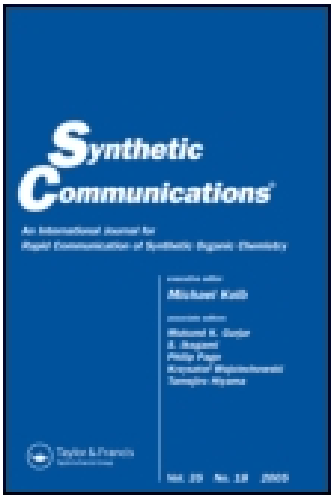


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of N-(2-(Methylamino)ethyl) Derivatives of 2H-Phthalazin-1-ones

Zbigniew Malinowski [a], Aleksandra K. Szcześniak [a], Wanda Pakulska [b], Dariusz Sroczyński [c], Elżbieta Czarnecka [b] & Jan Epsztajn [a]

[a] Faculty of Chemistry, Department of Organic Chemistry, University of Łódź, Łódź, Poland

[b] Faculty of Pharmacy, Department of Pharmacodynamics, Medical University of Łódź, Łódź, Poland

[c] Faculty of Chemistry, Department of Inorganic and Analytical Chemistry, University of Łódź, Łódź, Poland

Accepted author version posted online: 08 Aug 2014.Published online: 15 Oct 2014.

To cite this article: Zbigniew Malinowski, Aleksandra K. Szcześniak, Wanda Pakulska, Dariusz Sroczyński, Elżbieta Czarnecka & Jan Epsztajn (2014) Synthesis of N-(2-(Methylamino)ethyl) Derivatives of 2H-Phthalazin-1-ones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:24, 3572-3581, DOI: 10.1080/00397911.2014.944269

To link to this article: http://dx.doi.org/10.1080/00397911.2014.944269

Synthetic Communications®, 44: 3572–3581, 2014

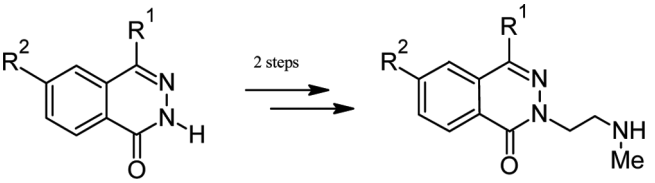
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2014.944269

SYNTHESIS OF *N*-(2-(METHYLAMINO)ETHYL) DERIVATIVES OF 2*H*-PHTHALAZIN-1-ONES

Zbigniew Malinowski,[1] Aleksandra K. Szcześniak,[1] Wanda Pakulska,[2] Dariusz Sroczyński,[3] Elżbieta Czarnecka,[2] and Jan Epsztajn[1]

[1]*Faculty of Chemistry, Department of Organic Chemistry, University of Łódź, Łódź, Poland*
[2]*Faculty of Pharmacy, Department of Pharmacodynamics, Medical University of Łódź, Łódź, Poland*
[3]*Faculty of Chemistry, Department of Inorganic and Analytical Chemistry, University of Łódź, Łódź, Poland*

GRAPHICAL ABSTRACT



Abstract *A series of new alkyl, tosyl, acetyl, and* tert-*butoxycarbonyl derivatives of 2-(2-aminoethyl)-phthalazinones were efficiently synthesized by reaction of lactams with* N-*Boc-,* N-*acetyl-, or* N,O-*ditosyl derivatives of* N-*methylethanolamine in the presence of MeONa or under Mitsunobu reaction conditions. Selected compounds were converted into corresponding 2-[2-(methylamino)ethyl]phthalazinones in good yields.*

Keywords Alkylation; amines; Mitsunobu reaction; phthalazinones; rotamers

INTRODUCTION

2*H*-Pyridazin-3-ones and their benzo- (*phthalazinones*) and pyrido- (*pyridopiryydazinones*) derivatives demonstrate a wide spectrum of biological properties. Compounds of these type show an interesting pharmacological action (e.g., adenosine A_1 receptor antagonist **I**,[1] antinociceptive agents **II**,[2–4] α_1-adrenoreceptors antagonist **III**,[5,6] and nonprostanoid PGI_2 agonist **IV**[7]; Fig. 1).

Especially interesting group of 2*H*-pyridazin-3-one derivatives are compounds substituted at the lactam nitrogen atom by ω-aminoalkyl group. These type of

Received May 22, 2014.

