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Synthesis of novel aza analogues of 2-substituted-2,3-dihydro-1,4-benzodioxins as potential new scaffolds for drug discovery

Encarna Matesanz,[a,*] Jesús Alcázar,[a] J. Ignacio Andrés,[a] Jose M. Bartolomé,[a] Marcel De Bruyn,[b] Javier Fernández[a] and Kristof Van Emelen[b]

[a]*Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen-Cilag S.A., Medicinal Chemistry Department, Jarama s/n, 45007 Toledo, Spain*

[b]*Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica N.V., Medicinal Chemistry Department, Turnhoutseweg 30, B-2340 Beerse, Belgium*

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Abstract—New synthesis approaches that have led to a series of novel aza analogues of the 2-substituted-2,3-dihydro-1,4-benzodioxin core, bearing versatile bromomethyl group on the non aromatic oxygenated ring, are described. According to their structures these novel scaffolds can be useful intermediates for the preparation of potential new therapeutic agents.

The 2,3-dihydro-1,4-benzodioxin core is present in the structure of several biologically interesting compounds.[1] Bioisosteric replacement of benzene by pyridine has proved to be one of the most useful tools for medicinal chemists over the years.[2] This replacement can often be done without any significant influence on the biological activity despite the different electronic distribution and the additional basic character of the pyridine ring.[2] For instance, Guillaumet and co-workers have demonstrated the generality of this approach by synthesizing the 1,4-dioxino[2,3-*b*]pyridine derivatives **3**,[3] **4**[4] and **5**[5] as bioanalogues of MDL 72832 **1** (5-HT_{1A} receptor agonist) and **2** (calcium antagonist) respectively with maintenance of the primary biological activity (Fig. 1).

In spite of these findings, and up to our knowledge, the only aza analogues of the 2,3-dihydro-1,4-benzodioxin skeleton, bearing a functional group amenable to derivatization (FG) on the non-aromatic ring, previously reported in the literature are 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines of general formulas **6**[3,6] and **7**[6,7] (Fig. 1).

As part of a Drug Discovery Program we were interested in the preparation of this kind of heterocycles as

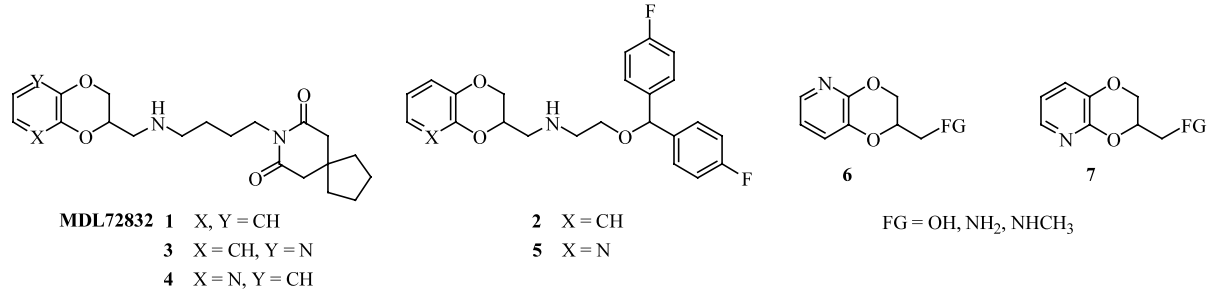

Figure 1.

Keywords: pyridine; heterocycles; 1,4-benzodioxin; 1,4-pyridodioxin; novel scaffolds.

* Corresponding author. Tel.: +34 925 245 750; fax: +34 925 245 771; e-mail: ematesan@prdes.jnj.com

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intermediates for the synthesis of more complex systems. In this communication we now report on the synthesis strategies for the preparation of three novel aza analogues of the 2,3-dihydro-1,4-benzodioxin core, substituted with a bromomethyl group in the 1,4-dioxane ring. According to their structures, these novel heterocycles can be useful intermediates for the synthesis of novel bioactive compounds.

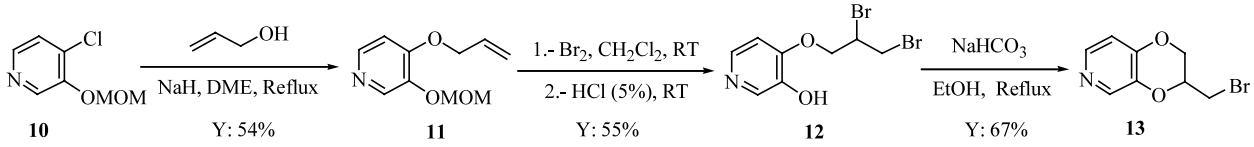
Within this general objective, our first efforts were devoted to the synthesis of the two unreported regioisomeric 2,3-dihydro-1,4-dioxino[2,3-*c*]pyridine scaffolds. In order to achieve this goal in both cases, and after prospection of several possible synthetic pathways, we followed the same strategy: to have a pyridine ring substituted with a conveniently protected oxygen and an allyloxy group in the appropriate positions (general formulas **8** and **9**) as starting point to generate the desired bicyclic systems (Fig. 2).

