Evaluation and synthesis of 7-arylhydroxymethyltriazolopyridines as potential cardiovascular agents

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Abstract

7-Arylhydroxymethyltriazolopyridines **3a-c** and **4a-d** were synthesized by regioselective lithiation of [1,2,3]triazolo[1,5-*a*]pyridines **1** and **2** and subsequent trapping of the 7-lithio-derivatives formed using aryl aldehydes as electrophiles. The structural relationship between compounds **3a-c** and **4a-d** and arylethanolamines suggested their consideration as potential cardiovascular agents. A preliminary evaluation as vascular smooth muscle relaxants was carried out. These compounds did not act as α_1-adrenoceptor antagonists and were unable to block calcium entry through voltage-dependent calcium channels.

Keywords: Triazolopyridines, lithiation reaction, α_1-adrenoceptor antagonism, calcium channels blockade

Introduction

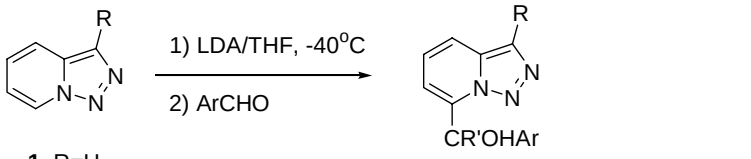
Phenylalkylamines and phenylethanolamines are well known cardiovascular agents. Related compounds such as benzyltetrahydroisoquinoline and bisbenzyltetrahydroisoquinoline alkaloids have the ability to block calcium channels and/or antagonize α_1-adrenoceptors, and may have applications in the treatment of cardiovascular disorders. Some aporphine alkaloids have been also reported to have a relaxant effect on vascular smooth muscle that is also related to their capacity to inhibit Ca^{+2} influx through voltage-operated Ca^{+2} channels or to block α_1-adrenoceptors.[1-4] The search for new compounds with activity in vascular pathologies is an interesting challenge, considering that these conditions are the major cause of death in the European Community. The idea that 7-arylhydroxymethyltriazolopyridines might be considered as structural analogues of the above mentioned compounds led us to synthesize a series of these

triazolopyridine derivatives and to carry out a preliminary evaluation of them as cardiovascular agents.

Results and Discussion

A. Chemistry

In the context of our work on synthesis and reactivity of [1,2,3]triazolo[1,5-*a*]pyridines **1** and **2**,[5] we have studied lithiation reactions that are regioselective at the 7 position. The 7-lithio derivatives are formed at –40ºC and can be trapped by electrophiles. We have now used aryl aldehydes as electrophiles and have synthesized the new 7-arylhydroxymethyltriazolopyridines **4a-d** in addition to the previously known **3a-c**.[6]



1, R=H
2, R=CH_3

3a, R=R'=H, Ar=*p*-MeOPh
3b, R=R'=H, Ar=*p*-NO_2Ph
3c, R=H, R'=Ar=Ph
4a, R=CH_3, R'=H, Ar=Ph
4b, R=CH_3, R'=H, Ar=*m*-MeOPh
4c, R=CH_3, R'=H, Ar=*p*-MeOPh
4d, R=CH_3, R'=H, Ar=2-Pyridyl

B. Biology

The activity of compounds **3a-c** and **4a-d** as relaxants of vascular smooth muscle was tested in isolated aortic rings precontracted by noradrenaline in order to determinate whether any of the compounds show activity as antagonists of the α_1–adrenoceptors present in this tissue and stimulated by the noradrenaline. Addition of 10 μM noradrenaline in Krebs solution induced a sustained contractile response in the intact rat aortic rings (753.8 ± 78.5 mg; n= 28). Compounds **3a-c** and **4a-d** were added in cumulative concentrations (0.0001 μM – 100 μM) to the contracted tissue, but changes in the tone were not observed (n = 4 for each compound). The lack of a relaxant action excludes the possibility that these compounds act as α_1–adrenoceptor antagonists.

In another set of experiments, addition of depolarising solution (KCl 80mM) to aortic rings induced a sustained contractile response in the absence of endothelium (658.8 ± 66.7 mg; n=28). In these conditions, opening of voltage-sensitive calcium channels and calcium entry promotes this contractile response. Subsequent addition of compounds **3a-c** or **4a-d** in cumulative concentrations (0.0001 μM – 100 μM), once the contractile plateau induced by depolarising solution had been reached, did not modify the tone (n = 4 for each compound), thus suggesting that none of the compounds tested can block calcium entry through voltage-dependent calcium channels.

Experimental Section

A. Chemistry

General Procedures. Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC250 instrument at 250 MHz (^{1}H) or 62.5 MHz (^{13}C) in $CDCl_3$ as solvent. HRMS (EI) were recorded on a VG Autospec Trio 1000 (Fisons) instrument. Infrared spectra were recorded in KBr discs on a Bio-Rad FTS-7.