Address correspondence to Zbigniew Malinowski, Faculty of Chemistry, Department of Organic Chemistry, University of Łódź, Tamka 12 Street, 91-403 Łódź, Poland. E-mail: zbigmal@uni.lodz.pl

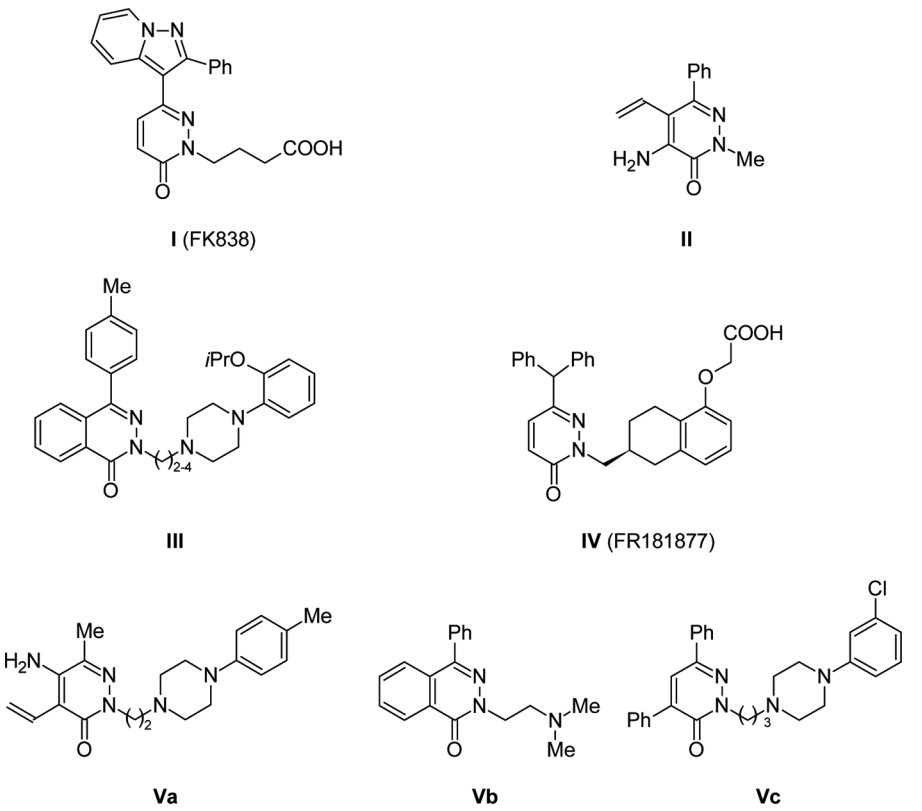


Figure 1. Structures of biologically active 2*H*-pyridazin-3-one derivatives **I**–**V**.

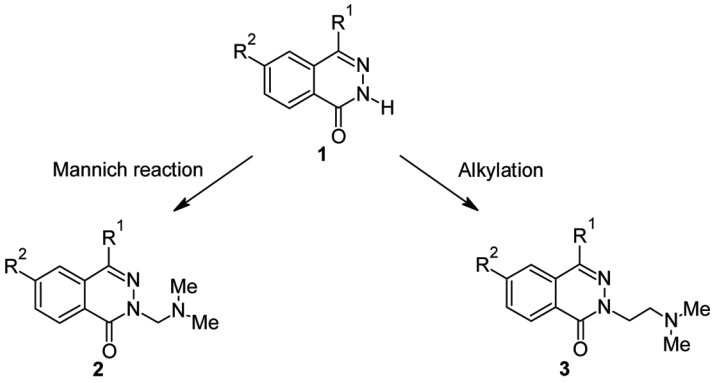
compounds can exhibit analgesic as well as nonsteroidal anti-inflammatory activity **Va–c**.[8–11]

In our previous articles we have described methodologies for the synthesis of novel (dimethylamino)methyl- and 2-(dimethylamino)ethyl- derivatives of phthalazinones and pyridopyridazinones (Scheme 1).[11,12] The synthetic methods applied in the preparation of these compounds were based on the Mannich reaction and on the reaction of lactams **1** with 2-chloro-*N,N*-dimethylethanamine.

