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Graphical Abstract

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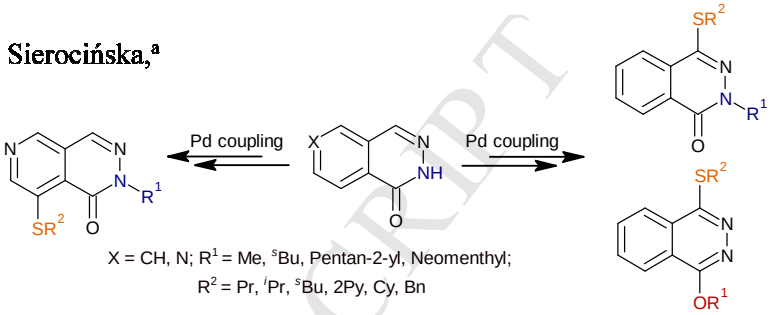

Synthesis of 4-alkylsulfanylphthalazin-1(2*H*)-ones via palladium catalyzed sulfanylation of substituted 4-bromophthalazin-1(2*H*)-ones

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Keywords:

Phthalazinones, Bromination, Mitsunobu reaction, Palladium catalyzed coupling reaction, Sulfanylation

Abstract

The synthesis of a series of new alkylsulfanyl phthalazinone and phthalazine derivatives ~~was~~ is described. The target compounds were efficiently synthesized in a four step sequence ~~steps reaction~~, consisting of *(1)* cyclization of 2-formylbenzoic acid with hydrazine hydrate to form phthalazinone, *(2)* the direct bromination of phthalazinone core with KBr_3, ~~then~~ *(3)* ~~the~~ alkylation ~~reactions~~ of the obtained 4-bromolactam (Mitsunobu procedure) to make *N*- and also *O*-alkyl derivatives and finally *(4)* ~~the~~ palladium-catalyzed coupling reactions of 2-alkyl-4-bromophthalazinone and 1-alkyloxy-4-bromophthalazine derivatives with aliphatic mercaptanes. Furthermore, the synthesis of 2-methyl-8-(propan-2-yl)sulfanyl-pyrido[3,4-*d*]pyridazin-1(2*H*)-one from 2-methyl-pyrido[3,4-*d*]pyridazin-1(2*H*)-one via bromination reaction with KBr_3 and subsequent sulfanylation by isopropyl mercaptan under catalyzed coupling reaction conditions ~~was~~ is also described.

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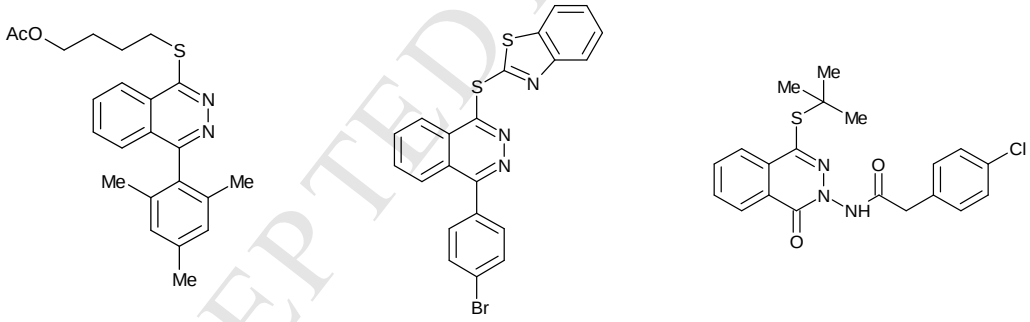
1. Introduction

Phthalazin-1(2*H*)-ones and phthalazines are nitrogen heterocycles which have aroused great interest ~~since~~ over many years, due to their important biological and pharmacological properties,[1] as well as due to their significance in other fields, ~~such as~~ *e.g.* ~~new~~ in materials chemistry.[2] It has been shown that phthalazinone derivatives exhibit ~~diverse biological activities~~, *e.g.* antidiabetic,[3] anticancer,[4] antiasthmatic,[5] anti-inflammatory, analgesic[6] or antimicrobial[7] activities. Some of them have been used in medicine to treat cancer (Olaparib) or diabetes (Zopolrestat).[8] In the recent years, much attention was devoted to the studies on the synthetic methods and properties of 4-substituted (alkyl, heteroaryl, amino) phthalazin-1(2*H*)-ones.[9-11] On the other hand, to date, the phthalazinones or phthalazines containing sulfide or sulfone functional groups are a relatively little-studied class of compounds. However, the literature review proves that some of them have shown interesting properties, *e.g.* mesitylphthalazine **I** (Fig. 1) has exhibited a good antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* (MIC = 12.5 μg/mL),[12] phthalazine **II** has exhibited a high cytotoxic activity (IC_{50} = 2.3 μM) against human breast cancer cell line (MCF-7)[13] and *tert*-butylsulfanylphthalazinone **III** has shown an activity as a modulator of KCNQ potassium channel.[14]



I **II** **III**

Fig. 1. Biologically tested phthalazinone and phthalazine derivatives containing sulfanyl moiety.

In continuing our work ~~in~~ on the synthesis of new polyazanaphthalene derivatives (phthalazinones, azaphthalazinones, quinazolinones),[15] and also taking into consideration the importance of sulfanyl compounds, ~~among other things~~ as biologically active molecules,[16] ~~already partially mentioned above,~~ we wished to ~~present the~~ investigate a route for the synthesis of 2-substituted-4-alkylsulfanylphthalazinones using palladium catalyzed C-S coupling reactions. The first report describing the palladium catalyzed C-S bond formation reaction was presented towards the end of 1970s by Migita.[17] Since then, many reviews describing the sulfanyl derivatives formation in reactions of aromatic halogenated species

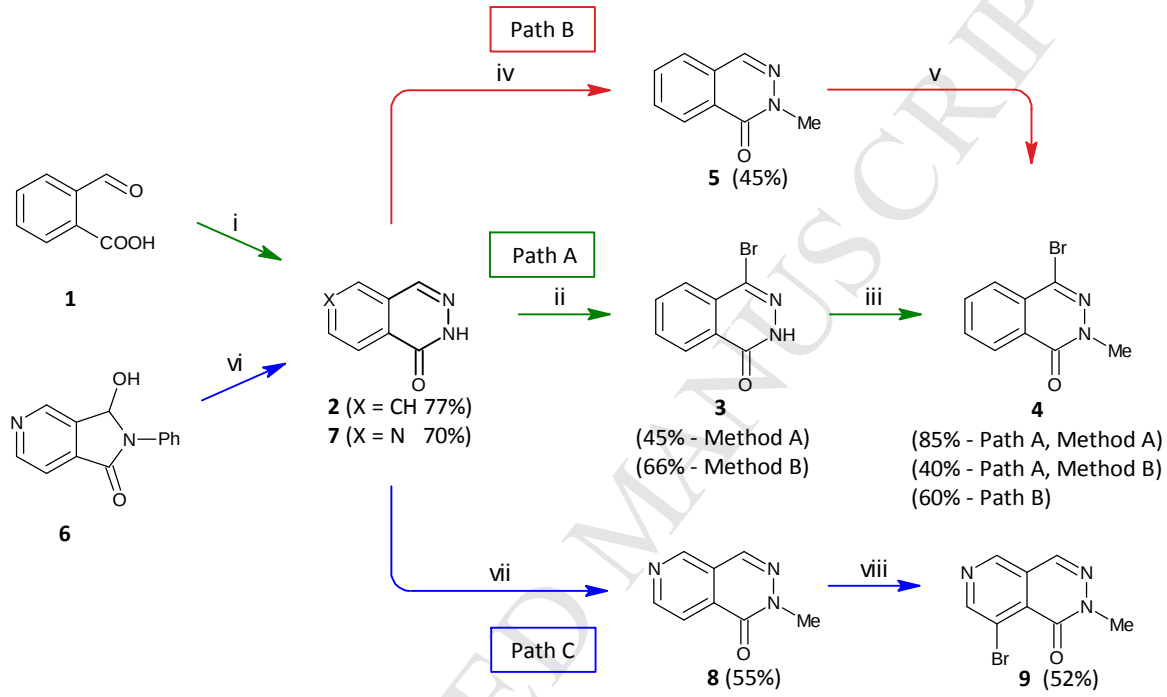
with various thiols have been published,[18] however these type of transformations were not used to the synthesis of phthalazinones, containing C-S bonds. As a key intermediate for our research, we chose 4-bromophthalazin-1(2*H*)-one (**3**, Scheme 1). Literature examples of the synthesis of **3**, usually involved condensation of phthalic anhydride with unsubstituted hydrazine, and next dibromination of formed phthalazine-1,4-dione, followed by monohydrolysis.[11] So far, synthetic utilities of 4-bromo- and also 4-triflate- phthalazinone derivatives ~~were~~ have been demonstrated, *e.g.* in ~~a~~ palladium or copper catalyzed coupling reactions with amines, aryl- (heteroaryl-) boronic acids or with aryl- (alkyl-) acetylenes.[11,~~17~~ 19]

2. Results and discussion

The planned synthetic route toward 4-bromophthalazinone (**3**) consisted of the two-steps~~, as~~ shown in Scheme 1 (Path A). The first step involved the condensation of 2-formylbenzoic acid (**1**) with hydrazine hydrate, in boiling propan-1-ol, yielding phthalazin-1(2*H*)-one (**2**)~~,~~ in 77% yield.[~~18~~ 20] In the next stage lactam **2** was subjected to bromination ~~reaction~~ with various ~~agents,~~ combinations of reagents[~~19~~ 21] such ~~as *e.g.*~~ NBS/$FeCl_3$ in MeCN, Br_2 in AcOH, Br_2/$FeBr_3$ in CCl_4 or Br_2/Na_2CO_3 in THF. Unfortunately, in most instances the results were not satisfying; only when NBS/$FeCl_3$ in MeCN and Br_2/Na_2CO_3 in THF were used the target bromo derivative **3** formed in a little amount (as judged by ^{1}H NMR, TLC). ~~,~~ ~~what made these methods useless in the further synthesis of target compounds~~. A literature survey revealed that ~~Br_2-KBr~~ various tribromide reagents, particularly potassium tribromide, can be ~~an~~ effective ~~reagent~~ agents for bromination of heterocyclic compounds.[~~20~~ 22] The treatment of phthalazin-1(2*H*)-one (**2**) with Br_2-KBr in water ~~as an environmentally friendly solvent~~, afforded a regioselectivity brominated product **3**, in a satisfactory yield (45%). ~~Moreover, an attempt to carry out the bromination of phthalazinone~~ ~~core~~ The use of Br_2-KBr in an acetate buffer solution resulted in an increase in a yield of **3** (66%). ~~The bromo derivative **3** was isolated from the post reaction mixture using flash chromatography. In addition to lactam **3**, every time some amount of starting phthalazinone **2** was also isolated from the crude material.~~ The position ~~substitution~~ of the bromine atom in ~~4 position of~~ pyridazinone moiety was ~~supported~~ confirmed by ^{1}H NMR spectroscopy. The spectrum of **3** revealed the absence of the singlet signal at 8.36 ppm (DMSO-d_6) of ~~4-H~~ H-4 ~~pyridazinone~~ proton, characteristic of an unsubstituted phthalazinone **2**.

