pot procedure previously described for salicylaldehyde.[15] This procedure involved Michael addition of the sodium salt of **14** to ethyl 2-diethylphosphonoacrylate **15**,[15] at room temperature, furnishing intermediate phosphonate anion **16**.[15] Subsequent heating of the reaction mixture at reflux temperature promoted intramolecular Wadswoth–Emmons cyclization of **16** to the corresponding bicyclic system **17**, obtained in low yield but easily purified by standard chromatographic procedures.[16] Finally, sequential ester group reduction of **17**, by treatment with $NaBH_4$, to the corresponding alcohol and palladium catalyzed double bond hydrogenation afforded the desired 3-hydroxymethyl-3,4-dihydro-2*H*-pyrano[3,2-*b*]pyridine **18** according to its spectroscopical and analytical data.[17]

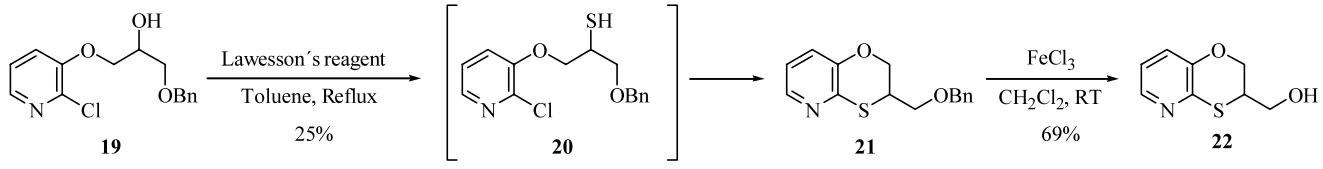
Once the synthesis of scaffolds **13** and **18** had been achieved our efforts were focused on the replacement of the oxygen atoms of the 1,4-dioxane ring by other heteroatoms. In this sense, chemical exploration of various synthetic routes towards these modifications is represented in Schemes 3 and 4.



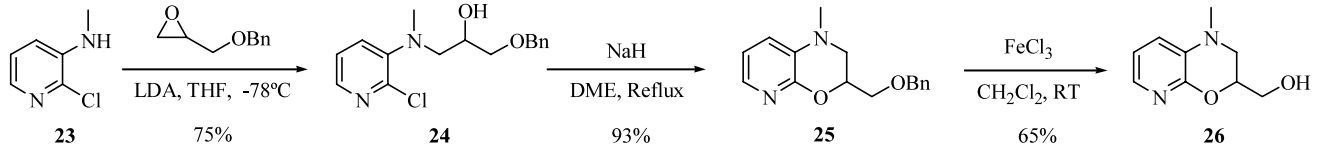
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

For the substitution of the oxygen atom at position 4 by sulphur we used the corresponding 2-chloropyridine derivative **19** as starting material, prepared according to a previously described procedure.[18] The 2,3-dihydro-[1,4]oxathiino[2,3-*b*]pyridine bicyclic core of **21** was prepared in one step from **19** by reaction with Lawesson's reagent in refluxing toluene. This step involved sequential conversion of the hydroxy group of **19** into the corresponding thiol intermediate that was not detected in the reaction media, followed by in situ intramolecular cyclization of **20**, furnishing system **21**.[19] The last step of the synthesis was the debenzylation of **21**, using $FeCl_3$[20] affording the corresponding 3-hydroxymethyl-2,3-dihydro[1,4]-oxathiino[2,3-*b*]pyridine **22** (Scheme 3).[21] The structure of this compound was confirmed by its ^1H NMR spectrum and analytical data.[21]

Finally, for the last modification reported, introduction of an amino methyl group at position 1, the synthetic scheme starts with the alkylation of 2-chloro-3-methylaminopyridine **23**[22] with 2-(benzyloxymethyl)oxirane, in the presence of LDA as base,[23] yielding the corresponding alcohol **24**. Intramolecular base-promoted cyclization of **24**, using NaH in refluxing 1,2-dimethoxyethane (DME) furnished compound **25** which already possesses the desired bicyclic nucleus. Finally, *O*-debenzylation of **25** using $FeCl_3$ led to the corresponding 3-hydroxymethyl-1-methyl-2,3-dihydro-1*H*-[1,4]oxazin[2,3-*b*]pyridine system **26** in good yield (Scheme 4). Confirmation of the structure of **26** was obtained by analysis of its NMR data.[24]

In summary, we have developed new synthetic schemes that have allowed the straightforward preparation of close analogues of the 2,3-dihydro-1,4-dioxino[2,3-*b*]-pyridine system containing a modified dioxane ring. These previously unattainable scaffolds have a derivatizable group (hydroxymethyl) on the non-aromatic ring that could allow their introduction into more complex systems. These new bicyclic cores may be considered as promising intermediates for the synthesis of novel potential therapeutic agents. Further derivatization of the reported systems is ongoing and will be described in due course.

