SYNTHESIS OF NEW ISOSTERIC HETEROTRICYCLIC DERIVATIVES: PYRAZOLO[3,4-*b*]THIENO[3,2-e]PYRIDINE, PYRAZOLO[3,4-*b*]PYRROLO[3,2-e]PYRIDINE AND FURO[2,3-*b*]PYRAZOLO[4,3-e]PYRIDINE

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Abstract- In this work we report the synthesis of new isosteric heterotricyclic derivatives, presenting the nucleus pyrazolo[3,4-*b*]thieno[3,2-*e*]pyridine 3a, pyrazolo[3,4-*b*]pyrrolo[3,2-*e*]pyridine 3b and furo[2,3-*b*]pyrazolo[4,3-*e*]pyridine 3c. Compounds 3a-c were obtained in good overall yields, exploring the 5-carboethoxy-6-hydroxy-3-methyl-1-phenyl-pyrazolo[3,4-*b*]pyridine 5 as key-intermediate.

In a research program aiming the development of new bioactive compounds, we have reported previously the synthesis of new functionalized heterotricyclic compounds, belonging to pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine 1a and their pyrrole 1b and furane 1c isosteres (1), starting from chloroester derivative 2. These compounds were useful in the synthesis of new antithrombotic PAF antagonists, presenting the thienyl-containing heterocycle 1a as the core nucleus (2). In this context, this paper describes the synthesis of novel functionalized heterotricyclic derivatives, corresponding to pyrazolo[3,4-*b*]thieno[3,2-e]pyridine 3a, pyrazolo[3,4-*b*]pyrrolo[3,2-e]pyridine 3b and furo[2,3-*b*]pyrazolo[4,3-e]pyridine 3c, structurally planned as position isomers of 1a-c, which are important synthons to access a new class of bioactive compounds (3) (Figure 1).

Considering our interest in construct the terminal five-member heterocycle (a, Figure 1) of desired compounds 3a-c, *i.e.* thiophene, pyrrole and furane rings, by applying a similar synthetic strategy to that used in preparation of 1a-c, *i.e.* nucleophilic displacement of chlorine atom of 2, followed by an one-pot Dieckmann cyclization, we elected the regioisomer of 2, ethyl 6-chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate 4 derivative as a key intermediate (Figure 1).

In order to obtain the chloro-ester derivative 4, we identify the corresponding hydroxy-ester derivative 5, as a suitable starting compound for our proposed synthesis (Figure 1). Compound 5 was prepared in 62 % overall yield, following a procedure previously described by Ahluwalia and Goyal (4), by exploring the modified Friedländer reaction of the appropriated *o*-amino-aldehyde-pyrazole 6, as an efficient key step to construction of these condensed bicyclic heterocycles, with unequivocal control of annelation direction by adequate location of functional groups in 6.