Furthermore, ~~it was found that~~ we observed that also 2-methylaphthalazin-1(2*H*)-one (**5**) (Scheme 1, Path B), ~~also~~ underwent the reaction ~~bromination~~ with potassium tribromide in

water, to give exclusively the monobrominated product **4**, substituted at 4 position of pyridazinone ring, in 60 % yield. On the other hand, the introduction of the nitrogen atom into the benzene ring condensed with pyridazinone moiety so significantly changed the reactivity of obtained system that ~~,~~ 2-methylpyridopyridazin-1(2*H*)-one **8**[21 23] (Scheme 1, Path C) ~~,~~ ~~under the same reaction conditions,~~ underwent bromination ~~reaction~~ only in the pyridine ring, leading to ~~afforded~~ 8-bromo derivative **9**, in 52% yield.



Reagents and conditions: Path A: i) NH_2NH_2, PrOH, Δ, ii) *Method A:* Br_2, KBr, H_2O, Δ, *Method B:* Br_2, KBr, acetate buffer, Δ; iii) *Method A:* MeI, K_2CO_3, acetone, Δ, *Method B:* MeI, K_2CO_3, acetone, MW; Path ~~C~~ B: iv) MeI, K_2CO_3, acetone, MW, v) Br_2, KBr, H_2O, Δ; Path ~~D~~ C: vi) NH_2NH_2, Δ, vii) MeI, KOH, methanol, Δ, viii) Br_2, KBr, H_2O, Δ.

Scheme 1. The direct bromination reaction of phthalazinone **2**, *N*-methylphthalazinone **5** and *N*-methylpyridopyridazinone **8** with KBr_3.

The mechanism of reaction KBr_3 with **2**, **5** and particularly with **8** is not obvious and demands additional studies but ~~,~~ it can be assumed that in the case of halogenation of lactam **2**, its lactim tautomeric form[22 24] plays ~~the~~ a significant role. ~~and~~ The possible mechanism of this transformation could be similar to the one proposed for the ~~bromination~~ reaction of cinnolin-4(1*H*)-one⇆4-hydroxycinnoline with bromine in AcOH or in AcOK/AcOH ~~,~~[23] ~~Likewise as for **2**, the bromination process of cinnolinone also~~ which proceeds selectively in the heterocyclic ring and leads to the formation of 3-bromo ~~derivative~~ cinnolinone.[25] On the other hand, phthalazinones could be treated like acyl hydrazones, which bromination leads to

~~the replacement of the methine hydrogen and~~ the formation of the corresponding hydrazonoyl bromides.[~~24~~ 26]

~~Nevertheless, the detailed mechanismtic investigations of these transformations demand additional studies and were not our main aim.~~

~~Two synthetic routes were employed for~~ The important part of our studies was the synthesis of the *N*-substituted phthalazinones and pyridopyridazinones. The conversion of 2*H*-pyridazin-3-one derivatives into corresponding *N*-alkyl ~~substituted~~ products ~~(Scheme 1 and Table 1).~~ was performed using two synthetic routes (Scheme 1, Table 1).

The first approach involved the reactions of lactams **2**, **3**, **8** with alkyl halides. It is known that phthalazinones as well as their azaanalogues can exist in two tautomeric forms (lactam⇆lactim) and thereby can be alkylated at the nitrogen or at the oxygen atom to produce both *N*- and *O*-substituted products, depending on the reaction conditions. ~~On the other hand, it is known that~~ It was found that potassium salts of phthalazinones selectively react with methyl iodide or ethyl iodide at the lactam nitrogen atom while their silver salts give mainly *O*-alkyl phthalazines.[~~22~~ 24] ~~Thus,~~ *N*-Methyl lactams **4** and **5** were prepared by direct alkylation of phthalazinones **2**, **3** with methyl iodide in the presence of K_2CO_3/dry acetone under microwave or conventional heating conditions (Scheme 1, Path A, B).[15] Unexpectedly, carrying out the reactions under MW conditions (55 ^oC, 3.5 h) turned out to be less effective than conventional heating and the products **4**, **5** were obtained in only moderate yields (40% and 45%, respectively). The change of the reaction conditions (60 ^oC, 8 h) led to an increase in a yield of **4** up to 85%. ~~Carrying out the reaction in dry acetone at 55 ^oC for 3.5 h under microwave conditions allow derivatives **4** (40%), **5** (45%) to be obtained in moderate yields. A considerable improvement of the yield of *N*-methyl lactam **4** (85%) was achieved when the reaction was carried out under conventional heating conditions.~~

2-Methylpyridopyridazinone **8** was prepared from pyridopyridazinone **7** according to previously described procedure (MeI, KOH/MeOH) in 55% yield.[~~21~~ 23] The formation of *N*-methylated product~~s~~ was confirmed on the ~~base~~ basis of their FTIR spectra, which exhibited band~~s~~ in the region 1648–1665 cm^{-1} attributable to C=O group of lactams.

~~Alternatively, the synthesis of alkyl 4-bromophthalazinone derivatives was performed using the Mitsunobu reaction~~.

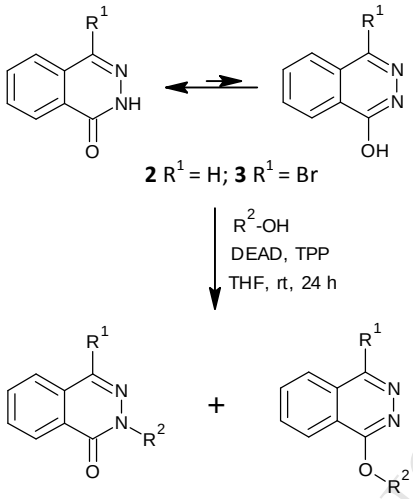
In the second approach the alkylation of phthalazine core was carried out under Mitsunobu reaction conditions. In our earlier paper, we ~~have~~ demonstrated ~~an~~ the effectiveness of this procedure as a synthetic tool for the alkylation of phthalazinone moieties

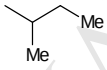
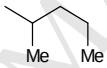
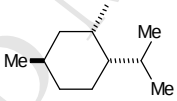
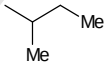
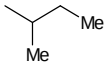
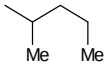
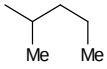
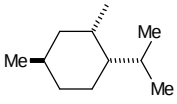
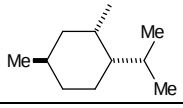
with the primary *N*-protected-aminoalcohols.[25] [27] In the present work, we focused on the application of secondary alcohols, like butan-2-ol, pentan-2-ol and (–)-menthol. It is well-known that in the case of secondary alcohols that the Mitsunobu reaction proceeds with the inversion of configuration at the stereogenic center and thus, the employ use of menthol leads to neomenthyl derivatives.[26] [28] Before attempting to synthesize *N*-alkylated bromophthalazinones **13-15** (Table 1), we there was investigated the behavior of unsubstituted phthalazinone **2** in the condensations with the mentioned secondary alcohols. All tests reactions were carried out in the presence of TPP and DEAD,[25,27] [27,29] at room temperature, in THF as solvent and were completed within 24 hours. At the beginning First, we applied the procedure described by Knaac[27] [29] (Experimental, Table 1, Method A); the analysis of the obtained post-reaction mixtures indicated the presence of Mitsunobu products, DEAD-H_2, triphenylphosphine oxide, unreacted starting compounds and others unidentified substances. Despite the fact that reactions mainly coursed at the phthalazinone nitrogen atom the outcomes were moderate and products **10a**-**12a** were isolated only in 30–48% yields (Table 1, Entry 1, 2, 3, 5, Method A). On the other hand, it is possible that also corresponding *O*-derivatives **10b**¸**11b** and **12b** were formed in trace amounts ((^{1}H NMR)), but they were not isolated. Next, we examined the effectiveness of an alkylation of phthalazinone **2** using modified Sammakia[28] [30] procedure conditions (Experimental, Table 1, Method B). Compounds **10a** and **11a** were received with meaningful better results (72% and 85%, respectively) but . unexpectedly, neomenthyl derivative **12a** was separated isolated in only 30% yield. The obtained results clearly showed that Therefore, in some cases, changes of in the reaction temperature as well as the order of reagent addition, can result in an increase of Mitsunobu products yields.

Finally, the condensations of 4-bromophthalazin-1(2*H*)-one (**3**) with butan-2-ol, pentan-2-ol and (–)-menthol secondary alcohols were performed using the second procedure (Method B, Table 1) the same reaction conditions as for **2** (Method B) and led to the formation of product mixtures of *N*-alkyl-bromophthalazinones **13a**-**15a** and *O*-alkyl-bromophthalazines **13b**-**15b** (Table 1), in which the former largely predominated.

Compounds **13a**-**15a**, **13b** and **15b** were separated by flash chromatography and identified by NMR and HRMS spectroscopy. Only, the phthalazine **14b** was isolated in the mixture with **14a**. The total yields of obtained products **13a**,**b**, **14a**,**b**, and **15a**,**b** were 54%, 31% and 57%, respectively.

