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XANTHONES IN HETEROCYCLIC SYNTHESIS. AN EFFICIENT AND GENERAL ROUTE FOR THE SYNTHESIS OF REGIOSELECTIVELY SUBSTITUTED PHTHALAZINES

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Abstract - Xanthone undergoes regioselective substitution and nucleophically - triggered ring opening to the corresponding ketone. Hydrazone of the latter oxidatively rearranges to *ortho*-diacylarenes, which, then, with hydrazine gives regioselectively substituted phthalazines. Molecular modeling analysis and ^{1}H NMR spectra indicate an intramolecular H-bonding engaging phenol OH and phthalazine N-3 atom.

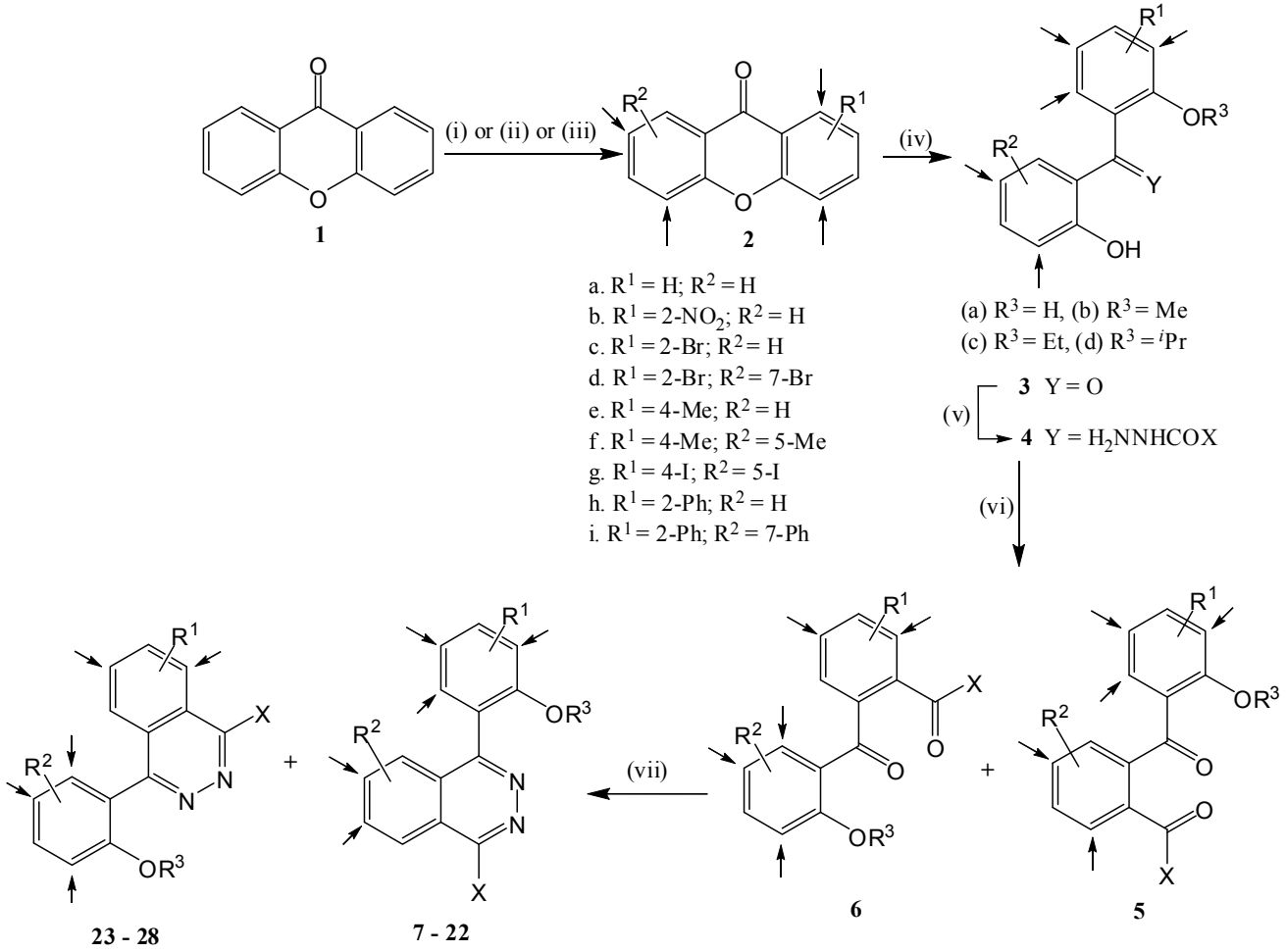
INTRODUCTION

Phthalazines, like the other members of the isomeric benzodiazine series, have found wide application as therapeutic agents.[1] Despite their significance, there are a rather limited number of efficient routes for their synthesis, especially when diverse substitution on both rings is required. Phthalazines bearing no substitution on the pyridazine ring can be prepared from *o*-phthalaldehydes through suitable precursors,[2] reductive[3] or oxidative[4] cleavage of heterocycles or lithiation followed by formylation.[5] 1- or 1,4-substituted congeners are usually accessible from their corresponding 1,2-diacyl arenes,[6] acid-catalyzed cyclodehydration of hydrazones,[7] acid-catalyzed rearrangement of Reissert compounds,[8] acid-catalyzed cyclization of azines,[9] thermally-induced cyclization of phthalanol,[10] reductive opening of γ-lactones[11] or Suzuki coupling of chloro-substituted phthalazines.[12] Drawbacks common to most of these

methods are multi-step schemes, rather forcing conditions and, most important, no diversity in substitution.

A phthalazine scaffold, incorporating a phenol ring directly attached to the heterocycle, has been essential to our needs for a recently developed project on selective binding at nicotinic acetylcholine receptor orthosteric sites. To that end, we report, herein, an efficient and general route for the synthesis of phthalazines, substituted or derivatized regioselectively, on either of the rings. The resulting structure can, thus, be a scaffold for a diverse array of analogues bearing at least one(het)aryl group. The diversity of phenols, their simple conversion to bromides[13] or triflates[14] and the value of these derivatives in coupling reactions, in addition to their well-known medical applications,[15] are a useful asset to the synthetic potential of the proposed route.

RESULTS AND DISCUSSION



