Tetrahedron 65 (2009) 1574–1580

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pyrazolo[3,4,5-*de*]phthalazine. Syntheses of a practically unknown heterocyclic system

Dolores Viña, Esther del Olmo *, José L. Lopez-Pérez, Arturo San Feliciano

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, CIETUS, University of Salamanca, 37007 Salamanca, Spain

ARTICLE INFO

Article history:
Received 23 September 2008
Received in revised form 17 December 2008
Accepted 23 December 2008
Available online 27 December 2008

ABSTRACT

Simple procedures for the synthesis of 1,3-dihydropyrazolo[3,4,5-*de*]phthalazines (**2**), a practically novel type of heterocyclic compounds, have been developed. Compounds equally substituted at positions N^1 and N^3 can be directly obtained from 4,7-dihalogenated benzalphthalides (**1**). Those with different R_2 and R_3 substituents are prepared through intermediate phthalazin-1-ones (**3**), whose synthesis is also considered.

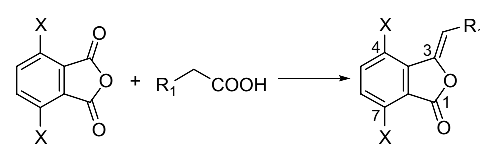
1. Introduction

The development of new efficient methods to synthesize structurally diverse azaheterocycles is of major interest for organic chemists.[1] Among a large variety of *N*-containing heterocycles, those having a bridgehead hydrazine fragment, or a pyrazole ring fused to any homocyclic or heterocyclic system, are common and continue receiving much attention from organic and medicinal chemists, mainly due to the pharmacological activities and clinical applications displayed by many of them. Notably, pyrazole-fused pyrimidines,[2] quinolines[3] and other systems,[4] and those structurally related to endogenous metabolites or drugs, have demonstrated their potential as chemotherapeutic or pharmacodynamic agents against disease. Pyrazolo[1,2-*b*]phthalazines are also well known and have been synthesized and bioevaluated as analgesic and anti-inflammatory.[5] However, pyrazolophthalazines with other ring fusion patterns are much less known. In the particular case of pyrazolo[3,4,5-*de*]phthalazines, only one procedure, based on the reaction between benzalthiocarbazone and tetrachloroquinone, describing the preparation of one unique compound of this type, seems to have been reported.[6]

Last year we described a general one-step procedure for the synthesis of indazoles, through copper oxide-catalyzed hydrazination of various types of *o*-halogeno-substituted aromatic carbonyls.[7] Such procedure seemed to be easily applicable on other types of halocarbonyl substrates, and, consequently, it could serve to synthesize novel heterocyclic systems, containing the hydrazine fragment as part of an additional fused ring. Thus, we report here on the research leading to a small library of pyrazolo[3,4,5-*de*]phthalazine derivatives (**2**), which configure a series of new heterocyclic compounds. They can be directly synthesized from 4,7-dihalogenophthalides (**1**) or through a one-pot two-step procedure from intermediate 5,8-dihalogenophthalazin-1-ones (**3**).

2. Results and discussion

To explore the possibilities of this methodology, a variety of benzalphthalides with different substituents on the aromatic rings were synthesized (Scheme 1).



1a-j

Scheme 1.

The classical synthesis of 3-arylmethylidenephthalides (**1**) consists of prolonged (4–6 h) heating (240–260 °C) of the phthalic anhydride derivative with the appropriate acid and KOAc as catalyst.[8] Yields achieved by this method are usually lower than 70% and tend to decrease, when thermally labile acids and/or substituted phthalic anhydrides are used. Attempts to have an easier access to the desired benzalphthalides using microwave (MW) irradiation resulted partially useful.[9] The method, while shortening the exposure of the mixture to high temperature, afforded reaction products cleaner than those from conventional heating, though yields were not substantially improved (Table 1).

As it is shown, the best yield in phthalide was achieved for the 4-chlorobenzylidene derivative **1b**, which subsequently was the most commonly used in the continued research. Yield attained for the difluoro derivative **1j** was lower than for the dichloro analogue **1b**.

* Corresponding author.
E-mail address: olmo@usal.es (E. del Olmo).

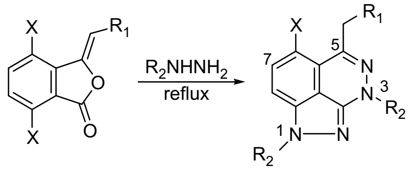
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.12.072

Table 1
Arylmethylidenephthalides synthesized under MW irradiation

Compd[a]	X	R_1	Yield[b]
1a	Cl	Ph	47
1b	Cl	4-ClPh	60
1c	Cl	4-FPh	41
1d	Cl	4-CH_3OPh	43
1e	Cl	2-CH_3OPh	29
1f	Cl	3,4,5-$(CH_3O)_3$Ph	48
1g	Cl	4-NO_2Ph	22
1h	Cl	1-Naphthyl	22
1i	Cl	2-Naphthyl	59
1j	F	4-ClPh	21

[a] All new compounds were characterized by ^{1}H/^{13}C NMR spectral data, elemental analysis and HRMS.
[b] % after crystallization.

The reaction of benzalphthalides **1a**–**j** with an excess of methylhydrazine, under reflux and without any catalyst (Scheme 2), directly led to the corresponding 1,3-dihydropyrazolo[3,4,5-*de*]phthalazines **2a**–**j** (Table 2).



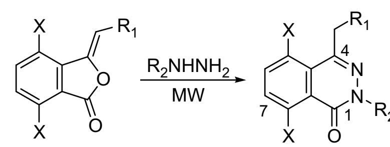
1a-j **2a-k**

Scheme 2.

The formation of this type of pyrazolophthalazines (**2**) should proceed through the intermediate 4-arylmethyl-5,8-dihalogenophthalazin-1-ones (**3**), followed by the cyclocondensation of a second methylhydrazine molecule with the β-halocarbonyl fragment of the substrate. We assumed that this one-pot reaction would similarly work with other hydrazine derivatives and confirmed this fact through the condensation of benzalphthalide **1b** with 2-hydroxyethylhydrazine that led to pyrazolophthalazine **2k**, with comparative better yield than in the case of the methyl derivative **2b**.

According to the proposed pathway, the use of a controlled sequential procedure for the preparation of pyrazolophthalazines should give access to a wider series of pyrazolophthalazines, having different substituents R_2 and R_3 at positions N^1 and N^3. The procedure would include arrest of the reaction at the phthalazin-1-one level and restart with a different hydrazine derivative. In this manner, pyrazolophthalazines **2m**, monosubstituted at N^1, and **2n** and **2o**, N^1,N^3-disubstituted alternately with methyl and hydroxyethyl groups, were prepared in good yields from the trichlorobenzalphthalide **1b** (Table 3).

In the case of equally N^1,N^3-disubstituted pyrazolophthalazines, the best yields were attained by the direct procedure. However, due to the easy formation and isolation of phthalazin-1-ones and mainly to their pharmacological interest as vasorelaxant,[10] polymerase inhibitors[11] and anxiolytic,[12] in most cases, we used the sequential procedure for studying conditions and results of the first reaction. Phthalazin-1-ones had previously been prepared by us through condensation of benzalphthalides with hydrazines under reflux.[13] In such conditions, dihalogenophthalides react completely with methylhydrazine, leading to the corresponding pyrazolo[3,4,5-*de*]phthalazines. Even, when equal number of equivalents of both reagents and soft heating were used, the pyrazolophthalazine was always present in the reaction crude. On the other hand, under MW irradiation (Scheme 3, Table 4), the reaction stopped at the phthalazinone, even in the presence of excess of hydrazine.[14]



1b R_1 = 4-ClPh
1d R_1 = 4-OCH_3
3i

Scheme 3.

The reaction of 4,7-dihalogenobenzalphthalides with methylhydrazine, under MW irradiation, readily led to the expected 2-methylphthalazin-1-ones in moderate to good yields.