Table 1. The alkylation reaction of phthalazinones **2**, **3** under Mitsunobu reaction conditions.



Entry	Compound	R^1	R^2	Yield (%)[a]	
				Method A	Method B
1	**10a**	H		30	72
2	**11a**	H		48	85
3	**12a**	H		40	30
4	**13a**	Br		–	48
5	**13b**	Br		–	6
6	**14a**	Br		–	28
7	**14b**	Br		–	3[b]
8	**15a**	Br		–	29
9	**15b**	Br		–	28

[a] Yield was given for isolated product after silica gel chromatography;
[b] Mixture with **14a** (^{1}H NMR).

The structures of *N*-, *O*- isomeric alkyl derivatives **13-15** were ~~explicitly~~ characterized based on the comparison of ^{1}H NMR spectra. The major diagnostic value in the identification of phthalazinone and phthalazine derivatives had the chemical shifts of H-8 aromatic proton and

methine proton of alkyl substituent, attached to carbon adjacent to nitrogen or oxygen atom. In the case of **13a**-**15a**, the H-8 proton signals were appreciably more downfield shifted (≈ 8.4 ppm), than in the instance of corresponding *O*-derivatives **13b**-**15b** (≈ 8.1 ppm) ~~(≈ 8.4 ppm and ≈ 8.1 ppm, respectively)~~, while the methine protons of alkyl groups were more upfield shifted for *N*-derivatives. For example, for *O*-derivative **15b** the methine proton signal was observed at ≈ 5.9~~2~~ ppm, while for **15a** at ≈ 5.4~~3~~ ppm. Furthermore, in the ^{13}C NMR spectra of ~~10b-12b~~ **13b**-**15b** signals corresponding to the carbon of O-Csp^3 and Csp^2-O moiety were observed at ≈ 74 ppm and ≈ 160 ppm, respectively. Whereas for *N*-derivatives **13a**-**15a**, signals of N-Csp^3 and C=O carbon atoms appeared at ≈ 53 ppm and ≈ 159 ppm, respectively. Likewise as in the case of *N*-methyl derivatives, the FTIR spectra of the *N*-substituted lactams **13a**, **14a**, **15a** showed ~~shown~~ the presence of C=O band ~~at~~ in the range 1653–1660 cm^{-1} characteristic of the lactam carbonyl group, which ~~were~~ was absent in the FTIR spectra of **13b**, **14b** and **15b**.

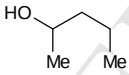
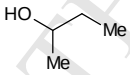
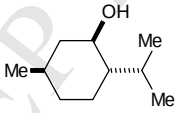
From achieved reaction results (Table 1) it become clear that the chemical nature of phthalazinones as ambident nucleophiles as well as alcohols can have an influence on the course of the Mitsunobu reaction and on the ratio of formed *N*-, *O*- isomeric products. In particular, ~~we have found, that~~ the bromine atom at the 4-position of the pyridazinone moiety in **3** clearly increased the formation of *O*-alkylated phthalazine in comparison with an unsubstituted phthalazinone. In addition, ~~in this case~~ an amount of the produced phthalazine derivative depended also on the kind of alcohol used for alkylation of **3** ~~process~~ (Table 1, Entry ~~8, 10, 12,~~ 5, 7, 9) and it was the largest for (–)-menthol.

A similar dual behavior of various ambident nucleophilic components in Mitsunobu reaction, was well documented in the literature,[~~29~~ 31] but ~~a lucid~~ an explanation of this phenomenon and especially the prediction of the amount~~s~~ of formed products is still problematic. The Hard and Soft Acids and Bases (HSAB) concept[~~30~~ 32] is one of more popular theory used for describing reactivity of ambident nucleophiles.~~, but its direct and uncritical application to organic chemistry should be circumspect due to sometimes erroneous deductions to which it can lead.~~[~~31~~] According to the HSAB principle, an intermediate formed from alcohol in Mitsunobu reaction, as hard electrophilic species should be preferentially attacked by harder nucleophilic atom (oxygen), but our experimental data showed ~~shown~~ the softer nucleophilic site in the ambident phthalazinone anion was mainly alkylated (Tables 1 and 2). Mayr[~~31~~ 33] as well Fletcher[~~32~~ 34] have written ~~in your papers paid attention~~ that Marcus theory better describes the behavior of amide type species in alkylation process. Despite the fact that, the value of

intrinsic barrier prefers the oxygen attack ~~(it is slight lower than for nitrogen)~~, the course of reaction through the nitrogen atom is thermodynamically favoured (amides are ~~typically~~ ~~80 kJ/mol~~ more stable than their tautomers).[33,34] ~~and it is in accordance with our experiment results~~. Thus, direct and uncritical application of the HSBA theory to organic chemistry can lead to wrong conclusions and it should be treated with caution.[33]

On the other hand, the HSAB-theory can ~~be with~~ give good results when applied to explain the influence of the alcohol (~~their~~ its hardness or softness, in fact) on the distribution of isomeric *N*-/*O*- alkylated products in the Mitsunobu reaction ~~obtained from **3**~~. Based on the methodology presented by Meier[~~33~~ 35] we closer examined the experimental data obtained for 4-bromoderivatives **13-15** (Tables 1 and 2). Approximately, the hardness/softness of an intermediate formed from alcohol in Mitsunobu reaction can be assessed based on the ^{13}C NMR chemical shift of the corresponding ~~HC-OH~~ alcohol carbon atom attached to the hydroxyl group.[~~33~~ 35] The more the HC-OH carbon atom signal is downfield, the harder it is likely to be and ~~harder~~ more *O*- derivative should be also appeared. ~~a carbocation-like center of an alcohol intermediate~~

Table 2. The ratio of *N*-/*O*- alkylation of lactam **3**.

Entry	Alcohol	HC-OH (ppm)[a]	Lactam	*N*-/*O*- alkylation ratio[b]
1		67.0	**3**	95:5
2		68.5		92:8
3		71.7		62:38

[a] - ^{13}C NMR chemical shift of HC-OH-carbon atom of alcohol;
[b] - The ratio of the formed *N*- and *O*- alkylated products was determined by ^{1}H NMR analysis of the crude mixture.

The obtained values of chemical shifts of HC-OH carbon for pentan-2-ol, butan-2-ol and (–)-menthol (Table 2) ~~were as follows: 67.0, 68.5 and 71.7 ppm. These data~~ implied that the C-1 carbon atom of menthol should be harder than the C-2 carbon atoms of butan-2-ol or pentan-2-ol and thereby, (–)-menthol can form more *O*- alkylated product. Indeed, these predictions are in conformity with experimental data.

~~The observed ratio of the formed *O*-alkylated 1-bromophthalazine to *N*-alkylated 4-bromophthalazinone increased from 5:95 (pentan-2-ol), 8:92 (butan-2-ol) to 38:62 ((-)-~~

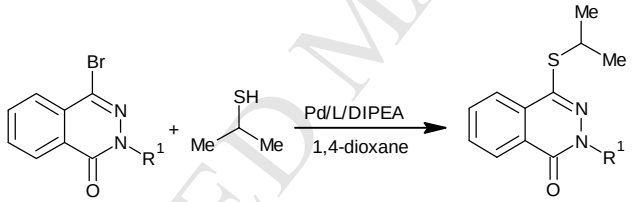
~~menthol). Therefore, the well thought out use of HSAB or Marcus theories can supply to conclusions in accordance with experimental data.~~

In the next step bromolactams **4**, **9**, **13a**, **14a** and **15a** ~~(Scheme 2)~~ were subjected to the palladium cross-coupling reaction with mercaptanes with a view to synthesize target 2-alkyl-4-sulfanyl- and 2-alkyl-8-sulfanyl- derivatives.

~~The first report describing the palladium catalyzed C-S bond formation reaction was presented towards the end of 1970s by Migita.[34] Since then, many reviews describing the sulfanyl derivatives formation in reactions of aromatic halogenated species with various thiols have been published in the literature,[35] however these type of transformations were not used to the synthesis of phthalazinones, containing C-S bonds.~~

To optimization of the reaction conditions for the palladium-catalyzed synthesis of sulfanyl derivatives, we initially investigated the reaction of 4-bromo-2-methylphthalazin-1(2*H*)-one **4** with isopropyl mercaptan in the presence of $Pd(OAc)_2$ as a palladium source and phosphine ligand, like: XantPhos, DPEPhos, DavePhos (Table 3).

Table 3. Optimization of the C-S coupling reaction conditions.



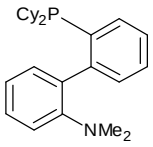
3 R^1 = H
4 R^1 = Me

16 R^1 = H
17 R^1 = Me

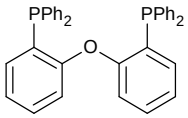
Entry	R^1	L	Pd	Pd/L ratio (mol%)	Yield (%)[a]	
					16	**17**
1	Me	DavePhos	$Pd(OAc)_2$	10 / 10	–	NR
2	Me	XantPhos	$Pd(OAc)_2$	10 / 10	–	NR
3	Me	DavePhos	$Pd(OAc)_2$	30 / 30	–	10
4	Me	XantPhos	$Pd(OAc)_2$	30 / 30	–	84[b]
5	Me	DPEPhos	$Pd(OAc)_2$	30 / 30	–	78
6	H	XantPhos	$Pd(OAc)_2$	30 / 30	16	–

Reaction conditions: 4-bromophthalazinone **3** (0.209 mmol) or 4-bromo-2-methylphthalazinone **4** (0.209 mmol), isopropyl thiol (0.418 mmol), DIPEA (0.7 mL), 1,4-dioxane (5 mL), 100 °C (26 h);

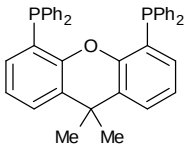
[a] Yield determined by ^{1}H NMR analysis of crude reaction mixture;
[b] Yield of isolated product;
NR - No reaction.