Scheme 1. (i) c. HNO_3/c. H_2SO_4/rt.[16] or (ii) a) $Br_2/AlCl_3/\Delta$ or b) Br_2 (10-fold excess)/AcOH/100 °C. or (iii) a) $SOCl_2$/DMF/Δ, b) NaOMe/MeOH-THF, c) ^{t}BuLi/THP/-13 – (-10) °C/H^+/H_2O.[16,17] (iv) 12N KOH/Δ/H^+ or NaOR (R = Me, Et, ^{i}Pr)/Δ sealed tube/H^+.[18] (v) $H_2NNHCOX/^i$PrOH/py/Δ/12 h. (vi) $Pb(OAc)_4$[19] or $PhI(OAc)_2$[19]/Et_2O or THF/0 °C to rt. (vii) H_2NNH_2/EtOH (or ^{i}PrOH)/ rt/45 min.

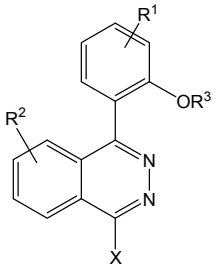
The proclivity of **1**[17,20] to substitution with a synthetically useful degree of regioselectivity allows its diverse functionalisation. Conventional electrophilic substitution, using nitration and bromination, has been detailed in a preceding report.[16] The NO_2 group is introduced at C-2 (or C-7). The bromine, on the other hand, enters C-2, predominantly but C-7 is also attacked to a lesser extend to give the dibromo derivative. Clearly, entries at C-2 and C-7 are facilitated by and directed from the pyran O lone pair. These entries serve as sites of further functionalisation. For example a phenyl group can be incorporated into **2c** or **2d** (Scheme 1), under Suzuki conditions, to give **2h** or **2i**, respectively. Complementary to the above functionalisation of **1** is a lithiation-electrophilic quench protocol[17] to C-1, C-4 and C-5 as the active sites for mono- or disubstitution (Scheme 1). Having **2** regioselectively substituted, it undergoes a nucleophilically-triggered ring opening to the ketone (**3**). The cleaving nucleophile, through an S_NAr process, ends up *ortho*- to the ketone carbonyl moiety. The cleavage is efficiently performed with alkali (yields up to 80%) whereas moderate yields of *ca*.50% are obtained when an alkoxide is used.[16] In the latter case one of the OH groups is protected as an alkyl ether (Scheme 1, **3b-d**).

Generation of hydrazone **4**, straightforward as would be expected, presented difficulties at first, presumably due to the interfering *intra*molecularly H-bonded OH groups. Protection by *O*-benzylation was initially carried out as the obvious means to remove the H-bonding effect. Having prepared the benzyl ether of **3**, the release of the OH groups was then attempted by either Mg/MeOH[21] or $MgBr_2$,[22] in both cases unsuccessfully. Deprotection was then accomplished by ammonium formate over Pd/C.[23] Removing the protection-deprotection steps adds to the elegance and performance of the scheme.[24] Thus, **4** was finally obtained very efficiently by simply heating unprotected **3** with the hydrazide in the presence of pyridine.