However, the reaction of **1b** with hydrazine hydrate, along with the expected phthalazinone **3p** (15%), gave the isoindolinone derivative **4a** as the major product (54%, Scheme 4, Tables 4 and 5),

Table 2
Directly one-pot synthesized N^1,N^3-disubstituted pyrazolophthalazines

Compd[a]	X	R_1	R_2	Yield[b]
2a	Cl	Ph	CH_3	26
2b	Cl	4-ClPh	CH_3	74
2c	Cl	4-FPh	CH_3	25
2d	Cl	4-CH_3OPh	CH_3	54
2e	Cl	2-CH_3OPh	CH_3	21
2f	Cl	3,4,5-$(CH_3O)_3$Ph	CH_3	29
2g	Cl	4-NO_2Ph	CH_3	34
2h	Cl	1-Naphthyl	CH_3	17
2i	Cl	2-Naphthyl	CH_3	20
2j	F	4-ClPh	CH_3	45
2k	Cl	4-ClPh	$(CH_2)_2OH$	80

[a] All new compounds were characterized by ^{1}H/^{13}C NMR spectral data, elemental analysis and HRMS.
[b] % after column chromatography.

Table 3
Differently substituted pyrazolo[3,4,5-*de*]phthalazine prepared sequentially from benzalphthalide **1b**

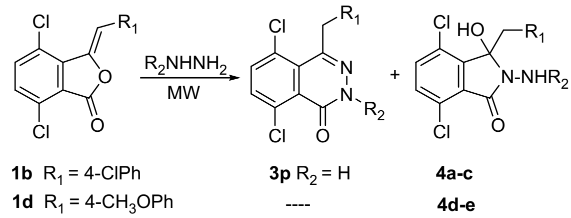
Compd[a]	R_2 (N^3)	R_3 (N^1)	Yield[b]
2m	H	$(CH_2)_2OH$	55
2n	CH_3	$(CH_2)_2OH$	57
2o	$(CH_2)_2OH$	CH_3	51

[a] All new compounds were characterized by ^{1}H/^{13}C NMR spectral data, elemental analysis and HRMS.
[b] % after column chromatography.

Table 4
5,8-Dihalogenated phthalazin-1-ones (**3**) prepared by MW irradiation

Compd[a]	X	R_1	R_2	Yield[b]
3a	Cl	Ph	CH_3	38
3b	Cl	4-ClPh	CH_3	46
3c	Cl	4-FPh	CH_3	30
3d	Cl	4-CH_3OPh	CH_3	46
3e	Cl	2-CH_3OPh	CH_3	65
3f	Cl	3,4,5-$(CH_3O)_3$Ph	CH_3	45
3g	Cl	4-NO_2Ph	CH_3	41
3h	Cl	1-Naphthyl	CH_3	59
3i	Cl	2-Naphthyl	CH_3	28
3j	F	4-ClPh	CH_3	63
3m	Cl	4-ClPh	$(CH_2)_2OH$	39
3p	Cl	4-ClPh	H	15[c]
3q	F	4-CH_3OPh	CH_3	77

[a] All new compounds were characterized by ^{1}H/^{13}C NMR spectral data, elemental analysis and HRMS.
[b] % after column chromatography.
[c] together with compound **4a** (Table 5).



Scheme 4.

Table 5
3-Hydroxyisoindolin-1-ones (**4**) derived from benzalphthalides **1b** and **1d**

Compd[a]	R_1	R_2	Yield[b]	
			MW	Reflux
4a	4-ClPh	H	54	—
4b	4-ClPh	*t*-Bu	18	—
4c	4-ClPh	Ph	55	—
4d	4-CH_3OPh	*t*-Bu	0	50
4e	4-CH_3OPh	Ph	47	93

[a] All new compounds are characterized by $^1H/^{13}C$ NMR spectral data, elemental analysis and HRMS.
[b] % after column chromatography.

while isoindolinones **4b** and **4c**, were, respectively, obtained as unique reaction products, when *tert*-butylhydrazine or phenylhydrazine were used as reagents.[15]

Similarly, changing the substrate to the 4-methoxybenzalphthalide **1d**, the reaction with phenylhydrazine in the mentioned conditions, and even at room temperature, led only to isoindolinone **4e**.

By contrast, previous unpublished results found by us demonstrated that, in absence of the halogen substituents (X) on the phthalide, both *tert*-butyl- and phenylhydrazine could lead to the corresponding phthalazinones, after refluxing with benzalphthalides. Finally, the treatment of 5,8-dichlorophthalazinone **3m** with excess of hydrazine hydrate, under reflux for two days, left mainly unchanged the starting phthalazinone, while a very small amount of the reduced 8-dechlorinated-**3m** could be isolated from the reacted product.

The mentioned failures in the formation of phthalazinones by MW irradiation, obviously, impede the subsequent progress towards the pyrazole-fused derivatives and more research must be done to overcome this problem. Nevertheless, these facts along with the absence of furo[1,2,3-*cd*]indazoles in the reaction products serve us to confirm the sequence phthalide–phthalazinone–pyrazolophthalazine as the actual synthetic pathway towards the final products.

3. Conclusions

In summary, the present findings show that the reaction of 4,8-dichlorobenzalphthalides with methylhydrazine has opened a way to one almost hitherto unknown series of heterocyclic compounds, 1,3-dihydropyrazolo[3,4,5-*de*]phthalazines. Much work for optimizing reaction conditions, enhancing yields and avoiding by-products remains to be performed. New research, focused on the application of this procedure on other substrates and reagents, aiming to prepare novel poly-fused hydrazine-based heterocyclic systems, is currently in progress.

4. Experimental

4.1. General

All NMR spectra were recorded on Bruker WP 200 SY (200 MHz for ^1H and 50.3 MHz for ^{13}C) or Bruker Avance 400 DRX (400 MHz for ^1H and 100 MHz for ^{13}C) or Bruker AMX (500 MHz for ^1H and 125.8 MHz for ^{13}C) spectrometers in $CDCl_3$ and DMSO-d_6 using TMS as internal reference. Chemical shift (δ) values are expressed in parts per million and coupling constants (J) are reported in hertz. High resolution mass spectra (HRMS) and the corresponding low resolution spectra (EIMS and FABMS) were obtained on a VG TS-250 spectrometer by EI and fast atom bombardment (FAB) working at 70 eV and using nitrobenzyl alcohol as the matrix with xenon as the fast atom. Column chromatography (CC) was performed on silica gel (Merck no. 9385). TLCs were carried out on silica gel 60 F_{254} (Merck, 0.25 mm thick) and were detected by UV. Solvents and reagents were purified by standard procedures as necessary.

4.2. General procedure for synthesis of benzalphthalides (1a–j)

4,7-Dichlorophthalic anhydride (1.5 mmol) and phenylacetic acid derivatives (2.7 mmol) were melted and KOAc (0.2 mmol) was added. The mixture was heated (the temperature is always maintained between 210 and 230 °C) under MW (350 W) 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 crystallization in CH_2Cl_2/MeOH to give the products as yellow to brown solids.

*4.2.1. 3-Benzylidene-4,7-dichloro-3H-isobenzofuran-1-one (**1a**)*

^1H NMR ($CDCl_3$) (δ): 7.26 (s, 1H, –CH=), 7.39–7.45 (m, 4H, Aryl-H), 7.63 (dd, 1H, Aryl-H, J=1.5 and 8.4 Hz), 7.88 (d, 2H, Aryl-H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) (δ): 113.7, 126.5, 128.9, 129.3, 131.0, 131.3, 132.4, 132.9, 136.7, 137.8, 141.5, 151.3, 162.8. HRMS (EI): (M+Na) calcd for $C_{15}H_8Cl_2O_2Na$: 312.9794, found: 312.9782. Mp: 205 °C.

