RSC Advances

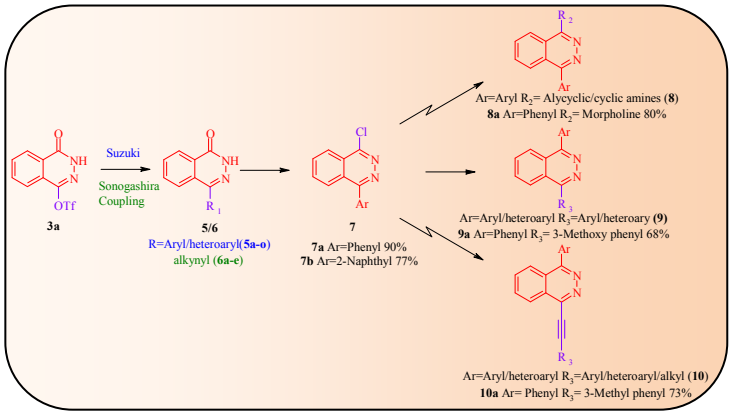
ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Synthesis of 1, 2-Dihydro-1-oxophthalazin-4-yl trifluoromethanesulfonate and its application in the Synthesis of 4-(aryl/heteroaryl/alkynyl)phthalazin-1(2*H*)-one

Ganesh Raosaheb Dhage, Santosh Rangnath Deshmukh and Shankar Ramchandra Thopate*

Biologically significant 4-aryl/heteroaryl/alkynyl phthalazinones have been reported via Suzuki and Sonogashira coupling reactions.



Synthesis of 1, 2-Dihydro-1-oxophthalazin-4-yl trifluoromethanesulfonate and its application in the Synthesis of 4-(aryl/heteroaryl/alkynyl)phthalazin-1(2*H*)-one

Ganesh Raosaheb Dhage, Santosh Rangnath Deshmukh and Shankar Ramchandra Thopate*

Department of Chemistry, Prof. John Barnabas Post Graduate School for Biological Studies, Ahmednagar College, Ahmednagar, Station Road, Ahmednagar, Maharashtra, India, 414001. Fax: (+) 91 241 2322415, E-mail: srthopate@gmail.com

The regioselective synthesis of 1,2-dihydro-1-oxophthalazin-4-yl trifluoromethanesulfonate (**3a**) has been reported. Reaction of Tf_2O (**2a**) with phthalhydrazide (**1a**) provided rapid access to **3a** in excellent yield and with high level of regioselectivity. The synthetic utility of this triflate is further enhanced by successful Suzuki and Sonogashira coupling reactions for the first time on **3a**, giving simple access to a range of biologically significant 4-aryl/heteroaryl/alkynyl phthalazinones in good yields.

Introduction

A realization of the intrinsic value of nitrogen heterocycles in medicinal and pharmaceutical chemistry enthralled researchers across the world. Nitrogen containing heterocycles are the cornerstone of many pharmaceutically active natural products. Furthermore, 59 % of approved drugs by US FDA contain nitrogen heterocycles, ranking them as the most privileged and haunted heterocycles by medicinal chemist.[1] Though nature has ascribed less importance to phthalazinone as a building block of natural products, it is often integrated in the synthesis of pharmaceuticals as shown in figure 1.

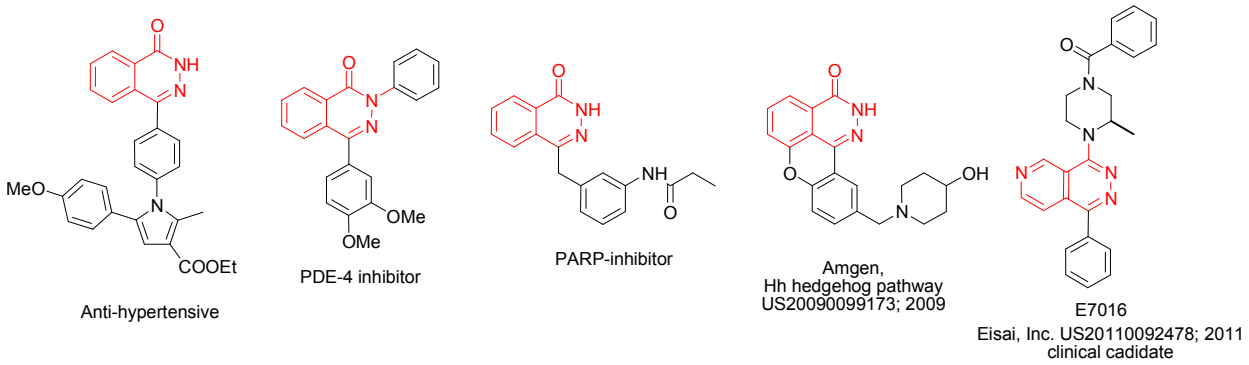


Fig. 1 Biologically important compounds containing phthalazinones and phthalazines.

Phthalazinone and class of compounds that contain elements of this pharmacophore are being developed preclinically for treatment of cancer, diabetes, hepatitis, asthma, and arrhythmia.[2] These compounds are also used as potent inhibitors of poly (ADP-ribose) polymerase-1 (PARP) and phosphodiesterase-4 (PDE-4).[2] The biological importance of 4-substituted phthalazinone (4SP) led to continuous development of various meritorious synthetic methods in this field. The most undemanding and widely used method is Friedel-craft acylation of phthalic anhydride followed by condensation with hydrazine,[3] cycloaddition,[4] multi component reaction for synthesis of 4-aminophthalazin-1(2*H*)-ones,[5,6] heteroarylation of arens[7] and condensation reaction of 3-substituted 3-hydroxyisoindolin-1-ones with hydrazine.[8a] However, all these methods generally suffer from significant drawbacks. Although 4SP's were effectively obtained by Friedel-Crafts (FC) acylation of phthalic anhydride and 1,4-dichlorophthalazine. But these reaction conditions were found to be amenable for only electron rich aromatic and heteroaromatic rings as Friedel-Crafts substrates hence allowing synthesis of specific compounds. Indeed, contributing to severely limiting structure activity relationship (SAR) studies of 4SP's and related heteroaromatics. Nguyen and coworkers [8] have developed an alternative, efficient and general method to prepare 4-substituted aryl/heteroaryl/alkyl phthalazinones. Their linear synthetic approach for 4SP's demands highly reactive, pyrophoric

reagents and tedious synthetic procedures. This methodology did not provide a suitable route to alkynyl substituted phthalazinones. Cross coupling reactions have not been employed in the 4SP's synthesis except a lonely report by Barreiro and coworkers[9] where they used tosylate of phthalhydrazide for Suzuki reaction limited to only phenylboronic acid. There is still a need for novel and more general methodologies to fulfill the increasing demands of modern drug discovery, such as combinatorial and parallel synthetic methods, that avoid harsh reaction conditions and allow for an efficient assembly of the phthalazinone core from readily available starting materials. Herein, we report our investigation in this field.