RESULTS AND DISCUSSION

In this article, we present methods for the preparation of 2-(*N*-methylamino)ethyl- derivatives of phthalazinones. Starting lactams **1** were synthesized from the appropriate 3-hydroxyisoindolinones or ketoacids upon reaction with hydrazine monohydrate, according to previously described methods.[11–14]

Our preliminary studies have shown that preparation of 2-(ω-aminoalkyl) phthalazinones by reaction of corresponding 2-halogenethylamines **4** (Scheme 2) with lactams **1** is not effective. If primary or secondary ω-halogenalkylamines **4a,b** were used to react with phthalazinones **1**, the outcomes were rather poor.[15]



Entry	Compound	R^1	R^2
1	3a	H	H
2	3b	Me	H
3	3c	2-(MeO)-C_6H_4	MeO
4	2a	4-Cl-C_6H_4	MeO
5	2b, 3d	2Py	MeO
6	2c, 3e	3Py	MeO
7	2d, 3f	4Py	MeO

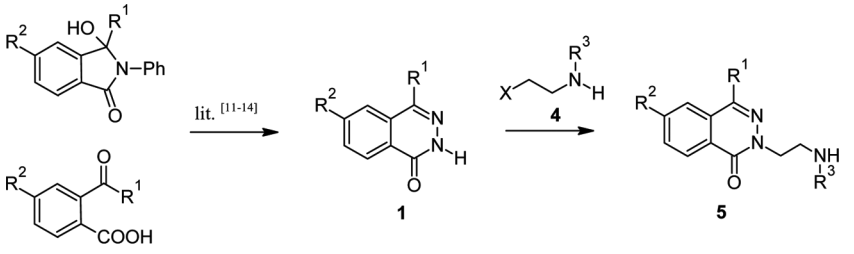
Scheme 1. Synthesis of (*N,N*-dimethylamino)alkyl phthalazinones **2** and **3**.[11,12]

N-Alkylated products **5** were formed in trace amounts only, if at all. The formation of compounds **5** was observed by NMR spectroscopy and they were not isolated in individual form. Therefore, practical application of the ω-halogenalkylamines as alkylating agents is limited and determined by the degree of substitution of amine nitrogen atom. In practice, this methodology plays a significant role in preparation of 2-(*N,N*-dialkylamino)ethyl-lactam derivatives type **3**,[11] solely (Scheme 1).

Based on these results, we focused on the synthesis of selected *N*-(2-aminoethyl)- phthalazinone derivatives substituted on the amine nitrogen atom by alkyl, tosyl, acetyl, and *tert*-butoxycarbonyl group. These derivatives can be effortlessly converted into the desired secondary amines (*N*-methylamines).[16,17] Easily accessible derivatives of 2-(methylamino)ethanol, types **6**, **7**, and **8** (Fig. 2),[18–20] were used as ω-aminoethylating agents.

Synthesis of *N*-2-(methylamino)ethyl lactams type **10** was carried out using two approaches as shown in Scheme 3. Initially, benzenesulfonamides **9** were synthesized, as precursors of corresponding 2-(methylamino)ethyl derivatives **10**.

Phthalazinones **1** after treatment with MeONa were converted into amides **9** by reaction with ditosylated 2-(methylamino)ethanol, in 40–64% yields. In the second



Entry	Compound	R^1	R^2	R^3	X
1	4a	–	–	H	Br
2	4b	–	–	Me	Cl
3	5a	H	H	H	–
4	5b	H	H	Me	–
5	5c	Me	H	H	–
6	5d	Ph	H	Me	–
7	5e	2-$MeOC_6H_4$	MeO	H	–
8	5f	2Py	MeO	Me	–

Scheme 2. Studies of synthesis of 2-(*N*-methylamino)ethyl- and 2-aminoethylphthalazinones **5**.

stage benzenesulfonamides **9** were hydrolyzed to corresponding amines **10** by heating with concentrated H_2SO_4 (110 °C). Desired amines were obtained in 56–78% yields. The structures of compounds **9** and **10** were determined by infrared (IR), ^{1}H NMR, and elemental analysis or mass spectroscopy (Table 1).

Unexpectedly, synthesis of amine **10d** via hydrolysis of appropriate *N*-tosyl derivative with H_2SO_4 ended in failure. For this reason, the synthesis of amine **10d** was carried out using the Mitsunobu reaction[21,22] as a key step, followed by deprotecion of the amine group. Alkylation of phthalazinone **1** with *N*-Boc-protected 2-(metylamino)ethanol using standard Mitsunobu conditions (TPP, DEAD) gave carbamic acid derivatives **11e** in satisfactory yields (Scheme 3). Cleavage of the Boc protecting group of compound **11e** with hydrochloric acid at rt gave the secondary amine **10d** in 55% yield. This protocol was successfully applied to