*4.2.2. 4,7-Dichloro-3-(4-chlorobenzylidene)-3H-isobenzofuran-1-one (**1b**)*

^1H NMR ($CDCl_3$) (δ): 7.19 (s, 1H, –CH=), 7.38 (d, 2H, Aryl-H, J=8.4 Hz), 7.42 (d, 1H, Aryl-H, J=8.0 Hz), 7.62 (d, 1H, Aryl-H, J=8.4 Hz), 7.79 (d, 2H, Aryl-H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 112.2, 122.3, 126.5, 129.1, 129.9, 131.6, 132.1, 132.5, 135.2, 136.8, 137.6, 141.7, 162.6. HRMS (EI): (M+Na) calcd for $C_{15}H_7Cl_3O_2Na$: 346.9404, found: 346.9408. Mp: 188 °C.

*4.2.3. 4,7-Dichloro-3-(4-fluorobenzylidene)-3H-isobenzofuran-1-one (**1c**)*

^1H NMR ($CDCl_3$) (δ): 7.10 (t, 2H, Aryl-H, J=8.4 Hz), 7.20 (s, 1H, –CH=), 7.40 (d, 1H, Aryl-H, J=8.4 Hz), 7.60 (d, 1H, Aryl-H, J=8.4 Hz), 7.85 (dd, 2H, Aryl-H, J=5.5 and 8.4 Hz). ^{13}C NMR ($CDCl_3$) (δ): 112.3, 116.0 (J=88.2 Hz), 126.4, 129.1, 131.3, 132.4 (J=29.4 Hz), 132.8, 136.7, 137.7, 141.0, 160.5, 162.6, 165.5. HRMS (EI): (M+Na) calcd for $C_{15}H_7O_2FCl_2Na$: 330.9699, found: 330.9680. Mp: 189 °C.

*4.2.4. 4,7-Dichloro-3-(4-methoxybenzylidene)-3H-isobenzofuran-1-one (**1d**)*

^1H NMR ($CDCl_3$) (δ): 3.87 (s, 3H, –OCH_3), 6.96 (d, 2H, Aryl-H, J=8.8 Hz), 7.24 (s, 1H, –CH=), 7.38 (d, 1H, Aryl-H, J=8.4 Hz), 7.60 (d, 1H, Aryl-H, J=8.4 Hz), 7.85 (d, 2H, Aryl-H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 55.4, 113.6, 114.4, 121.9, 125.7, 126.1, 130.7, 132.2, 132.7, 136.5, 137.9, 139.9, 160.5, 163.0. HRMS (EI): (M+Na) calcd for $C_{16}H_{10}Cl_2O_3Na$: 342.9899, found: 342.9897. Mp: 178 °C.

*4.2.5. 4,7-Dichloro-3-(2-methoxybenzylidene)-3H-isobenzofuran-1-one (**1e**)*

^1H NMR ($CDCl_3$) (δ): 3.92 (s, 3H, –OCH_3), 6.91 (dd, 1H, Aryl-H, J=1.1 and 8.4 Hz), 7.05 (td, 1H, Aryl-H, J=1.1 and 7.7 Hz), 7.29–7.37 (m, 1H, Aryl-H), 7.38 (d, 1H, Aryl-H, J=8.4 Hz), 7.60 (d, 1H, Aryl-H, J=8.4 Hz), 7.77 (s, 1H, –CH=), 8.24 (dd, 1H, Aryl-H, J=1.5 and 7.7 Hz). ^{13}C NMR ($CDCl_3$) (δ): 55.9, 107.5, 110.6, 121.1, 121.9, 126.5, 130.7 (2C), 130.9, 131.8, 132.1, 136.6, 138.1, 141.2, 157.6, 163.1. HRMS (EI): (M+Na) calcd for $C_{16}H_{10}Cl_2O_3Na$: 342.9899, found: 342.9921. Mp: 190 °C.

4.2.6. *4,7-Dichloro-3-(3,4,5-trimethoxybenzylidene)-3H-isobenzofuran-1-one (**1f**)*

^{1}H NMR (CDCl$_3$) (δ): 3.91 (s, 3H, –OCH$_3$), 3.94 (s, 6H, –OCH$_3$), 7.08 (s, 2H, Aryl-H), 7.15 (s, 1H, =CH–), 7.38 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.59 (d, 1H, Aryl-H, *J*=8.4 Hz). ^{13}C NMR (CDCl$_3$) (δ): 56.3, 61.0, 108.2, 113.5, 122.0, 126.3, 128.4, 131.1, 132.4, 136.6, 137.7, 139.4, 140.9, 153.3, 162.5. HRMS (EI): (M+Na) calcd for $C_{18}H_{14}Cl_2O_5Na$: 403.0110, found: 403.0133. Mp: 200 °C.

4.2.7. *4,7-Dichloro-3-(4-nitrobenzylidene)-3H-isobenzofuran-1-one (**1g**)*

^{1}H NMR (CDCl$_3$) (δ): 7.31 (s, 1H, –CH=), 7.50 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.69 (d, 1H, Aryl-H, *J*=8.4 Hz), 8.02 (d, 2H, *J*=8.8 Hz), 8.28 (d, 2H, *J*=8.8 Hz). ^{13}C NMR (CDCl$_3$) (δ): 110.4, 123.6, 124.0, 126.6, 127.1, 129.8, 130.5, 131.3, 131.5, 132.5, 137.1, 139.2, 165.8. HRMS (EI): (M+H) calcd for $C_{15}H_8Cl_2NO_4$: 335.9786, found: 336.0303. Mp: 192–197 °C.

4.2.8. *4,7-Dichloro-3-(naphth-1-yl)methylidene-3H-isobenzofuran-1-one (**1h**)*

^{1}H NMR (CDCl$_3$) (δ): 7.44 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.50–7.64 (m, 3H, Aryl-H), 7.67 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.86–7.92 (m, 2H, Aryl-H), 8.07 (s, 1H, –CH=), 8.16 (d, 1H, Aryl-H, *J*=8.4 Hz), 8.32 (d, 1H, Aryl-H, *J*=8.4 Hz). ^{13}C NMR (CDCl$_3$) (δ): 109.6, 123.2, 124.8, 125.4, 125.9, 126.1, 126.8, 127.0, 128.8, 129.1, 129.8, 131.4, 131.8, 132.4, 133.7, 136.7, 137.3, 142.4, 165.5. HRMS (EI): (M+Na) calcd for $C_{19}H_{10}Cl_2O_2Na$: 362.9950, found: 362.9976. Mp: 218 °C.

4.2.9. *4,7-Dichloro-3-(naphth-2-yl)methylidene-3H-isobenzofuran-1-one (**1i**)*

^{1}H NMR (CDCl$_3$) (δ): 7.42 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.46 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.50 (m, 1H, Aryl-H), 7.53 (s, 1H, –CH=), 7.63 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.88 (m, 3H, Aryl-H), 8.06 (d, 1H, Aryl-H, *J*=8.8 Hz), 8.29 (br s, 1H, Aryl-H). ^{13}C NMR (CDCl$_3$) (δ): 113.8, 126.6, 126.7, 127.2, 127.6, 127.7, 128.2, 128.6 (2C), 128.7, 130.3, 130.6, 131.3, 132.4, 133.1, 133.4, 136.7, 143.2, 165.8. HRMS (EI): (M+Na) calcd for $C_{19}H_{10}Cl_2O_2Na$: 362.9950, found: 362.9981. Mp: 209 °C.

4.2.10. *3-(4-Chlorobenzylidene)-4,7-difluoro-(3H)-isobenzofuran-1-one (**1j**)*

^{1}H NMR (CDCl$_3$) (δ): 6.64 (s, 1H, –CH=), 7.16 (td, 1H, Aryl-H, *J*=1.1, 3.3 and 8.8 Hz), 7.40 (d, 2H, Aryl-H, *J*=8.8 Hz), 7.59 (t, 1H, Aryl-H, *J*=5.5 Hz), 7.78 (d, 2H, Aryl-H, *J*=8.8 Hz). ^{13}C NMR (CDCl$_3$) (δ): 112.4 (d, *J*=29.4 Hz), 117.9 (dd, *J*=29.4 and 88.2 Hz), 123.5 (dd, *J*=29.4 and 88.2 Hz), 126.8 (t, *J*=58.8 Hz), 129.2, 131.7, 135.2, 140.6, 151.9, 155.1, 157.3, 158.2, 161.9. HRMS (EI): (M+Na) calcd for $C_{15}H_8F_2ClO_2$: 293.0136, found: 293.0158. Mp: 145 °C.