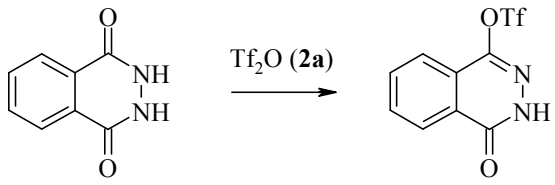
Result and Discussion

The study was initiated with selective *O*-triflation of phthalhydrazide by investigating the reaction of phthalhydrazide (**1a**) and trifluoromethanesulphonic anhydride (**2a**) (Table 1). Initially, the reaction failed to give the triflate **3a** after 36 h in dichloromethane and pyridine (1.1eq.) at room temperature (Table1, entry 1). When the same reaction was performed in acetonitrile and pyridine (1.1eq.) at -50 °C, it provided **3a** in less than 5% and 15-30% yield when performed at 0 °C to room temperature (Table 1, entry 2, 3). The biggest challenge for this reaction was solubility of **1a** and so we used pyridine as a solvent and this resulted in 80-90% yield of **3a** in 2-3 h at -50 °C to room temperature (Table 1, entry 4). The best result was obtained when 20% pyridine was used in acetonitrile which gave **3a** in 90-95% yield (Table 1, entry 8). In present protocol, triflation occurred selectively and exclusively at one of the carbonyl oxygen giving *O*-sulfonate rather than any of amidic nitrogen of 2, 3-dihydrophthalazine-1, 4-dione/phthalhydrazide (**1a**).

After a successful *O*-triflation, next this triflate was subjected to couple of cross coupling reactions namely Suzuki and Sonogashira coupling reactions aimed to access the biologically

relevant phthalazinone motif in library fashion. Thus for Suzuki cross coupling reaction triflate **3a** (1.69 mmol), phenylboronic acid (1.78 mmol), Pd (0) catalyst (10 mol%) and K_2CO_3 (2.54 mmol) in acetonitrile was stirred at rt for 12 h under nitrogen atmosphere, product **5a** was

Table 1. Optimization of the reaction conditions.[a]



1a **3a**

Entry	Solvent	Base	Base Equivalent/proportion	Temp. °C	Yield (%)
1	Dichloromethane	Pyridine	1.1	rt	NR
2	Acetonitrile	Pyridine	1.1	-50	5
3	Acetonitrile	Pyridine	1.1	0 to rt	15-30
5	Pyridine			-50 to rt	80-90
6	Acetonitrile	Pyridine	1:1	0	80-90
7	Acetonitrile	Pyridine	2:1	0	80-90
8	Acetonitrile	Pyridine	4:1	0	90-95

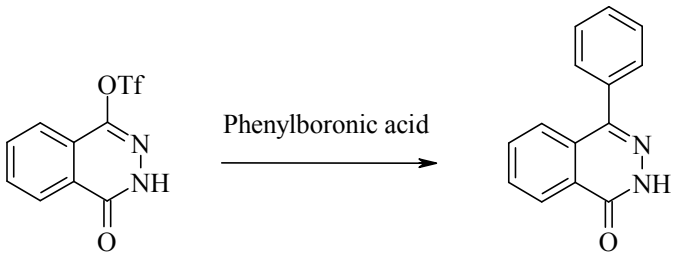
[a]Isolated yield

obtained in less than 30% yield (Table 2, entry 1). The same reaction when refluxed in acetonitrile for 2-3 h resulted in 15% yield (Table 2, entry 2). Even a change of solvent from acetonitrile to 1,4-dioxane did not show much impact on the yield, either at room or reflux temperature (Table 2, entry 3,4). In these reactions, we observed that triflate **3a** was consumed but phenylboronic acid was not. So we postulated that, this may be due to K_2CO_3 induced cleavage of triflate **3a**, which depends on temperature. But, when we used mild base like K_3PO_4 we observed an improvement in reaction profile in terms of proportionate consumption of both triflate and phenylboronic acid. Several other solvents were investigated but they did not show considerable improvement in term of yields and reaction profile (Table 2, entry 5-11). The screening of different Pd (II) catalysts demonstrated that $PdCl_2$(dppf) was best suitable for this reaction conditions, and the product **5a** was obtained in 74% yield (Table 2, entries 12-14). With

the optimized reaction condition in hand, the scope and generality of reaction was explored using various arylboronic acids **4a** (Table 3). Arylboronic acids bearing electron donating groups at *para*, *meta* and *ortho* positions such as –OMe were smoothly coupled with **3a** to give corresponding products **5b** (77%), **5c** (70%) and **5d** (60%) respectively. Boronic acids with halogen substituents, such as chlorine on the benzene ring, were found compatible for this coupling reaction (**5j**, 75% and **5k**, 73%). Boronic acids having electron withdrawing functional groups, such as 2-CF_3- and 4-CHO-, were also well tolerated to give the desired products **5h** (59%) and **5e** (72%) respectively. In addition, steric effect was observed since boronic acid with *ortho*-substituent led to relatively lower yields compared to *para* and *meta* substituted variants (Table 3, entries 4, 8) and, further, boronic acid having 2-CHO- group was failed in our hand to give the desired product. Heteroarylboronic acids, such as 3-pyridyl, 3-thienyl and benzo [*b*] thien-2-yl were also coupled smoothly with **3a** to give **5l** (72%), **5m** (71%) and **5n** (69%) respectively. Using this methodology we have effectively incorporated 3-substituted (Table 3, entries 3, 6-7, 9 and 11) and electron deficient aromatic rings (Table 3, entries 5-8) in Suzuki coupled products (**5)** which are not easily accessible through traditional methods (*vide supra*).

To extend the scope further, in synthetic manipulations, we carried out Sonogashira cross coupling reaction on **3a** in library fashion to get completely new 4-Alkynyl phthalazin-1(2*H*)-one (Table 3, entries 16-20). Phenyl acetylene, 3-methyl phenyl acetylene and 3-amino phenyl acetylene were coupled smoothly giving **6a** (85%), **6b** (80%) and **6c** (76%) respectively.