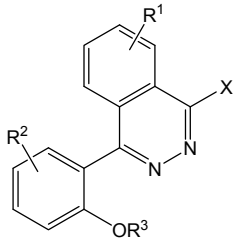
Treatment of **4** with either lead(IV) acetate (LTA)[19] or phenyliododiacetate (PIDA)[19] induces an oxidative rearrangement leading to **5** (and **6**). This reaction encompasses[25] a ligand coupling followed by a series of rearrangements. The overall process is a C-O to C-C bond conversion. The last step of the scheme is a simple condensation of **5** (or **6**) with hydrazine hydrate (stirring for 45 min in isopropanol at room temperature) to **7-28** (Table 1).

From the scheme and the tabulated results certain features emerge: (a) the cleavage of **2** introduces the desired phenol, regioselectively substituted or not, ultimately at C-1 (or C-4) of the phthalazine structure. (b) when unsubstituted, **3** leads to a single phthalazine isomer (Table 1, entries **7-9** and **17**, **19**, **20** and **22**). Similarly the alkyl ether of **3** also leads to a single isomer (Table 1, entries **10-12**), (c) the type of hydrazide used to form **4** determines the *o*-diacyl arene substitution pattern and ultimately that of phthalazine isomer(s) formed, (d) **5** and **6** need not be separated but can be reacted as a mixture to yield **7-28**, (e) **13-16** and **21** as well as their regioisomers **23-26** and **28** are generated from the alternative modes of oxidative rearrangement of **4** whereas **17**, **19**, **20** and **22**, being symmetrically substituted, yield only one isomer.

Table 1. Regioselectively Substituted Phthalazines **7-22** and **23-28**



7 - 22



23 - 28

Entry	R^1	R^2	R^3	X	Yield %	(mp °C)	Entry	R^1	R^2	R^3	X	Yield %	(mp °C)
7	H	H	H	Me	88	(168)							
8	H	H	H	Ph	90	(222)							
9	H	H	H	2′-py	90	(172)							
10	H	H	Me	Me	84	(oil)							
11	H	H	Et	Ph	88	(64)							
12	H	H	^{i}Pr	2′-py	81	(61)							
13	5′-NO_2	H	H	Me	52	(164)	**23**	6- NO_2	H	H	Me	22	(136)
14	5′-NO_2	H	H	Ph	58	(178)	**24**	6- NO_2	H	H	Ph	26 [a)]	
15	5′-Br	H	H	Me	42	(116)	**25**	6-Br	H	H	Me	44 [a)]	
16	5′-Br	H	H	Ph	44	(127)	**26**	6-Br	H	H	Ph	47[a)]	
17	5′-Br	6 -Br	H	Ph	89	(153)							
18	3′-Me	H	H	Ph	43	(76)	**27**	8-Me	H	H	Ph	38[a)]	
19	3′-Me	8-Me	H	Ph	88	(94)							
20	3′-I	8-I	H	Ph	90	(228)							
21	5′-Ph	H	H	Ph	45	(231)	**28**	6-Ph	H	H	Ph	42[a)]	
22	5′-Ph	6-Ph	H	Ph	85	(246)							

[a)] Not isolated. Identified by ^{1}H NMR spectra.

A molecular modeling analysis[26] was performed on **9** to depict inherent conformational features (Figure 1). Indeed, lowest energy conformers A-D exhibit the potential of an *intra*molecular H-bonding interaction between the phenolic OH and the nearest ring N atom. This is in concert with a ^{1}H NMR signal at δ = 9.05 ppm and an IR absorption at 3360 cm^{-1} attributed to the OH bonded proton. A very modest elongation of 0.001Å, observed in A-D conformers lends support to a weak such interaction. The bond length shows a more notable increase of 0.003Å when compared to that of parent phenol.[27]