4.3. General procedure for the synthesis of pyrazolo[3,4,5-*de*]phthalazines (2a–k)

Method A. Benzalphthalides (**1a**–**j**) were dissolved in *N*-alkylhydrazine (1:30 mmol) and refluxed overnight. The mixture was cooled to room temperature, EtOAc was added and washed with H_2O and NaCl solution until pH=7. Organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The resulting solid was purified by flash chromatography (hexane/EtOAc as eluent) to provide the desired products (**2a**–**k**).

Method B. Phthalazinones (**3b**, **3m**, **3p**) were treated under conditions mentioned in method A, affording the corresponding pyrazolo[3,4,5-*de*]phthalazines (**2m**–**o**).

4.3.1. *5-Benzyl-6-chloro-1,3-dimethyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2a**)*

^{1}H NMR (CDCl$_3$) (δ): 3.62 (s, 3H, –CH$_3$), 3.77 (s, 3H, –CH$_3$), 4.30 (s, 2H, –CH$_2$–), 6.63 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.07 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.19–7.29 (m, ArylH, 5H). ^{13}C NMR (CDCl$_3$) (δ): 35.6, 39.2 (2C), 107.0, 110.8, 123.0, 126.2, 128.3, 128.6, 133.5, 139.1, 139.7, 146.0, 155.6, 159.2. HRMS (EI): (M+H) calcd for $C_{17}H_{16}ClN_4$: 311.1058, found: 311.1072. Anal. Calcd for $C_{17}H_{15}ClN_4$: C, 65.70; H, 4.86; N, 18.03. Found: C, 65.66; H, 4.83; N, 17.96. Mp: 104 °C.

4.3.2. *6-Chloro-5-(4-chlorobenzyl)-1,3-dimethyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2b**)*

^{1}H NMR (CDCl$_3$) (δ): 3.60 (s, 3H, –CH$_3$), 3.77 (s, 3H, –CH$_3$), 4.24 (s, 2H, –CH$_2$–), 6.64 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.08 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.23 (m, 4H, Aryl-H). ^{13}C NMR (CDCl$_3$) (δ): 35.6, 38.7, 39.3, 107.2, 110.6, 122.9, 128.5, 130.0, 132.0, 133.4, 137.6, 139.1, 146.0, 155.6, 159.2. HRMS (EI): (M+H) calcd for $C_{17}H_{15}Cl_2N_4$: 345.0668, found: 345.0667. Anal. Calcd for $C_{17}H_{14}Cl_2N_4$: C, 59.14; H, 4.09; N, 16.23. Found: C, 59.07; H, 4.01; N, 16.19. Mp: 150 °C.

4.3.3. *6-Chloro-5-(4-fluorobenzyl)-1,3-dimethyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2c**)*

^{1}H NMR (CDCl$_3$) (δ): 3.61 (s, 3H, –CH$_3$), 3.77 (s, 3H, –CH$_3$), 4.25 (s, 2H, –CH$_2$–), 6.65 (d, 1H, Aryl-H, *J*=8.4 Hz), 6.96 (t, 2H, Aryl-H, *J*=8.8 Hz), 7.08 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.24 (dd, 2H, Aryl-H, *J*=5.5 and 8.8 Hz). ^{13}C NMR (CDCl$_3$) (δ): 35.6, 38.4, 39.2, 107.1, 110.6, 115.1 (*J*=23.7 Hz), 130.0 (*J*=33.0 Hz), 133.4, 134.7, 139.0, 139.5, 145.9, 159.1, 163.2. HRMS (EI): (M+H) calcd for $C_{17}H_{15}FClN_4$: 329.0964, found: 329.0959. Anal. Calcd for $C_{17}H_{14}ClFN_4$: C, 62.10; H, 4.29; N, 17.04. Found: C, 62.13; H, 4.20; N, 16.97. Mp: 115 °C.

4.3.4. *6-Chloro-5-(4-methoxybenzyl)-1,3-dimethyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2d**)*

^{1}H NMR (CDCl$_3$) (δ): 3.61 (s, 3H, –CH$_3$), 3.77 (s, 6H, –(CH$_3$)$_2$), 4.23 (s, 2H, –CH$_2$–), 6.63 (d, 1H, Aryl-H, *J*=8.4 Hz), 6.82 (d, 2H, Aryl-H, *J*=8.8 Hz), 7.07 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.22 (d, 2H, Aryl-H, *J*=8.8 Hz). ^{13}C NMR (CDCl$_3$) (δ): 35.5, 38.3, 39.2, 55.2, 107.0, 110.8, 113.7, 123.0, 129.6, 131.0, 131.3, 133.5, 139.0, 140.0, 146.0, 158.1. HRMS (EI): (M+H) calcd for $C_{18}H_{18}ClN_4O$: 341.1164, found: 341.1157. Anal. Calcd for $C_{18}H_{17}ClN_4O$: C, 63.44; H, 5.03; N, 16.44. Found: C, 63.40; H, 5.06; N, 16.39. Mp: 122 °C.

4.3.5. *6-Chloro-5-(2-methoxybenzyl)-1,3-dimethyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2e**)*

^{1}H NMR (CDCl$_3$) (δ): 3.60 (s, 3H, –CH$_3$), 3.79 (s, 3H, –CH$_3$), 3.86 (s, 3H, –CH$_3$), 4.24 (s, 2H, –CH$_2$–), 6.66 (d, 1H, Aryl-H, *J*=8.8 Hz), 6.86 (t, 2H, Aryl-H, *J*=7.3 Hz), 6.98 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.09 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.20 (td, 1H, Aryl-H, *J*=2.2 and 7.3 Hz). ^{13}C NMR (CDCl$_3$) (δ): 33.9, 35.6, 39.4, 55.5, 106.9, 110.1, 111.3, 120.4, 122.8, 123.3, 127.3, 127.9, 128.3, 133.7, 139.0, 139.7, 145.9, 157.2. HRMS (EI): (M+H) calcd for $C_{18}H_{18}ClN_4O$: 341.1164, found: 341.1163. Anal. Calcd for $C_{18}H_{17}ClN_4O$: C, 63.44; H, 5.03; N, 16.44. Found: C, 63.38; H, 4.96; N, 16.35. Mp: 108 °C.

4.3.6. *6-Chloro-5-(3,4,5-trimethoxybenzyl)-1,3-dimethyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2f**)*

^{1}H NMR (CDCl$_3$) (δ): 3.62 (s, 3H, –CH$_3$), 3.74 (s, 3H, –OCH$_3$), 3.80 (s, 6H, (OCH$_3$)$_2$), 4.22 (s, 2H, –CH$_2$–), 6.56 (s, 2H, Aryl-H), 6.65 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.11 (d, 1H, Aryl-H, *J*=8.8 Hz). ^{13}C NMR (CDCl$_3$) (δ): 35.6, 39.1, 39.3, 56.2, 60.9, 105.8, 107.1, 110.7, 122.9, 133.6, 134.7, 136.1, 136.6, 139.0, 139.6, 145.9, 153.1. HRMS (EI): (M+H) calcd for $C_{20}H_{22}ClN_4O_3$: 401.1375, found: 401.1388. Anal. Calcd for $C_{20}H_{21}ClN_4O_3$: C, 59.92; H, 5.28; N, 13.98. Found: C, 59.95; H, 5.23; N, 13.88. Mp: 102 °C.