For the preparation of the 3-substituted-2,3-dihydro-1,4-dioxin[2,3-*c*]pyridine **13** (Scheme 1), we used as starting material the MOM protected 4-chloro-3-hydroxypyridine **10**, prepared according to a previously described procedure.[8] The introduction of the allyloxy group by aromatic nucleophilic substitution was carried out by reaction of **10** with allyl alcohol in 1,2-dimethoxyethane (DME) using NaH as base yielding intermediate **11**.[9] Then, quantitative double bond bromination of **11**, by treatment with bromine in CH_2Cl_2, and subsequent *O*-MOM deprotection in acidic medium afforded compound **12**. Finally, cyclization of **12** in refluxing EtOH, in absence of base or using a weak base such as $NaHCO_3$ furnished the desired 3-bromomethyl-2,3-dihydro-1,4-dioxino[2,3-*c*]-pyridine **13** in good yield.[10] The regiochemistry of the cyclization step was confirmed by analysis of the NMR data of compound **13**.[11]

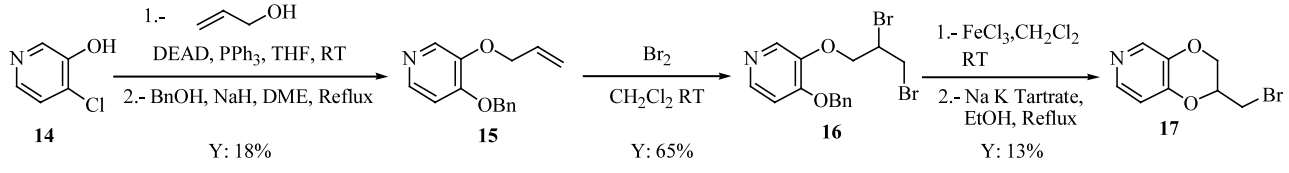
Figure 2.

The starting material for the synthesis of 2-substituted-2,3-dihydro-1,4-dioxino[2,3-*c*]pyridine **17** (Scheme 2) was 4-chloro-3-hydroxypyridine **14**.[8] The corresponding *O*-protected-3-allyloxy-4-hydroxypiridine intermediate **15** was prepared in two steps. Firstly, introduction of the allyloxy group in 3 position by reaction of **14** with allyl alcohol, under standard Mitsunobu conditions,[12] yielded an intermediate which proved to be unstable and had to be used immediately after its synthesis. In second place, the introduction of the benzyloxy group at the 4 position by aromatic nucleophilic substitution with benzyl alcohol led to the desired compound **15**. Then, bromination of the double bond of **15** afforded **16**, which was debenzylated using $FeCl_3$ as deprotection agent[13] to give the corresponding hydroxy intermediate. This compound was cyclized, without purification, in refluxing EtOH using potassium sodium tartrate both to remove iron complexes that interfere in the reaction and as weak base, furnishing the expected system **17** as confirmed by its NMR data.[14]

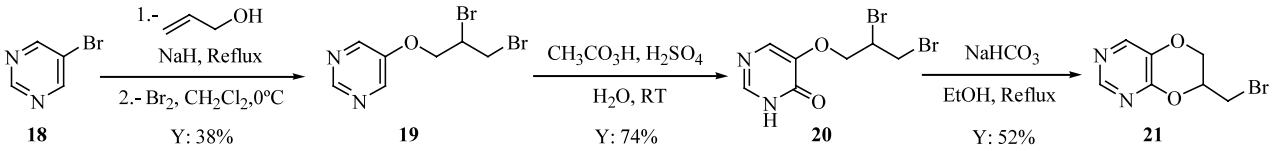
After the obtention of systems **13** and **17**, our work focused on the introduction of a second nitrogen atom in the aromatic ring of the 2-substituted-2,3-dihydro-1,4-dioxino[2,3-*c*]pyridine skeleton, modification that remained unpublished as well. In this sense, among all the possible isomers, we considered the synthesis of the corresponding 6,7-dihydro-1,4-dioxino[2,3-*d*]pyrimidine core as the most feasible. For this purpose, we decided to pursue a synthesis methodology similar to the one previously used for the preparation of **13** and **17** (Scheme 3). Thus, dibrominated derivative **19** was prepared, in moderate yield, by aromatic nucleophilic substitution of allyl alcohol on 5-bromopyrimidine **18** using NaH as base in absence of solvent,[15] followed by reaction with bromine in CH_2Cl_2. Subsequent oxidation of the pyrimidine ring, using the CH_3CO_3H/H_2SO_4 system as oxidant,[16] produced the pyrimidin-4-one **20** in good yield. Finally, intramolecular cyclization of **20** was achieved in refluxing EtOH in the presence of $NaHCO_3$ affording, according to its NMR data, 7-bromomethyl-6,7-dihydro-1,4-dioxino[2,3-*d*]pyrimidine **21**.[17]



