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A comparative synthesis of 6-benzyl-2,3-dihydroimidazo[2,1-*a*]phthalazine and 2*H*-7-benzyl-3,4-dihydropyrimido[2,1-*a*]phthalazine

Javier Munín [a,b], Lourdes Santana [b], Eugenio Uriarte [b], Fernanda Borges [c], Elías Quezada [c,*]

[a] Departamento de Farmacologia, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain
[b] Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain
[c] Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua Campo Alegre 687, 4169-007 Porto, Portugal

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ABSTRACT

Two new synthetic strategies have been developed for the synthesis of a new class of cyclophthalazine derivatives. 6-Benzyl-2,3-dihydroimidazo[2,1-*a*]phthalazine and 2*H*-7-benzyl-3,4-dihydropyrimido[2,1-*a*]phthalazine were obtained (i) by intramolecular cyclization of the 2-(aminoalkyl)-4-benzyl-2*H*-phthalazin-1-one or (ii) by intramolecular cyclization of the corresponding 2-(4-benzylphthalazin-1(2*H*)-ylideneamino)alcohols previously prepared. The second of the described routes afforded the desired derivatives in high yields.

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Some methodologies have been previously reported to obtain dihydroimidazo and dihydropyrimido derivatives fused to other heterocycles as phthalazines. These methods involve the reaction of an aromatic heterocycle such as the phthalazinone (**I**) which is made to react with phosphorus oxychloride to give the chloro derivative (**II**). This chloro derivative (**II**) reacts with ethanolamine affording the hydroxyalkylamine (**III**) and finally, by treating with thionyl chloride and a base furnishes the tricycle (**IV**).[1,2] Alternatively, the phthalazinone (**I**) reacts with 2-aminoethylammonium tosylate at 200–250 °C resulting in the formation of tricycle (**IV**) (Scheme 1).[3]

Furthermore, the treatment of the either hydroxyalkylamine (**V**) with mineral acids,[4] or their corresponding tosyl[5] and acyloxy[6] derivatives (**VI**), leads to tricyclic skeleton (**VII**), (Scheme 2).

However, the previously described methodology to obtain **IV** from **I** was not an effective procedure, as it resulted in practically complete destruction of the starting material under the reaction conditions while the other methodologies resulted in very low yield.[1–6] Because of these drawbacks, our goal was to optimize a new synthetic route in order to get subsequently a large and selected series of these tricyclic systems bearing a benzyl group at the contiguous position to the nitrogen atom (compounds **6** and **7** in Scheme 3) and to study their potential beneficial cardiovascular effects.

In this work, we evaluate the efficiency to prepare 6-benzyl-2,3-dihydroimidazo[2,1-*a*]phthalazine (**6**) and 2*H*-7-benzyl-3,4-dihydropyrimido[2,1-*a*]phthalazine (**7**) through two different pathways depicted in Scheme 3.

(i) To obtain the 2-(aminoalkyl)-4-benzyl-2*H*-phthalazin-1-one by reaction of a benzalphthalide[7,8] with an appropriate aminoalkylhydrazine followed by intramolecular cyclization according to the published procedure above.[9]
(ii) To obtain the corresponding 2-(4-benzylphthalazin-1(2*H*)-ylideneamino)alcohols by reaction of benzalphthalide with hydrazine to yield the benzylphthalazinona[7,8] followed by reaction with an appropriate aminoalcohol and final cyclization.[10]

Benzalphthalide **3** was secured by reacting phthalic anhydride with phenylacetic acid in the presence of catalytic amounts of potassium acetate using microwave irradiation (350 W, 15 min (at 1 min intervals)), in 71% yield.[11]

Following the route (i), reaction, at room temperature overnight, of benzalphthalide **3** with an excess of 2-hydrazinoethanamine (synthesized via aziridine)[12,13] dissolved in ethanol, resulted in 2-(2-aminoethyl)-4-benzyl-2*H*-phthalazin-1-one (**4**)[14]

* Corresponding author. Tel.: +351 34881814936; fax: +351 34881594912.
E-mail address: elias.quezada@usc.es (E. Quezada).

