



ONE-POT GREEN SYNTHESIS OF 3-AMINO-1-(5-NITRO-1H-INDOL-2-YL)-5,10-DIOXO-5,10-DIHYDRO-1H-PYRAZOLO[1,2-*b*]PHTHALAZINE-2-CARBONITRILE AND RELATED COMPOUNDS

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Synthesis of 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitriles by a one-pot green and an eco-friendly reaction of phthalic acid, hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of Et₃N as catalyst and Glycerol mediated at 100-105 °C for 45-60 min. This one-pot reaction proceeded in a short time with good yields and the desired products obtained without using column purifications.

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INTRODUCTION

Multi-component reactions (MCRs) are one-pot processes in which three or more compounds react in a single reaction vessel to form a product containing substantial components of all the reactants.¹ Thus, design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of steps in the synthesis of compounds with interesting properties is essential for drug discovery and synthesis of natural products.² MCRs have attracted much attention in combinatorial and medicinal chemistry and have been designed to produce biologically active compounds.^{3,4}

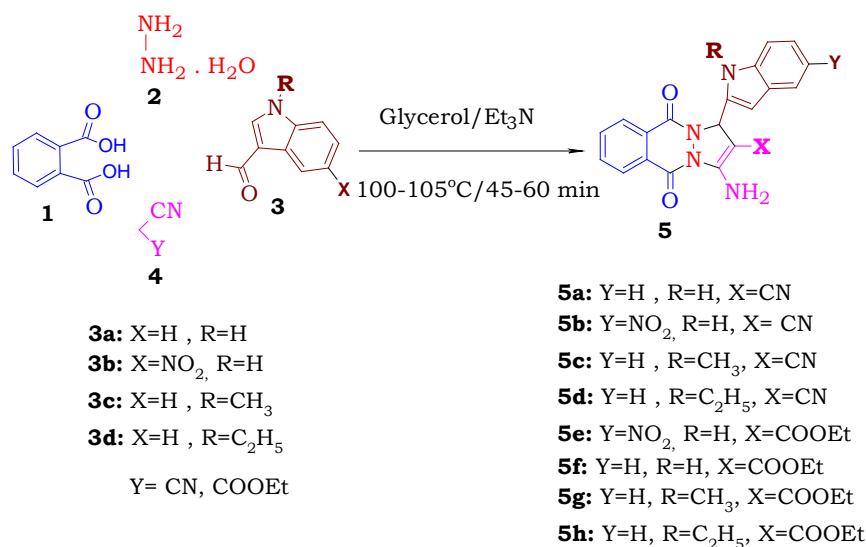
Phthalazines are important heterocycles that are known to possess multiple biological activities such as antimicrobial, anticonvulsant, antifungal, anticancer and anti-inflammatory.⁵ Carling et al. reported⁶ the synthesis of 3-phenyl-6-(2-pyridyl)methoxy-1,2,4-triazolo[3,4-*a*]phthalazines and analogs which were found to be a critical structural element of specific CNS - active drugs. Jain et al. reported⁷ the synthesis of keto-glutamine tetrapeptide analogs containing a 2-oxopyrrolidine ring as a glutamine side chain mimic which showed improved inhibition against hepatitis A virus 3C proteinase. Grasso et al. reported⁸ the synthesis of 6,7-methylenedioxyphtalazin-1(2H)-ones which were found to be potent anticonvulsant agents. Nomoto et al. reported⁹ the synthesis of 6,7-dimethoxyphthalazine derivatives which showed relatively potent cardiotoxic activity comparable to that of amrinone. Watanabe et al. reported¹⁰ the synthesis of 4-benzylamino-1-chloro-6-substituted phthalazines which were found to be vasorelaxant and some methods have been reported for the synthesis of phthalazine derivatives.¹¹ Therefore, it was considered worthwhile to synthesize phthalazine moiety containing 4H-pyrans.

Keeping above discussion in our mind, we now wish to report 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile derivatives by reaction of phthalic acid, hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of Et₃N as catalyst and glycerol as a medium at 100-105 °C for 30-60 min.