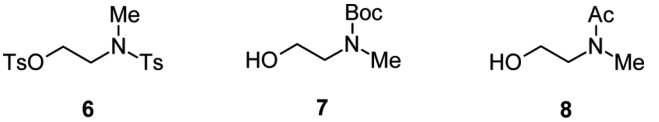
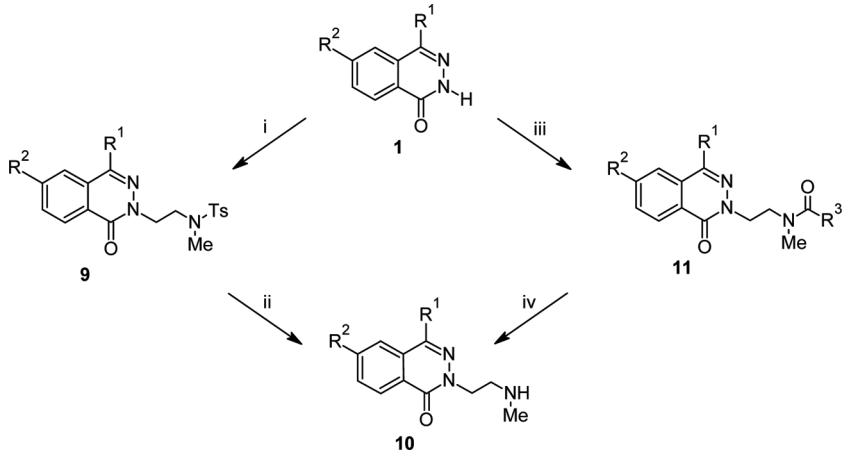


Figure 2. Structures of ω-aminoethylating agents.



Scheme 3. Synthesis of compounds **9**, **10**, and **11**. Reagents and conditions: (i) (a) MeONa/MeOH, Δ 30 min, (b) $TsOCH_2CH_2N(Me)Ts$ (**6**), Δ 7 h; (ii) H_2SO_4, Δ 6 h; (iii) Mitsunobu procedure: (a) TPP, DEAD, −10 °C, (b) $HOCH_2CH_2N(Me)R^3$ **7** or **8**, rt 20 h; (iv) HCl (20%$_{aq}$), MeOH, rt 30 h.

Table 1. Synthesis of compounds **9**, **10**, and **11**

Entry	Compound	R^1	R^2	R^3	Yield (%)
1	**9a**	H	H	—	50
2	**9b**	Me	H	—	45
3	**9c**	Ph	H	—	64
4	**9d**	4-(MeO)-C_6H_4	H	—	47
5	**9e**	4-Cl-C_6H_4	H	—	40
6	**9f**	2Py	MeO	—	45
7	**10a**	H	H	—	78
8	**10b**	Me	H	—	65
9	**10c**	Ph	H	—	56
10	**10d**	2Py	MeO	—	55
11	**11a**	H	H	Ac	30
12	**11b**	H	H	Boc	45
13	**11c**	Ph	H	Ac	55
14	**11d**	Ph	H	Boc	50
15	**11e**	2Py	MeO	Boc	55

preparation of *N*-(*tert*-butoxycarbonyl) derivatives **11b,d** and *N*-acetyl analogs **11a,c** using *N*-(2-hydroxyethyl)-*N*-methylacetamide as a starting material, too. Therefore, presented methods for synthesis of *N*-methylaminoethyl derivatives of phthalazinones are complementary to one another but application of Mitsunobu methodology allows the reaction to be carried out under milder conditions.

CONCLUSIONS

In conclusion, we described an efficient synthesis of new *N*-substituted phthalazinones derivatives containing (2-{methyl[(4-methylphenyl)sulfonyl]amino}ethyl)- and

{2-[(*tert*-butoxy carbonyl)(methyl)amino]ethyl}- moiety by reaction of series phthalazinones with readily accessible 2-(methylamino)ethanol derivatives. This, coupled with an effective conversion of compounds **9** and **11** to the corresponding 2-[2-(methylamino)ethyl]-2*H*-phthalazin-1-ones **10**, should allow to access a wide variety of these types of compounds.

EXPERIMENTAL

The melting points were determined on a Boetius hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz on a Varian Gemini 200 BB spectrometer with tetramethylsilane (TMS) as an internal reference. IR spectra were recorded on a Nexus FT-IR spectrometer. Mass spectra analyses were performed on a MAT95-Finnigan mass spectrometer. The analytical thin-layer chromatography tests (TLC) were carried out on Merck silica gel plates (Kiselgel 60 F_{254}, layer thickness 0.2 mm) and the spots were visualized using an ultraviolet lamp.