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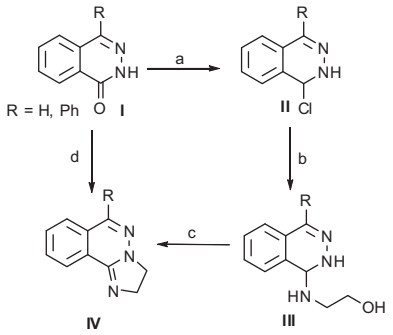
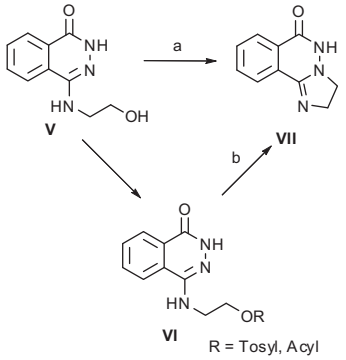


Scheme 1. Reagents and conditions: (a) $POCl_3$, rt; (b) $H_2NCH_2CH_2OH$, 95 °C; (c) $SOCl_2$, K_2CO_3; (d) $H_2NCH_2CH_2NH_3^+p$-$MeC_4H_4SO_3^-$, 200–250 °C.



Scheme 2. Reagents: (a) H^+; (b) Δ.

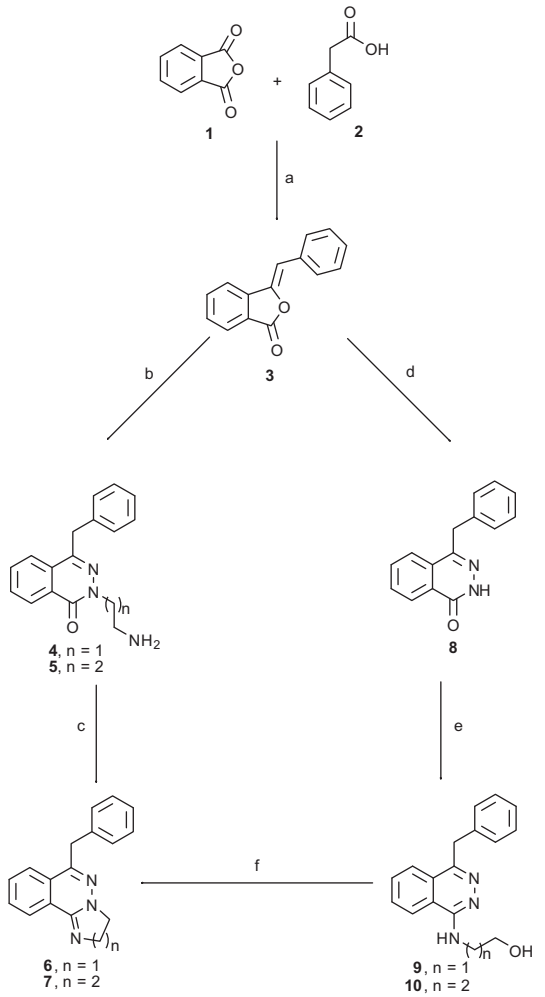
in a low yield (24%), which may be probably due to the instability of the hydrazinoethanamine. However reaction of **3** with 3-hydrazinopropan-1-amine[15] under the above described conditions afforded 2-(3-aminopropyl)-4-benzyl-2*H*-phthalazin-1-one (**5**)[14] in a markedly better yield (76%) due to the greater stability of 3-hydrazinopropan-1-amine.

The 2-(aminoalkyl)-4-benzyl-2*H*-phthalazin-1-ones **4** and **5** were dissolved in ethylene glycol monomethyl ether[9] and heated under reflux overnight to afford, respectively, 6-benzyl-2,3-dihydroimidazo[2,1-*a*]phthalazine (**6**)[16] in 6% yield and 2*H*-7-benzyl-3,4-dihydropyrimido[2,1-*a*]phthalazine (**7**)[16] in 11% yield. Probably, these low yields can be explained by the low stability of the 2-(aminoalkyl)-4-benzyl-2*H*-phthalazin-1-ones **4** and **5** under these reaction conditions.