DavePhos



DPEPhos

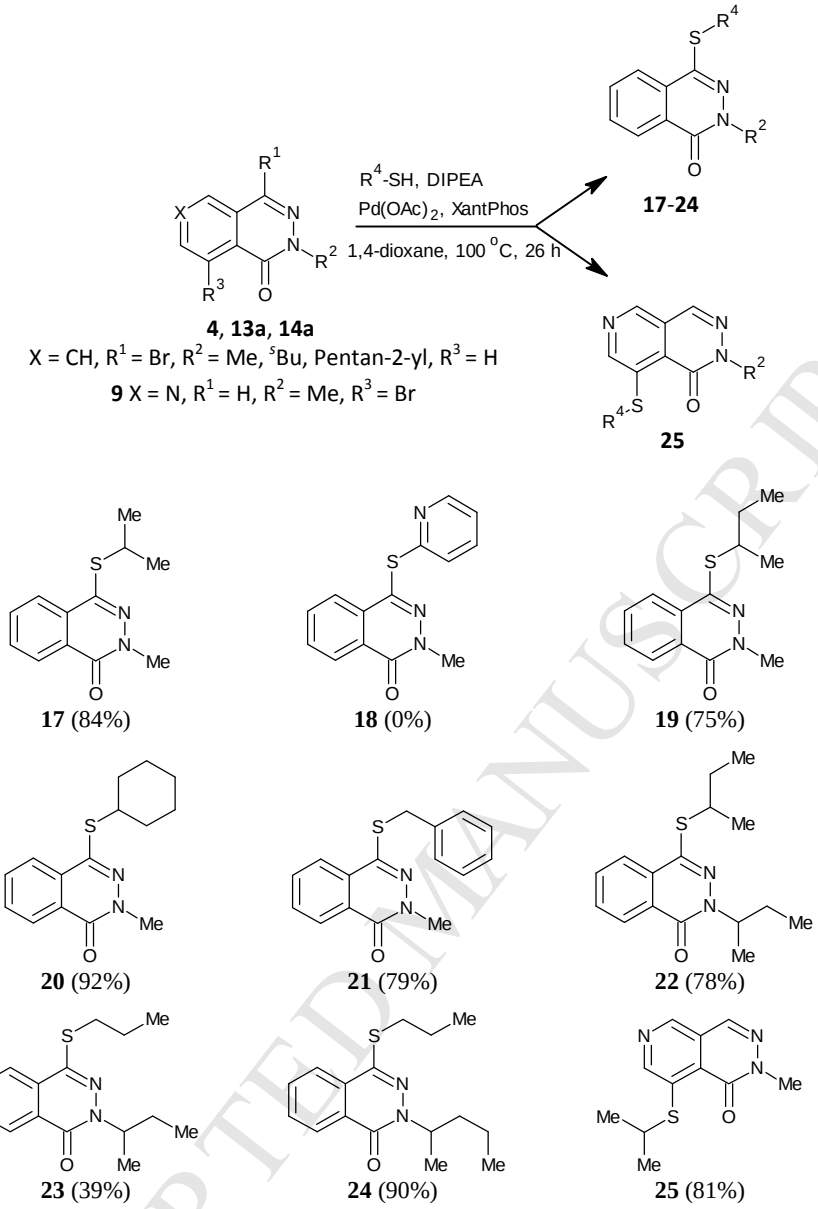


XantPhos

When the combination of $Pd(OAc)_2$ with DavePhos (Entry 1), or $Pd(OAc)_2$ with XantPhos (Entry 2) in the ratio 10 mol%/10 mol% as catalytic system were used ~~to~~ for the coupling **4** with mercaptan, the production of **17** was not observed. ~~The~~ Further investigations showed that ~~the~~ an increased ~~an~~ amount of $Pd(OAc)_2$ and DavePhos up to 30 mol%/30 mol% (Entry 3) resulted in the production of **17**, which was observed in 10% yield by ^{1}H NMR. In the presence of $Pd(OAc)_2$ and XantPhos used in the same ratio (Entry 4) sulfide **17** was formed as the major product, and finally was isolated in 84% yield. The replacement of the XantPhos by DPEPhos led to a slight decrease in the reaction yield (78%, ^{1}H NMR, Entry 5). Although both catalytic systems worked, $Pd(OAc)_2$/XantPhos proved to be more productive and gave the higher yield of the target product **17**. Moreover, in this case the starting lactam **4** was observed only in trace amount, in the crude reaction mixtures by ^{1}H NMR.

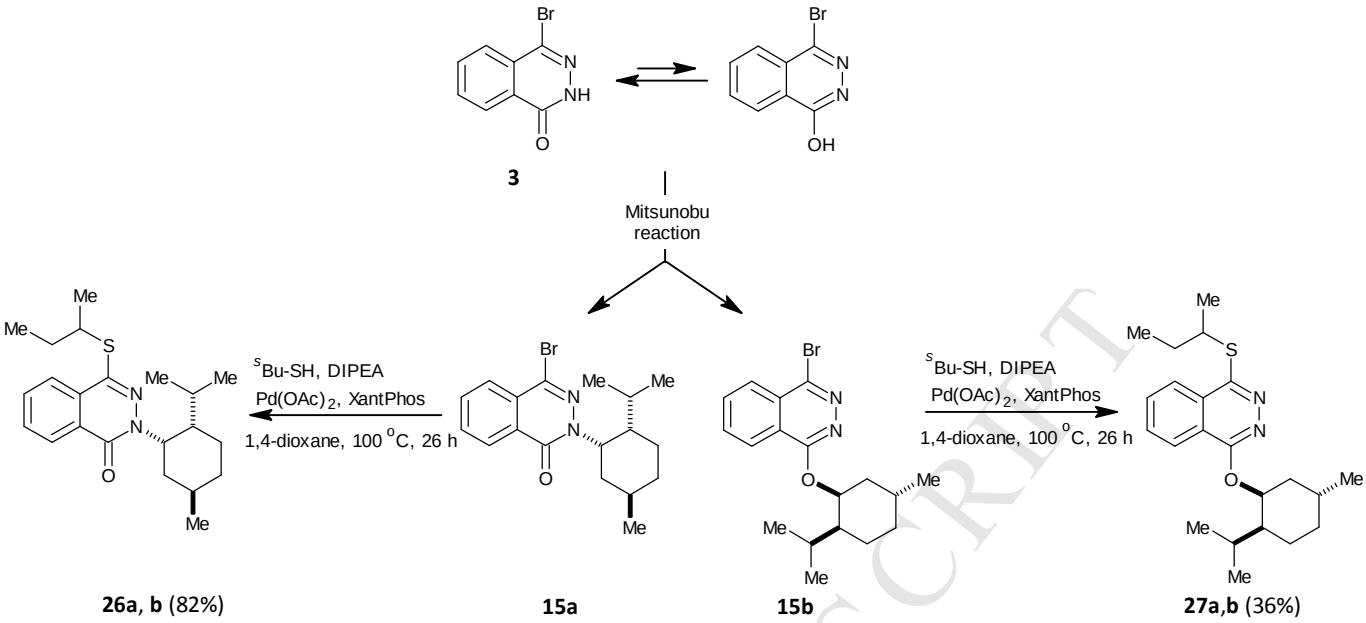
In addition, ~~we~~ it was observed that ~~the corresponding~~ 4-bromophthalazinone **3** (Entry 6) also underwent sulfanylation in the presence of $Pd(OAc)_2$/XantPhos system in the ratio 30 mol%/30 mol% and gave **16**, in 16% (^{1}H NMR) yield. Attempts to separation of **16** by flash chromatography ~~was~~ were failed, and finally it was obtained as a mixture with **3** and characterized by ^{1}H NMR spectroscopy.

Based on the results presented in Table 3, bromolactams **4**, **9**, **13a**, **14a** were subjected to coupling reactions with various mercaptanes. As can be seen from Scheme 2, the palladium catalyzed sulfanylation of **4**, **9**, **13a** and **14a** proceeded excellent with primary as well as secondary aliphatic mercaptanes. Unexpectedly, 2-mercaptopyridine was unreactive towards **4** and product **18** was not observed. The target alkylsulfanyl derivatives **17**, **19-22**, **24** were isolated in 75–92% yields. The reaction of **13a** with propyl mercaptan surprisingly processed in lower yield ~~than in other cases~~ and derivative **23** was isolated in 39% yield.



Scheme 2. Synthesis of sulfanyl phthalazinone and pyridopyridazinone derivatives.

Apart from bromophthalazinones, 1-bromophthalazines may be also transformed into sufanyl derivatives. The treatment of **15a** as well, **15b** with *sec*-butyl mercaptan in the presence of the previously used catalytic system led to alkylsulfanylphthalazinone **26** and alkylsulfanylphthalazine **27** (Scheme 3) in 82% and 36% yields, respectively. Sulfanylderivatives **26**, **27** were obtained as mixtures of two diastereomers (dr = 1:1, ^{1}H NMR) each, due to the presence of an additional stereogenic center from the *sec*-butyl thiol. ~~Curiously, the coupling reactions of bromoderivatives **15a**, **15b** with ^{s}Bu-SH proceeded without any diastereoselectivity effect, despite the presence of the neomenthyl moiety in both molecules.~~



Scheme 3. Synthesis of neomenthyl derivatives **26**, **27**.

Successful synthesis of **25** and **27** has confirmed our conjectures that the described above strategy could be a useful tool for modifications of various heterocyclic systems.

~~The proposed structures of all new compounds were confirmed using spectroscopic analyses (NMR, FTIR and HRMS).~~

3. Conclusion

In conclusion, we have demonstrated an efficient synthesis of 2-alkyl-4-alkylsulfanyl phthalazinones **17**, **19**-**24**, **26** and 1-alkyloxy-4-alkylsulfanyl phthalazine **27** via the direct bromination of phthalazin-1(2*H*)-one (**2**) with potassium tribromide, followed by alkylation of 4-bromophthalazinone **3** with methyl iodide or selected secondary alcohols in the presence of TPP and DEAD (Mitsunobu reaction) and further palladium-catalyzed sulfanylation of lactams **4**, **13a**-**15a** and phthalazine **15b** with aliphatic mercaptanes. Furthermore, we have demonstrated that 2-methylphthalazinone **5** and 2-methylazaphthalazinone **8** can be also brominated with KBr_3, thereby providing for the possibility of the further synthesis of new compounds under metal catalyzed coupling reactions.