RESULTS AND DISCUSSION:

Firstly, we have initiated the optimization of the one-pot four-component reaction by using phthalic acid (**1**) and hydrazine hydrate (**2**) to in-situ formation of phthalic hydrazide as intermediate in the presence of Et₃N and glycerol medium. To this reaction mixture, 5-nitroindole-3-carboxaldehyde (**3a**) and malononitrile (**4a**) were added for preparation of 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5a**) in the presence of different solvents (glycerol, ethylene glycol and DMF) and different bases (Et₃N and pyridine) at different temperature (RT, 50 °C, 100 °C and 120 °C) as a simple model reaction (Table 1 entries 1-3). However, it was found that the one-pot reaction of **1** (10 mM), **2** (10 mM), **3a** (10 mM) and **4a** (10 mM) in the presence of Et₃N (2 mM) as catalyst and glycerol (50 ml) as medium for 45 min at 100 °C gave the highest yield (88 %) and clean product (**5a**) (Table 1, entry 1). ¹H-NMR, IR and mass spectroscopy have confirmed the structure of the compound **5a**.

In order to examine the quantity of Et₃N, the one-pot reaction has been carried out at different quantity (1 mM, 2 mM and 5 mM) of Et₃N with respect of phthalic acid **1**. However, it was found that the one-pot reaction of **1** (10 mM), **2** (10 mM), **3a** (10 mM) and **4a** (10 mM) in the presence of Et₃N (2 mM) as catalyst and glycerol medium (50 ml) for 45 min at 100-105 °C gave the highest yield (88 %) (Table 2, entry 2).



Scheme 1. The general reaction route to prepare the pyrazolo[1,2-b]phthalazine derivatives

In the next step, the scope of the reaction process was explored, using the best-optimized conditions by changing the phthalic acid, the aldehyde & the nitrile (Table 3). The results are displayed in Table 3. The structures of the products were assigned on the basis of their spectral properties - IR, NMR and mass spectra (for details, please see the experimental section).

Table 1. Effect of solvent/catalyst and temperature on the one-pot reaction of 1, 2, 3a and 4a at RT yielding 5a.

No.	Solvent/Catalyst	T, °C	Time, min	Yield 5a, %
1	Glycerol/Et ₃ N	100	45	88
2	Ethylene glycol /Et ₃ N	100	55	80
3	DMF/Et ₃ N	100	100	80
4	Glycerol/pyridine	100	40	80
5	Ethylene glycol/pyridine	100	50	78
6	DMF/pyridine	100	90	72
7	Glycerol/Et ₃ N	RT	300	85
8	Ethylene glycol/Et ₃ N	RT	320	82
9	DMF/Et ₃ N	RT	450	78
10	Glycerol/Et ₃ N	50	80	82
11	Ethylene glycol/Et ₃ N	50	85	81
12	DMF/Et ₃ N	50	100	79
13	Glycerol/Et ₃ N	120	40	75
14	Ethylene glycol/Et ₃ N	120	45	70
15	DMF/Et ₃ N	120	60	73

A schematic mechanism for the catalytic activity of Et₃N in the synthesis of titled compounds **5** can be postulated as shown in Scheme 2. This mechanism contains three steps. In the first step, the formation of phthalic hydrazide (**X1**) by nucleophilic addition of hydrazine hydrate (**2**) to phthalic acid (**1**) takes place followed by dehydration. The second step involves forming heterodiene (**Y1**) by standard Knoevenagel condensation of indole-3-carboxaldehyde (**3**) and malononitrile/ethyl cyanoacetate (**4**). Then, in the third step, Michael-type addition of the phthalic hydrazide **X1** to

heterodiene **Y1** takes place forming the intermediary iminomethylene derivative **Z** which undergoes cyclisation affording **5**.