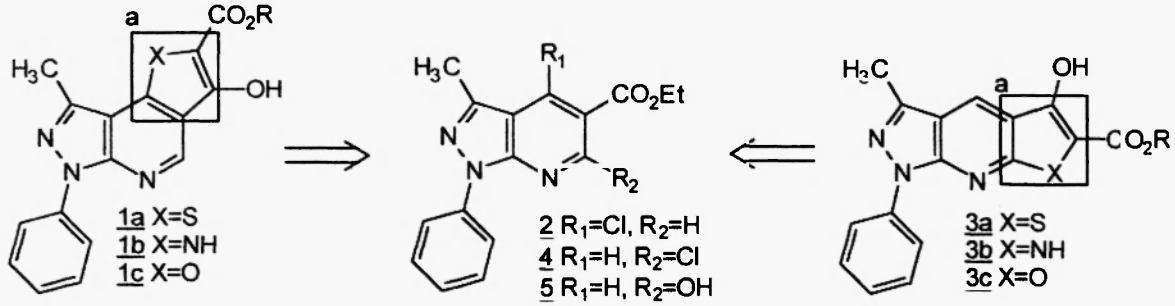


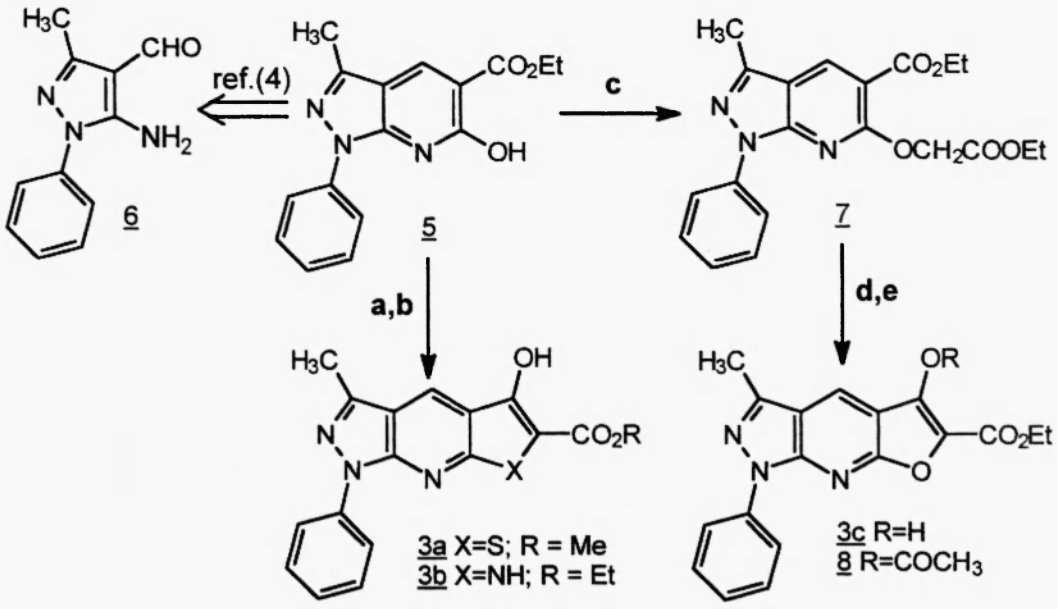
Figure 1

With an efficient method to obtain compound 5 in hands, we promote the next conversion of 5 in the desired chloro-ester derivative 4 by treatment with phosphorous oxychloride at reflux. Unfortunately, in spite to evidence of the total comsuption of 5 after 3 h, the isolation of hydroxy-halogen replacement product 4 was not accomplished even using other variants (*e.g.*, $POCl_3$-PCl_5, PCl_5 and $POCl_3$-Py) (5,6). Otherwise, we are able to detect that the treatment of the reaction residue, after careful remotion of $POCl_3$ excess, with methyl thioglycolate followed by addition of NaOMe, promotes the formation of the desirable product 3a in 65% yield, indicating that the product formed by treatment of 5 with $POCl_3$ could be an unstable phosphate ester (7). The preparation of pyrrole analogue 3b from 5 was accomplished in 71% yield, employing ethyl glycinate and *t*-BuOK as base, in order to avoid the formation of transesterification product evidenced in the previous work from this laboratory(1). In contrast, attempts to obtain the desired oxa-isoster compound 3c employing the same reaction conditions over 5, using the ethyl glycolate oxa-anion, were unsuccessful (Scheme 1). In order to circumvent this unexpected behaviour, we promote the construction of furane ring present in compound 3c, exploring a two steps sequence. Initially, the hydroxy ester intermediate 5 was *O*-alkylated, in 95% yield, with ethyl 2-bromo-acetate, using potassium carbonate in acetone (8).

The structure of all new tricyclic compounds 3a, 3b and 8 were supported by their spectral and elemental analyses data. The synthetic methodologies described herein represents a useful procedure for the synthesis of this new isosteric polyciclic compounds, as an attractive synthons to construct new bioactive derivatives.