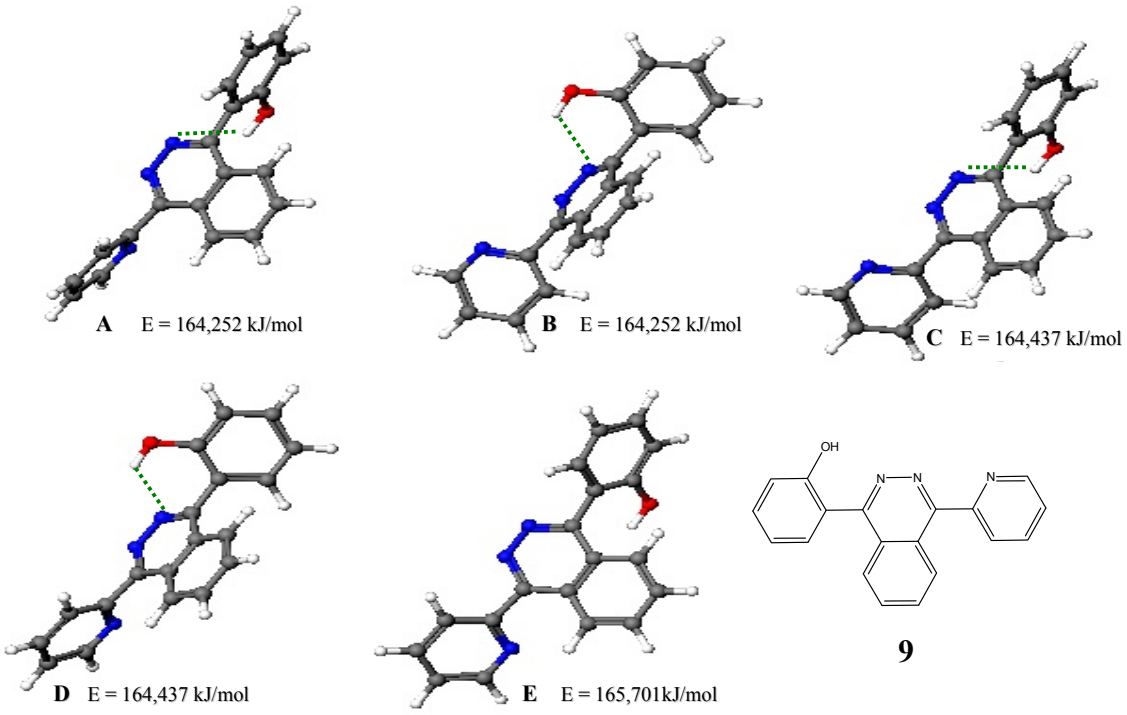


Figure 1. Conformers A-D of **9** forming intramolecular hydrogen bond (green dashed lines). The potential energy of each conformer is depicted under each one of them.

Interestingly, the H-bonded sites, particularly in conformers B and D, as well as those in conformers B and C, having the pyridine and phthalazine N atoms in-phase, are in effect bidentate sites, available for metal chelation or *inter*molecular H-bonding. Sites of this type are important for interaction with a protein's "hinge" region.[28]

In conclusion, an efficient protocol for the synthesis of regioselectively substituted phthalazines has been developed. Key features, integrated in the scheme, signifying its scope and potential are (a) the regioselectivity of substitution pattern of xanthone (**1**) that secures and extends regioselectivity for all ensuing structures and eventually the target phthalazines (not accessible by other methods) (b) the nucleophilically–triggered cleavage of xanthone **2**, (c) C-arylation of phenols[29] and thence molecular harpoons[30] (d) the oxidative rearrangement of hydrazones **4** to phthalazines **7-28** and (d) the effect of the nature and pattern of substitution on the isolation of a single or both possible phthalazine isomers. Credence to the value of this protocol are the simplicity and efficiency of its individual transformations.

It is clear at the outset that the derivatization potential of **1**, as exemplified by this protocol, sets the scene for various transformations on **7-28**, hence inviting for a diverse array of heterocyclic structures with a phthalazine scaffold. Work on this line will be reported in due course.

EXPERIMENTAL

Melting points were measured on an Electrothermal IA9000 Series apparatus and are uncorrected. Infrared spectra were recorded or an FT/IR-5300 spectrometer as KBr discs. Elemental analyses were performed on a Carlo Erba 1106 analyser. NMR spectra were measured on a Bruker Avance 400MHz and a Varian 600 MHz spectrometers, in $CDCl_3$ or DMSO-d_6 solutions. Mass spectra were recorded by Micromass - Platform LC or JEOL JMS-AX505W low or high resolution instruments. Analytical TLC was run on Fluka Silica Gel F254. Preparative Flash Chromatography was run on MERCK 9385 Silica Gel. Reagents were used as commercially purchased while solvents such as CH_2Cl_2, EtOAc, hexane and MeOH were purified and dried according to standard procedures.

Xanthones (2): prepared and identified as described in recent reports.[16,17]

2,2′Dihydroxybenzophenones (3): prepared and identified as described in recent reports.[19]

Hydrazones (4). Typical procedure: To a solution of **3** in isopropanol the hydrazide (3-fold excess) andpyridine (5-fold excess) were added and the mixture was heated for 12 h. Cooling to room temperature, addition of xylene and concentration *in vacuo* was followed by column chromatography (ethylacetate/petroleum ether 3:1) to give **4** as a pale yellow solid (yields 65-72%).