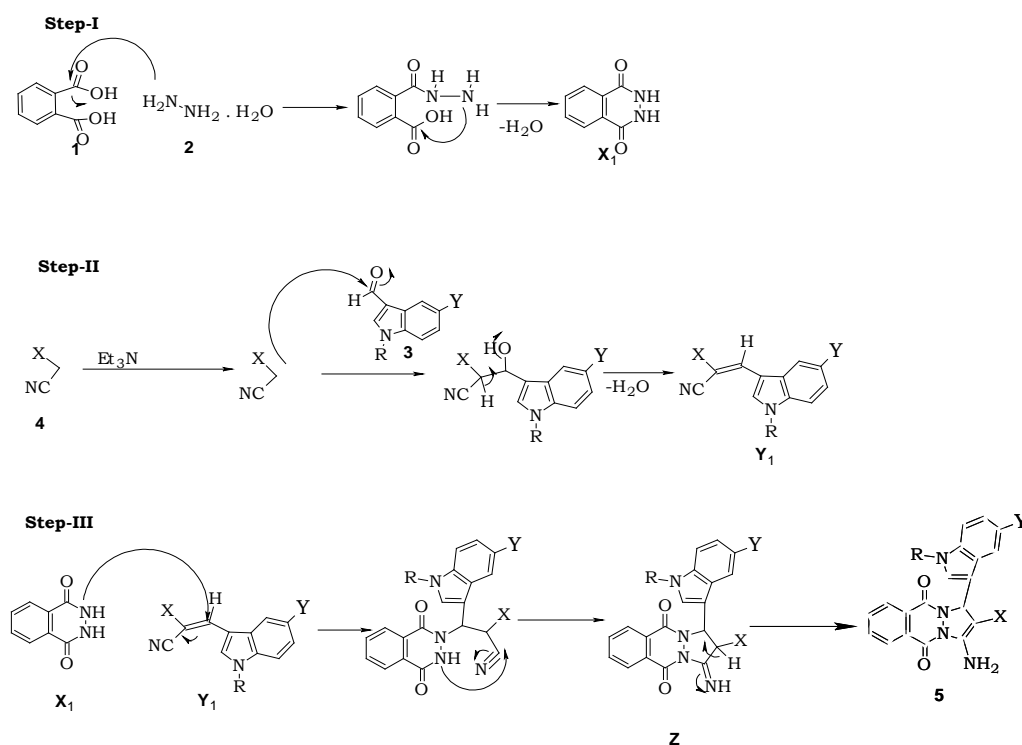
Table 2. Effect of Et₃N catalyst quantity on the one-pot reaction of 1, 2, 3a and 4a at 100-105 °C yielding 5a in glycerol.

No.	Catalyst concentration	T, °C	Time, min	Yield, 5a, %
1	1 mM	100	120	75
2	2 mM	100	45	88
3	5 mM	100	40	78

Table 3. Characterization data, reaction time and yields of **5** obtained from **1**, **2**, **3** and **4** via one-pot, four component synthesis.

Starting materials (1, 2, 3 and 4)	Product	Time, min	Yield, %
3a (R=H, Y=NO ₂)	4a (X=CN)	5a	45 88
3b (R=H, Y=H)	4a (X=CN)	5b	48 86
3c (R=CH ₃ , Y=H)	4a (X=CN)	5c	50 85
3d (R=C ₂ H ₅ , Y=H)	4a (X=CN)	5d	55 84
3a (R=H, Y=NO ₂)	4b (X=COOEt)	5e	50 87
3b (R=H, Y=H)	4b (X=COOEt)	5f	60 86
3c (R=CH ₃ , Y=H)	4b (X=COOEt)	5g	60 84
3d (R=C ₂ H ₅ , Y=H)	4b (X=COOEt)	5h	60 86

≠ Refers to yields of crude products only.



Scheme 2. A plausible mechanism for **5** from **1**, **2**, **3** and **4**.

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined in open capillary tubes in a sulphuric acid bath. TLC was run on silica gel-G and visualization were done using iodine vapor or UV light. IR spectra were recorded using a Perkin-Elmer 1000 instrument in KBr pellets. ^1H NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard at 400 MHz operating frequency. Mass spectra were recorded on an Agilent-LC-MS instrument.