4-Methoxyphenyl-[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanol 3a, 4-nitrophenyl[1,2,3] triazolo[1,5-a]pyridin-7-ylmethanol 3b and diphenyl-[1,2,3]triazolo[1,5-a]pyridin-7-yl methanol 3c. Prepared as described.[6]

General procedure for lithiation of 3-methyl-[1,2,3]triazolo[1,5-a]pyridine 2

A solution of *n*-butyllithium in hexane (2.4mL, 1.6M) was added to diisopropylamine (0.53mL), freshly distilled from KOH, at -40ºC under argon. A solution of 3-methyl-[1,2,3]triazolo[1,5-a]pyridine **2** (0.5g) in anhydrous THF was added with stirring. A deep red colour developed. The mixture was kept at -40ºC for 6h. Treatment with an equimolar amount of the co-reagent changed the colour to yellow. The reaction mixture was left at room temperature overnight, and quenched with a saturated aqueous solution of ammonium chloride. Extraction with dichloromethane gave, after drying and evaporation of the organic solvent, a residue which was purified by chromatography over silica gel. The conditions of the purification are given for each compound.

Phenyl-3-methyl[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanol (4a). The co-reagent was benzaldehyde (0.39g). Elution with ethyl acetate/hexane (1:1) gave a white solid identified as 4a (50% yield). Mp 165-166 ºC (AcOEt/hexane). HRMS found M^+ 239.1063; $C_{14}H_{13}N_3O$ requires 239.1058. ν_{max} (KBr) (cm^{-1}) 3300-3200 (broad, OH), 1650-1600 (C=C). ^{1}H NMR δ 7.52-7.47 (m, 3H), 7.35-7.27 (m, 3H), 7.07 (dd, J_1= 6.9, J_2= 8.8Hz, 1H), 6.56 (d, J= 6.9Hz, 1H), 6.43 (d, $J_{C\underline{H}OH}$= 4.0Hz, 1H), 4.08 (d, $J_{CHO\underline{H}}$= 4.0Hz, 1H), 2.55 (s, 3H). ^{13}C NMR δ 139.88 (C), 138.60 (C), 134.74 (C), 132.03 (C), 128.48 (2 CH), 128.36 (2 CH), 127.13 (CH), 124.04 (CH), 116.38 (CH), 112.94 (CH), 71.73 (CH), 10.31 (CH_3). MS m/z (%), 239 (53), 211 (100), 194 (12), 134 (9), 104 (55), 77 (75).

3-Methoxyphenyl-3-methyl[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanol (4b). The co-reagent was *m*-anisaldehyde (0.51g). Elution with ethyl acetate/hexane (1:2) gave a yellow solid identified as **4b** (70% yield). Mp 140-141 ºC ($CHCl_3$/hexane). HRMS found M^+ 269.1158; $C_{15}H_{15}N_3O_2$ requires 269.1164. ν_{max} (KBr) (cm^{-1}) 3300-3200 (broad, OH), 1600 (C=C). ^{1}H NMR δ 7.57 (d, J= 8.8Hz, 1H), 7.30 (dd, J_1= 8.8, J_2= 7.0Hz, 1H), 7.17-7.08 (m, 3H), 6.89 (dd, J_1= 2.0, J_2= 7.5Hz, 1H), 6.64 (d, J= 7.0Hz, 1H), 6.47 (s, 1H, C<u>H</u>OH), 5.10 (br s, 1H, CHO<u>H</u>), 3.80 (s, 3H, OCH_3), 2.62 (s, 3H). ^{13}C NMR δ 159.69 (C), 140.32 (C), 139.84 (C), 134.62 (C), 131.95 (C), 129.40 (CH), 124.02 (CH), 119.38 (CH), 116.27 (CH), 113.85 (CH), 112.88 (CH), 112.54

(CH), 71.01 (CH), 55.15 (CH_3), 10.23 (CH_3). MS m/z (%), 269 (57), 241 (84), 224 (42), 198 (24), 134 (100), 104 (68), 77 (58).

4-Methoxyphenyl-3-methyl[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanol (4c). The co-reagent was *p*-anisaldehyde (0.51g). Elution with ethyl acetate/hexane (2:3) gave a white solid identified as **4c** (70% yield). Mp 152-154 ºC (AcOEt/hexane). HRMS found M^+ 269.1123; $C_{15}H_{15}N_3O_2$ requires 269.1164. ν_{max} (KBr) (cm^{-1}) 3300-3200 (broad, OH), 1600 (C=C). ^{1}H NMR δ 7.46 (d, J= 8.8Hz, 1H), 7.38 (d, J= 7.9Hz, 2H), 7.09 (dd, J_1= 8.8, J_2= 7.0Hz, 1H), 6.80 (d, J= 7.9Hz, 2H), 6.68 (d, J= 7.0Hz, 1H), 6.38 (s, 1H, C<u>H</u>OH), 4.88 (br s, 1H, CHO<u>H</u>), 3.71 (s, 3H, OCH_3), 2.51 (s, 3H). ^{13}C NMR δ 159.50 (C), 140.23 (C), 134.29 (C), 131.27 (C), 130.81 (C), 128.42 (2 CH), 124.01 (CH), 116.17 (CH), 113.80 (2 CH), 112.57 (CH), 70.83 (CH), 55.18 (OCH_3), 10.26 (CH_3). MS m/z (%), 269 (75), 241 (74), 240 (43), 224 (29), 212 (100), 198 (33), 134 (30), 104 (48), 77 (44).