All compounds were identified by their IR or ^{1}H NMR spectra and were compared with literature data.[19]

4b: R_f = 0.43. Mp 137 ^{o}C. IR (KBr) 3317, 3280, 1649 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.97 (br, 6H, aromatic), 7.20 (dd, 1H, *J* = 7.6 Hz, aromatic), 7.10 (d, 1H, *J* = 8.0 Hz, aromatic), 7.05-6.95 (m, 3H, aromatic), 6.84 (dd, 1H, *J* = 7.67 Hz, aromatic), 6.81-6.72 (m, 1H, aromatic). ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.4, 161.5, 161.0, 155.7, 133.0, 132.5, 130.7, 130.0, 129.3, 128.9, 127.8, 127.6, 121.5, 120.0, 118.0, 117.9, 117.5. ESMS (M+H): *m/z* 333.

4c: R_f = 0.23. Mp 165 ^{o}C. IR (KBr): 3320, 3270, 1647 cm.$^{-1}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.06 (s, 1H, OH), 8.75-8.02 (m, 2H, aromatic), 7.55-7.47 (m, 2H, aromatic), 7.41 (dd, 1H, *J* = 7.72 Hz, aromatic), 7.29 (dd, 1H, *J* = 7.72 Hz, aromatic), 7.19 (d, 1H, *J* = 6.53 Hz, aromatic), 7.08 (d, 1H, *J* = 8.24 Hz, aromatic), 7.03-6.6.96 (m, 2H, aromatic), 6.85-6.74 (m, 3H, aromatic). ^{13}C NMR (100MHz, $CDCl_3$): δ 161.3, 161.1, 157.6, 155.6, 151.3, 147.6, 137.5, 133.0, 132.4, 131.0, 126.7, 124.5, 122.1, 121.4, 121.1, 118.4, 117.9, 117.6. ESMS (M+H): *m/z* 334.

***Ortho*-Diacylbenzenes (5)** (and (**6**)). Typical procedure: To a solution of 4 in THF, $Pb(OAc)_4$ (or $PhI(OAC)_2$) (in 25% excess) was added portiorwise, under stirring, over 15 min. at ca.0-5 ^{o}C. The mixture was, then, allowed to reach room temperature and was stirred for 3-4 h. Filtration, concentration of filtrate and column chromatography (ethylacetate/petroleum ether 5:1) gave **5** and **6** as off- white solids (yields 74-86%). All compounds were identified by their IR or ^{1}H NMR spectra and were compared with literature data.[19]

Where isomers are formed they may not be isolated and can be reacted as a mixture to generate phthalazine isomers (**7**) and (**8**).

5c: R_f = 0.53. Mp 142 °C. IR (KBr) 3241, 1687, 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H, OH), 8.07 (d, 1H, *J* = 7.91 Hz), 7.73-7.65 (m, 2H, aromatic), 7.61 (d, 1H, *J* = 7.17 Hz), 7.43-7.40 (m, 3H, aromatic), 7.22 (s, 1H, aromatic), 7.51-7.44 (m, 2H, aromatic), 7.00 (d, 1H, *J* = 8.55 Hz, aromatic), 6.82 (dd, 1H, *J* = 7.61 Hz, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 189.3, 162.2, 155.1, 151.6, 148.2, 143.8, 137.5, 133.9, 133.2, 133.0, 132.3, 127.7, 126.3, 124.1, 123.9, 120.5, 117.5. ESMS (M+H): *m/z* 304.

5d: R_f = 0.72. Viscous oil. IR (KBr) 1680, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1 7.64-7.40 (m, 4H, aromatic), 7.40-7.30 (m, 5H, aromatic), 6.90-6.70 (m, 4H, aromatic), 3.80 (s, 3H, OMe), ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 189.6, 161.1, 151.2, 138.7, 137.4, 135.6, 134.4, 133.6, 133.1, 132.3, 128.4, 127.1, 126.2, 124.1, 123.1, 121.6, 121.2, 119.0, 116.4, 57.6. ESMS (M+H): *m/z* 317.

1-Methyl-4-[2′-hydroxyphenyl]phthalazine (7): off-white microcrystals, Mp 168 °C. IR (KBr) ν_{max} cm^{-1}. 3350 (OH), 3045, 1605. ^1H NMR ($CDCl_3$) δ: 2.71, (s, 3H), 6.88-6.55 (m, 2H), 7.25-7.15 (m, 2H), 7.41 (d, 2H, *J* = 7.6 Hz), 7.65-7.60 (m, 2H), 7.75 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.1, 152.1, 133.5, 133.2, 130.1, 129.5, 129.1,128.8, 127.6, 126.5, 126.4,121.4, 120.6, 115.7, 44.2. ESMS (M+H): *m/z* 237. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.08; N, 11.86. Found: C, 76.03; H, 4.89; N, 11.70%.