4. Experimental section

Melting points were determined on a Boetius hot stage apparatus and were uncorrected. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker Advance III spectrometer at 600 MHz and 150 MHz respectively. The residual $CDCl_3$ or DMSO-d_6 signal was used for reference ($CDCl_3$ at

7.26 ppm or DMSO-d_6 at 2.50 ppm for ^{1}H NMR and $CDCl_3$ at 77.16 ppm or DMSO-d_6 at 39.52 ppm for ^{13}C NMR).[36] 2D Homonuclear ^{1}H, ^{1}H COSY spectra and heteronuclear ^{1}H, ^{13}C COSY spectra (HSQC and HMBC) were used to assign the proton and carbon signals. IR spectra were recorded on a Nexus FT-IR spectrometer. Microwave reactions were performed in a Synthos 3000 microwave reactor from Anton Paar. LC/HRMS analyses were performed using an Agilent Technologies HPLC 1200 coupled to an Agilent Technologies 6530 Accurate Mass Q-TOF LC-MS mass spectrometer equipped with a JetStream Technology ion source housed in the Institute of Nuclear Chemistry and Technology, Warsaw, Poland (internal mass calibration was enabled, reference ions of m/z 121.0509 and 922.0098 were used) in the case of compounds **3**, **4**, **9**, **13a**, **14a**, **15a**, **15b**, **10a**, **11a**, **12a**, **17**, **19**, **21** and using an Agilent Technologies HPLC 1200 coupled to an Agilent Technologies 6538 UHD Accurate Mass Q-TOF LC-MS mass spectrometer equipped with a HPLC chip-cube ion source housed in The Children's Memorial Health Institute, Warsaw, Poland (internal mass calibration was unenabled) for compounds **13b**, **20**, **22**, **23**, **24**, **25**, **26**, **27**. The analytical thin layer chromatography tests (TLC) were carried out on Merck silica gel plates (Kiselgel 60 F254, layer thickness 0.2 mm) and the spots were visualised using UV lamp. The flash column chromatography purifications were performed on Fluka silica gel (Silica gel 60, 0.035-0.070 mm). All reactions with organopalladium compounds were performed under an argon atmosphere using standard Schlenk technique. Tetrahydrofuran (THF) and 1,4-dioxane were distilled from sodium benzophenone ketyl prior to use. Commercially available reagents: 2-formylbenzoic acid, hydrazine monohydrate, *N*-bromosuccinimide (NBS), methyl iodide (MeI), butan-2-ol, pentan-2-ol, (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol ((–)-menthol), benzyl mercaptan, propyl mercaptan, (*sec*-butyl mercaptan, isopropyl mercaptan, cyclohexyl mercaptan, 2-mercaptopyridine, triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD), *N*,*N*-diisopropylethyl amine (DIPEA), palladium(II) acetate ($Pd(OAc)_2$), 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), 2-dicyclohexylphosphino-20-(*N*,*N*-dimethylamino)biphenyl (DavePhos), (oxydi-2,1-phenylene)-bis-(diphenylphosphine) (DPEPhos) were purchased from Sigma-Aldrich and were used without further purification.

*4.1. Synthesis of phthalazin-1(2H)-one (**2**).*

A mixture of 2-formylbenzoic acid (**1**) (~~1.00 g,~~ 6.66 mmol) and hydrazine monohydrate (3 mL), in propan-1-ol (15 mL) was heated with stirring under reflux for 8 h. After the

completion of the reaction (TLC check) the mixture was cooled and all volatile materials were removed under reduced pressure. To the residue water was added and neutralized with acetic acid. The separated solid was collected by filtration, washed with water and then dried by vacuum suction to give the pure product **2**.

White solid; Yield: 750 mg, 77%; Mp: 186–187 ^{o}C, (lit. 182–184 ^{o}C[37]); FTIR (KBr): ν = 3162, 3103, 1659 (C=O), 1559, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.75 (s, 1H, NH), 8.45 (d, *J* = 7.9 Hz, 1H, 8 Ar-H), 8.18 (s, 1H, 4-pyrid), 7.87–7.83 (m, 1H, Ar-H), 7.81–7.78 (m, 1H, Ar-H), 7.73 (d, *J* = 7.9 Hz, 1H, 5 Ar-H); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.62 (s, 1H, NH), 8.36 (s, 1H, 4-pyrid), 8.22 (d, *J* = 7.8 Hz, 1H, 8 Ar-H), 7.94–7.90 (m, 2H, Ar-H), 7.87–7.82 (m, 1H, Ar-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 159.6 (C=O), 138.2, 133.6, 131.7, 129.9, 127.5, 126.7, 125.3 ppm.

*4.2. General procedure for the reaction of phthalazinones **4** (Path A) and **5** (Path B) with methyl iodide*

Method A.

A mixture of 4-bromophthalazin-1(2*H*)-one (**3**) (~~0.50 g,~~ 2.22 mmol), potassium carbonate (~~0.92 g,~~ 6.66 mmol) in dry acetone (20 mL) was heated to boiling for 30 min and next methyl iodide (~~0.47 g,~~ 3.33 mmol) was added. The reaction mixture was heated and stirred under reflux for 8 h.

Method B.

A mixture phthalazin-1(2*H*)-one (**2**) (~~0.50 g,~~ 3.42 mmol), caesium carbonate (~~1.34 g,~~ 4.11 mmol) in dry acetone (20 mL) was charged to PTFE tubes, sealed in ceramic cases and placed in the rotor. The reaction mixture was heated to 55 ^{o}C, held for 0.5 h at 55 ^{o}C and then cooled to 25 ^{o}C. In the next step the methyl iodide (~~0.56 g,~~ 0.23 mL, 3.77 mmol) was added and the reaction was continued at 55 ^{o}C for 3.5 h.

After cooling to room temperature the separated solid was collected by filtration and washed with acetone (5 mL). The filtrate was concentrated under reduced pressure and then the crude product was purified by flash chromatography.

*4.2.1. 4-Bromo-2-methylphthalazin-1(2H)-one (**4**) (Path A).* White solid; Yield: 451 mg, 85% (Method A), 327 mg, 40% (Method B); Mp: 101–104 ^{o}C; R_f ($CHCl_3$) = 0.34; FTIR (KBr): ν = 3036, 2906, 1652 (C=O), 1572 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.29 (d, *J* = 7.9 Hz,

1H, 8 Ar-H), 8.06–8.00 (m, 1H, Ar-H), 7.98–7.92 (m, 2H, Ar-H), 3.71 (s, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.2 (C=O), 134.4, 133.2, 129.6, 128.1, 127.7, 127.5, 126.7, 38.9 ppm; HRMS (ESI) m/z: calcd for $C_9H_8BrN_2O$ $[M + H]^+$ 238.9814, found 238.9813.

*4.2.2. 2-Methylphthalazin-1(2H)-one (**5**) (Path B).* White solid; Yield: 247 mg, 45% (Method B); Mp: 111–114 °C, (lit. 112–114 °C[37]); R_f ($CHCl_3$/AcOEt/PE 6:1:1.5) = 0.46; FTIR (KBr): ν = 3036, 2942, 1641 (C=O), 1590 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.40 (s, 1H, 4-pyrid), 8.25 (d, J = 8.0 Hz, 1H, Ar-H), 7.96–7.89 (m, 2H, Ar-H), 7.88–7.83 (m, 1H, Ar-H), 3.72 (s, 3H, Me); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 158.7 (C=O), 137.8, 133.4, 132.1, 129.6, 127.0, 126.8, 125.6, 39.0 ppm.

*4.3. Synthesis of 2-methylpyrido[3,4-d]pyridazin-1(2H)-one (**8**)*[~~21~~,23]

N-Methylpyridopyridazinone **8**, pyridopirydazinone **7** and hydroxyazaisoindolinone **6** were prepared according to the procedure reported in literature 21.

*4.3.1. 2-methylpyrido[3,4-d]pyridazin-1(2H)-one (**8**) (Path C).* Canary yellow solid; Yield: 197 mg, 55%; Mp: 175–177 °C (lit. 180–182 °C[~~21~~ 23]); FTIR (KBr): ν = 1665 (C=O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.14 (s, 1H, 5 A-H), 8.96 (d, J = 5.3 Hz, 1H, 7 Ar-H), 8.25 (s, 1H, 4-pyrid), 8.20 (d, J = 5.3 Hz, 1H, 8 Ar-H), 3.87 (s, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.4, 151.3, 149.6, 135.6, 132.8, 124.4, 119.00, 39.9 ppm.

*4.4. General procedure for bromination of phthalazinones **2**, **5** and pyridopyridazinone **8***
*Synthesis of compounds **3** (Path A), **4** (Path B) and **9** (Path C).*

The reaction was carried out in a round-bottom flask fitted with a magnetic stirrer bar. To a suspension of phthalazin-1(2*H*)-one (**2**) or 2-methylphthalazin-1(2*H*)-one (**5**) or pyridopyridazinone **8** (6.84 mmol) in water (55 mL) (Method A) or in the acetate buffer solution pH = 5.8 (55 mL) (Method B), was added potassium bromide (8.44 mmol) and bromine (8.44 mmol) at an ambient temperature. The mixture was then stirred for 6 h at an ambient temperature, and next the whole was heated to boiling and stirred for 25 h until the bromine colour entirely disappeared. After cooling to an ambient temperature (in the case of **9** the mixture was adjusted to pH 7 with saturated $NaHCO_3$) the separated solid was collected by filtration and washed with water (5 mL). The crude product was purified by flash chromatography.