*4.3.7. 6-Chloro-1,3-dimethyl-5-(4-nitrobenzyl)-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2g**)*

^{1}H NMR ($CDCl_3$) (δ): 3.61 (s, 3H, $-CH_3$), 3.77 (s, 3H, $-CH_3$), 4.18 (s, 2H, $-CH_2-$), 6.63 (d, 1H, Aryl-H, J=8.8 Hz), 6.67 (d, 2H, Aryl-H, J=8.4 Hz), 7.07 (d, 1H, Aryl-H, J=8.8 Hz), 7.10 (d, 2H, Aryl-H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) (δ): 35.5, 38.2, 39.2, 106.9, 115.2, 123.0, 128.6, 128.8, 129.0, 129.2, 129.4, 133.4, 138.9, 140.1, 144.5. HRMS (EI): (M+H) calcd for $C_{17}H_{14}ClN_5O_2$: 356.0914, found: 356.1717. Anal. Calcd for $C_{17}H_{14}ClN_5O_2$: C, 57.39; H, 3.97; N, 19.68. Found: C, 57.31; H, 3.88; N, 19.57. Mp: 146 °C.

*4.3.8. 6-Chloro-1,3-dimethyl-5-(naphth-1-yl)methyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2h**)*

^{1}H NMR ($CDCl_3$) (δ): 3.58 (s, 3H, $-CH_3$), 3.81 (s, 3H, $-CH_3$), 4.71 (s, 2H, $-CH_2-$), 6.67 (d, 1H, Aryl-H, J=8.6 Hz), 7.07 (d, 1H, Aryl-H, J=8.6 Hz), 7.18 (dd, 1H, Aryl-H, J=0.9 and 7.1 Hz), 7.34 (m, 1H), 7.50–7.55 (m, 2H, Aryl-H), 7.73 (d, 1H, Aryl-H, J=8.2 Hz), 7.87 (d, 1H, Aryl-H, J=8.0 Hz), 8.10 (d, 1H, Aryl-H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) (δ): 35.6, 36.7, 39.7, 107.0, 111.2, 122.9, 123.2, 123.6, 124.6, 124.7, 125.4, 125.5, 125.9, 126.8, 128.8, 132.1, 133.7, 135.3, 139.0, 139.1, 146.0. HRMS (EI): (M+H) calcd for $C_{21}H_{18}ClN_4$: 361.1215, found: 361.1231. Anal. Calcd for $C_{21}H_{17}ClN_4$: C, 69.90; H, 4.75; N, 15.53. Found: C, 69.81; H, 4.70; N, 15.47. Mp: 176 °C.

*4.3.9. 6-Chloro-1,3-dimethyl-5-(naphth-2-yl)methyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2i**)*

^{1}H NMR ($CDCl_3$) (δ): 3.65 (s, 3H, $-CH_3$), 3.78 (s, 3H, $-CH_3$), 4.46 (s, 2H, $-CH_2-$), 6.62 (d, 1H, Aryl-H, J=8.8 Hz), 7.06 (d, 1H, Aryl-H, J=8.8 Hz), 7.38–7.49 (m, 3H, Aryl-H), 7.66–7.80 (m, 4H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 35.6, 39.3 (2C), 107.1, 110.8, 123.0, 125.3, 125.8, 126.7, 127.5, 127.6, 127.9, 132.3, 133.5, 133.6, 135.0, 136.0, 136.7, 139.0, 139.5, 146.0. HRMS (EI): (M+H) calcd for $C_{21}H_{18}ClN_4$: 361.1215, found: 361.1231. Anal. Calcd for $C_{21}H_{17}ClN_4$: C, 69.90; H, 4.75; N, 15.53. Found: C, 69.83; H, 4.69; N, 15.49. Mp: 145 °C.

*4.3.10. 5-(4-Chlorobenzyl)-6-fluoro-1,3-dimethyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2j**)*

^{1}H NMR ($CDCl_3$) (δ): 3.59 (s, 3H, $-CH_3$), 3.75 (s, 3H, $-CH_3$), 3.96 (s, 2H, $-CH_2-$), 6.62 (dd, 1H, Aryl-H, J=2.6 and 8.8 Hz), 6.92 (dd, 1H, Aryl-H, J=8.8 and 10.6 Hz), 7.36 (m, 4H, Aryl-H). HRMS (EI): (M+Na) calcd for $C_{17}H_{14}FClN_4$: 351.0789, found: 351.0702. Anal. Calcd for $C_{17}H_{14}ClFN_4$: C, 62.10; H, 4.29; N, 17.04. Found: C, 62.02; H, 4.17; N, 16.98.

*4.3.11. 6-Chloro-5-(4-chlorobenzyl)-1,3-bis(2-hydroxyethyl)-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2k**)*

^{1}H NMR ($CDCl_3$) (δ): 3.98–4.05 (m, 4H, $(-CH_2-)_2$), 4.12 (s, 2H, $-CH_2-$), 4.21 (t, 2H, $-CH_2-$, J=5.1 Hz), 4.33 (s, 2H, $-CH_2-$), 6.83 (d, 1H, Aryl-H, J=8.8 Hz), 7.21 (m, 5H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 38.7, 51.0, 54.0, 59.9, 61.0, 108.1, 111.3, 122.3, 122.5, 128.4, 130.0, 132.0, 133.8, 137.0, 139.3, 140.3, 145.9. HRMS (EI): (M+H) calcd for $C_{19}H_{19}Cl_2N_4O_2$: 405.0880, found: 405.0888. Anal. Calcd for $C_{18}H_{16}Cl_2N_4O$: C, 57.61; H, 4.30; N, 14.93. Found: C, 57.49; H, 4.25; N, 14.90. Mp: 172 °C.

*4.3.12. 6-Chloro-5-(4-chlorobenzyl)-1-(2-hydroxyethyl)-3H-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2m**)*

^{1}H NMR ($CDCl_3$+CD_3OD) (δ): 3.88 (s, 2H, $-CH_2-$), 4.09 (t, 2H, $-CH_2-$, J=5.5 Hz), 4.19 (s, 2H, $-CH_2-$), 6.73 (d, 1H, Aryl-H, J=8.8 Hz), 7.06 (d, 1H, Aryl-H, J=8.8 Hz), 7.13 (d, 2H, Aryl-H, J=8.8 Hz), 7.21 (d, 2H, Aryl-H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$+CD_3OD) (δ): 42.6, 54.8, 64.8, 112.3, 115.3, 132.3, 132.5, 133.9, 135.9, 137.9, 139.4, 141.2, 142.6, 143.7, 149.1. HRMS (EI): (M+H) calcd for $C_{17}H_{15}Cl_2N_4O$: 362.0617, found: 362.0625. Anal. Calcd for $C_{17}H_{14}Cl_2N_4O$: C, 56.52; H, 3.91; N, 15.51. Found: C, 56.56; H, 3.82; N, 15.48. Mp: 194 °C.

*4.3.13. 6-Chloro-5-(4-chlorobenzyl)-1-(2-hydroxyethyl)-3-methyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2n**)*

^{1}H NMR ($CDCl_3$) (δ): 3.62 (s, 3H, $-CH_3$), 4.02 (s, 2H, $-CH_2-$), 4.17 (m, 2H, $-CH_2-$), 4.26 (s, 2H, $-CH_2-$), 6.71 (d, 1H, Aryl-H, J=8.8 Hz), 7.12 (d, 1H, Aryl-H, J=8.8 Hz), 7.23 (m, 4H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 38.6, 39.5, 50.7, 62.1, 107.5, 111.4, 122.6, 122.8, 128.5, 130.0, 132.1, 134.0, 137.3, 139.2, 139.8, 146.0. HRMS (EI): (M+Na) calcd for $C_{18}H_{17}Cl_2N_4O$: 375.0774, found 375.0785. Anal. Calcd for $C_{18}H_{16}Cl_2N_4O$: C, 57.61; H, 4.30; N, 14.93. Found: C, 57.54; H, 4.26; N, 14.81. Mp: 186 °C.