General procedure for preparation of **5**

Phthalic acid (**1**) (10 mM) and hydrazine hydrate (**2**) (10 mM) were charged in glycerol (50 ml) in the presence of Et_3N (3 mM) and heated for 10 min at 100-105 °C to form phthalic acid hydrazide. Then, 5-nitroindole-3-carboxaldehydes (**3a**) (10 mM) and malononitrile/ethylcyano acetate (**4**) (10 mM) were added to this reaction mixture and again heated for 20-35 min (until no starting materials could be detected on thin-layer chromatography). After the reaction was completed, cold water was added to the reaction mixture and solid part was separated by filtration. The product was recrystallised from ethanol solvent to obtain **5**.

3-Amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5a**)

M.p.: >220 °C; IR (KBr): 3116-3440 cm^{-1} (broad, medium, -NH group), 2218 (sharp, strong, -CN group), 1669 cm^{-1}

(sharp, strong, -CO of amide group), 1686 cm^{-1} (sharp, strong, -CO of amide group);

^1H -NMR (DMSO-d_6 , 400 MHz): δ 5.67 (s, 1H, -CH), 7.26-8.68 (m, 10H, Ar-H and NH_2), δ 11.87 (s, 1H, -NH); ^{13}C -NMR (DMSO-d_6 , 100 MHz): δ 61.5, 69.1, 110.6, 111.5, 115.8, 115.9, 119.2, 122.9, 123.6, 127.6, 134.6, 135.6, 138.4, 144.6, 145.8, 161.6, 164.5; $[\text{M}+\text{H}]^+$: 400

3-Amino-1-(1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5b**)

M.p.: >220 °C; IR (KBr): 3116-3440 cm^{-1} (broad, medium, -NH group), 2218 (sharp, strong, -CN group), 1669 cm^{-1} (sharp, strong, -CO of amide group), 1686 cm^{-1} (sharp, strong, -CO of amide group); ^1H -NMR (DMSO-d_6 , 400 MHz): δ 5.67 (s, 1H, -CH), 7.26-8.68 (m, 11H, Ar-H and NH_2), δ 11.87 (s, 1H, -NH); ^{13}C -NMR (DMSO-d_6 , 100 MHz): δ 61.0, 69.0, 110.1, 111.5, 115.9, 119.2, 122.9, 123.9, 127.3, 134.6, 135.8, 138.4, 144.6, 145.8, 161.0, 164.5; $[\text{M}+\text{H}]^+$: 356

3-Amino-1-(1-methyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5c**)

M.p.: >220 °C; IR (KBr) 2213 (sharp, strong, -CN group), 1668 cm^{-1} (sharp, strong, -CO- of amide group), 1682 cm^{-1} (sharp, strong, -CO of amide group); ^1H -NMR (DMSO-d_6 , 400 MHz): δ 2.20 (s, 3H, - CH_3), 5.30 (s, 1H, -CH), 7.21-8.68 (m, 11H, Ar-H and NH_2); ^{13}C -NMR (DMSO-d_6 , 400 MHz): δ 23.4, 60.1, 68.1, 111.3, 111.4, 114.8, 118.1, 122.9,

123.6, 127.4, 133.5, 134.7, 138.3, 144.2, 145.9, 161.4, 164.4; [M+H]⁺: 370

3-Amino-1-(1-ethyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5d)

M.p.: >220 °C; IR (KBr) 2216 (sharp, strong, -CN group), 1663 cm⁻¹ (sharp, strong, -CO of amide group), 1678 cm⁻¹ (sharp, strong, -CO of amide group); ¹H-NMR (DMSO-d₆, 400 MHz): δ 1.81 (t, 3H, CH₃), 2.22 (q, 2H, -CH₂), 5.26 (s, 1H, -CH), 7.21-8.94 (m, 11H, Ar-H and NH₂); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 19.2, 23.2, 60.4, 68.5, 111.2, 111.5, 114.2, 118.2, 122.4, 123.2, 127.1, 133.0, 134.3, 138.2, 144.0, 145.2, 161.5, 164.9; [M+H]⁺: 384

Ethyl-3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5e)