*4.4.1. 4-Bromophthalazin-1(2H)-one (**3**) (Path A).* White solid; Yield: 693 mg, 45% (Method A), 1.02 g, 66 % (Method B); Mp: 279–281 ^{o}C, (lit. 277–279 °C,[20] [22] 273 ^{o}C[38]); R_f (DCM/AcOEt/Hex 6:1:1) = 0.24; FTIR (KBr): ν = 3022, 2931, 2892, 1671, 1659 (C=O), 1581 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.94 (s, 1H, NH), 8.26 (d, J = 7.9 Hz, 1H, 8 Ar-H), 8.06–8.01 (m, 1H, Ar-H), 7.97–7.91 (m, 2H, Ar-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 159.1 (C=O), 134.8, 133.1, 129.9, 129.4, 128.2, 127.6, 126.5 ppm; HRMS (ESI) m/z: calcd for $C_8H_6BrN_2O$ $[M + H]^+$ 224.9658, found 224.9658.

*4.4.2. 4-Bromo-2-methylphthalazin-1(2H)-one (**4**) (Path B).* White solid; Yield: 981 mg, 60% (Method A); Mp: 101-104 ^{o}C; R_f (AcOEt/Hex 1:1) = 0.6.

*4.4.3. 8-Bromo-2-methylpyrido[3,4-d]pyridazin-1(2H)-one (**9**) (Path C).* Cream solid; Yield: 854 mg, 52% (Method A); Mp: 220–222 ^{o}C; R_f (AcOEt/Hex 10:3) = 0.56; FTIR (KBr): ν = 3062, 2927, 1653 (C=O) cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.22 (s, 1H, 5 Ar-H), 9.08 (s, 1H, 7 Ar-H), 8.54 (s, 1H, 4-pyrid), 3.70 (s, 3H, Me); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 155.8 (C=O), 154.1, 149.6, 135.4, 129.0, 126.0, 116.6, 39.5 ppm; HRMS (ESI) m/z: calcd for $C_8H_7BrN_3O$ $[M + H]^+$ 239.9767, found 239.9765.

*4.5. General procedure for the Mitsunobu reaction of phthalazin-1(2H)-ones **2** and **3** with the secondary alcohols. Synthesis of compounds **10**-**15**.*

Method A

The Mitsunobu reaction was carried out under argon. Diethyl azodicarboxylate (1.03 mmol, solution in toluene c ≈ 40%) was slowly added to a stirred solution of triphenylphosphine (1.03 mmol) in dry THF (10 mL) at the temperature between –10 ^{o}C and –5 ^{o}C. Then a solution of phthalazinone **2** (0.684 mmol) in THF (10 mL) was added dropwise. The whole lot was mixed for 15 min at this temperature and next the appropriate alcohol (0.753 mmol) in THF (5 mL) was added at –10 - –5 ^{o}C. The mixture was stirred during 2 h at this conditions, after which time the reaction mixture was warmed to ambient temperature and stirred in this conditions for 24 h. All volatile materials were removed under reduced pressure, ethyl ether (5 mL) was added to the residue, and the whole lot was stirred for 0.5 h at an ambient temperature. The separate white solid was collected by flirtation and washed with ether, and

the filtrate was evaporated to dryness. The product was separated and purified by flash chromatography.

Method B

The Mitsunobu reaction was carried out under argon. To a round bottom flask were added phthalazinone **2** or **3** (1.78 mmol), alcohol (2.67 mmol), triphenylphosphine (2.67 mmol) and THF (40 mL). Then, the solution was cooled to the temperature –20 ^{o}C for 15 min. and diethyl azodicarboxylate (2.67 mmol, solution in toluene c ≈ 40%) was added dropwise to the solution. The reaction was stirred at –20 ^{o}C for 1 h, and then the cold bath allowed to slowly warm to an ambient temperature and stirred in this conditions for 24 h. All volatile materials were removed under reduced pressure, diethyl ether (15 mL) was added to the residue, and the whole lot was stirred for 0.5 h at an ambient temperature. The separate white solid was collected by flirtation and washed with ether, and the filtrate was evaporated to dryness. The product was separated and purified by flash chromatography.

*4.5.1. 2-(Butan-2-yl)phthalazin-1(2H)-one (**10a**).* Straw oil; Yield: 41.5 mg, 30% (Method A), 259 mg, 72% (Method B); R_f (AcOEt/Hex 1:3) = 0.5; FTIR (thin film): ν = 3044, 2968, 2933, 1644 (C=O), 1591 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, J = 7.8 Hz, 1H, 8 Ar-H), 8.20 (s, 1H, 4-pyrid), 7.80–7.71 (m, 2H, Ar-H), 7.67 (d, J = 8.2 Hz, 1H, 5 Ar-H), 5.38–5.06 (m, 1H, N-CH), 1.95–1.86 (m, 1H, CH_2), 1.77–1.68 (m, 1H, CH_2), 1.37 (d, J = 6.8 Hz, 3H, Me), 0.84 (t, J = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.6 (C=O), 137.7, 133.0, 131.5, 129.4, 128.0, 127.1, 125.9, 54.1 (N-CH), 28.4, 19.4, 10.9 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{15}N_2O$ $[M + H]^+$ 203.1179, found 203.1179.

*4.5.2. 2-(Pentan-2-yl)phthalazin-1(2H)-one (**11a**).* Yellow oil; Yield: 71.0 mg, 48% (Method A), 327 mg, 85% (Method B); R_f (Hex/AcOEt 3:1) = 0.56; FTIR (thin film): ν = 3051, 2960, 2331, 1653 (C=O), 1589 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.44 (d, J = 7.8 Hz, 1H, 8 Ar-H), 8.21 (s, 1H, 4-pyrid), 7.81–7.77 (m, 1H, Ar-H), 7.77–7.72 (m, 1H, Ar-H), 7.68 (d, J = 8.0 Hz, 1H, 5 Ar-H), 5.37–5.27 (m, 1H, N-CH), 1.97–1.87 (m, 1H, CH_2), 1.71–1.62 (m, 1H, CH_2), 1.38 (d, J = 6.7 Hz, 3H, Me), 1.35–1.28 (m, 1H, CH_2), 1.25–1.17 (m, 1H, CH_2), 0.90 (t, J = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.5 (C=O), 137.7, 133.0, 131.5, 129.4, 128.0, 127.2, 125.9, 52.4 (N-CH), 37.6, 19.8, 19.7, 14.0 ppm; HRMS (ESI) m/z: calcd for $C_{13}H_{17}N_2O$ $[M + H]^+$ 217.1335, found 217.1331.

*4.5.3. 2-[(1S,2S,5R)-5-Methyl-2-(propan-2-yl)cyclohexyl]phthalazin-1(2H)-one (**12a**).* White solid; Yield: 77.8 mg, 40% (Method A), 152 mg, 30% (Method B); Mp: 144–147 ^{o}C; R_f (Hex/AcOEt 5:1) = 0.58; FTIR (KBr): ν = 3066, 2952, 2930, 1638 (C=O), 1587 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.45 (d, J = 7.9 Hz, 1H, 8 Ar-H), 8.13 (s, 1H, 4-pyrid), 7.80–7.76 (m, 1H, Ar-H), 7.75–7.71 (m, 1H, Ar-H), 7.66 (d, J = 7.7 Hz, 1H, 5 Ar-H), 5.63–5.38 (m, 1H, N-CH), 2.26–2.15 (m, 1H, CH_2), 1.97–1.86 (m, 3H, CH_2), 1.78–1.72 (m, 1H, CH_2), 1.46–1.35 (m, 3H, CH_2), 1.06–0.97 (m, 1H, CH_2), 0.86 (d, J = 6.3 Hz, 3H, Me), 0.83–0.80 (m, 6H, 2xMe); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.7 (C=O), 135.6, 132.9, 131.2, 129.4, 128.0, 127.2, 125.6, 52.5 (N-CH), 47.0, 40.5, 35.6, 29.3, 25.8, 25.7, 22.8, 21.5, 21.3 ppm; HRMS (ESI) m/z: calcd for $C_{18}H_{25}N_2O$ $[M + H]^+$ 285.1961, found 285.1960.

*4.5.4. 4-Bromo-2-(butan-2-yl)phthalazin-1(2H)-one (**13a**).* Yellow oil; Yield: 240 mg, 48% (Method B), R_f (AcOEt/Hex 1:10) = 0.25; FTIR (thin film): ν = 3074, 2968, 2933, 1660 (C=O), 1576 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.44 (dd, J = 7.9, 0.8 Hz, 1H, 8 Ar-H), 7.93 (dd, J = 8.0, 0.5 Hz, 1H, 5 Ar-H), 7.87–7.83 (m, 1H, 7 Ar-H), 7.82–7.77 (m, 1H, 6 Ar-H), 5.31–4.98 (m, 1H, N-CH), 1.96–1.86 (m, 1H, CH_2), 1.79–1.70 (m, 1H, CH_2), 1.39 (d, J = 6.7 Hz, 3H, Me), 0.87 (t, J = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.0 (C=O), 133.7, 132.4, 130.0, 129.2, 128.6, 127.8, 127.7, 54.9 (N-CH), 28.4, 19.4, 10.9 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{14}BrN_2O$ $[M + H]^+$ 281.0284, found 281.0285.

*4.5.5. 1-Bromo-4-[(butan-2-yl)oxy]phthalazine (**13b**).* White solid; Yield: 30.0 mg, 6% (Method B), Mp: 88–90 ^{o}C; R_f (AcOEt/Hex 1:10) = 0.32; FTIR (KBr): ν = 2966, 2919, 1537, 1408 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.21 (d, J = 7.9 Hz, 1H, Ar-H), 8.17–8.10 (m, 2H, Ar-H), 8.11–8.07 (m, 1H, Ar-H), 5.60–5.27 (m, 1H, O-CH), 1.90–1.82 (m, 1H, CH_2), 1.82–1.74 (m, 1H, CH_2), 1.42 (d, J = 6.2 Hz, 3H, Me), 0.99 (t, J = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.0 (C-O), 142.3, 134.3, 133.9, 128.5, 126.8, 123.3, 121.0, 74.9 (O-CH), 28.3, 18.8, 9.4 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{14}BrN_2O$ $[M + H]^+$ 281.0284, found 281.0289.