Commercially available (Aldrich, Fluka) hydrazine monohydrate, *N,N,N′*, *N′*-tetramethylethylenediamine, triphenylphosphite (TPP), diethyl azodicarboxylate (DEAD), 2-acetylbenzoic acid, and 2-benzoilbenzoic acid were used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. ω-Aminoethylating agents **6**, **7**, and **8** were prepared by standard methods[18–20] from the commercially available 2-(methylamino)ethanol.

2*H*-Phthalazin-1-ones **1** were prepared according to an already reported procedure from appropriate 3-hydroxy-1*H*-isoindolin-1-ones or ketoacids.[11–14]

General Procedure for Preparation of Benzenesulfonamides 9

2*H*-Phthalazin-1-one **1** (0.0153 mol) was added to a solution of sodium methoxide (0.0165 mol) in dry MeOH (70 ml). The mixture was heated to boiling for 30 min. Afterward, toluene-4-sulfonic acid 2-[methyl-(toluene-4-sulfonyl)-amino]-ethyl ester (**6**) (0.0230 mol) was added and heating was continued for the next 7 h. After this time, the mixture was cooled to ambient temperature. The separated product was filtrated off, washed with dry methanol, and purified by crystallization or column chromatography.

The FTIR spectra of the benzenesulfonamides **9** displayed characteristic absorption of the C=O in the region 1640–1650 cm^{-1}. Besides, bands of SO_2 between 1150 and 1340 cm^{-1} were observed. The ^{1}H NMR spectra of amides **9** showed the presence of two singlets at 2.31–2.34 ppm and 2.91–2.93 ppm corresponding to methyl group of 4-toluenesulfonyl moiety and N-Me protons, respectively. The signals of the ethylene bridge were displayed as two triplets at 4.36–4.50 and 3.51–3.59 ppm.

4,*N*-Dimethyl-*N*-[2-(1-oxo-4-phenyl-1*H*-phthalazin-2-yl)-ethyl] benzenesulfonamide (9c)

Yield 64%; mp 128–131 °C (MeOH); FT-IR (KBr, cm^{-1}) ν: 1654 (C=O), 1336, 1163 (SO_2); ^{1}H NMR (200 MHz, $CDCl_3$, ppm) δ: 8.46–8.51 (m, 1H, 8-ArH),

7.82–7.72 (m, 3H, Ph, ArH), 7.67–7.52 (m, 7H; Ph, Ar, TsH), 7.15 (m, 2H, TsH), 4.48 (t, 2H, CH_2, $J = 6.0$ Hz), 3.59 (t, 2H, CH_2, $J = 6.0$ Hz), 2.93 (s, 3H, NMe), 2.31 (s, 3H, TsMe); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ: 159.1, 142.9, 135.0, 134.9, 132.7, 131.2, 129.4, 129.0, 128.5, 127.9, 127.0, 126.6, 48.1, 34.8, 21.4. Anal. calcd. for ($C_{24}H_{23}N_3O_3S$): C, 66.49; H, 5.35; N, 9.69; S, 7.40%. Found: C, 66.45; H, 5.42; N, 9.73; S, 7.47%.

General Procedure for Preparation of Acetyl- and *tert*-Butoxycarbonyl-Derivatives of 2-[(Methylamino)ethyl]-2*H*-phthalazin-1-ones 11 (Mitsunobu Procedure)

The Mitsunobu reaction was carried out under argon. DEAD (0.0102 mol, solution in toluene c ≈ 40%) was slowly added to a stirred solution of TPP (0.0102 mol) in dry THF (10 ml) at −10 °C. Then a solution of phthalazinone **1** (0.0068 mol) in THF (44 ml) was added dropwise. The whole lot was mixed for 15 min at −10 °C and next the appropriate derivative of *N*-methylethanolamine **7** or **8** (0.00748 mol) in THF (5 ml) was added at −10 °C. The mixture was stirred during 2 h at −10 °C, after which time the reaction mixture was warmed to ambient temperature and stirred in this condition for 20 h. All volatile materials were removed under reduced pressure, ethyl ether (20 ml) was added to the residue, and the whole lot was stirred for 0.5 h at ambient temperature. The separate white solid was collected by flirtation and washed with ether, and the filtrate was evaporated to dryness. The residue was subjected to column chromatography to give the pure product **11**.