1-Phenyl-4-[2′-hydroxyphenyl]phthalazine (8): off-white powder, Mp 222 °C. IR (KBr): 3360 (OH), 3030, 1602 cm^{-1}. ^1H NMR ($CDCl_3$)δ: 7.40 (s, 2H, *J* = 7.8 Hz) 7.66-7.55 (m, 3H), 7.82-7.44 (m, 3H), 8.40-7.90 (m, 2H), 10.21(brs, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.3, 152.2, 152.1, 133.4, 133.2, 133.1, 131.5, 130.1, 129.5, 129.2, 128.8, 127.6, 127.4, 126.6, 126.4,121.9, 121.4, 120.6, 117.9. ESMS (M+H): *m/z* 299. Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.53; H, 4.69; N, 9.38. Found: C, 80.25; H, 4.50; N, 9.10%.

1-[2′-Pyridyl]-4-[2′-hydroxyphenyl]phthalazine (9): Mp 172 °C. IR: 3360 (OH), 3082, 1602 cm^{-1}. ^1H NMR ($CDCl_3$). δ: 7.06-7.11 (m, 1H), 7.41-7.44 (m, 1H), 7.46-7.49 (m, 1H), 7.55-7.61 (m, 1H), 7.74 (dd, 1H, *J* = 7.81 Hz, *J* = 1.59 Hz), 7.93-8.01 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 155.6, 155.3, 152.3,149.3, 137.5, 133.5, 133.3, 131.2, 126.9, 126.8, 126.6, 124.8, 124.6,124.2,123.8, 123.4, 121.8, 120.7, 117.8. ESMS (M+H): *m/z* 300. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 76.25; H, 4.34; N, 14.04. Found: C, 76.02; H, 4.18; N, 13.86%.

1-Methyl-4-[2′-methoxyphenyl]phthalazine (10): viscous oil. IR (KBr): 3050, 1605 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.70 (t, 3H), 4.30 (q, 2H), 7.45 (d, 2H, *J* = 7.8 Hz), 7.70-7.60 (m, 3H), 7.85-7.75 (m, 3H), 8.50-7.90 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 159.8, 152.4, 133.2, 133.1, 131.4, 130.1, 129.4, 128.8, 127.6, 127.4, 126.4,126.2, 121.9, 120.5, 114.0, 82.0, 54.50, 44.0. ESMS (M+H): *m/z* 265. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.27; H, 6.06; N, 10.60. Found: C, 77.01; H, 5.88; N, 10.36%.

1-Phenyl-4-[2′-ethoxyphenyl]phthalazine (11): off-white powder, Mp 64 °C. IR (KBr): 3050, 1605cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.30 (t , 3H), 4.3 (m, 1H), 7.50 (d, 2H, *J* = 7.9 Hz), 7.65-7.60 (m, 3H), 7.80-7.75 (m, 3H), 8.40-7.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 155.3, 152.3, 133.4, 133.2, 133.1, 129.9, 129.6, 128.8, 127.6, 126.7, 126.4,126.2, 126.0, 121.8, 121.5, 121.2 ,120.0, 117.4, 115.5, 78.0, 43.0. ESMS (M+H): *m/z* 341. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.17; H, 5.88; N, 8.23. Found: C, 80.89; H, 5.68; N, 8.01%

1-[2′Pyridyl]-4-[2′-isopropoxyphenyl]phthalazine (12): off-white powder, Mp 61 °C. IR (KBr): 3030, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.20 (dd, 6H), 4.2 (m, 1H), 7.10-7.06 (m, 1H), 7.45-7.40 (m, 1H), 7.60-7.50 (m, 1H), 7.65-7.60 (m, 1H), 7.757.50 (dd, 1H, *J* = 7.9 Hz, *J* = 1.60 Hz), 8.0-7.90 (m, 2H), 8.13-8.06 (m, 1H), 8.20-8.15 (m, 1H), 8.50 (dd, 1H, *J* = 6.8 Hz, *J* = 2.4 Hz), 8.80 (dd, 1H, *J* = 4.8 Hz, *J* = 1.5Hz). ^{13}C NMR ($CDCl_3$) δ: 155.6, 155.3, 152.3, 149.3, 137.5, 133.5, 133.3, 131.2, 126.9, 126.7, 126.4, 124.8, 124.6,124.2, 123.8, 123.4,121.8 ,120.7, 117.8, 76.4, 44.5. ESMS (M+H): *m/z* 341. Anal. Calcd. for $C_{22}H_{19}N_2O$: C, 77.19; H, 5.55; N, 12.28. Found: C, 77.01; H, 5.39; N, 11.99%

1-Methyl-4-[2′-hydroxy-5′-nitrophenyl]phthalazine (13): pale yellow flakes, Mp 164 °C. IR (KBr): 3360 (OH), 1610, 152 5 (NO_2), 1340 (NO_2) cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$) δ: 2.80 (s, 3H), 8.23 (m, 2H), 8.73 (s, 1H), 6.90-6.60 (m, 2H), 7.25-7.20 (m, 2H), 7.75 (brs, 1H,OH). ^{13}C NMR (DMSO-*d*$_6$) δ: 155.2, 152.2, 148.3, 134.3, 133.5, 130.1, 129.4, 129.2, 128.6, 126.4, 124.2, 121.4, 120.5, 115.4, 44.5. ESMS (M+H): *m/z* 282. Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.91; N, 14.94. Found: C, 63.88; H, 3.69; N,14.77%.