Experimental

Melting points were determined with a Quimis 340 apparatus and are uncorrected. ^{1}H NMR spectrum were determined in deuterated chloroform containing *ca.* 1% tetramethylsilane as an internal standard, with Brucker AC 200 or Varian GEMINI 200 at 200 MHz. ^{13}C NMR spectrum were determined in the same spectrometers described above at 50 MHz, employing the same solvents. IR spectra were obtained with Phillips PYE UNICAM SP3-100 and Nicolet 505 Magna spectrophotometers by using sodium chloride cell. Microanalysis data was obtained with Perkin Elmer 240 analyzer, using Perkin Elmer AD-4 balance. The usual work-up means that the organic extracts prior to concentration under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred as to brine, dried over anhydrous sodium sulfate and filtered.



a) $POCl_3$ exc.; **b)** $HSCH_2CO_2Me$, MeONa, MeOH, rt, 2h (65%) or $H_2NCH_2CO_2Et.HCl$, *t*-BuOK, THF, rt, 3h (71%); **c)** K_2CO_3, acetone, rt, 5 min, then $BrCH_2CO_2Et$, rt, 4h (95%); **d)** *t*-BuOK, THF, rt, 3h; **e)** Ac_2O, Py, DMAP, CH_2Cl_2, rt, 16h (41% two steps).

Scheme 1

Ethyl 3-methyl-6-hydroxy-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate 5 (4)

m.p. 285-6°C; ^{1}H-NMR (200 MHz, $CDCl_3$): d 1.4 (t, 3H, J = 7 Hz, CH_2CH_3), 2.6 (s, 3H, CH_3), 4.4 (q, 2H, J = 7.1 Hz, CH_2CH_3), 7.35 (t, 1H, J=7.3 Hz, H-4'), 7.5 (t, 2H, J=7.5 Hz), 8.2 (d, 2H, J= 7.6 Hz, H-2'), 8.6 (s, 1H, H-4), 12.1 (br., 1H, OH, D_2O exchangeable) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): d 12.29 (Ar-CH_3), 14.07 (CH_2CH_3), 62.20 (CH_2CH_3), 103.21 (C-6), 112.38 (C-4), 120.69 (C-3'), 125.73 (C-4'), 128.87 (C-2'), 134.49 (C-5), 138.72 (C-3), 144.67 (C-9), 150.97 (C-1'), 164.65 (C-7), 169.39 (COO) ppm; IR 3330 (NH), 1660 (C=O), Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.59; H, 5.05; N, 14.18

Methyl 5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]thieno[3,2-e]pyridine-6-carboxylate 3a

A mixture of 0.5 g of the compound 5 (1.68 mmol) and 3.5 mL of phosphorous oxychloride containing 0.1 mL of *N,N*-dimethylaniline was refluxed for 3 hours, and the excess of phosphorous oxychloride was carefully distilled at reduced pressure. To the remained residue was added 0.78 mL of methyl thioglycolate (8.53 mmol, 0.905 g). After 2 h, a sodium methoxide solution [prepared from 196 mg of Na° and 15 mL of methanol] was added and the resulting mixture stirred at room temperature for 4 h. After remotion of the volatile solvents, 15 mL of water was added and the mixture formed was extracted with hexane (3 X 20 mL). The aqueous phase was acidified at pH = 3.0 with concentrated HCl, and extracted with dichloromethane (3 x 20 mL). The organic layer was submitted at the usual work-up furnishing a crude solid residue, that after purification by SiO_2 flash chromatography (hexane/ethyl acetate 5%), give 0.37 g (65%) of the compound 3a, as white crystals, m.p. 162-163°C. ^{1}H NMR (200 MHz, $CDCl_3$): d 2.6 (s, 3H, Ar-CH_3), 4.0 (s, 3H, $COOCH_3$), 7.3 (m, 1H, H-4'), 7.5 (m, 2H, H-3'), 8.2 (m, 2H, H-2'), 8.59 (s, 1H, H-4), 11.91 (s, 1H, D_2O exchangeable)

ppm; ^{13}C NMR (50 MHz, $CDCl_3$): d 12.18 (Ar-$\underline{C}H_3$), 52.73 (COO$\underline{C}H_3$), 102.93 (C-6), 112.16 (C-4a), 112.38 (C-3a), 120.62 (C-3'), 125.70 (C-4'), 128.84 (C-2'), 134.49 (C-4), 138.71 (C-1'), 144.65 (C-3), 150.94 (C-8a), 155.0 (C-7a), 164.47 (<u>C</u>OOCH$_3$), 169.68 (C-5) ppm; IR 3448 (n OH) 3019 (n C-H), 1676 (n C=O). Anal Calcd. for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found: C, 60.21; H, 3.91; N, 12.35.