^{1}H NMR spectra of compounds **11** showed doubled singlets of methyl groups connected with nitrogen atoms and derived from acetyl or *tert*-butoxycarbonyl moieties. This fact may indicate that amides **11** coexist as mixtures of rotamers.[23]

N-Methyl-*N*-[2-(1-oxo-4-phenyl-1*H*-phthalazin-2-yl)-ethyl]-acetamide (11c)

Yield: 55%; mp 138–140 °C; $R_f = 0.12$ (CH_2Cl_2-acetone = 9:1); FT-IR (KBr, cm^{-1}) ν: 1652, 1649 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$, ppm, mixture of rotamers) δ: 8.53–8.50 (m, 1H, ArH), 7.81–7.72 (m, 3H, ArH), 7.61–7.50 (m, 5H, ArH), 4.50 (m, 2H, CH_2), 3.93–3.77 (m, 2H, CH_2), 3.04, 3.02 (2 × s, 3H, NMe, two rotamers), 2.02, 1.97 (2 × s, 3H, Ac-Me, two rotamers); ^{13}C NMR (50 MHz, $CDCl_3$, ppm, mixture of rotamers) δ: 171.1, 170.9, 159.4, 159. 3, 147.8, 147.1, 135.1, 134.8, 133.1, 132.8, 131.7, 131.3, 129.4, 129.3, 129.0, 128.7, 128.6, 127.1, 126.7, 49.0, 48.6, 46.2, 36.7, 33.5, 21.7, 20.9. Anal. calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07%. Found: C, 70.88; H, 5.99; N, 12.81%.

General Procedure for Preparation of 2-[(Methylamino)ethyl]-2*H*-phthalazin-1-ones 10

Method A: Hydrolysis of benzenesulfonamides 9. The benzenesulfonamide **9** (0.0106 mol) and H_2SO_4 (98%, 0.0318 mol) were heated up to 100–110 °C over a period of 6 h. After this time the reaction mixture was cooled to ambient temperature, alkalized with 20% aqueous solution of NaOH, and next extracted with

CH_2Cl_2 (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated to dryness. The amine was separated by column chromatography.

Method B: Hydrolysis of *tert*-butyl methyl[2-(1-oxo-1*H*-phthalazin-2-yl) ethyl]-carbamates 11. Carbamate **11** (0.00275 mol) was added to a solution of HCl_{aq} (20%, 36 ml). The mixture was stirred for 30 h at room temperature. Next reaction mixture was alkalized with 20% aqueous solution of NaOH and extracted with CH_2Cl_2 (3 × 50 ml). The combined extracts were dried over $MgSO_4$ and concentrated under vacuum. The amine was isolated by column chromatography.

In the case of amines **10** FTIR spectra showed NH bands at ≈3320 cm^{-1} and strong C=O bands at 1652 cm^{-1}. In the ^1H NMR spectra of amines **10** (Scheme 3) the signals of the 2-(methylamino)ethyl moiety were displayed as two triplets at ≈4.42 and ≈3.11 ppm corresponding to CH_2 protons of ethylene chain, whereas the protons of NMe and NH groups exhibited as two singlets between 1.52 and 2.51 ppm.

2-[2-(Methylamino)-ethyl]-4-phenyl-2*H*-phthalazin-1-one (10c). Yield: 56% (method A); mp 96–98 °C; $R_f = 0.01$ (AcOEt–MeOH = 1:1 next MeOH); FT-IR (KBr, cm^{-1}) ν: 1652 (C=O), 3332 (NH). ^1H NMR (200 MHz, $CDCl_3$, ppm) δ: 8.57–8.53 (m, 1H, ArH), 7.82–7.76 (m, 3H, ArH), 7.62–7.53 (m, 6H, ArH), 4.49 (t, 2H, CH_2, $J = 6.1$ Hz), 3.16 (t, 2H, CH_2, $J = 6.1$ Hz), 2.51 (s, 3H, NMe), 2.29 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ: 159.2, 146.9, 135.0, 132.6, 131.2, 129.3, 128.9, 128.4, 127.0, 126.5, 50.3, 50.2, 36.1. Anal. calcd. for ($C_{17}H_{17}N_3O$): C, 73.10; H, 6.13; N, 15.04%. Found: C, 73.11; H, 5.98; N, 15.11%.