1-Methyl-4-[2′-hydroxyphenyl]-6-nitrophthalazine (23): pale yellow flakes, Mp 136 °C. IR (KBr): 3400 (OH), 3040, 1530 (NO_2), 1340 (NO_2) cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$) δ: 2.80 (s, 3H), 6.96 (d, 2H, *J* = 8.1 Hz), 8.14 (d, 2H, *J* = 8.4 Hz), 7.65-7.60 (m, 2H), 7.45-7.40 (m, 2H), 11.10 (s, 1H, OH). ^{13}C NMR (DMSO-*d*$_6$) δ: 155.2, 148.3, 134.7, 133.2, 131.1, 130.1, 129.4, 129.2, 126.6, 126.4, 123.4, 121.5, 120.1, 115.4, 44.8. ESMS (M+H): m/z 282. Anal. Calcd for $C_{15}H_{14}N_3O_3$: C, 64.05; H, 3.91; N, 14.94. Found: C, 63.90; H, 3.71; N, 14.74%

1-Phenyl-4′-[2′-hydroxy-5′-nitrophenyl]phthalazine (14): Mp 178 °C. IR (KBr): 3423, 3078, 1620, 1510, 1340 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 3.06 (s, 3H), 7.07 (t, 1H, *J* = 7.4 Hz), 7.11 (d, 2H, *J* = 8.2 Hz), 7.42 (dd, 1H, *J* = 7.4 Hz, *J* = 1.5 Hz), 7.46-7.49 (m, 1H), 8.44 (d, 1H, *J* = 2.2 Hz), 8.54 (d, 1H, *J* = 9.0 Hz), 8.68 (dd, 1H, *J* = 9.0 Hz, *J* = 2.2 Hz), 9.99 (s, 1H). ^{13}C NMR (DMSO-*d*$_6$) δ: 155.3, 149.4, 133.5, 133.3, 131.5, 131.2, 130.1, 129.5, 129.2, 128.8, 128.1, 127.2, 126.8, 126.5, 126.4, 126.1, 124.8, 124.2, 120.6, 117.9. ESMS (M+H): *m/z* 282. Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.06; H, 3.91; N, 14.94%. Found: C, 63.88; H, 3.74; N, 14.65%

1-Methyl-4-[2′-hydroxy-5′-bromophenyl]phthalazine (15): off-white needles, Mp 116 °C. IR (KBr): 3360, 3040, 1610cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.70 (s, 3H), 6.90-6.60 (m, 2H), 7.25-7.20 (m, 2H),

7.50-7.40 (m, 2H), 7.55(s, 1H),7.75(s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.2, 152.3, 133.6, 133.2, 131.5, 130.0, 129.5, 128.6, 127.0, 126.6, 126.4, 122.6, 121.0, 115.6, 45.6. ESMS (M+H): *m/z* 316. Anal. Calcd for $C_{15}H_{11}BrN_2O$: C, 57.14; H, 3.49; N, 8.88. Found: C, 56.90; H, 3.28; N, 8.70%

1-Phenyl-4-[2′-hydroxy-5′-bromophenyl]phthalazine (16): white powder, Mp 127 °C. IR (KBr): 3365, 3040, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.90(d, 1H, *J* = 8.10 Hz), 7.40-7.30 (m, 2H), 7.25-7.15 (m, 2H), 7.20 (d, 2H, *J* = 8.0 Hz), 7.80 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.2, 152.3, 133.4, 133.2, 131.4, 130.0, 129.6, 129.4, 128.8, 127.4, 126.4, 126.2, 123.4, 123.1, 122.6, 121.0, 120.0, 117.4, 115.5. ESMS (M+H): *m/z* 378. Anal. Calcd for $C_{20}H_{13}BrN_2O$: C, 63.66; H, 3.44; N, 7.42. Found: C, 63.50; H, 3.28; N, 7.30%.

1-Phenyll-4-[2′-hydroxy-5′-bromophenyl]-6-bromophthalazine (17): white needles, Mp 153 °C. IR (KBr): 3360, 3040, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.85 (d, 1H, *J* = 7.90 Hz), 7.45-7.30 (m, 3H), 7.20 (d, 2H, *J* = 7.85 Hz), 7.95 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.2, 152.1, 133.4, 133.2, 133.1, 131.5, 130.0, 129.4, 128.6, 127.4, 127.0, 126.4, 126.2, 123.4, 123.1, 122.6, 121.0, 120.1, 117.4, 115.4. ESMS (M+H): *m/z* 457. Anal. Calcd for $C_{20}H_{12}Br_2N_2O$: C, 52.63; H, 2.63; N, 6.14. Found: C, 52.50; H, 2.48; N, 5.98%.