2-Piridyl-3-methyl[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanol (4d). The co-reagent was 2-pyridylcarbaldehyde (0.45g). Elution with ethyl acetate/hexane (1:3) gave a white solid identified as **4d** (30% yield). Mp 113-115 ºC (CH_2Cl_2/hexane). HRMS found M^+ 240.1011; $C_{13}H_{12}N_4O$ requires 240.1011. ν_{max} (KBr) (cm^{-1}) 3300-3200 (broad, OH), 1600 (C=C). ^{1}H NMR δ 8.45 (d, J= 4.7Hz, 1H), 7.77 (d, J= 7.7Hz, 1H), 7.56 (dd, J_1= J_2= 7.7Hz, 1H), 7.47 (d, J= 8.8Hz, 1H), 7.13 (dd, J_1= 7.7, J_2= 4.7Hz, 1H), 7.11 (dd, J_1= 8.8, J_2= 6.6Hz, 1H), 6.98 (d, J= 6.6Hz, 1H), 6.60 (s, 1H, C<u>H</u>OH), 5.77 (br s, 1H, CHO<u>H</u>), 2.53 (s, 3H). ^{13}C NMR δ 157.44 (C), 148.32 (C), 139.44 (C), 137.06 (CH), 134.59 (C), 132.07 (CH), 124.13 (CH), 123.31 (CH), 121.96 (CH), 116.18 (CH), 112.43 (CH), 70.01 (CH), 10.32 (CH_3). MS m/z (%), 240 (21), 212 (73), 195 (100), 169, (8), 134 (57), 104 (35), 77 (14).

B. Biological Evaluation

Wistar rats of both sexes, weighing 200-220g were decapitated and the thoracic aorta was isolated. The connective tissue was removed and the vessels were cut into rings of about 5 mm in length which were suspended in a 10 ml organ bath containing Krebs-bicarbonate solution (KBS), maintained at 37ºC and gassed with 95% O_2 and 5% CO_2. An initial load of 1 g was applied and maintained throughout a 75-90 min equilibration period. Tension was recorded isometrically on a polygraph (Grass M7) via force-displacement transducers (Grass FT03). KBS had the following composition (mM): NaCl 118, KCl 4.75, $CaCl_2$ 1.8, $MgCl_2$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25 and glucose 11. For experiments with Ca^{2+}-free solution $CaCl_2$ was omitted and EDTA (0.1 mM) was added. Depolarizing solution, 80mM, was prepared by equimolar substitution of NaCl by KCl in the Krebs solution. Endothelium-denuded aortic rings were prepared by rubbing the entire intimal surface. To test for the presence of vascular endothelium, acetylcholine (100 μM) was added to preparations pre-contracted with noradrenaline (1 μM).[7] Acetylcholine-induced-relaxation was expressed as a percentage of the maximum increase in tension obtained by NA addition. Segments with relaxant responses lower than 20% were considered as endothelium-denuded preparations. Concentration-response relaxation curves were

obtained by addition of cumulative concentrations of each compound to vascular rings pre-contracted by noradrenaline (1 μM) or depolarizing solution.[1]

(-)-Noradrenaline bitartrate was from Sigma, St. Louis MO, U.S.A.; other reagents were of analytical grade. Compounds **3a-c** and **4a-d** were dissolved in ethanol and diluted in deionized water. The other drugs were dissolved in deionized water. All solutions were prepared daily and the pH was adjusted to 7.0.

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References

1. Chuliá, S.; Ivorra, M. D.; Martinez, S.; Elorriaga, M.; Valiente, M.; Noguera, M A.; Lugnier, C.; Advenier, Ch.; D'Ocón, P. *Br. J. Pharmacol.* **1997**, *122*, 409.
2. Madrero, M.; Elorriaga, M.; Martinez, S.; Noguera, M A.; Cassels, B. K.; D'Ocón, P.; Ivorra, M. D. *Br. J. Pharmacol.* **1996**, *119*, 1563.
3. Chuliá, S.; Ivorra, M. D.; Lugnier, C.; Vila, E.; Noguera, M A.; D'Ocón, P. *Br. J. Pharmacol.* **1994**, *113*, 1377.
4. Ivorra, M. D.; Chuliá, S.; Lugnier, C., D'Ocón, P. *Eur. J. Pharmacol.* **1993**, *231*, 165.
5. Last part in the series: Abarca, B.; Ballesteros, R.; Elmasnaouy, M. *ARKIVOC* **2002**, *(v)*, 145.
6. Jones, G.; Sliskovic, D.R. *J. Chem. Soc., Perkin 1* **1982**, 967.