*4.3.14. 6-Chloro-5-(4-chlorobenzyl)-3-(2-hydroxyethyl)-1-methyl-1,3-dihydropyrazolo[3,4,5-de]phthalazine (**2o**)*

^{1}H NMR ($CDCl_3$) (δ): 3.75 (s, 3H, $-CH_3$), 3.96–4.02 (m, 4H, $-(CH_2-)_2$), 4.26 (s, 2H, $-CH_2-$), 6.67 (d, 1H, Aryl-H, J=8.8 Hz), 7.10 (d, 1H, Aryl-H, J=8.8 Hz), 7.19 (d, 2H, Aryl-H, J=8.8 Hz), 7.26 (d, 2H, Aryl-H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 35.6, 39.0, 54.6, 61.2, 107.6, 111.1, 122.5, 122.8, 128.6, 130.1, 132.2, 133.7, 136.9, 138.9, 140.2, 145.6. HRMS (EI): (M+Na) calcd for $C_{18}H_{16}Cl_2N_4O$: 375.0774, found: 375.0797. Anal. Calcd for $C_{18}H_{16}Cl_2N_4O$: C, 57.61; H, 4.30; N, 14.93. Found: C, 57.50; H, 4.27; N, 14.79. Mp: 143 °C.

4.4. General procedure for the synthesis of phthalazinones (3a–j, 3m and 3p,q) and isoindolinones (4a–e)

A solution of benzalphthalide (**1a**–**k**) and *N*-alkylhydrazine in CH_2Cl_2 was absorbed on silica gel, 10:1 rate silica/benzalphthalide, evaporated to dryness and heated under MW (350 W), the temperature was maintained between 70 and 110 °C for 45 s. Phthalazinones were extracted from the silica washing with EtOAc. Then solvent was evaporated to dryness and the residue purified by flash chromatography (hexane/EtOAc).

*4.4.1. 4-Benzyl-5,8-dichloro-2-methyl-2H-phthalazin-1-one (**3a**)*

^{1}H NMR ($CDCl_3$) (δ): 3.81 (s, 3H, $-CH_3$), 4.67 (s, 2H, $-CH_2-$), 7.09 (m, 2H, Aryl-H), 7.24 (m, 3H, Aryl-H), 7.56 (d, 1H, Aryl-H, J=8.8 Hz), 7.61 (d, 1H, Aryl-H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 39.9, 42.4, 126.3, 126.7, 128.1, 128.5, 129.4, 129.9, 134.5, 134.7, 136.0, 138.8, 142.0, 157.0. HRMS (EI): (M+Na) calcd for $C_{16}H_{12}Cl_2N_2ONa$: 341.0219, found: 341.0228. Mp: 101 °C.

*4.4.2. 5,8-Dichloro-4-(4-chlorobenzyl)-2-methyl-2H-phthalazin-1-one (**3b**)*

^{1}H NMR ($CDCl_3$) (δ): 3.79 (s, 3H, $-CH_3$), 4.62 (s, 2H, $-CH_2-$), 7.02 (d, 2H, Aryl-H, J=8.6 Hz), 7.22 (d, 2H, Aryl-H, J=8.6 Hz), 7.58 (d, 1H, Aryl-H, J=8.8 Hz), 7.63 (d, 1H, Aryl-H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 39.8, 41.7, 126.6, 128.5, 129.1, 129.5, 129.6, 132.1, 134.5, 134.8, 136.3, 137.1, 141.5, 156.8. HRMS (EI): (M+Na) calcd for $C_{16}H_{11}Cl_3N_2ONa$: 374.9829, found: 374.9839. Mp: 111 °C.

*4.4.3. 5,8-Dichloro-4-(4-fluorobenzyl)-2-methyl-2H-phthalazin-1-one (**3c**)*

^{1}H NMR ($CDCl_3$) (δ): 3.80 (s, 3H, $-CH_3$), 4.62 (s, 2H, $-CH_2-$), 6.96 (dt, 2H, Aryl-H, J=2.6 and 8.8 Hz), 7.02 (dt, 2H, Aryl-H, J=5.8 and 8.8 Hz), 7.58 (d, 1H, Aryl-H, J=8.4 Hz), 7.62 (d, 1H, Aryl-H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) (δ): 39.9, 41.6, 115.3 (J=80.9 Hz), 126.7, 129.2, 129.7 (J=29.4 Hz), 134.3, 134.6, 134.8, 136.1, 141.9, 156.9, 159.1, 164.0. HRMS (EI): (M+Na) calcd for $C_{16}H_{11}FCl_2N_2ONa$: 359.0125, found: 359.0133. Mp: 120 °C.

*4.4.4. 5,8-Dichloro-4-(4-methoxybenzyl)-2-methyl-2H-phthalazin-1-one (**3d**)*

^{1}H NMR ($CDCl_3$) (δ): 3.76 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-CH_3$), 4.60 (s, 2H, $-CH_2-$), 6.79 (d, 2H, Aryl-H, J=8.8 Hz), 7.00 (d, 2H, Aryl-H, J=8.8 Hz), 7.57 (d, 1H, Aryl-H, J=8.6 Hz), 7.62 (d, 1H, Aryl-H, J=8.6 Hz). ^{13}C NMR ($CDCl_3$) (δ): 39.9, 41.4, 55.3, 113.9, 126.4, 126.7, 129.2, 129.4, 129.8, 130.7, 132.6, 134.5, 134.7, 136.0, 142.5, 158.1. HRMS (EI): (M+Na) calcd for $C_{17}H_{14}Cl_2N_2O_2Na$: 371.0325, found: 371.0332. Mp: 133 °C.

4.4.5. *5,8-Dichloro-4-(2-methoxybenzyl)-2-methyl-2H-phthalazin-1-one (**3e**)*

^{1}H NMR ($CDCl_3$) (δ): 3.75 (s, 3H, –OCH_3), 3.84 (s, 3H, –CH_3), 4.57 (s, 2H, –CH_2–), 6.68 (d, 1H, Aryl-H, *J*=7.3 Hz), 6.79 (t, 1H, Aryl-H, *J*=7.3 Hz), 6.88 (d, 1H, Aryl-H, *J*=7.7 Hz), 7.20 (t, 1H, Aryl-H, *J*=7.7 Hz), 7.58 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.61 (d, 1H, Aryl-H, *J*=8.4 Hz). ^{13}C NMR ($CDCl_3$) (δ): 37.2, 39.9, 55.4, 110.1, 120.4, 126.6, 127.5, 127.9, 128.2, 129.8, 130.3, 134.4, 134.5, 136.0, 142.1, 156.9, 157.0. HRMS (EI): (M+Na) calcd for $C_{17}H_{14}Cl_2N_2O_2Na$: 371.0325, found: 371.0323. Mp: 142 °C.

4.4.6. *5,8-Dichloro-4-(3,4,5-trimethoxybenzyl)-2-methyl-2H-phthalazin-1-one (**3f**)*

^{1}H NMR ($CDCl_3$) (δ): 3.75 (s, 6H, –$(OCH_3)_2$), 3.80 (s, 3H, –OCH_3), 3.81 (s, 3H, –CH_3), 4.60 (s, 2H, –CH_2–), 6.29 (s, 2H, Aryl-H), 7.63 (s, 2H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 39.9, 42.4, 56.2, 60.9, 105.5, 126.6, 129.5, 129.9, 134.4, 134.6, 134.8, 136.1, 136.7, 142.0, 153.3, 157.0. HRMS (EI): (M+H) calcd for $C_{19}H_{19}Cl_2N_2O_4$: 409.0716, found 409.0701. Mp: 161 °C.

4.4.7. *5,8-Dichloro-2-methyl-4-(4-nitrobenzyl)-2H-phthalazin-1-one (**3g**)*

^{1}H NMR ($CDCl_3$) (δ): 3.79 (s, 3H, –CH_3), 4.75 (s, 2H, –CH_2–), 7.26 (d, 2H, Aryl-H, *J*=8.8 Hz), 7.60 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.66 (d, 1H, Aryl-H, *J*=8.4 Hz), 8.14 (d, 2H, Aryl-H, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 40.0, 42.5, 123.8, 126.7, 129.1, 129.6, 134.3, 134.9, 135.1, 136.1, 140.5, 146.5, 146.7, 156.1. HRMS (EI): (M+H) calcd for $C_{16}H_{12}Cl_2N_3O_3$: 364.0211, found: 364.0203. Mp: 235 °C.