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10. When the reaction was tried using NaH in DMF at room temperature or sodium methoxide in MeOH both, at room temperature and under reflux only starting material was recovered unaltered.
11. In spite of the low yield, **12** was obtained in pure form after standard flash column chromatography over silica gel eluting sequentially with CH_2Cl_2, CH_2Cl_2/acetone (25/1) and CH_2Cl_2/MeOH (25/1).
12. Longer reaction times afforded mainly decomposition.
13. Analytical data for **13**: syrup; ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ 7.63 (dd, $J=5.4$ and 1.4 Hz, 1H, Ar), 6.95 (dd, $J=7.6$ and 1.4 Hz, 1H, Ar), 6.74 (dd, $J=7.6$ and 5.4 Hz, 1H, Ar), 6.28 (t, $J=4.3$ Hz, 1H, C$\underline{H}$), 3.77 (d, $J=4.3$ Hz, 2H, C$\underline{H}_2$OH), 1.93–1.62 (bs, 1H, O$\underline{H}$); MS (electrospray+) $C_7H_7NO_3$: MW 153; found $(M+H)^+$: 154.
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16. Flash column chromatography over silica gel eluting first with CH_2Cl_2 and then with CH_2Cl_2/acetone (9/1 and 4/1).
17. Analytical data for **18**: foam; ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ 8.12 (dd, $J=4.5$ and 1.5 Hz, 1H, Ar), 7.09 (dd, $J=8.2$ and 1.5 Hz, 1H, Ar), 7.04 (dd, $J=8.2$ and 4.5 Hz, 1H, Ar), 4.30 (d, $J=10.7$ Hz, 1H, OC$\underline{H}_2$), 3.89 (dd, $J=10.7$ and 7.2 Hz, 1H, OC$\underline{H}_2$), 3.13–3.07 (m, 2H, C$\underline{H}_2$OH), 3.04 (dd, $J=17.2$ and 3.3 Hz, 1H, C$\underline{H}_2$CH), 2.68 (dd, $J=17.2$ and 7.4 Hz, 1H, C$\underline{H}_2$CH), 2.39–2.32 (m, 1H, C$\underline{H}$), 1.87–1.57 (bs, 1H, O$\underline{H}$); MS (electrospray+) $C_9H_{11}NO_2$: MW 165; found $(M+H)^+$: 166.

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19. Intermediate **20** was obtained after two consecutive flash column chromatographies over silica gel. The first one, eluted with CH_2Cl_2/acetone (9/1), to remove Lawesson's reagent by-products obtained in the course of the reaction and the second one, eluted with hexane/acetone (9/1), to obtain the pure compound.
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21. Analytical data for **22**: foam; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 8.07 (dd, $J=4.6$ and 1.5 Hz, 1H, Ar), 7.01 (dd, $J=8.2$ and 1.5 Hz, 1H, Ar), 6.93 (dd, $J=8.2$ and 4.6 Hz, 1H, Ar), 4.79 (dd, $J=11.4$ and 4.7 Hz, 1H, OCH_2), 4.30 (dd, $J=11.4$ and 2.2 Hz, 1H, OCH_2), 3.75–3.68 (m, 2H, CH_2OH), 3.65–3.59 (m, 1H, CH), 1.98–1.67 (bs, 1H, OH); MS (electrospray+) $C_8H_9NO_2S$: MW 183; found $(M+H)^+$: 184.
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23. When the epoxide opening was tried in the absence of base or using weaker bases, such as Cs_2CO_3 or NaH, no reaction took place.
24. Analytical data for **26**: syrup; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 7.58 (dd, $J=4.7$ and 1.7, 1H, Ar), 6.89 (dd, $J=7.8$ and 1.7 Hz, 1H, Ar), 6.84 (dd, $J=7.8$ and 4.7 Hz, 1H, Ar), 4.53–4.47 (m, 1H, CH), 3.93 (dd, $J=12.0$ and 4.1 Hz, 1H, OCH_2), 3.84 (dd, $J=12.0$ and 5.0 Hz, 1H, OCH_2), 3.28–3.22 (m, 2H, CH_2OH), 2.88 (s, 3H, NCH_3), 2.04–1.59 (bs, 1H, OH); MS (electrospray+) $C_9H_{12}N_2O_2$: MW 180; found $(M+H)^+$: 181.