*4.5.6. 4-Bromo-2-(pentan-2-yl)phthalazin-1(2H)-one (**14a**).* Yellow oil; Yield: 147 mg, 28% (Method B), R_f (Hex/AcOEt 5:1) = 0.62; FTIR (thin film): ν = 3037, 2960, 2931, 1655 (C=O), 1576 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.44 (dd, J = 7.9, 0.7 Hz, 1H 8 Ar-H),

7.92 (d, *J* = 8.0 Hz, 1H, 5Ar-H), 7.87–7.83 (m, 1H, Ar-H), 7.82–7.78 (m, 1H, Ar-H), 5.29–5.21 (m, 1H, N-CH), 1.95–1.87 (m, 1H, CH_2), 1.71–1.62 (m, 1H, CH_2), 1.39 (d, *J* = 6.7 Hz, 3H, Me), 1.36–1.29 (m, 1H CH_2), 1.29–1.20 (m, 1H CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.8 (C=O), 133.6, 132.3, 129.9, 129.0, 128.5, 127.6, 127.5, 52.9 (N-CH), 37.3, 19.6, 19.5, 13.9 ppm; HRMS (ESI) m/z: calcd for $C_{13}H_{16}BrN_2O$ $[M + H]^+$ 295.0440, found 295.0438.

*4.5.7. 1-Bromo-4-[(pentan-2-yl)oxy]phthalazine (**14b**).* (The crude mixture with **14a** after chromatography); Yellow oil; Yield: 15.8 mg, 3% (^{1}H NMR, Method B), R_f (Hex/AcOEt 5:1) = 0.59, 0.62; 1H NMR (600 MHz, $CDCl_3$) δ = 8.46–8.42 (m, 1H, Ar-H, **14a**), 8.23–8.19 (m, 1H, Ar-H), 8.14–8.11 (m, 1H, Ar-H), 7.96–7.83 (m, 4H, Ar-H, **14a**, **14b**), 7.82–7.77 (m, 1H, Ar-H, **14a**), 5.69–5.57 (m, 1H, O-CH), 5.28–5.19 (m, 1H, N-CH, **14a**), 1.95–1.85 (m, 2H, CH_2, **14a**, **14b**), 1.74–1.63 (m, 2H, CH_2, **14a**, **14b**), 1.53–1.41 (m, 5H, CH_2, Me), 1.39 (d, *J* = 6.7 Hz, 3H, Me, **14a**), 1.36–1.20 (m, 2H, CH_2, **14a**), 0.96 (t, *J* = 7.4 Hz, 3H, Me), 0.91 (t, *J* = 7.4 Hz, 3H, Me, **14a**); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.5, 158.8 (**14a**), 142.7, 133.6 (**14a**), 133.0, 132.7, 132.3 (**14a**), 129.9 (**14a**), 129.4, 129.0 (**14a**), 128.5 (**14a**), 128.1, 127.7 (**14a**), 127.6 (**14a**), 127.3, 123.7, 74.1 (O-CH), 52.9 (**14a**, N-CH), 38.3, 37.3 (**14a**), 19.7, 19.6 (**14a**), 19.5 (**14a**), 18.7, 14.1, 13.9 (**14a**) ppm.

*4.5.8. 4-Bromo-2-[(1S,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]phthalazin-1(2H)-one (**15a**).* White solid; Yield: 188 mg, 29% (Method B), Mp: 80–82 ^{o}C; R_f (Hex/ AcOEt 5:1) = 0.60; FTIR (KBr): ν = 2951, 2924, 1653 (C=O), 1576 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.45 (dd, *J* = 7.9, 0.7 Hz, 1H, 8 Ar-H), 7.92 (d, *J* = 8.0 Hz, 1H, 5 Ar-H), 7.87–7.84 (m, 1H, 7 Ar-H), 7.81–7.76 (m, 1H, 8 Ar-H), 5.51–5.34 (m, 1H, N-CH), 2.22–2.12 (m, 1H, CH_2), 1.97–1.88 (m, 3H, CH_2), 1.79–1.73 (m, 1H CH_2), 1.46–1.36 (m, 3H, CH_2), 1.05–0.96 (m, 1H, CH_2), 0.89 (d, *J* = 6.3 Hz, 3H, Me), 0.83 (d, *J* = 6.3 Hz, 3H, Me), 0.82 (d, *J* = 6.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.1 (C=O), 133.7, 132.2, 130.0, 128.6, 127.9, 127.4, 126.8, 53.0 (N-CH), 46.8, 40.3, 35.5, 29.3, 25.5, 25.5, 22.8, 21.4 ppm; HRMS (ESI) m/z: calcd for $C_{18}H_{24}BrN_2O$ $[M + H]^+$ 363.1067, found 363.1065.

*4.5.9. 1-Bromo-4-{[(1S,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}phthalazine (**15b**).* White solid; Yield: 181 mg, 28% (Method B), Mp: 109–112 ^{o}C; R_f (Hex/ AcOEt 5:1) = 0.70; FTIR (KBr): ν = 2955, 2919, 1535, 1408 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.19 (d, *J* =

7.9 Hz, 1H, Ar-H), 8.14 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.96–7.85 (m, 2H, Ar-H), 5.94–5.89 (m, 1H, O-CH), 2.40 (dd, *J* = 14.5, 2.6 Hz, 1H, CH_2), 1.94–1.83 (m, 2H, CH_2), 1.76–1.61 (m, 3H, CH_2), 1.24–1.13 (m, 2H, CH_2), 1.08–1.00 (m, 1H, CH_2), 0.95 (d, *J* = 6.7 Hz, 3H, Me), 0.89 (d, *J* = 6.7 Hz, 3H, Me), 0.84 (d, *J* = 6.6 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.4, 142.8, 133.2, 132.9, 129.7, 127.5, 123.7, 122.4, 74.4 (O-CH), 47.7, 38.1, 35.2, 29.9, 27.1, 25.6, 22.3, 21.2, 21.1 ppm; HRMS (ESI) m/z: calcd for $C_{18}H_{24}BrN_2O$ $[M + H]^+$ 363.1067, found 363.1067.

4.6. General procedure for the palladium-catalyzed synthesis of 4-sulfanylphthalazinones ***17****,* ***19-26*** *and 4-sulfanylphthalazine* ***27****.*

The reaction was carried out under an argon atmosphere in an oven-dried resealable Schlenk flask. A resealable Schlenk flask was charged with appropriate 2-substituted-4-bromophthalazinone **4**, **10a**-**12a** or 8-bromo-2-methylpyridopyridazinone **9** or 1-bromophthalazine **12b** (0.418 mmol), 5 mL freshly distilled 1,4-dioxane, $Pd(OAc)_2$ (30 mol%), XantPhos (30 mol%), DIPEA (1.5 mL), and the appropriate mercaptan (0.836 mmol). The whole mixture was stirred and heated in an oil bath at 100 ^{o}C for 26 h. After this time, the reaction mixture was cooled to an ambient temperature and diluted with 5 mL chloroform. The solid was removed by filtration and washed with 5 mL chloroform. The filtrate was concentrated to dryness and the residue was purified by flash chromatography to give pure product.

*4.6.1. 2-Methyl-4-[(propan-2-yl)sulfanyl]phthalazin-1(2H)-one (****17****).* Pale yellow solid; Yield: 82.3 mg, 84%, Mp: 80–82,5 ^{o}C; R_f (AcOEt/$CHCl_3$/PE 1:9:6) = 0.70; FTIR (KBr): ν = 3072, 2960, 2923, 1648, 1576 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.7 Hz, 1H, 8 Ar-H), 7.90 (d, *J* = 7.4 Hz, 1H, 5 Ar-H), 7.79–7.70 (m, 2H, Ar-H), 3.96–3.88 (m, 1H, S-CH), 3.83 (s, 3H, N-Me), 1.45 (d, *J* = 6.8 Hz, 6H, 2×Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.0 (C=O), 144.2, 132.8, 131.7, 130.0, 127.5, 127.2, 124.6, 39.5, 36.0, 23.1 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{15}N_2OS$ $[M + H]^+$ 235.0900, found 235.0897.

*4.6.2. 4-[(Butan-2-yl)sulfanyl]-2-methylphthalazin-1(2H)-one (****19****).* Light yellow solid; Yield: 77.9 mg, 75%, Mp: 40–42 ^{o}C; R_f (AcOEt/$CHCl_3$/PE 1:9:6) = 0.45; FTIR (thin film): ν = 3067, 2959, 2926, 1652, 1576 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.44 (dd, *J* = 7.0, 2.1 Hz, 1H, 8 Ar-H), 7.93 (dd, *J* = 7.1, 1.9 Hz, 1H, 5 Ar-H), 7.79–7.71 (m, 2H, Ar-H), 3.84 (s,

3H, Me), 3.83–3.76 (m, 1H, S-CH), 1.85–1.78 (m, 1H, CH_2), 1.76–1.69 (m, 1H, CH_2), 1.44 (d, J = 6.8 Hz, 3H, Me), 1.06 (t, J = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.1 (C=O), 144.3, 132.9, 131.7, 130.1, 127.5, 127.2, 124.6, 42.3, 39.5, 29.7, 20.6, 11.6; HRMS (ESI) m/z: calcd for $C_{13}H_{17}N_2OS$ $[M + H]^+$ 249.1056, found 249.1052.

*4.6.3. 4-(Cyclohexylsulfanyl)-2-methylphthalazin-1(2H)-one (**20**).* Yellow solid; Yield: 106 mg, 92%; Mp: 111–114 ^{o}C; R_f (DCM/AcOEt/Hex 6:1:1) = 0.54; FTIR (KBr): ν = 3030, 2943, 2918, 1651 (C=O), 1574 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.45–8.41 (m, 1H, 8 Ar-H), 7.95–7.92 (m, 1H, 5 Ar-H), 7.79–7.71 (m, 2H, Ar-H), 3.84 (s, 3H, Me), 3.80–3.73 (m, 1H, S-CH), 2.16–2.09 (m, 2H, CH_2), 1.84–1.78 (m, 2H, CH_2), 1.69–1.62 (m, 1H, CH_2), 1.60–1.51 (m, 2H CH_2), 1.49–1.41 (m, 2H, CH_2), 1.40–1.31 (m, 1H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.1 (C=O), 143.9, 132.9, 131.7, 130.2, 127.5, 127.2, 124.7, 44.0, 39.6, 33.3, 26.2, 26.0 ppm; HRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2OS$ $[M + H]^+$ 275.1213, found 275.1220.