Alternatively compounds **6** and **7** were prepared from the benzalphthalide (**3**) in three steps following the route (ii).

Firstly, reaction of **3** with hydrazine (1 M in THF) at room temperature for 2 h followed by heating at 60 °C for 4 h, provided 4-benzyl-2*H*-phthalazin-1-one (**8**)[17] in almost quantitative yield. The high yield of this reaction, allowed us to purify **8** by crystallization from EtOAc.

The 2-(4-benzylphthalazin-1(2*H*)-ylideneamino)alcohols (**9**) and (**10**) were prepared in nearly quantitative yields (98% and 97%, respectively) by reaction under reflux of the benzylphthalazinone (**8**) with 2-aminoethanol and 3-aminopropan-1-ol, respectively.[18] The high yields of these reactions, allowed to **9** and **10** to be purified by crystallization from CH_3CN. Finally the reaction of the 2-(4-benzylphthalazin-1(2*H*)-ylideneamino)alcohols **9** and **10** with carbon tetrabromide and triphenylphosphine refluxing in CH_2Cl_2 overnight resulted in the 6-benzyl-2,3-dihydroimidazo[2,1-*a*]phthalazine (**6**) and 2*H*-7-benzyl-3,4-dihydropyrimido[2,1-*a*]phthalazine (**7**), in yields of 60% and 72%, respectively.



Scheme 3. Reagents and conditions: (a) AcOK, MW 350 W, 15 min, 71%; (b) $H_2N(CH_2)_nCH_2NHNH_2$, EtOH, rt, 12 h, $n = 1$ (24%), $n = 2$ (76%); (c) $CH_3OCH_2CH_2OH$, reflux, 12 h, $n = 1$ (6%), $n = 2$ (11%); (d) H_2NNH_2/THF, 2 h, rt and 4 h, 60 °C, 99%; (e) $H_2NCH_2(CH_2)_nOH$, reflux, 48 h, $n = 1$ (98%), $n = 2$ (97%); (f) CBr_4, $P(Ph)_3$, CH_2Cl_2, reflux, 12 h, $n = 1$ (60%), $n = 2$ (72%).

In summary, two new cyclophthalazine derivatives 6-benzyl-2,3-dihydroimidazo[2,1-*a*]phthalazine (**6**) and 2*H*-7-benzyl-3,4-dihydropyrimido[2,1-*a*]phthalazine (**7**) have been synthesized using two different synthetic strategies. Based on the obtained yields, the selected route for the preparation of new derivatives should be the intramolecular cyclization of the corresponding 2-(4-benzylphthalazin-1(2*H*)-ylideneamino)alcohols. 2-(4-Benzylphthalazin-1(2*H*)-ylideneamino)alcohols were previously prepared starting from benzalphthalide and condensation with hydrazine gave the benzylphthalazinone. These reactions were performed in nearly quantitative yields. The reaction of the benzylphthalazinone with an appropriate aminoalcohol afforded after cyclization compounds **6** and **7**.

Acknowledgments

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11. *Synthesis of (Z)-3-Benzyliden-3H-isobenzofuran-1-one* (**3**): Phthalic anhydride (**1**) (1.0 g, 6.75 mmol) and 2-phenylacetic acid (**2**) (1.102 g, 8.10 mmol) were melted and KOAc (66 mg, 0.675 mmol) was added. The mixture was heated (the temperature is always maintained between 210 and 230 °C) under MW (350 W) for 15 min in 1 min periods until change of colour, then extracted with ethyl acetate and washed with Na_2CO_3 10% and H_2O until pH = 7. Residue was purified by flash chromatography with silica gel (35–70 mesh) using hexane/EtOAc (97:3) as the eluent to give **3**: White solid, mp 90–91 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (dt, J = 1.8; 7.7 Hz, 1H), 7.84 (dt, J = 1.5; 8.5 Hz, 2H), 7.73 (m, 2H), 7.54 (m, 1H), 7.34 (m, 3H), 6.41 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 107.00, 119.76, 123.31, 125.49, 128.36, 128.71 (2C), 129.72, 130.06 (2C), 133.02, 134.44, 140.52, 144.50, 167.01; HR-MS calcd for $C_{15}H_{10}O_2$ $(M)^+$: 222.0681, found 222.0680.