M.p.: >220 °C; IR (KBr): 3076-3360 cm⁻¹ (broad, medium, -NH group), 2297 (sharp, strong, -CN group), 1660 cm⁻¹ (sharp, strong, -CO of amide group), 1666 cm⁻¹ (sharp, strong, -CO of amide group); ¹H NMR (DMSO-d₆, 400 MHz): δ 1.32 (t, 3H, -CH₃), 4.46 (q, 2H, -CH₂), 6.02 (s, 1H, -CH), 7.20-8.69 (m, 10H, Ar-H and NH₂), δ 11.79 (s, 1H, -NH); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 14.0, 61.9, 69.1, 74.0, 110.6, 111.1, 115.8, 115.9, 119.1, 122.9, 123.6, 127.1, 134.6, 135.7, 140.6, 143.7, 151.6, 155.6; [M+H]⁺: 402

Ethyl-3-amino-1-(1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5f)

M.p.: >220 °C; IR (KBr): 3112-3453 cm⁻¹ (broad, medium, -NH group), 2204 (sharp, strong, -CN group), 1668 cm⁻¹ (sharp, strong, -CO of amide group), 1672 cm⁻¹ (sharp, strong, -CO of amide group); ¹H NMR (DMSO-d₆, 400 MHz): δ 1.24 (t, 3H, -CH₃), 4.18 (q, 2H, -CH₂), 5.42 (s, 1H, -CH), 7.22-8.68 (m, 11H, Ar-H and NH₂), δ 11.78 (s, 1H, -NH); ¹³C NMR (DMSO-d₆, 400 MHz): δ 15.3, 55.2, 60.5, 68.1, 110.3, 111.4, 115.0, 117.2, 122.0, 123.5, 127.2, 133.0, 134.9, 137.3, 142.5, 144.5, 150.1, 156.4; [M+H]⁺: 403

Ethyl-3-amino-1-(1-methyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5g)

M.p.: >220 °C; IR (KBr) 2213 (sharp, strong, -CN group), 1664 cm⁻¹ (sharp, strong, -CO of amide group), 1683 cm⁻¹ (sharp, strong, -CO of amide group); ¹H NMR (DMSO-d₆, 400 MHz): δ 1.12 (t, 3H, -CH₃), 2.24 (s, 3H, -CH₃), 4.00 (q, 2H, -CH₂), 5.42 (s, 1H, -CH), 7.22-8.64 (m, 11H, Ar-H and NH₂); ¹³C NMR (DMSO-d₆, 400 MHz): δ 15.3, 22.5, 56.3, 61.4, 67.0, 111.4, 113.5, 114.7, 118.0, 122.0, 122.7, 125.0, 132.4, 134.6, 138.0, 144.1, 143.5, 152.2, 153.5; [M+H]⁺: 417

Ethyl-3-amino-1-(1-ethyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5h)

M.p.: >220 °C; IR (KBr): 2215 cm⁻¹ (sharp, strong, -CN group), 1666 cm⁻¹ (sharp, strong, -CO of amide group),

1673 cm⁻¹ (sharp, strong, -CO of amide group); ¹H NMR (DMSO-d₆, 400 MHz): δ 1.18 (t, 3H, -CH₃), 1.69 (t, 3H, CH₃), 2.39 (q, 2H, -CH₂), 4.15 (q, 2H, -CH₂), 5.26 (s, 1H, -CH), 7.22-8.93 (m, 11H, Ar-H and NH₂); ¹³C NMR (DMSO-d₆, 400 MHz): δ 15.2, 19.4, 23.6, 54.3, 60.2, 68.4, 111.5, 111.7, 114.0, 118.1, 122.3, 124.1, 126.8, 133.4, 134.9, 138.1, 144.2, 145.5, 151.6, 154.6; [M+H]⁺: 431

CONCLUSION

In summary, a novel method to prepare 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile and related derivatives have been developed by the reaction of phthalic acid, hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of Et₃N and glycerol mediated at 100-105 °C for 30-60 min. This one-pot reaction proceeds in a short time with good yields and the desired products obtained without using column chromatographic purifications.