Table 2. Optimization of the reaction conditions[a]

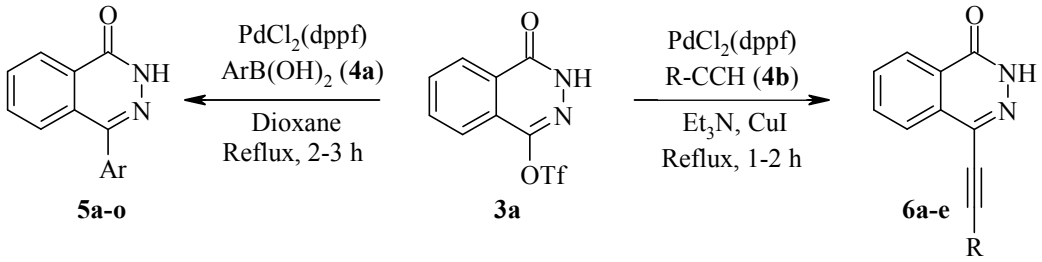


3a **5a**

Entry	Catalyst[a]	Solvent	Base[b]	Time	Temp	Yield[c] %
1	$Pd(PPh_3)_4$	Acetonitrile	K_2CO_3	12 h	rt	30
2	$Pd(PPh_3)_4$	Acetonitrile	K_2CO_3	2-3 h	Reflux	15
3	$Pd(PPh_3)_4$	1,4-dioxane	K_2CO_3	12 h	rt	35
4	$Pd(PPh_3)_4$	1,4-dioxane	K_2CO_3	2-3 h	Reflux	10
5	$Pd(PPh_3)_4$	Acetonitrile	K_3PO_4	12 h	rt	35
6	$Pd(PPh_3)_4$	Acetonitrile	K_3PO_4	2-3 h	Reflux	30
7	$Pd(PPh_3)_4$	1,4-dioxane	K_3PO_4	12 h	rt	35
8	$Pd(PPh_3)_4$	1,4-dioxane	K_3PO_4	2-3 h	Reflux	40
9	$Pd(PPh_3)_4$	Ethanol	K_3PO_4	2-3 h	Reflux	30
10	$Pd(PPh_3)_4$	Dimethylformamide	K_3PO_4	2-3 h	Reflux	NR[d]
11	$Pd(PPh_3)_4$	Acetonitrile:Ethanol	K_3PO_4	2-3 h	Reflux	15
12	$Pd_2(dba)_3$	1,4-dioxane	K_3PO_4	2-3 h	Reflux	NR[d]
13	$PdCl_2(PPh_3)_2$	1,4-dioxane	K_3PO_4	2-3 h	Reflux	NR[d]
14	$PdCl_2(dppf)$	1,4-dioxane	K_3PO_4	2-3 h	Reflux	74

[a]Reaction conditions: unless otherwise noted, all reactions were carried out with 10 mmol % of catalyst in 5.0 mL of solvent under an nitrogen. [b]1.5 equiv of base was used. [c]Isolated yield. [d]No reaction

Table 3. Synthesis of novel 4SP's from triflate (**3a**)



5a-o **3a** **6a-e**

Entry	Ar/R	Compound	Yields (%)
1	Phenyl	5a	74
2	4-Methoxy phenyl	5b	77
3	3-Methoxy phenyl	5c	70
4	2-Methoxy phenyl	5d	60
5	4-Formyl phenyl	5e	72

6	3-Formyl phenyl	5f	62
7	3-Trifluoromethyl phenyl	5g	69
8	2-Trifluoromethyl phenyl	5h	59
9	3-Hydroxy phenyl	5i	74
10	4-Chloro phenyl	5j	75
11	3-Chloro phenyl	5k	73
12	3-Pyridyl	5l	72
13	3-Thienyl	5m	71
14	Benzo[*b*]thien-2-yl	5n	69
15	2-naphthyl	5o	69
16	Phenyl	6a	85
17	3-Methyl phenyl	6b	80
18	3-Amino phenyl	6c	76
19	n-Pentyl	6d	70
20	n-Hexyl	6e	69

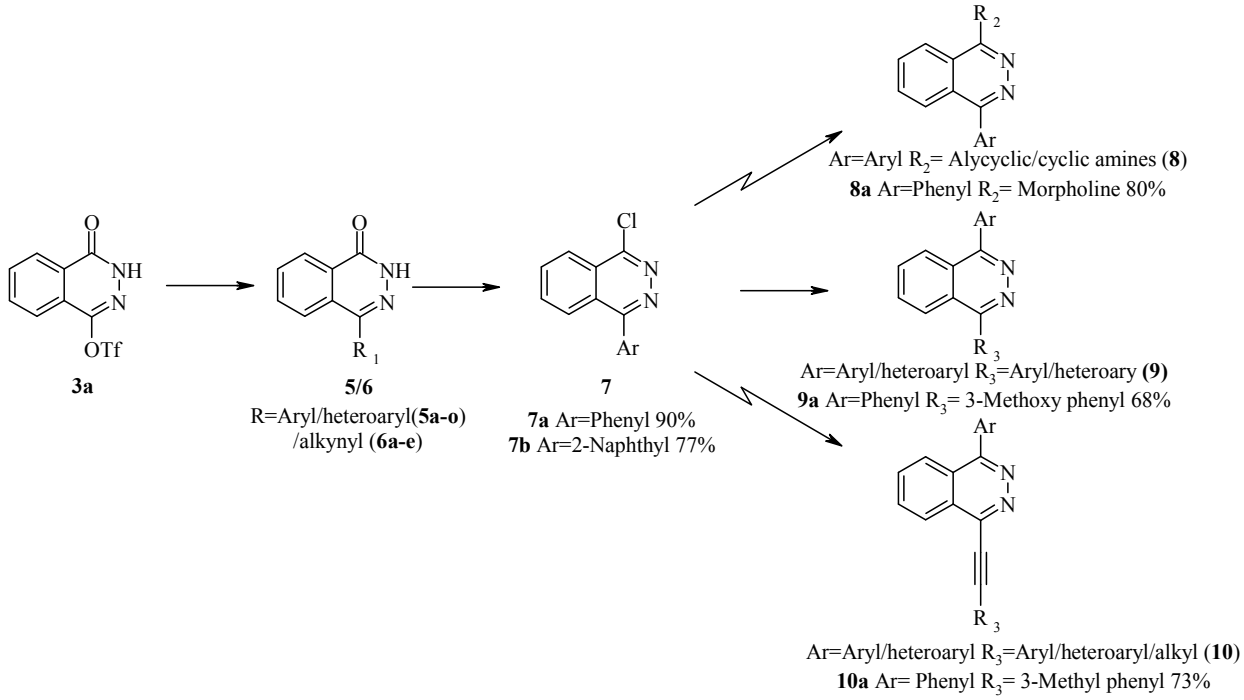


Fig.2. Scope of **3a** in combinatorial synthesis.