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14. *General procedure for the synthesis of 2-(alkylamine)-4-benzyl-2H-phthalazin-1-ones* **4** and **5**. A solution of 3-benzyliden-3*H*-isobenzofuran-1-one (**3**) (1.8 mmol) and hydrazinoalkylamine (4.5 mmol) in EtOH (10 mL) was stirred for 12 h at rt. The solvent was removed under vacuum and the residue was purified by HPLC with Partisil 10 (Whatman column, 9 × 900 mm, 5 μm) using $CHCl_3$/iPrOH (7:3) as eluent. *2-(2-Aminoethyl)-4-benzyl-2H-phthalazin-1-one* (**4**): White solid, mp 109–110 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.44 (d, J = 6.0 Hz, 1H), 7.71 (m, 3H), 7.27 (m, 5H), 4.34 (t, J = 6.0 Hz, 2H), 4.30 (s, 2H), 3.20 (t, J = 6.0 Hz, 2H), 1.67 (br s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 38.88, 41.02, 53.52, 125.05, 126.70, 127.22, 128.17, 128.34 (2C), 128.68 (2C), 129.05, 131.17, 132.82, 137.71, 145.30, 159.63; HR-MS (ESI) calcd for $C_{17}H_{18}N_3O$ (M^+H^+): 280.1444, found 280.1453. *2-(3-Aminopropyl)-4-benzyl-2H-phthalazin-1-one* (**5**): Yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (d, J = 7.5, 1H), 7.67 (m, 3H), 7.24 (m, 5H), 4.36 (t, J = 6.7, 2H), 4.30 (s, 2H), 2.77 (t, J = 6.7, 2H), 2.17 (br s, 2H), 2.04 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.94, 38.74, 38.89, 47.97, 125.03, 126.66, 127.16, 128.09, 128.30 (2C), 128.64 (2C), 129.06, 131.12, 132.75, 137.74, 145.26, 159.38; HR-MS calcd for $C_{18}H_{19}N_3O$ $(M)^+$: 293.1528, found 293.1521.