4.4.8. *5,8-Dichloro-2-methyl-4-(naphth-1-yl)methyl-2H-phthalazin-1-one (**3h**)*

^{1}H NMR ($CDCl_3$) (δ): 3.77 (s, 3H, –CH_3), 5.05 (s, 2H, –CH_2–), 6.82 (d, 1H, Aryl-H, *J*=7.0 Hz), 7.29 (t, 1H, Aryl-H, *J*=7.7 Hz), 7.49–7.57 (m, 2H, Aryl-H), 7.56 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.64 (d, 1H, Aryl-H, *J*=8.4 Hz), 7.73 (m, 1H, Aryl-H), 7.89 (m, 1H, Aryl-H), 8.06 (m, 1H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 39.8, 40.0, 123.2, 124.6, 125.5, 125.8, 126.3, 126.7, 127.1, 128.9, 129.8, 130.2, 131.7, 133.8, 134.5, 134.8, 135.6, 136.1, 141.7, 157.0. HRMS (EI): (M+H) calcd for $C_{20}H_{15}Cl_2N_2O$: 369.0556, found: 369.0537. Mp: 172 °C.

4.4.9. *5,8-Dichloro-2-methyl-4-(naphth-2-yl)methyl-2H-phthalazin-1-one (**3i**)*

^{1}H NMR ($CDCl_3$) (δ): 3.84 (s, 3H, –CH_3), 4.81 (s, 2H, –CH_2–), 7.30 (dd, 1H, Aryl-H, *J*=1.5 and 8.4 Hz), 7.37 (s, 1H, Aryl-H), 7.39–7.43 (m, 2H, Aryl-H), 7.54 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.60 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.65–7.78 (m, 3H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 40.0, 42.6, 125.6, 126.1, 126.2, 126.8, 127.1, 127.6 (2C), 128.1, 129.5, 130.0, 132.2, 133.5, 134.6, 134.7, 136.1, 136.5, 142.0, 157.0. HRMS (EI): (M+Na) calcd for $C_{20}H_{14}Cl_2N_2ONa$: 391.0375, found: 391.0368. Mp: 160 °C.

4.4.10. *4-(4-Chlorobenzyl)-5,8-difluoro-2-methyl-2H-phthalazin-1-one (**3j**)*

^{1}H NMR ($CDCl_3$) (δ): 3.83 (s, 3H, –CH_3), 4.24 (d, 1H, –CH_2–, *J*=12.0 Hz), 4.34 (d, 1H, –CH_2–, *J*=12.0 Hz), 7.15 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.28 (d, 2H, Aryl-H, *J*=8.8 Hz), 7.23–7.38 (m, 2H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 39.5, 40.6 (*J*=40 Hz), 117.5, 119.3 (*J*=40 and 92 Hz), 120.0 (*J*=28 Hz), 120.9 (*J*=36 and 104 Hz), 128.5, 129.7, 132.4, 136.3, 140.5 (*J*=24 Hz), 154.5, 155.5, 156.4 (*J*=20 Hz), 159.0 (*J*=24 Hz). HRMS (EI): (M+Na) calcd for $C_{16}H_{11}F_2ClN_2ONa$: 343.0420, found: 343.0436. Mp: 127–131 °C.

4.4.11. *4-(4-Chlorobenzyl)-5,8-dichloro-2-(2-hydroxyethyl)-2H-phthalazin-1-one (**3m**)*

^{1}H NMR ($CDCl_3$) (δ): 3.99 (t, 2H, –CH_2–, *J*=5.1 Hz), 4.33 (t, –CH_2–, *J*=5.1 Hz), 4.63 (s, 2H, –CH_2–), 7.03 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.25 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.64 (s, 2H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 42.1, 53.8, 61.4, 126.7, 128.8, 129.4, 129.8, 130.4, 132.4, 134.9, 135.3, 136.3, 136.7, 142.6, 157.5. HRMS (EI): (M+Na) calcd for $C_{17}H_{13}Cl_3N_2O_2Na$: 404.9940, found 404.9917. Mp: 123 °C.

4.4.12. *4-(4-Chlorobenzyl)-5,8-dichloro-2H-phthalazin-1-one (**3p**)*

^{1}H NMR ($CDCl_3$) (δ): 4.61 (s, 2H, –CH_2–), 7.04 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.24 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.65 (s, 2H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 42.0, 127.0, 128.7, 129.8, 130.0, 130.9, 132.4, 134.8, 135.1, 136.9, 143.4, 149.9, 157.5. HRMS (EI): (M+Na) calcd for $C_{15}H_9Cl_3N_2ONa$: 360.9673, found: 360.9673. Mp: 211 °C.

4.4.13. *5,8-Difluoro-4-(4-methoxybenzyl)-2-methyl-2H-phthalazin-1-one (**3q**)*

^{1}H NMR ($CDCl_3$) (δ): 3.75 (s, 3H, –OCH_3), 3.82 (s, 3H, –CH_3), 4.20 (d, 1H, –CH_2–, *J*=12.0 Hz), 4.30 (d, 1H, –CH_2–, *J*=12.0 Hz), 6.80 (d, 2H, Aryl-H, *J*=1.8 and 8.8 Hz), 7.13 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.31 (m, 2H, Aryl-H). ^{13}C NMR ($CDCl_3$) (δ): 39.5, 40.4 (*J*=37 Hz), 55.3, 113.9, 119.2 (*J*=37 and 96 Hz), 120.9 (*J*=37 and 96 Hz), 129.4, 129.9, 134.9, 141.4 (*J*=29 Hz), 151.0 (*J*=29 Hz), 155.1, 156.0, 158.4, 160.4. HRMS (EI): (M+Na) calcd for $C_{17}H_{14}F_2N_2O_2Na$: 339.0921, found: 339.0913. Mp: 181 °C.

4.4.14. *2-Amino-4,7-dichloro-3-(4-chlorobenzyl)-3-hydroxyisoindolin-1-one (**4a**)*

^{1}H NMR ($CDCl_3$) (δ): 2.85 (br s, 2H, NH_2+OH), 3.59 (d, 1H, –*H*CH–, *J*=13.5 Hz), 3.72 (d, 1H, –*H*CH–, *J*=13.5 Hz), 6.79 (d, 2H, Aryl-H, *J*=8.4 Hz), 6.98 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.22 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.39 (d, 1H, Aryl-H, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 38.7, 90.1, 128.4, 128.6, 129.9, 130.3, 130.5, 132.5, 132.7, 133.4, 133.9, 141.9, 162.5. HRMS (EI): (M+Na) calcd for $C_{15}H_{11}Cl_3N_2O_2Na$: 378.9784, found: 378.9740. Mp: 197–202 °C.

4.4.15. *2-tert-Butylamino-4,7-dichloro-3-(4-chlorobenzyl)-3-hydroxyisoindolin-1-one (**4b**)*

^{1}H NMR ($CDCl_3$) (δ): 1.20 (t, 9H, $C(CH_3)_3$), 3.60 (d, 1H, –*H*CH–, *J*=13.2 Hz), 3.86 (d, 1H, –HC*H*–, *J*=13.2 Hz), 4.43 (br s, 1H, OH), 6.79 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.00 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.28 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.44 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.58 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) (δ): 28.9, 38.7, 55.8, 91.3, 127.8, 128.4, 129.6, 130.8, 132.4, 132.6, 133.1, 134.0, 136.7, 142.1, 164.4. HRMS (EI): (M+Na) calcd for $C_{19}H_{19}Cl_3N_2O_2Na$: 435.0404, found: 435.0440. Mp: 159–162 °C.