Aliphatic alkynes such as 1-heptyne and 1-octyne also coupled effectively to give desired products **6d** (70%) and **6e** (69%) respectively. However, yields of aromatic alkynes were relatively higher as compared to aliphatic alkynes.

Figure 2, furthermore, elaborates the scope of **3a** in combinatorial and diversity oriented synthesis to enrich compound's bank with diversity around phthalazin-1(2*H*)-one core. For this purpose, when 4-arylphthalazin-1(2*H*)-ones were treated with $POCl_3$ corresponding chlorides were obtained,[8] Thus we effectively chlorinated **5a** and **5o** to **7a** (90%) and **7b** (77%) respectively. These chlorinated intermediates (**7a-b)** would be effectively employed in diversity oriented synthesis to get 4-aminophthalazin-1(2*H*)-one (**8)** by nucleophilic displacement reactions with various 1°/2° aliphatic and alicyclic amines. Furthermore, symmetrically or non-symmetrically 1,4 substituted phthalazines (**9**) and 1-aryl,4-alkynyl phthalazines (**10**) are also accessible by Suzuki and Sonogashira cross coupling reactions respectively. We have exemplified this diversity oriented synthesis by reaction of **7a** to get corresponding 1-morpholino-4-phenylphthalazine (**8a**) in 80% yield, 1-(3-methoxyphenyl)-4-phenylphthalazine (**9a**) in 68% yield and 1-phenyl-4-(2-*m*-tolylethynyl) phthalazine (**10a**) in 73% yield respectively.

Conclusions

In conclusion, we have demonstrated that 1,2-dihydro-1-oxophthalazin-4-yl trifluoromethanesulfonate (**3a**) can be synthesized exclusively from **1a** with high efficacy thereby providing a platform for further synthetic manipulations. The present protocol provides straight forward access to library oriented synthesis of 4-aryl/heteroaryl/alkynyl phthalazinones from **3a** by metal catalyzed cross coupling reactions such as Suzuki and Sonogashira reactions in good yields. In addition, we have done refinement of existing protocols and developed completely new reaction parameters which can afford non-obvious lead "hits" *viz.* 4-(3-substituted-aryl) phthalazin-1(2*H*)-one, 4-alkynyl phthalazin-1(2*H*)-one and 1-aryl-4-alkynyl phthalazine that might otherwise remain unexplored. This helps to fill gaps in SAR of 4SP's and

related heteroaromatics. Diversity oriented synthesis on 1-chloro-4-arylphthalazine can lead to an entire library of new chemical compounds such as 1-aryl,4-alkynyl phthalazines (**10**), symmetrically or non-symmetrically substituted 1,4 substituted phthalazines (**9**) and 4-aminophthalazin-1(2*H*)-one (**8**). The utility of the present protocol in the synthesis of biologically important phthalazinones containing heterocycles is currently underway in our laboratory.

Experimental Section

General Information:

All reactions were performed in oven dried glassware and under a N_2 atmosphere. Solvents were dried and degassed by standard methods before use. Thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ (0.25 mm thickness) plates and were visualized under short (254 nm) and long (365 nm) UV light. Column chromatography was performed using silica gel 200-400 mesh. Melting points (Mp) were determined in open capillary tubes using paraffin oil bath and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 and 500 MHz NMR spectrometer using $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts δ are reported in ppm relative to Me_4Si internal standard. The multiplicity of signals is designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). FT-IR was recorded on IR-Affinity1 Shimadzu DRS-8000A instrument. High-resolution mass spectra (HRMS) were obtained using micromass-Q-TOF machine operating in electrospray ionization (ESI) mode.

Synthesis of 1,2-dihydro-1-oxophthalazin-4-yl trifluoromethanesulfonate (3a):

Compound **1a** (2.00 g, 12.33 mmol) was taken in 20 mL acetonitrile and 5 mL of pyridine after 10 min stirring at 0 °C triflic anhydride (12.95 mmol) was added and stirred 0 °C to rt. After completion of reaction (TLC check, 3-4 h), reaction mixture was poured in ethyl acetate (100 mL) and to it water (50 mL) was added then stirred for 30 min to avoid emulsion. Organic layer was washed with 5% HCl, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to get crude compound which was purified by column chromatography using ethyl acetate: n-hexane (25-30%) as eluent to yield pure product as white solid (3.45 g, 95%).

Mp: 186-188 °C; IR (neat): ῡ = 3174, 1681, 1602, 1423, 1321, 1056, 873, 744 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.82 (s, 1H, -NH), 8.31 (d, J = 7.6 Hz, 1H, Ar-H), 8.06-8.01 (m, 1H, Ar-H), 7.98-7.95 (m, 1H, Ar-H), 7.80 ppm (d, J = 7.6 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): 163.1, 159.1, 142.7, 135.7, 134.5, 133.4, 129.0, 129.0, 127.0, 124.39, 123.6, 122.6, 119.6, 116.4 ppm; HRMS (ESI) *m/z:* calcd for $C_9H_6F_3N_2O_4S$ $[M + H]^+$ 294.9995, found 294.9995.

General procedure for synthesis of 4-Aryl phthalazin-1(2*H*)-one (5a-o).

Compound **3a** (0.5 g, 1.69 mmol), $PdCl_2$(dppf) (10 mol%), **4a** arylboronic acid (1.78 mmol) and K_3PO_4 (2.54 mmol) was dissolved in 5 mL of 1,4-dioxane and refluxed for 2-3 h under inert atmosphere. After completion of reaction mixture (TLC check) was poured in (25 mL) water and extracted with ethyl acetate (3 x 25 mL). Organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to get crude compound which was purified by column chromatography using ethyl acetate: n-hexane (40-60%) as eluent to yield product as white solid (59-77%).

4-Phenylphthalazin-1(2*H*)-one (5a):

White solid; Mp: 224-226 °C; lit.[10] IR (neat): ῡ = 3057, 1678, 1489, 1336, 1153, 898, 750, 543cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.1 (s, 1H, -NH), 8.59-8.55 (m, 1H, Ar-H), 7.85-782 (m, 3H, Ar-H), 7.63-7.61 (m, 2H, Ar-H), 7.57-7.54 ppm (m, 3H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5, 148.3, 135.0, 133.5, 131.6, 129.8, 129.4, 129.3, 128.7, 128.4, 127.1, 127.0 ppm; HRMS (ESI) *m/z:* calcd for $C_{14}H_{11}N_2O$ $[M + H]^+$ 223.0866, found 223.0861.