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16. *General procedure for the synthesis of benzyl dihydroimidazo and dihydropyrimido[2,1-a]phthalazine*. A solution of 2-(alkylamine)-4-benzyl-2*H*-phthalazin-1-one (**4**) (0.72 mmol) in ethylene glycol monomethyl ether (5 mL) was refluxed for 12 h under N_2 atmosphere and then the solvent was evaporated under vacuum. The product was purified by flash chromatography with silica gel (35–70 mesh) using EtOAc/$(CH_3)_2CO$ (8:2; 7:3 and 6:4) as the eluent. *6-Benzyl-2,3-dihydroimidazo[2,1-a]phthalazine* (**6**) and: White solid, mp 220–221 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.94 (d, J = 9.1 Hz, 1H), 8.01 (m, 3H), 7.29 (m, 5H), 4.88 (t, J = 10.0 Hz, 2H), 2.44 (s, 2H), 4.37 (t, J = 10.0 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 38.61, 42.40, 52.00, 117.92, 126.49, 127.18, 127.81, 128.22 (2C), 128.40, 128.87 (2C), 134.03, 135.98, 136.52, 152.79, 153.31; HR-MS calcd for $C_{17}H_{15}N_3$ $(M)^+$: 261.1266, found 261.1267. *2H-7-Benzyl-3,4-dihydropyrimido[2,1-a]phthalazine* (**7**): White solid, mp 210–211 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.44 (d, J = 9.2 Hz, 1H), 7.87 (m, 3H), 7.28 (m, 5H), 4.52 (t, J = 6.0 Hz, 2H), 4.37 (s, 2H), 3.91 (t, J = 6.0 Hz, 2H), 2.36 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.43, 38.38, 39.01, 52.73, 121.33, 125.78, 126.03, 127.01, 127.11, 128.21 (2C), 128.73 (2C), 133.63, 134.92, 136.03, 148.89, 150.57; HR-MS calcd for $C_{18}H_{17}N_3$ $(M)^+$: 275.1422, found 275.1423. Alternatively, compounds **6** and **7** were prepared by adding triphenylphosphine (0.81 mmol) to a mixture of alcohol **9** or **10** (0.54 mmol) and CBr_4 (0.81 mmol) in dry CH_2Cl_2 (10 mL). After stirring at reflux overnight, the mixture was concentrated to dryness. The crude product was purified by flash chromatography with silica gel (35–70 mesh) using EtOAc/$(CH_3)_2CO$ (8:2; 7:3 and 6:4) as the eluent.
17. *Synthesis of 4-benzyl-2H-phthalazin-1-one* (**8**). 3-Benzyliden-3*H*-isobenzofuran-1-one (**3**) (4.5 mmol) was dissolved in hydrazine 1M in THF (9.0 mL, 9.0 mmol). The mixture was stirred for 2 h at room temperature and for 4 h at 60 °C, in a sealed tube. The mixture was cooled to room temperature and evaporated to dryness. The resulting solid was purified by crystallization in EtOAc, to give **8**: white solid, mp 200–201 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.46 (br s, 1H), 8.48 (d, J = 7.4 Hz, 1H), 7.73 (m, 3H), 7.25 (m, 5H), 4.32 (s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 38.85, 125.36, 126.73, 126.95, 128.24, 128.44 (2C), 128.68 (2C), 129.78, 131.26, 133.40, 137.62, 146.38, 160.93. HR-MS calcd for $C_{15}H_{12}N_2O$ $(M)^+$: 236.095, found 236.0947.
18. *General procedure for the synthesis of (4-Benzylphthalazin-1(2H)-ylideneamino)alcohol* (**9**) and (**10**). 4-Benzyl-2*H*-phthalazin-1-one (**8**) (1.27 mmol) was dissolved in the corresponding aminoalcohol (12.7 mmol) and refluxed for 48 h. The mixture was cooled to room temperature, CH_2Cl_2 (100 mL) was added and washed with H_2O and brine. Organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The resulting solid was purified by crystallization using CH_3CN. *2-(4-Benzylphthalazin-1(2H)-ylideneamino)ethanol* (**9**): White solid, mp 171–172 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.26 (d, J = 6.7 Hz, 1H), 7.95 (d, J = 6.8 Hz, 1H), 7.77 (m, 2H), 7.38 (br s, 1H), 7.20 (m, 5H), 4.94 (br s, 1H), 4.43 (s, 2H), 3.65 (m, 4H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 38.43, 43.97, 59.73, 118.32, 122.47, 124.73, 125.70, 126.10 (2C), 128.38 (2C), 130.81 (2C), 131.43, 139.69, 149.91, 153.47; HR-MS (ESI) calcd for $C_{17}H_{18}N_3O$ (M^+H^+): 280.1444, found 280.1439. *3-(4-Benzylphthalazin-1(2H)-ylideneamino)propan-1-ol* (**10**): White solid, mp 150–151 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.25 (d, J = 6.9 Hz, 1H), 7.96 (d, J = 6.8 Hz, 1H), 7.77 (m, 2H), 7.35 (br s, 1H), 7.21 (m, 5H), 4.71 (br s, 1H), 4.43 (s, 2H), 3.60 (t, J = 6.2 Hz, 2H), 3.52 (t, J = 6.2 Hz, 2H), 1.85 (m, 2H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 32.05, 38.27, 38.44, 58.78, 118.31, 122.39, 124.74, 125.67, 126.10 (2C), 128.39 (2C), 130.80 (2C), 131.39, 139.71, 149.75, 153.43. HR-MS (ESI) calcd for $C_{18}H_{20}N_3O$ (M^+H^+): 294.1601, found: 294.1591.