6-Methoxy-2-[2-(methylamino)-ethyl]-4-(pyridin-2-yl)-2*H*-phthalazin-1-one (10d). Yield: 55% (method B); mp 94–96 °C; $R_f = 0.0$ (AcOEt next MeOH); FT-IR (KBr, cm^{-1}) ν: 1652 (C=O), 3316 (NH); ^1H NMR (200 MHz, $CDCl_3$, ppm) δ: 8.75–7.24 (m, 1H, ArH), 8.42 (d, 1H, ArH, $J = 8.8$ Hz), 7.95–7.86 (m, 3H, ArH), 7.42–7.28 (m, 2H, ArH), 4.44 (t, 2H, CH_2, $J = 6.1$ Hz), 3.88 (s, 3H, OMe), 3.10 (t, 2H, CH_2, $J = 6.1$ Hz), 2.47 (s, 3H, NMe), 1.52 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ: 162.9, 159.3, 154.9, 148.4, 143.3, 137.1, 130.4, 128.9, 124.2, 123.4, 121.9, 120.2, 108.6, 55.5, 50.3, 50.2, 36.0. Anal. calcd. for ($C_{17}H_{18}N_3O_2$): C, 65.79; H, 5.85; N, 18.05%. Found: C, 65.52; H, 5.78; N, 17.93%.

FUNDING

This work was financially supported by the Polish Ministry of Science and Higher Education, Grant No. 3 T09A 015 29 and University of Łódź.

SUPPORTING INFORMATION

Full experimental details, ^1H and ^{13}C NMR, and IR spectra can be accessed on the publisher's website.

REFERENCES

1. Kuroda, S.; Takamura, F.; Tenda, Y.; Itani, H.; Tomishima, Y.; Akahane, A.; Sakane, K. Design, synthesis, and biological evaluation of a novel series of potent, orally active adenosine A1 receptor antagonists with high blood–brain barrier permeability. *Chem. Pharm. Bull.* **2001**, *49*, 988–998.
2. Dal Piaz, V.; Cianini, G.; Turco, G.; Giovannoni, M.P.; Mideli, M.; Pirisino, R.; Perretti, M. 5-Acyl-6-aryl-4-nitro-3(2*H*)-pyridazinones and related 4-amino compounds: synthesis and pharmacological evaluation. *J. Pharm. Sci.* **1991**, *80*, 341–348.
3. Dal Piaz, V.; Giovannoni, M. P.; Ciciani, G.; Barlocco, D.; Giardina, G.; Petrone, G.; Clarke, G. D. 4,5-Functionalized 6-phenyl-3(2*H*)-pyridazinones: synthesis and evaluation of antinociceptive activity. *Eur. J. Med. Chem.* **1996**, *31*, 65–70.
4. Takaya, M.; Sato, M.; Terashima, H.; Tanizawa, H.; Maki, Y. A new nonsteroidal analgesic-antiinflammatory agent: Synthesis and activity of 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone and related compounds. *J. Med. Chem.* **1979**, *22*, 53–58.
5. Montesano, F.; Barlocco, D.; Dal Piaz, V.; Leonardi, A.; Poggesi, E.; Fanelli, F.; De Benedetti, P. G. Isoxazolo-[3,4-*d*]-pyridazin-7-(6*H*)-ones and their corresponding 4,5-disubstituted-3-(2*H*)-pyridazinone analogues as new substrates for α1-adrenoceptor selective antagonists: synthesis, modeling, and binding studies. *Bioorg. Med. Chem.* **1998**, *6*, 925–935.
6. (a) Strappaghetti, G.; Brodi, C.; Giannaccini, G.; Betti, L. New 4-(4-methyl-phenyl) phthalazin-1(2*H*)-one derivatives and their effects on α1-receptors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2575–2579 (b) Betti, L.; Botta, M.; Corelli, F.; Floridi, M.; Fossa, P.; Giannaccini, G.; Manetti, F.; Strappaghetti, G.; Corsano, S. α1-Adrenoceptor antagonists: Rational design, synthesis and biological evaluation of new trazodone-like compounds. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 437–440.
7. Tsubaki, K.; Taniguchi, K.; Tabuchi, S.; Okitsu, O.; Hattori, K.; Seki, J.; Sakanea, K.; Tanaka, H. A novel pyridazinone derivative as a nonprostanoid PGI_2 agonist. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2787–2790.
8. Rohet, F., Rubat, C.; Coudert, P.; Albuisson, E.; Couquelet, J. Synthesis and trazodone-like analgesic activity of 4-phenyl-6-aryl-2-[3-(4-arylpiperazin-1-yl)propyl]pyriazin-3-ones. *Chem. Pharm. Bull.* **1996**, *44*, 980–986.
9. Gokce, M.; Dogruer, D.; Fethi Sahin, M. Synthesis and antinociceptive activity of 6-substituted-3-pyridazinone derivatives. *Farmaco* **2001**, *56*, 233–237.
10. Dal Piaz, V.; Vergelli, C.; Giovannoni, M. P.; Scheideler, M. A.; Petrone, G.; Zaratin, P. 4-Amino-3(2*H*)-pyridazinones bearing arylpiperazinylalkyl groups and related compounds: Synthesis and antinociceptive activity. *Farmaco* **2003**, *58*, 1063–1071.
11. Pakulska, W.; Malinowski, Z.; Szcześniak, A. K.; Czarnecka, E.; Epsztajn, J. Synthesis and pharmacological evaluation of *N*-(dimethylamino)ethyl derivatives of benzo- and pyridopyridazinones. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 41–47.
12. Epsztajn, J.; Malinowski, Z.; Urbaniak, P.; Andrijewski, G. A practical approach for preparation of 2-[(dialkylamino)-methyl]-4-aryl-2*H*-phthalazin-1-ones via Mannich reaction of 4-aryl-2*H*-phthalazin-1-ones. *Synth. Commun.* **2005**, *35*, 179–192.
13. Brzeziński, J.; Epsztajn, J.; Bakalarz, A. D.; Łajszczak, A.; Malinowski, Z. Application of organolithium and related reagents in synthesis, part 22: Synthetic strategies based on *ortho*-aromatic metallation: A concise regiospecific conversion of benzoic acids into the 4-pyridyl-2*H*-phthalazin-1-ones. *Synth. Commun.* **1999**, *29*, 457–473.
14. Epsztajn, J.; Malinowski, Z.; Brzeziński, J.; Karzatka, M. Application of organolithium and related reagents in synthesis, part 26: Synthetic strategies based on directed *ortho*-metalation: Synthesis of 4-methyl-2*H*-phthalazin-1-ones. *Synthesis* **2001**, *14*, 2085–2090.