1-Phenyll-4-[2′-hydroxy-3′-methylphenyl]phthalazine (18): white microcrystals, Mp 76 °C. IR (KBr): 3360, 3035, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.60(s, 3H), 6.68-6.80 (m, 3H), 7.80-7.75(m, 2H), 8.40-8.0 (m, 2H), 7.25-7.20 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 155.2, 152.3, 137.8, 133.4, 133.2, 133.0, 129.2, 128.6, 128.4, 127.4, 126.6, 126.2, 126.0, 125.5, 123.0, 122.4, 121.2, 117.4, 115.5, 55.2. ESMS (M+H) : *m/z* 313. Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.76; H, 5.12; N, 8.97. Found: C, 80.60; H, 4.98; N, 8.81%.

1-Methyl-4-[2′-hydroxy-3′-methylphenyl]-6-methyphthalazine (19): off-white powder, Mp 94 °C. IR (KBr): 3280, 3040, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.55 (s, 3H), 2.65 (m, 3H), 6.90-6.80 (m, 3H), 7.60-7.50 (m, 3H), 7.25-7.20 (m, 5H), 7.80 (brs, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.3, 152.2, 137.6, 133.4, 133,1, 131.0, 130.1, 129.4, 128.8, 128.4, 127.2, 126.6, 126.2, 125,4, 123.4, 122.6, 121.0, 117.5, 115.6, 55.0. ESMS (M+H): *m/z* 327. Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.98; H, 5.52; N, 8.58. Found: C, 80.75; H, 5.40; N, 8.38%.

1-Phenyll-4-[2′-hydroxy-3′-iodophenyl]-8-iodophthalazine (20): off-white amorphous solid, Mp 228 °C. IR (KBr): 3380, 3040, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.80 (d, 1H, *J* = 8.0 Hz), 7.40-7.30 (m, 3H), 7.20 (d, 2H, *J* = 7.9 Hz), 7.25-7.20 (m, 5H), 7.85 (brs, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.3, 152.1, 137.2, 133.6, 133.2, 131.4, 130.1, 129.6, 129.2, 128.8, 127.0, 126.6, 126.4, 123.4, 122.6, 121.4, 120.4, 115.5, 94.5, 87.0. ESMS (M+H): m/z 551. Anal. Calcd for $C_{20}H_{12}I_2N_2O$: C, 43.63; H, 2.18; N, 5.09. Found: C, 43.40; H, 2.02; N,4.95%.

1-Phenyll-4-[2′-hydroxy-5′-phenylphenyl]phthalazine (21): off-white microcrystals, Mp 231 °C. IR (KBr):3360, 3030, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.30-7.25 (m, 5H), 7.25-7.20 (m, 5H), 7.25-7.15 (m,

3H), 7.15-6.80 (m, 4H), 7.70 (brs, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 155.3, 152.3, 152.2, 133.6, 133.4, 133.1, 131.4, 130.2,130.0, 129.6, 129.4, 129.0, 128.6, 128.4, 127.2, 126.6, 126.4, 126.2, 126.0, 123.4, 122.6, 121.0, 120.4, 117.5, 115.5. ESMS (M+H): *m/z* 375. Anal. Calcd for $C_{26}H_{18}N_2O$: C, 83.42; H, 4.81; N, 7.48. Found: C, 83.20; H, 4.68; N, 7.28%.

1-Phenyl-4-[2′-hydroxy-5′-phenylphenyl]-6-phenylphthalazine (22): off-white amorphous solid, Mp 246 ^{o}C. IR (KBr):3360, 3030, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.25-7.20 (m, 5H), 7.30-7.25 (m, 5H), 7.20-7.15 (m, 5H), 7.15-7.0 (m, 3H), 7.10-6.90 (m, 3H), 7.70 (s,1H,OH). ^{13}C NMR ($CDCl_3$) δ: 155.1, 138.4, 133.8, 133.4, 133.2, 133.1, 131.4, 131.1, 130.6, 130.2, 130.0, 129.8, 129.6, 129.2, 128.8, 128.4, 127.6, 127.2, 127.0, 126.4, 126.0, 123.4, 122.4, 121.6,121.4, 121.1, 120.8, 117.4, 117.2, 115.5. 115.0. ESMS (M+H): *m/z* 451. Anal. Calcd for $C_{32}H_{22}N_2O$: C, 85.33; H, 4.88; N, 6.22. Found: C, 85.15; H, 4.72; N, 6.01%.

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