Ethyl 5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyrrolo[3,2-*e*]pyridine 6-carboxylate 3b

A mixture of 0.23 g of the compound 5 (0.79 mmol) and 3 mL of phosphorous oxychloride containing 0.1 mL of *N,N*-dimethylaniline was refluxed for 3 hours, and the excess of phosphorous oxychloride was carefully distilled at reduced pressure. After suspension of the residue in anhydrous THF (15 mL), ethyl glycinate hydrochloride (0.40 g, 3.96 mmol) and *t*-BuOK (0.88 g, 7.93 mmol) were added. The resulting mixture stirred at room temperature for 16 h. After remotion of the volatile solvents, 15 mL of water was added and the mixture was acidified at pH = 3.0 with concentrated HCl, furnishing a white precipitate that was filtered out and purified by SiO_2 flash chromatography (hexane/ethyl acetate 10%), to give 0.19 g (71%) of the compound 3b, as white crystals, m.p. 191-192°C. ^{1}H NMR(200 MHz, $CDCl_3$): d 1.48 (t, 3H, J = 7 Hz, $CH_2\underline{C}H_3$), 2.5 (s, 3H, Ar-$\underline{C}H_3$), 4.58 (q, 2H, J = 7 Hz, $\underline{C}H_2CH_3$), 7.2 (m, 1H, H-4'), 7.42 (m, 2H, H-3'), 8.13 (m, 2H, H-2'), 8.64 (s, 1H, H-4) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): d 12.34 (Ar-$\underline{C}H_3$), 14.25 (COOCH$_2\underline{C}H_3$), 63.96 (COO$\underline{C}H_2CH_3$), 108.52 (C-6), 112.37 (C-3a), 112.4 (C-4a), 120.05 (C-3'), 125.57 (C-4'), 128.88 (C-2'), 137.08 (C-4), 139.01 (C-1'), 144.61 (C-8a), 149.52 (C-7a), 161.35 (C-5), 165.57 (C-3), 165.75 (COO) ppm; IR 3444 (n OH) 3062 (n C-H), 1703 (n C=O). Anal.Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.22; H, 4.81; N, 16.70.

Ethyl 2-(5-ethyloxycarbonyl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yloxy)acetate 7

A mixture of 0.59 g (2 mmol) of compound 5 and 0.55 g (4 mmol) of potassium carbonate dissolved in 20 mL of acetone was stirred at room temperature for 5 min. After this time, when the solution acquires a yellow color, 0.2 g (0.13 mL, 2.4 mmol) of ethyl bromo-acetate was added and the reaction was stirred for additional 3 h, until that tlc analysis indicated the total comsuption of starting material. Then, solvent was removed at reduced pressure and the residue obtained was poured into water and extracted with ethyl acetate (3 x 20 mL). Usual work-up of the organic layer furnish a crude residue that after purification by SiO_2 flash chromatography (hexane/ethyl acetate 10%), yield 0.72 g (95%) of the compound 9, as a yellow crystals, m.p. 105°C. ^{1}H NMR (200 MHz, $CDCl_3$): d 1.2 (t, 3H, J = 7.1 Hz, ArCOOCH$_2\underline{C}H_3$), 1.45 (t, 3H, J=7.2 Hz, -OCH$_2$COOCH$_2\underline{C}H_3$), 2.6 (s, 3H, Ar-$\underline{C}H_3$), 4.2 (q, 2H, J = 7 Hz, ArCOOC$\underline{H}_2$CH$_3$), 4.4 (q, 2H, J = 7.1 Hz, -OCH$_2$COOC$\underline{H}_2$CH$_3$), 5.05 (s, 2H, OC$\underline{H}_2$COO), 7.3 (m, 1H, H-4'), 7.45 (m, 2H, H-3'), 8.1 (m, 2H, H-2'), 8.6 (s, 1H, H-4) ppm; ^{13}C NMR(50 MHz, $CDCl_3$): d 12.26 (Ar-$\underline{C}H_3$), 13.94 (ArCOOCH$_2\underline{C}H_3$), 14.16 (-OCH$_2$COOCH$_2\underline{C}H_3$), 60.96 (ArCOO$\underline{C}H_2$CH$_3$), 61.03 (-OCH$_2$COO$\underline{C}H_2$CH$_3$), 63.65 (OC$\underline{H}_2$COO), 148.74 (C-7a), 112.28 (C-3a), 109.29 (C-5), 120.01 (C-3'), 125.51 (C-4'), 128.71 (C-2'), 136.11 (C-4), 138.86 (C-1'), 160.76 (C-6), 144.28 (C-3), 164.29 (<u>C</u>OOCH$_2$CH$_3$), 168.23 (<u>C</u>OOCH$_2$CH$_3$) ppm; 3072 (n C-H), 1728 (n C=O), 1618 (n C=C); Anal. calcd. for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.59; H, 5.48; N, 10.92.