*4.6.4. 4-(Benzylsulfanyl)-2-methylphthalazin-1(2H)-one (**21**).* Beige solid; Yield: 93.2 mg, 79%; Mp: 121–123 ^{o}C; R_f ($CHCl_3$/PE/AcOEt 9:6:1) = 0.54; FTIR (KBr): ν = 3059, 2925, 1644 (C=O), 1574 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.45–8.40 (m, 1H, 8 Ar-H), 7.87–7.81 (m, 1H, 5 Ar-H), 7.80–7.69 (m, 2H, Ar-H), 7.44 (d, J = 7.5 Hz, 2H, Ar-H), 7.36–7.29 (m, 2H, Ar-H), 7.29–7.23 (m, 1H, Ar-H),4.39 (s, 2H, S-CH_2), 3.85 (s, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.1 (C=O), 143.6, 137.1, 132.9, 131.8, 129.4, 129.4, 128.7, 127.6, 127.5, 127.3, 124.2, 39.3, 34.8 ppm; HRMS (ESI) m/z: calcd for $C_{16}H_{15}N_2OS$ $[M + H]^+$ 283.0900, found 283.0895.

*4.6.5. 2-(Butan-2-yl)-4-[(butan-2-yl)sulfanyl]phthalazin-1(2H)-one (**22**).* Brown-yellow oil; Yield: 94.7 mg, 78%; Diastereoisomers ratio = 1:1; R_f (AcOEt/Hex 1:4) = 0.44; FTIR (thin film): ν = 3056, 2962, 2922, 1652 (C=O), 1575 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.48–8.41 (m, 1H, 8 Ar-H), 7.92–7.86 (m, 1H, 5 Ar-H), 7.78–7.69 (m, 2H, Ar-H), 5.27–5.15 (m, 1H, N-CH), 3.85–3.76 (m, 1H, S-CH), 1.96–1.88 (m, 1H, CH_2), 1.87–1.81 (m, 1H, CH_2), 1.76–1.67 (m, 2H, CH_2), 1.47–1.42 (m, 3H, Me), 1.40–1.35 (m, 3H, Me), 1.09–1.04 (m, 3H, Me), 0.88–0.85 (m, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.7 (C=O), 144.0, 144.0, 132. 8, 131.5, 129.3, 127.6, 127.5, 124.2, 54.1, 41.8, 41.8, 29.7, 29.6, 28.6, 28.5, 20.5, 20.4,

19.7, 19.6, 11.6, 11.6, 11.0, 10.9 ppm; HRMS (ESI) m/z: calcd for $C_{16}H_{23}N_2OS$ $[M + H]^+$ 291.1526, found 291.1534.

*4.6.6. 2-(Butan-2-yl)-4-(propylsulfanyl)phthalazin-1(2H)-one (**23**).* Dark yellow oil; Yield: 45.1 mg, 39%, R_f (Hex/AcOEt 5:1) = 0.44; FTIR (KBr): ν = 3057, 2964, 2929, 1653 (C=O), 1578 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.46 (d, J = 7.7 Hz, 1H, 8 Ar-H), 7.88 (d, J = 7.6 Hz, 1H, 5 Ar-H), 7.80–7.71 (m, 2H, Ar-H), 5.26–5.16 (m, 1H, N-CH), 3.16 (t, J = 7.2 Hz, 2H, S-CH_2), 1.95–1.87 (m, 1H, CH_2), 1.84–1.78 (m, 2H, CH_2), 1.78–1.70 (m, 1H, CH_2), 1.38 (d, J = 6.6 Hz, 3H, NCH-Me), 1.08 (t, J = 7.4 Hz, 3H, Me), 0.87 (t, J = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.8 (C=O), 143.7, 132.8, 131.6, 129.0, 127.7, 127.5, 124.0, 54.2, 32.0, 28.5, 22.8, 19.6, 13.7, 11.0 ppm; HRMS (ESI) m/z: calcd for $C_{15}H_{21}N_2OS$ $[M + H]^+$ 277.1369, found 277.1379.

*4.6.7. 2-(Pentan-2-yl)-4-(propylsulfanyl)phthalazin-1(2H)-one (**24**).* Brown-orange oil; Yield: 109 mg, 90%, R_f (Hex/AcOEt 5:1) = 0.44; FTIR (thin film): ν = 3066, 2962, 2931, 1653 (C=O), 1578 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.44 (d, J = 7.4 Hz, 1H, 8 Ar-H), 7.87 (d, J = 7.7 Hz, 1H, 5 Ar-H), 7.81–7.69 (m, 2H, Ar-H), 5.38–5.22 (m, 1H, N-CH), 3.23–3.06 (m, 2H, S-CH), 1.96–1.87 (m, 1H, CH_2), 1.84–1.75 (m, 2H, CH_2), 1.69–1.59 (m, 1H, CH_2), 1.37 (d, J = 6.6 Hz, 3H, SCH-Me), 1.34–1.27 (m, 1H, CH_2), 1.25–1.18 (m, 1H, CH_2), 1.08 (t, J = 7.4 Hz, 3H, Me), 0.90 (t, J = 7.4 Hz, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.6 (C=O), 143.6, 132.8, 131.6, 129.0, 127.6, 127.5, 123.9, 52.4, 37.6, 32.0, 22.8, 19.9, 19.6, 14.1, 13.7 ppm; HRMS (ESI) m/z: calcd for $C_{16}H_{23}N_2OS$ $[M + H]^+$ 291.1526, found 291.1536.

*4.6.8. 2-Methyl-8-[(propan-2-yl)sulfanyl]pyrido[3,4-d]pyridazin-1(2H)-one (**25**).* Yellow solid; Yield: 79.7 mg, 81%; Mp: 94–96 ^oC; R_f ($CHCl_3$/AcOEt/Hex 6: 1:1) = 0.22; FTIR (KBr): ν = 3076, 2969, 2929, 1644 (C=O), 1594 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.74 (s, 1H, 5 Ar-H), 8.66 (s, 1H, 7 Ar-H), 8.13 (s, 1H, 4-pyrid), 3.79 (s, 3H, Me), 3.75–3.66 (m, 1H, CH), 1.47 (d, J = 6.6 Hz, 6H, 2×Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.6 (C=O), 145.1, 142.5, 137.8, 135.4, 128.8, 125.5, 39.8, 34.3, 22.4 ppm; HRMS (ESI) m/z: calcd for $C_{11}H_{14}N_3OS$ $[M + H]^+$ 236.0852, found 236.0852.

*4.6.9. 4-[(Butyl-2-yl)sulfanyl]-2-[(1S,2S,5R)-5-Methyl-2-(propan-2-yl)cyclohexyl]phthalazin-1(2H)-one (**26a**, **26b**).* Brown oil; Yield: 128 mg, 82%; Diastereoisomers ratio = 1:1; R_f (Hex/AcOEt 5:1) = 0.48; FTIR (thin film): ν = 2956, 2924, 1653 (C=O), 1578 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.45 (dd, *J* = 7.7, 1.2 Hz, 1H, 8 Ar-H), 7.97–7.92 (m, 1H, 5 Ar-H), 7.79–7.68 (m, 2H, 6, 7 Ar-H), 5.58–5.52 (m, 1H, O-CH), 3.98–3.65 (m, 1H, S-CH), 2.16–2.08 (m, 1H, CH_2), 1.99–1.63 (m, 6H, CH_2), 1.51–1.34 (m, 6H, CH_2, Me), 1.10–0.99 (m, 4H, CH_2), 0.88–0.84 (m, 3H, Me), 0.84–0.79 (m, 6H, 2xMe); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.0 (C=O), 142.7, 142.6, 132.8, 131.5, 129.5, 129.5, 127.7, 127.7, 127.6, 124.6, 124. 6, 52.5, 52.4, 46.6, 46.5, 41.9, 41.7, 40.5, 40.4, 35.4, 35.4, 29.9, 29.9, 29.8, 29.3, 29.3, 25.9, 25.9, 25.8, 25.8, 22.7, 22.7, 21.5, 21.2, 21.2, 21.1, 20.9, 11.6, 11.6 ppm; HRMS (ESI) m/z: calcd for $C_{22}H_{33}N_2OS$ $[M + H]^+$ 373.2308, found 373.2316.

*4.6.10. 4-[(Butan-2-yl)sulfanyl]-1-{[(1S,2S,5R)-5-methyl-2-(propan-2-yl)cyclo-hexyl]oxy} phthalazine (**27a**, **27b**).* White solid; Yield: 79.7 mg, 36%; Diastereoisomers ratio = 1:1; Mp: >315 ^oC (decomposition); R_f (AcOEt/Hex 1:10) = 0.68; ^1H NMR (600 MHz, DMSO-d_6): δ = 8.19–8.16 (m, 1H, Ar-H), 8.06–8.02 (m, 1H, Ar-H), 8.02–7.97 (m, 2H, Ar-H), 5.78–5.72 (m, 1H, O-CH), 4.17–4.07 (m, 1H, S-CH), 2.23 (d, *J* = 13.6 Hz, 1H, CH_2), 1.87–1.55 (m, 7H, CH_2), 1.46–1.40 (m, 3H, Me), 1.25–1.14 (m, 2H, CH_2), 1.08–0.98 (m, 4H, CH_2, Me), 0.92 (d, *J* = 6.7 Hz, 3H, Me), 0.86–0.83 (m, 3H, Me), 0.81 (d, *J* = 6.6 Hz, 3H, Me); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 158.0, 154.0, 133.0, 133.0, 127.3, 123.3, 123.0, 119.1, 72.4, 46.6, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.1, 29.3, 28.9, 26.4, 24.8, 22.0, 20.8, 20.5, 20.5, 11.3 ppm; HRMS (ESI) m/z: calcd for $C_{22}H_{33}N_2OS$ $[M + H]^+$ 373.2308, found 373.2317.

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