4-(4-Methoxyphenyl)phthalazin-1(2*H*)-one (5b):

White solid; Mp: 238-240 °C; lit.[3] IR (neat): ῡ = 3099, 1668, 1608, 1516, 1255, 1028, 873, 682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.78 (s, 1H, -NH), 8.36-8.34 (m, 1H, Ar-H), 7.87-7.84 (m, 2H, Ar-H), 7.74-7.71 (m, 1H, Ar-H), 7.53-7.50 (m, 2H, Ar-H), 7.10-7.07 (m, 2H, Ar-H), 3.86 ppm (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.6, 159.2, 146.1, 133.2, 131.2, 130.5, 129.2, 128.0, 127.3, 126.5, 126.0, 113.8, 55.1 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0971, found 253.0968.

4-(3-Methoxyphenyl)phthalazin-1(2*H*)-one (5c):

White solid; Mp: 182-184 °C; IR (neat): ῡ = 3070, 1662, 1598, 1485, 1159, 860, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.83 (s, 1H, -NH), 8.36-8.35 (m, 1H, Ar-H), 7.87-7.85 (m, 2H, Ar-H), 7.74-7.71 (m, 1H, Ar-H), 7.47-7.43 (m, 1H, Ar-H), 7.14-7.07 (m, 3H, Ar-H), 3.83 ppm (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2, 159.2, 146.1, 136.3, 133.2, 131.3, 129.4, 129.0, 127.9, 126.4, 126.0, 121.4, 114.6, 114.4, 55.1 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0971, found 253.0973.

4-(2-Methoxyphenyl)phthalazin-1(2*H*)-one (5d):

White solid; Mp: 240-242 °C; IR (neat): ῡ = 3022, 1658, 1606, 1153, 1024, 889, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.78 (s, 1H, -NH), 8.33-8.31 (m, 1H, Ar-H), 7.81-7.77 (m, 2H, Ar-H), 7.53-7.49 (m, 1H, Ar-H), 7.33 (dd, *J* = 1.7, 7.4 Hz, 1H, Ar-H), 7.29-7.27 (m, 1H, Ar-H), 7.17 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.12-7.08 (m, 1H, Ar-H), 3.70 ppm (s, 3H, $-OCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.5, 157.1, 144.9, 133.0, 131.1, 130.8, 130.6, 129.8, 127.4, 126.7, 125.5, 123.9, 120.5, 111.2, 55.2 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0971, found 253.0974.

4-(4-Formylphenyl)phthalazin-1(2*H*)-one (5e):

White solid; Mp: 280-282 °C; IR (neat): ῡ = 3159, 2845, 1703, 1666, 1606, 1336, 1209, 833, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.96 (s, 1H, -NH), 10.14 (s, 1H, -CHO), 8.39-8.37 (m, 1H, Ar-H), 8.09 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.90-7.87 (m, 2H, Ar-H), 7.82 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.72-7.69 ppm (m, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.3, 159.2, 145.2, 140.7, 136.1, 133.4, 131.5, 130.0, 129.5, 128.6, 127.9, 126.1, 126.1 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{11}N_2O_2$ $[M + H]^+$ 251.0815, found 251.0815.

4-(3-Formylphenyl)phthalazin-1(2*H*)-one (5f):

White solid; Mp: 256-258 °C; IR (neat): ῡ = 3179, 2895, 1701, 1674 1338, 1184, 796, 684 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.92 (s, 1H, -NH), 10.12 (s, 1H, -CHO), 8.40-8.37 (m, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 8.07 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.94-7.86 (m, 3H, Ar-H), 7.79-7.75 (m, 1H, Ar-H), 7.72-7.69 ppm (m, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.4,

159.3, 145.2, 136.3, 136.0, 135.0, 133.4, 131.5, 130.3, 129.5, 129.3, 128.7, 128.0, 126.14,126.1 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{11}N_2O_2$ $[M + H]^+$ 251.0815, found 251.0814.

4-(3-(Trifluoromethyl)phenyl)phthalazin-1(2*H*)-one (5g):

White solid; Mp: 272-274 °C; lit.[8a] IR (neat): ῡ = 3150, 1668, 1313, 1182, 1134, 688, 549 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.86 (s, 1H, -NH), 8.37-8.35 (m, 1H, Ar-H), 7.90 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.85-7.74 (m, 4H, Ar-H), 7.56 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.15 ppm (d, *J* = 7.4 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3, 144.2, 133.1, 132.0, 131.7, 131.3, 130.0, 129.5, 128.8, 128.5, 127.5, 126.4, 126.4, 126.3, 126.0, 125.7, 125.0 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{10}F_3N_2O$ $[M + H]^+$ 291.0740, found 291.0741.

4-(2-(Trifluoromethyl)phenyl)phthalazin-1(2*H*)-one (5h):

White solid; Mp: 278-280 °C; IR (neat): ῡ = 3161, 1668, 1606, 1313, 1180, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.89 (s, 1H, -NH), 8.36 (dd, *J* = 1.4, 7.8 Hz, 1H, Ar-H), 7.91 (d, 7.4 Hz, 1H, Ar-H), 7.87-7.75 (m, 4H, Ar-H), 7.58 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.15 ppm (d, *J* = 7.5 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3, 144.2, 133.2, 133.1, 133.1, 132.1, 131.8, 131.4, 130.0, 129.5, 128.7, 128.4, 127.5, 126.4, 126.4, 126.1, 125.8, 125.0, 122.3 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{10}F_3N_2O$ $[M + H]^+$ 291.0740, found 291.0740.

4-(3-Hydroxyphenyl)phthalazin-1(2*H*)-one (5i):

White solid; Mp: 274-276 °C; IR (neat): ῡ = 3213, 3053, 1651, 1589, 1471, 1354, 1201, 794, 704 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.75 (s, 1H, -NH), 9.57 (s, 1H, -OH), 8.38-8.35 (m, 1H, Ar-H), 7.88-7.83 (m, 2H, Ar-H), 7.79-7.75 (m, 1H, Ar-H), 7.78 (m, 1H, Ar-H), 6.98-6.97

(m, 2H, Ar-H), 6.94-6.91 ppm (m, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3, 157.4, 146.4, 136.2, 133.0, 131.1, 129.2, 129.0, 128.0, 126.4, 125.9, 119.8, 116.1, 115.8 ppm; HRMS (ESI) *m/z:* calcd for $C_{14}H_{11}N_2O_2$ $[M + H]^+$ 239.0815, found 239.0813.