Ethyl 5-acetoxy-3-methyl-1-phenyl-1*H*-furo[2,3-*b*]pyrazolo[4,3-*e*]pyridine-6-carboxylate 8

A mixture of 0.25 g (0.655 mmol) of di-ester derivative 9 and 0.29 g of *t*-BuOK (2.62 mmol) in 10 mL of anhydrous THF were refluxed for 3 hours. The volatile components were removed and the crude residue added, to a mixture of 0.16 mL of pyridine, 0.16 mL of acetic anhydride and 0.005 g of DMAP in 10 mL of dichloromethane. The resulting mixture was stirred at room temperature for 16 h. The organic solution was then extracted with a 5% aq. copper sulfate solution (3 x 20 mL), and submitted to usual work-up. The residue obtained was purified by SiO_2 column chromatography (hexane/ethyl acetate 10%), yelding 0.13 g (41%) of the compound 10 as yellow crystals, m.p. 163°C. ^{1}H NMR (200 MHz, $CDCl_3$): d 1.42 (t, 3H, J = 4.7 Hz, CH_2CH_3), 2.10 (s, 3H, $OOCCH_3$), 2.46 (s, 3H, Ar-CH_3), 4.43 (q, 2H, J=4.7 Hz, CH_2CH_3), 7.26 (m, 1H, H-4'), 7.50 (m, 2H, H-3'), 8.31 (m, 2H, H-2'), 8.18 (s, 1H, H-4) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): d 12.34 (Ar-CH_3), 14.24 ($COOCH_2CH_3$), 20.55 ($OOCCH_3$), 61.60 ($COOCH_2CH_3$), 110.51 (C-4a), 116.53 (C-3a), 120.46 (C-3'), 123.38 (C-6), 125.68 (C-4'), 129.02 (C-2'), 133.62 (C-4), 138.18 (C-1'), 139.04 (C-3), 143.67 (C-8a), 157.99 ($COOCH_2CH_3$), 158.24 (C-7a), 167.28 ($OOCCH_3$), 169.68 (C-5) ppm; IR 3064 (n C-H), 1758 (n C=O), 1722 (n C=O), 1612 (n C=C) ; Anal. Calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.28; H, 4.55; N, 11.07.

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7. Various attempts to obtain compound 4 were made and we are able to isolate and characterize it, by treatment of 5 with boiling phosphorous oxychloride containing 10% of *N,N'*-dimethylaniline. After a long reaction time (3 days), isolation and purification by column chromatography in basic alumina, furnished only 2% of compound 4, m.p. 188-9°C. ^{1}H NMR (200 MHz, $CDCl_3$): d 1.45 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 2.65 (s, 3H, Ar-CH_3), 4.45 (q, 2H, J = 7.1 Hz, $COOCH_2CH_3$), 7.31 (m, 1H, H-4'), 7.51 (m, 2H, H-3'), 8.18 (d, 2H, H-2'), 8.56 (s, 1H, H-4) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) d 12.63 ($COOCH_2CH_3$), 14.40 (Ar-CH_3), 62.12 ($COOCH_2CH_3$), 115.48 (C-5), 119.97 (C-3a), 120.93 (C-3'), 126.49 (C-4'), 129.32 (C-2'), 134.74 (C-4), 138.73 (C-3), 144.20 (C-6), 149.47 (C-1'), 149.64 (C-7a), 164.93 (COO) ppm; IR:

2976 (n C-H), 1731 (n C=O), 1594 (n C=C); Anal. Calcd. for $C_{16}H_{14}N_3O_2Cl$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.89; H, 4.49; N, 13.37.

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