Scheme 1.



Scheme 2.



Scheme 3.

In conclusion, we have developed a new synthesis strategy that has allowed us the straightforward preparation of previously unattainable scaffolds, more precisely close analogues of 2,3-dihydro-1,4-benzodioxin containing nitrogen atoms on the phenyl ring. All these novel systems have a derivatizable group (bromomethyl) on the oxygenated non-aromatic ring allowing their introduction in more complex systems. According to their structures these new bicyclic cores may be promising intermediates in the synthesis of new potential therapeutic agents. Further derivatization of the reported systems is on going and will be matter of further publications.

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9. When DMF was used as solvent the allyloxygroup of **11** underwent spontaneous isomerization to the corresponding enol–ether.
10. Cyclization step was tried in different conditions concerning solvent, base and temperature: using either Et_3N in $CHCl_3$ at reflux or NaH in DMF at room temperature, a mixture of two compounds was obtained. In both cases the desired product was the minor fraction while the structure of the major fraction could not be determined.
11. Analytical data for **13**: foam; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 8.23 (s, 1H, Ar), 8.07 (d, $J=5.4$ Hz, 1H, Ar), 6.84 (d, $J=5.4$ Hz, 1H, Ar), 4.45 (m, 2H, C$\underline{H}$ and OC$\underline{H}_2$), 4.25 (dd, $J=11.3$ and 6.2 Hz, 1H, OC$\underline{H}_2$), 3.60 (dd, $J=10.9$ and 4.9 Hz, 1H, C$\underline{H}_2$Br), 3.52 (dd, $J=10.9$ and 7.4 Hz, 1H, C$\underline{H}_2$Br); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 149.6 (C), 144.0 (CH), 140.6 (C), 140.1 (CH), 112.5 (CH), 72.2 (CH), 66.8 (CH_2), 28.6 (CH_2); MS (electrospray +) $C_8H_8BrNO_2$: *Mw* 230; found $(M+H)^+$: 230.
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14. Analytical data for **17**: syrup; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H, Ar), 8.02 (d, $J=5.3$ Hz, 1H, Ar), 6.87 (d, $J=5.3$ Hz, 1H, Ar), 4.46 (m, 1H, C$\underline{H}$), 4.37 (dd, $J=11.8$ and 2.3 Hz, 1H, OC$\underline{H}_2$), 4.17 (dd, $J=11.8$ and 6.2 Hz, 1H, OC$\underline{H}_2$), 3.52 (dd, $J=11.0$ and 5.1 Hz, 1H, C$\underline{H}_2$Br), 3.47 (dd, $J=11.0$ and 7.3 Hz, 1H, C$\underline{H}_2$Br); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 148.8 (C), 143.3 (CH), 139.6 (C), 139.3 (CH), 112.2, 71.4 (CH), 65.6 (CH_2), 27.9 (CH_2); MS (electrospray +) $C_8H_8BrNO_2$: *Mw* 230; found $(M+H)^+$: 230.
15. When the reaction was carried out on DMF or DMSO as solvents the yield of the process dramatically decreased.
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17. Analytical data for **21**: foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H, Ar), 8.29 (s, 1H, Ar), 4.70 (m, 1H, C$\underline{H}$), 4.48 (dd, $J=11.9$ and 2.4 Hz, 1H, OC$\underline{H}_2$), 4.25 (dd, $J=11.9$ and 6.4 Hz, 1H, OC$\underline{H}_2$), 3.68 (dd, $J=11.0$ and 4.5 Hz, 1H, C$\underline{H}_2$Br), 3.55 (dd, $J=11.0$ and 8.1 Hz, 1H, C$\underline{H}_2$Br); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 154.2 (C), 151.6 (CH), 144.7 (CH), 137.7 (C), 73.9 (CH), 65.4 (CH_2), 27.3 (CH_2); MS (electrospray +) $C_7H_7BrN_2O_2$: *Mw* 231; found $(M+H)^+$: 231.