4-(4-Chlorophenyl)phthalazin-1(2*H*)-one (5j):

White solid; Mp: 256-258 °C; lit.[8a] IR (neat): ῡ = 3159, 1666, 1598, 1483, 1153, 877, 761, 686 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.8 (s, 1H, -NH), 8.37-8.34 (m, 1H, Ar-H), 7.89-7.84 (m, 2H, Ar-H), 7.70-7.67 (m, 1H, Ar-H), 7.62-7.56 ppm (m, 4H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2, 145.2, 135.9, 133.8, 133.3, 131.4, 130.9, 128.7, 128.4, 127.9, 126.2, 126.0 ppm; HRMS (ESI) m/z: calcd for $C_{14}H_{10}ClN_2O$ [M + H]+ 257.0476, found 257.0480.

4-(3-Chlorophenyl)phthalazin-1(2*H*)-one (5k):

White solid; Mp: 216-218 °C; IR (neat): ῡ = 3161, 1666, 1473, 1217, 887, 788, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + D_2O): δ = 8.49-8.48 (m, 1H, Ar-H), 7.82-7.80 (m, 2H, Ar-H), 7.71-7.70 (m, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.48-745 ppm (m, 3H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 147.0, 136.6, 134.6, 134.5, 133.7, 131.9, 130.9, 129.9, 129.5, 129.4, 127.6, 126.9, 126.6, 123.4 ppm; HRMS (ESI) *m/z:* calcd for $C_{14}H_{10}ClN_2O$ $[M + H]^+$ 257.0476, found 257.0473.

4-(Pyridin-3-yl)phthalazin-1(2*H*)-one (5l):

White solid; Mp: 242-244 °C; IR (neat): ῡ = 3072, 1681, 1487, 1328, 1153, 821, 686, 632 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.96 (s, 1H, -NH), 8.80-8.79 (m, 1H, Ar-H), 8.74-8.72 (m,

1H, Ar-H), 8.39-8.36 (m, 1H, Ar-H), 8.03-8.02 (m, 1H, Ar-H), 7.91-7.88 (m, 2H, Ar-H), 7.69-7.67 (m, 1H, Ar-H), 7.59-7.56 ppm (m, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2, 149.7, 149.5, 143.7, 136.5, 133.5, 131.6, 130.9, 128.8, 127.9, 126.1, 126.0, 123.3 ppm; HRMS (ESI) *m/z:* calcd for $C_{13}H_{10}N_3O$ $[M + H]^+$ 224.0818, found 224.0815.

4-(Thiophen-3-yl)phthalazin-1(2*H*)-one (5m):

White solid; Mp: 230-232 °C; IR (neat): ῦ = 3105, 1660, 1554, 1350, 1190, 792, 679 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.76 (s, 1H, -NH), 8.36-8.34 (m, 1H, Ar-H), 7.93-7.80 (m, 4H, Ar-H), 7.66-7.64 (m, 1H, Ar-H), 7.40-7.39 ppm (m, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2, 142.0, 135.8, 133.3, 131.2, 129.1, 128.3, 127.8, 126.2, 126.1, 126.0, 125.9 ppm; HRMS (ESI) *m/z:* calcd for $C_{12}H_9N_2OS$ $[M + H]^+$ 229.0430, found 229.0432.

4-(Benzo[b]thiophen-2-yl)phthalazin-1(2*H*)-one (5n):

White solid; Mp: 228-230 °C; lit.[8a] IR (neat): ῦ = 3097, 1660, 1575, 1352, 1197, 914, 792, 746 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.00 (s, 1H, -NH), 8.39 (d, J = 7.76 Hz, 1H, Ar-H), 8.32 (d, J = 8.04 Hz, 1H, Ar-H), 8.03-7.88 (m, 5H, Ar-H), 7.45-7.41 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9, 140.1, 139.6, 138.9, 137.5, 135.8, 133.7, 131.6, 128.2, 127.8, 126.3, 125.9, 125.2, 125.0, 124.5, 124.2, 122.0 ppm; HRMS (ESI) *m/z:* calcd for $C_{16}H_{11}N_2OS$ $[M + H]^+$ 279.0587, found 279.0584.

4-(Naphthalen-3-yl)phthalazin-1(2*H*)-one (5o):

White solid; Mp: 248-250 °C; IR (neat): ῦ = 2899, 1666, 1494, 1348, 1153, 781 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.92 (s, 1H, -NH), 8.40-8.38 (m, 1H, Ar-H), 8.14 (s, 1H, Ar-H),

8.06 (d, *J* = 8.5 Hz, 1H, Ar-H), 8.02-7.99 (m, 2H, Ar-H), 7.89-7.85 (m, 2H, Ar-H), 7.79-7.77 (m, 1H, Ar-H), 7.71 (dd, *J* = 1.7, 8.4 Hz, 1H, Ar-H), 7.59 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3, 146.3, 133.3, 132.8, 132.6, 132.5, 131.3, 129.1, 128.6, 128.2, 128.0, 127.9, 127.5, 126.7, 126.7, 126.5, 126.5, 126.1 ppm; HRMS (ESI) *m/z:* calcd for $C_{18}H_{13}N_2O$ [M + H]$^+$ 273.1022, found 273.1027.

General procedure for synthesis of 4-Alkynyl phthalazin-1(2*H*)-one (6a-e):

Compound **3a** (0.5 g, 1.69 mmol), $PdCl_2$(dppf) (10 mol%), **4b** terminal alkynes (1.71 mmol) and copper iodide (5 mol%) was dissolved in 5 mL of triethylamine and refluxed for 1-2 h under inert atmosphere. After completion of reaction (TLC check) mixture was poured in water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude product which was purified by column chromatography using ethyl acetate: n-hexane (30-40%) as eluent to yield pure product as white solid.

4-(2-Phenylethynyl)phthalazin-1(2*H*)-one (6a):

White solid; Mp: 200-202 °C; IR (neat): ῡ = 3151, 2225, 1660, 1496, 1338, 1022, 807, 756 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.00 (s, 1H, -NH), 8.30 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.17 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.03-7.99 (m, 1H, Ar-H), 7.91-7.88 (m, 1H, Ar-H), 7.73-7.70 (m, 2H, Ar-H), 7.50-7.47 ppm (m, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6); δ = 159.0, 133.9, 131.9, 131.7, 131.1, 129.7, 129.5, 128.7, 127.1, 125.8, 125.8, 121.0, 92.9, 82.7 ppm; HRMS (ESI) *m/z:* calcd for $C_{16}H_{11}N_2O$ [M + H]$^+$ 247.0866, found 247.0863.