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REFERENCES

- Montagne, C., Shiers, J. J., Shipman, M. Rapid generation of molecular complexity using "sequenced" multi-component reactions: one-pot synthesis of 5,5'-disubstituted hydantoins from methyleneaziridines, *Tetrahedron Lett.* **2006**, *47*, 9207. <https://doi.org/10.1016/j.tetlet.2006.10.135>
- Bienayme, H.; Multicomponent Reactions, Wiley-VCH, Weinheim, **2005**, 311-341. <https://doi.org/10.1016/j.tetlet.2006.10.135>
- Braese, S., Gil, C., Knepper, K. The recent impact of solid-phase synthesis on medicinally relevant benzoannulated nitrogen heterocycles, *Bioorg. Med. Chem.* **2002**, *10*, 2415. [https://doi.org/10.1016/S0968-0896\(02\)00025-1](https://doi.org/10.1016/S0968-0896(02)00025-1)
- Hailes, H. C., Reaction Solvent Selection: The Potential of Water as a Solvent for Organic Transformations, *Org. Process Res. Dev.*, **2007**, *11*, 114. DOI: 10.1021/op060157x
- El-Sakka, S. S.; Soliman, A. H.; Imam, A. M., Synthesis, antimicrobial activity and Electron Impact of Mass Spectra of Phthalazine-1,4-dione Derivatives, *Afinidad.* **2009**, *66*, 167. <https://core.ac.uk/download/pdf/39152404.pdf>
- Carling, R. W., Moore, K. W., Street, L. J., Wild, D., Isted, C., Leeson, P. D., Thomas, S., O'Connor, D., McKernan, R. M., Quirk, K., Cook, S. M., Atack, J. R., Waftord, K. A., Thompson, S. A., Dawson, G. R., Ferris, P., Castro, J. L., 3-Phenyl-6-(2-pyridyl)methoxy-1,2,4-triazolo[3,4-*a*]phthalazines and Analogues: High-Affinity γ -Aminobutyric Acid-A Benzodiazepine Receptor Ligands with α 2, α 3, and α 5-Subtype Binding Selectivity over α 1, *J. Med. Chem.* **2004**, *47*, 1807; DOI: 10.1021/jm031020p
- Jain, R., Vederas, J. C., Structural variations in keto-glutamines for improved inhibition against hepatitis A virus 3C proteinase, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3655. <https://doi.org/10.1016/j.bmcl.2004.05.021>
- Grasso, S., DeSarro, G., Micale, N., Zappala, M., Puia, G., Baraldi, M., Demicheli, C., Synthesis and Anticonvulsant Activity of Novel and Potent 6,7-Methylenedioxyphthalazin-

- 1(2*H*)-ones, *J. Med. Chem.* **2000**, *43*, 2851; DOI: [10.1021/jm001002x](https://doi.org/10.1021/jm001002x)
- ⁹Nomoto, Y., Obase, H., Takai, H., Teranishi, M., Nakamura, J., Kubo, K., Studies on Cardiotonic Agents. II.: Synthesis of Novel Phthalazine and 1,2,3-Benzotriazine Derivatives, *Chem. Pharm. Bull. (Tokyo)* **1990**, *38*, 2179. <https://doi.org/10.1248/cpb.38.2179>
- ¹⁰Watanabe, N., Kabasawa, Y., Takase, Y., Matsukura, M., Miyazaki, K., Ishihara, H., Kodama, K., Adachi, H., 4-Benzylamino-1-chloro-6-substituted Phthalazines: Synthesis and Inhibitory Activity toward Phosphodiesterase 5, *J. Med. Chem.* **1998**, *41*, 3367. DOI: [10.1021/jm970815r](https://doi.org/10.1021/jm970815r)
- ¹¹Sheradsky, T., Moshenberg, R., Bridgehead hydrazines. Unusual photorearrangement of 1,4-diphenylpyridazino[1,2-b]phthalazine-6,11-dione, *J. Org. Chem.* **1986**, *51*, 3123. DOI: [10.1021/jo00366a008](https://doi.org/10.1021/jo00366a008)

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