4.4.16. *4,7-Dichloro-3-(4-chlorobenzyl)-3-hydroxy-2-phenylaminoisoindolin-1-one (**4c**)*

^{1}H NMR ($CDCl_3$) (δ): 3.36 (br s, 1H, OH), 3.57 (d, 1H, –*H*CH–, *J*=11.0 Hz), 3.78 (d, 1H, –*H*CH–, *J*=11.0 Hz), 6.10 (br s, 1H, NH), 6.74 (d, 2H, Aryl-H, *J*=6.8 Hz), 6.96 (m, 5H, Aryl-H), 7.17 (dd, 2H, Aryl-H, *J*=5.1 and 6.9 Hz), 7.28 (d, 1H, Aryl-H, *J*=6.9 Hz), 7.46 (d, 1H, Aryl-H, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$) (δ): 39.6, 90.8, 115.1, 122.5, 127.8, 128.2, 128.8, 129.2, 130.3, 130.5, 132.0, 133.0, 133.5, 134.6, 141.7, 146.8, 162.8. HRMS (EI): (M+Na) calcd for $C_{21}H_{15}Cl_3N_2O_2Na$: 455.0097, found: 455.0119. Mp: 206 °C.

4.4.17. *4,7-Dichloro-3-hydroxy-3-(4-methoxybenzyl)-2-phenylaminoisoindolin-1-one (**4e**)*

^{1}H NMR ($CDCl_3$) (δ): 3.56 (d, 1H, –*H*CH–, *J*=13.9 Hz), 3.66 (s, 3H, OCH_3), 6.21 (br s, 1H, OH), 3.79 (d, 1H, –HC*H*–, *J*=13.9 Hz), 6.59 (d, 2H, Aryl-H, *J*=8.4 Hz), 6.77 (d, 2H, Aryl-H, *J*=8.4 Hz), 6.98 (m, 3H, Aryl-H), 7.19 (d, 2H, Aryl-H, *J*=8.4 Hz), 7.31 (d, 1H, Aryl-H, *J*=8.8 Hz), 7.50 (d, 1H, Aryl-H, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) (δ): 39.4, 55.1, 91.1, 113.2, 114.0, 114.9, 122.2, 125.4, 128.0, 128.2, 129.2, 130.1, 130.2, 132.8, 134.4, 142.0, 147.0, 158.8, 162.8. HRMS (EI): (M+Na) calcd for $C_{22}H_{18}Cl_2N_2O_3Na$: 451.0587, found: 451.0560. Mp: 202–204 °C.

Acknowledgements

Financial support from Spanish ISCIII, through the RICET Thematic Network (RD06-0021-0022) and grant No. FIS-PI060782, is gratefully acknowledged.

References and notes

1. (a) Padwa, A.; Waterson, A. G. *Curr. Org. Chem.* **2000**, *4*, 175; (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (c) Kirsch, G.; Hesse, S.; Comel, A. *Curr. Org. Chem.* **2004**, *1*, 47.
2. (a) Manetti, F.; Brullo, C.; Magnani, M.; Mosci, F.; Chelli, B.; Crespan, E.; Schenone, S.; Naldini, A.; Bruno, O.; Trincavelli, M. L.; Maga, G.; Carraro, F.; Martini, C.; Bondavalli, F.; Botta, M. *J. Med. Chem.* **2008**, *51*, 1252; (b) Schenone, S.; Bruno, O.; Bondavalli, F.; Ranise, A.; Mosti, L.; Menozzi, G.; Fossa, P.; Manetti, F.; Morbidelli, L.; Trincavelli, L.; Martini, C.; Lucacchini, A. *Eur. J. Med. Chem.* **2004**, *39*, 153; (c) Baraldi, P. G.; Fruttarolo, F.; Tabrizi, M. A.; Preti, D.; Romagnoli, R.; El-Kashef, H.; Moorman, A.; Varani, K.; Gessi, S.; Merighi, S.; Borea, P. A. *J. Med. Chem.* **2003**, *46*, 1229; (d) Selleri, S.; Bruni, F.; Costagli, C.; Costanzo, A.; Guerrini, G.; Ciciani, G.; Gratteri, P.; Bonaccini, C.; Malmberg, A. P.; Besnard, F.; Renard, S.; Costa, B.; Martini, C. *J. Med. Chem.* **2003**, *46*, 310; (e) Quintela, J. M.; Peinadora, C.; Moreira, M. J.; Alfonso, A.; Botana, L. M.; Riguera, R. *Eur. J. Med. Chem.* **2001**, *36*, 321; (f) Kryštof, V.; Moravcová, D.; Paprskářová, M.; Barbier, P.; Peyrot, V.; Alice Hlobilková, A.; Havlíček, H.; Strnad, M. *Eur. J. Med. Chem.* **2006**, *41*, 1405.
3. (a) Calabri, F. R.; Colotta, V.; Catarzi, D.; Varano, F.; Lenzi, O.; Filacchioni, G.; Costagli, C.; Galli, A. *Eur. J. Med. Chem.* **2005**, *40*, 897; (b) Bekhit, A. A.; El-Sayed, O. A.; Aboul-Enein, H. Y.; Siddiqui, Y. M.; Al-Ahdal, M. N. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 33.
4. (a) Martinez, R.; Chacon-Garcia, L. *Curr. Med. Chem.* **2005**, *12*, 127; (b) Xia, B.; Ma, W.; Zheng, B.; Zhang, X.; Fan, B. *Eur. J. Med. Chem.* **2008**, *43*, 1489.
5. (a) D'alò, G.; Conti, G.; Cadel, S.; Vedova, R. D. *Farmaco* **1978**, *33*, 106; (b) Akitada, K.; Shozo, K. *Chem. Pharm. Bull.* **2002**, *18*, 1526; (c) Al'-Assar, F.; Zelenin, K. N.; Lesiovskaya, E. E.; Bezhan, I. P.; Chakchir, B. A. *Pharm. Chem. J.* **2002**, *36*, 598; (d) Nunes da Silva, E. *Res. J. Chem. Environ.* **2007**, *11*, 90.
6. Hassan, A. A.; Mohamed, N. K.; Aly, A. A.; Mourad, A.-F. E. *Monatsh. Chem.* **1997**, *128*, 61.
7. Viña, D.; del Olmo, E.; Lopez-Perez, J. L.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525.
8. (a) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 921; (b) Muller, E. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 423; (c) Del Olmo, E.; García, M.; López-Pérez, J. L.; Grace, R.; Vargas, F.; Giménez, A.; Deharo, E.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2755.
9. Lácová, M.; Chovancová, J.; Veverková, E.; Toma, S. *Tetrahedron* **1996**, *52*, 14995.
10. (a) Cherkez, S.; Herzig, J.; Yellin, H. *J. Med. Chem.* **1986**, *29*, 947; (b) Del Olmo, E.; Barboza, B.; Ybarra, M. I.; López-Pérez, J. L.; Carrón, R.; Sevilla, M. A.; Boselli, C.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2786.
11. (a) Loh, V. M., Jr.; Cockcroft, X.; Dillon, K. J.; Dixon, L.; Drzewiecki, J.; Eversley, P. J.; Gomez, S.; Hoare, J.; Kerrigan, F.; Matthews, I. T. W.; Menear, K. A.; Martin, N. M. B.; Newton, R. F.; Paul, J.; Smith, G. C. M.; Vile, J.; Whittle, A. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2235; (b) Cockroft, X.; Dillon, K. J.; Dixon, L.; Drzewiecki, J.; Kerrigan, F.; Loh, V. M., Jr.; Martin, N. M. B.; Menear, K. A.; Smith, G. C. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1040.
12. Zamilpa, A.; Herrera-Ruiz, M.; del Olmo, E.; Lopez-Perez, J. L.; Tortoriello, J.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3483.
13. Fuson, R. C.; Hammann, W. C. *J. Am. Chem. Soc.* **1952**, *74*, 1626.
14. (a) Zhang, L.; Walter, E. M.; Watson, E. J.; Gibson, E. P. *Tetrahedron Lett.* **1994**, *35*, 3675; (b) Magnano, A.; Sparapani, S.; Lucciarini, R.; Michela, M.; Amantini, C.; Santoni, G.; Antonini, I. *Bioorg. Med. Chem.* **2004**, *12*, 5941.
15. Scartoni, V.; Morelli, I.; Marsili, A.; Catalana, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2332.