4-(2-*m*-Tolylethynyl)phthalazin-1(2*H*)-one (6b):

White solid; Mp: 232-234 °C; IR (neat): ῡ = 3101, 2220, 1662, 1577, 1494, 1332, 1155, 777, 682 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.99 (s, 1H, -NH), 8.29 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.17 (d, *J* = 7.84 Hz, 1H, Ar-H), 8.03-7.99 (m, 1H, Ar-H), 7.91-7.87 (m, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.50 (d, *J* = 7.56 Hz, 1H, Ar-H), 7.37-7.33 (m, 1H, Ar-H), 7.29 ppm (d, *J* = 7.64 Hz, 1H, Ar-H), 2.38 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 138.1, 133.9, 132.0, 131.9, 131.2, 130.3, 129.7, 128.8, 128.5, 127.1, 125.8, 125.8, 120.8, 93.2, 82.1 ppm; HRMS (ESI) *m/z:* calcd for $C_{17}H_{13}N_2O$ $[M + H]^+$ 261.1022, found 261.1020.

4-(2-(3-Aminophenyl)ethynyl)phthalazin-1(2*H*)-one (6c):

White solid; Mp: 274-276 °C; IR (neat): ῡ = 3414, 3161, 2218, 1668, 1598, 1348, 1159, 856, 773 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.96 (s, 1H, -NH), 8.30 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.13 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.03-8.0 (m, 1H, Ar-H), 7.91-7.87 (m, 1H, Ar-H), 7.14-7.10 (m, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.86 (d, *J* = 7.5 Hz, 1H, Ar-H), 6.72 (d, *J* = 8.0 Hz, 1H, Ar-H), 5.27 ppm (s, 2H, -NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 148.8, 133.9, 131.9, 131.3, 129.8, 129.2, 127.1, 125.8, 121.1, 119.2, 116.4, 115.5, 94.2, 81.4 ppm; HRMS (ESI) *m/z:* calcd for $C_{16}H_{12}N_3O$ $[M + H]^+$ 262.0975, found 262.0974.

4-(Hept-1-ynyl)phthalazin-1(2*H*)-one (6d):

White solid; Mp: 138-140 °C; IR (neat): ῡ = 3155, 2231, 1660, 1583, 1330, 1149, 906, 776 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.80 (s, 1H, -NH), 8.28-8.23 (m, 1H, , Ar-H), 8.02 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.98-7.93 (m, 1H, Ar-H), 7.88-7.84 (m, 1H, Ar-H), 2.58-2.54 (m, 2H, -CH_2), 1.70-1.63 (m, 2H, -CH_2), 1.51-1.45 (m, 2H, -CH_2), 1.43-1.33 (m, 2H, -CH_2), 0.94-0.91 ppm (t,

3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 133.6, 131.7, 131.6, 129.9, 127.1, 125.8, 125.7, 95.2, 74.3, 30.6, 27.5, 21.6, 18.6, 13.8 ppm; HRMS (ESI) *m/z:* calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1335, found 241.1334.

4-(Oct-1-ynyl)phthalazin-1(2*H*)-one (6e):

White solid; Mp: 118-120 °C; IR (neat): ῡ = 3153, 2231, 1660, 1471, 1334, 1149, 904, 786 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.81 (s, 1H, -NH), 8.26 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.02 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.98-7.94 (m, 1H, Ar-H), 7.90-7.85 (m, 1H, Ar-H), 2.58-2.54 (m, 2H, -CH_2), 1.67-1.61 (m, 2H, -CH_2), 1.50-1.46 (m, 2H, -CH_2),1.35-1.31 (m, 4H, -CH_2), 0.91-0.89 ppm (m, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9, 133.7, 131.8, 131.6, 129.9, 127.1, 125.8, 121.7, 95.3, 74.3, 30.7, 28.0, 27.8, 22.0, 18.6, 13.8 ppm; HRMS (ESI) *m/z:* calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1492, found 255.1491

General procedure for synthesis of 1-Chloro-4-arylphthalazine (7):

Compound **5** (3.0 g, 13.50 mmol) was taken 20 mL of acetonitrile to it at room temperature $POCl_3$ (12.63 mL, 135.09 mmol) was added and then refluxed for 5-6 h. After completion (TLC check), reaction mixture was neutralized by aqueous saturated $NaHCO_3$ solution and then extracted with ethyl acetate (3 x 25 mL). Organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude compound which was purified by column chromatography using ethyl acetate: n- hexane (15-20%) as eluent to get pure product as white solid (2.8 g, 86%).

1-Chloro-4-phenylphthalazine (7a): White solid; Mp: 138-142 °C; lit.[8b] IR (neat): ῡ = 3041, 1527, 1446, 1292, 1174, 781, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.38 (d, *J* = 8 Hz, 1H, Ar-H), 8.18-8.14 (m, 1H, Ar-H), 8.11-8.03 (m, 2H, Ar-H), 7.73-7.70 (m, 2H, Ar-H), 7.64-7.62 ppm (m, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.9, 153.7, 134.9, 134.0, 133.8, 129.7, 129.5, 128.4, 126.6, 126.6, 125.5, 124.8 ppm; HRMS (ESI) *m/z:* calcd for $C_{14}H_{10}ClN_2$ $[M + H]^+$ 241.0532, found 241.0537.

1-Chloro-4-(naphthalen-3-yl)phthalazine (7b): White solid; Mp: 178-180 °C; IR (neat): ῡ = 3072, 1568, 1527, 1471, 746, 678, 634 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.28 (s, 1H, Ar-H), 8.19-8.03 (m, 6H, Ar-H), 7.84-7.82 (m, 1H, Ar-H), 7.65-7.61 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.9, 153.8, 134.1, 133.9, 133.1, 132.5, 132.4, 129.7, 128.4, 128.1, 127.6, 127.1, 126.9, 126.8, 126.7, 126.7, 125.5, 124.9 ppm; HRMS (ESI) *m/z:* calcd for $C_{18}H_{12}ClN_2$ $[M + H]^+$ 291.0683, found 291.0685.

Synthesis of 1-Morpholino-4-phenylphthalazine (8a):

This compound was synthesized according to the reported method[11] in 81% yield.

White solid; Mp: 190-192 °C; lit.[11] IR (neat): ῡ = 3047, 2852, 1529, 1444, 1408, 1111, 889, 706 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.20 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.97-7.88 (m, 3H, Ar-H), 7.69-7.66 (m, 2H, Ar-H), 7.61-7.55 (m, 3H, Ar-H), 3.93 (t, *J* = 4.5 Hz, 4H, $-OCH_2$), 3.48 ppm (t, *J* = 4.5 Hz, 4H, $-OCH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.8, 155.8, 136.3, 131.3, 131.9, 131.6, 129.6, 128.7, 128.3, 126.5, 126.2, 124.4, 120.8, 66.1, 51.3 ppm; HRMS (ESI) *m/z:* calcd for $C_{18}H_{18}N_3O$ $[M + H]^+$ 292.1444, found 292.1444.