15. Strappaghetti, G.; Corsano, S.; Barbaro, R.; Lucacchini, A.; Giannaccini, G.; Betti, L. Adenosine receptors: Synthesis, structure–activity relationships, and biological activity of new 6-amino purine derivatives. *Eur. J. Med. Chem.* **1998**, *33*, 501–508.
16. Epsztajn, J.; Czarnecka, E.; Szcześniak, A.; Pakulska, W.; Malinowski, Z. Benzo- and pyridopyridazinones with analgesic and antiinflammatory activity. WO Patent Application 051504 A1, 2009.
17. Bencini, A.; Bianchi, A.; Garcia-Espana, E.; Fusi, V.; Micheloni, M; Paoletti, P.; Ramirez, J. A.; Rodriguez A.; Valtancolia, B. Synthesis and protonation behaviour of the macrocyclic ligand 1,4,7,13-tetramethyl-1,4,7,10,13,16-hexaazacyclooctadecane and of its bicyclic derivative 4,7,10,17,23-pentamethyl-1,4,7,10,13,17,23-heptaazabicyclo[11.7.5]-pentacosane: A potentiometric and ^{1}H and ^{13}C NMR study. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1059–1065.
18. Herold, P.; Mah, R.; Tschinke, V.; Behnke, D.; Marti, Ch.; Jotterand, N.; Stutz, S. Substituted piperidines as therapeutic compounds. European Patent Application EP 1987834 A2, 2008.
19. Basel, Y.; Hassner, A. Di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine revisited: Their reactions with amines and alcohols. *J. Org. Chem.* **2000**, *65*, 6368–6380.
20. Yadav, V. K.; Ganesh Babu, K. Reactions on a solid surface: A simple, economical, and efficient acylation of alcohols and amines over Al_2O_3. *J. Org. Chem.* **2004**, *69*, 577–580.
21. Knaack, M.; Fleischhauer, I.; Charpentier, P.; Emig, P.; Kutcher, B.; Mueller, A. Ringumlagerungen bei der Mitsunobu-alkylierung von phthalazinonen und indazololen. *Liebigs Ann.* **1996**, *9*, 1477–1482.
22. Procopiou, P. A.; Browning, C.; Buckley, J. M.; Clark, K. L.; Fechner, L.; Gore, P. M.; Hancock, A. P.; Hodgson, S. T.; Holmes, D. S.; Kranz, M.; Looker, B. E.; Morriss, K. M. L.; Parton, D. L.; Russell, L. J.; Slack, R. J.; Sollis, S. L.; Vile, S.; Watts, C. J. The discovery of phthalazinone-based human H_1 and H_3 single-ligand antagonists suitable for intranasal administration for the treatment of allergic rhinitis. *J. Med. Chem.* **2011**, *54*, 2183–2195.
23. Kim, Y. J.; Park, Y.; Park, K. K. Rotational isomers of *N*-alkyl-*N*-(o-acylphenyl) acetamides. *J. Mol. Struct.* **2006**, *783*, 61–65.