Synthesis of 1-(3-Methoxyphenyl)-4-phenylphthalazine (9a):

Compound **7a** (0.5 g, 2.07 mmol), $PdCl_2$(dppf) (10 mol%), 3-Methoxyphenylboronic acid (2.09 mmol) and K_3PO_4 (3.11 mmol) was dissolved in 5 mL of 1,4-dioxane and refluxed for 2-3 h under inert atmosphere. After completion (TLC check), reaction mixture was poured in 25 mL of water and extracted with ethyl acetate (3 x 25 mL). Organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude compound which was purified by column chromatography using ethyl acetate: n-hexane (25-35%) as eluent to yield product as white solid (452 mg, 69%).

Mp: 168-170 °C; IR (neat): ῡ = 3072, 1589, 1489, 1253, 1159, 1041, 790, 705 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.08-8.05 (m, 1H, Ar-H), 8.05-8.01 (m, 3H, Ar-H), 7.77 (dd, J = 2, 4.7 Hz, 2H, Ar-H), 7.67-7.61 (m, 3H, Ar-H), 7.61-7.54 (m, 1H, Ar-H), 7.33-7.32 (m, 2H, Ar-H), 7.20-7.18 (m, 1H, Ar-H), 3.86 ppm (s, 3H, $-OCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2, 158.6, 158.4, 137.3, 136.0, 132.9, 129.8, 129.6, 129.3, 128.5, 126.1, 126.0, 124.9, 124.9, 122.1, 115.2, 115.0, 55.2 ppm; HRMS (ESI) *m/z:* calcd for $C_{21}H_{17}N_2O$ $[M + H]^+$ 313.1335, found 313.1336.

Synthesis of 1-Phenyl-4-(2-*m*-tolylethynyl)phthalazine (10a):

Compound **7a** (0.5 g, 2.07 mmol), $PdCl_2$(dppf) (10 mol%), 1-ethynyl-3-methylbenzene (2.09 mmol) and copper iodide (5 mol%) was dissolved in 5 mL of triethylamine and refluxed for 1-2 h under inert atmosphere. After completion (TLC check), reaction mixture was poured in 25 mL of water and extracted with ethyl acetate (3 x 25 mL). Organic layer was dried over anhydrous Na_2SO_4 concentrated under reduced pressure to give crude compound which was purified by

column chromatography using ethyl acetate: n-hexane (25-30%) as eluent to yield pure product as white solid (490 mg, 73%).

Mp: 164-166 °C; IR (neat): ῡ = 3043, 2218, 1508, 1384, 1259, 1078, 788, 709 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (d, *J* = 8.5 Hz, 1H, Ar-H), 8.19-8.15 (m, 1H, Ar-H), 8.10-8.04 (m, 2H, Ar-H), 7.78-7.76 (m, 2H, Ar-H), 7.69 (s, 1H, Ar-H), 7.64-7.63 (m, 4H, Ar-H), 7.45-7.42 (m, 1H, Ar-H), 7.38 (d, *J* = 7.5Hz, 1H, Ar-H), 2.39 ppm (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.0, 144.9, 138.4, 135.6, 133.8, 133.6, 132.5, 131.0, 130.0, 129.5, 129.3, 128.9, 128.5, 126.9, 126.1, 125.5, 123.7, 120.5, 96.8, 83.8, 20.7 ppm; HRMS (ESI) *m/z:* calcd for $C_{23}H_{17}N_2$ $[M + H]^+$ 321.1386, found 321.1387

Acknowledgments

We would like to thank Council of Scientific and Industrial Research (CSIR), (No: 02(0001)/11/EMR-II) New Delhi- 110 001 and Board of Colleges and University Development (BCUD), (No: OSD/BCUD/360/36) Savitribai Phule Pune University, Pune-411 007, MS, India for supporting this work. Ganesh Dhage thanks CSIR, New Delhi for a fellowship. We wish thank to Dr. R. J. Barnabas (The Principal, Ahmednagar College, Ahmednagar) for helpful discussions and suggestions.

References

1 E. Vitaku, D.T. Smith and J. T. Njardarson, *J. Med. Chem.* 2014, **57**, 10257-10274.

2 N. Vila, P. Besada, T. Costas, M. C. Costas-Lago and C. Terán, *E. J. Med. Chem.* 2014. doi:10.1016/j.ejmech.2014.11.043 and references there in.

3 M. Yamaguchi, K. Kamei, T. Koga, M. Akima, T. Kuroki and N. Ohi, *J. Med. Chem.* 1993, **36**, 4052-4060.

4 (a) H. Wang, J. Cai, H. Huang and G.-J. Deng, *Org. Lett.* 2014, **16**, 5324-5327; (b) X.-F. Wu, H. Neumann, S. Neumann and M. Beller, *Chem. Eur. J.* 2012, **18**, 8596-8599.

5 T. Vlaar, E. Ruijter, A. Znabet, E. Janssen, F. J. J. de Kanter, B. U. W. Maes and R. V. A. Orru, *Org. Lett.* 2011, **13**, 6496-6499.

6 T. Vlaar, P. Mampuys, M. Helliwell, B. U. W. Maes, R. V. A. Orru and E. Ruijter, *J. Org. Chem.* 2013, **78**, 6735-6745.

7 M. Pal, V. R. Batchu, K. Parasuraman and K. R. Yeleswarapu, *J. Org. Chem.* 2003, **68**, 6806-6809.

8 (a) H. N. Nguyen, V. J. Cee, H. L. Deak, B. Du, K.P. Faber, H. Gunaydin, B. L. Hodous, S. L. Hollis, P. H. Krolikowski, P. R. Olivieri, V. F. Patel, K. Romero, L. B. Schenkel and S. D. Geuns-Meyer, *J. Org. Chem.* 2012, **77**, 3887-3906; (b) M. M. Hemdan, S. M. Taha, A. M. Gabr, M. Y. Elkady, *J. Chem. Res.* 2010, **34**, 102-105.

9 A. E. Kümmerle, M. M. Vieira, M. Schmitt, A. L. P. Miranda, C. A. M. Fraga, J-J. Bourguignon and E. J. Barreiro, *Bioorg. Med. Chem. Lett*. 2009, **19**, 4963–4966.

10 M. F. Ismail, F. A. El-Bassiouny, H. A. Younes, *Tetrahedron* 1984, **40**, 2983-2984.

11 H. M. Holava, Jr., R. A. Partyka, *J. Med. Chem.* 1969, **12**, 555-556.