A convenient synthesis of 4-diarylmethyl-, 4-(α-hydroxy-α-aryl/naphthyl)methyl- and 4-(benzoyl/naphthanoyl)-1-(2H)-phthalazinones from ninhydrin

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Refluxing of 2,2-diaryl-1,3-indanediones in hydrazine hydrate for a brief period affords 4-diarylmethyl-1-(2H)-phthalazinones in very high yield. A series of 4-(α-hydroxy-α-aryl/naphthyl)methyl- and 4-(benzoyl/naphthanoyl)-1-(2H)-phthalazinones also have been synthesized simply by stirring 2-hydroxy-2-aryl/naphthyl-1,3-dioxoindanes in hydrazine hydrate (99%) at room temperature in very high yields. All the ninhydrin adducts, 2,2-diaryl-1,3-indanediones and 2-hydroxy-2-aryl/naphthyl-1,3-dioxoindanes are prepared by stirring ninhydrin and the appropriate aromatic hydrocarbons in acid medium.

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The diverse biological activities of various functional derivatives of 4-substituted alkyl-1-(2H) phthalazinones are well known. It has been reported that various functional derivatives of 4-substituted alkyl-1-(2H)phthalazinone-2-acetates, such as corresponding acids, amides, and hydrazides have variety of biological activities like hypnotic,1 anticonvulsive,1 antibacterial,2 antifungal,3 antianaphilactic,3 nootropic,3 and inhibition of aldose reductase6 etc. The phthalazinone nucleus has been proved to be a versatile system in medicinal chemistry. Various derivatives of it are well recognized pharmacophores that show a wide range of biological activities. The development of new and efficient methodologies for the synthesis of such potentially bioactive phthalazinone derivatives are important. Despite the useful nature of phthalazinones, there are only a limited number of synthetic approaches to achieve substitution on these rings and, therefore, functionalisation of the nucleus continues to be of synthetic interest.

Very few methods are known in literature for the synthesis of 4-phenyl- and 4-substituted alkyl-1-(2H)phthalazinones and their 2-acetate derivatives.5,11 Generally 4-alkyl-1-(2H)phthalazinones are synthesized by refluxing 2-acyl benzoic acids with hydrazine hydrate (Scheme I, Eqn-1). However, this method is not suitable for the synthesis of compounds like 4-diarylmethyl-, 4-(α-hydroxy-α-aryl/naphthyl)-methyl- and 4-(benzoyl/naphthanoyl)-1-(2H) phthalazinones, as corresponding starting material viz., 2-substituted benzoic acids A, B and C (Scheme I) are not easily available. Moreover, B and C type of compounds may not produce the desired 4-substituted phthalazinones upon refluxing with hydrazine hydrate due to other possible side reactions. From synthetic point of view, 4-(α-hydroxy-α-aryl/naphthyl)methyl- and 4-(benzoyl/naphthanoyl)-1-(2H)phthalazinones are important as the α-hydroxy and keto groups can be easily elaborated further. In connection with our ongoing research to find out suitable and facile methodologies for the synthesis of potentially bioactive phthalazinone and phthalazine derivatives from the easily available starting material, we have recently reported a novel synthesis of 4-diarylmethyl-1-(2H)phthalazinones in a communication.12 In the present paper we wish to present a full account of the facile synthesis of 4-diarylmethyl-, 4-(α-hydroxy-α-aryl/naphthyl)methyl- and 4-(benzoyl/naphthanoyl)-1-(2H)phthalazinones starting from easily available ninhydrin.

Results and Discussion

It was realized that the chemical reaction of 2,2-diaryl-1,3-indanediones and 2-hydroxy-2-aryl-1,3-indanediones with hydrazine hydrate might be similar to that of 2-acylbenzoic acid. In case of ninhydrin, the advantage is that the C-2 position of it can be suitably arylated in acid medium to derive the ninhydrin adducts. Various reports established that the C-2 position of ninhydrin is very reactive to nitrogen-, sulfur-,
The highly electrophilic character of the C-2 position of ninhydrin has been exploited to prepare various ninhydrin adducts. The substrates 2,2-diaryl-1,3-indanediones 1a-e (Scheme II) were prepared from ninhydrin following the reported procedure. It was observed that due to steric reason, the electrophilic attack of the carbocation at the C-2 position of ninhydrin takes place to the para position of the monosubstituted aromatic hydrocarbons such as toluene, halobenzenes etc. Other substrates, 1f and 1g were prepared by stirring the appropriate hydrocarbons (Ar-H, anisole, 1,3-dimethoxybenzene) with ninhydrin in acid medium for 1 hr. Then it was possible to derive 2,2'-diaryl-1,3-indanediones such as 3a and 3b (Scheme II), where the two aryl groups are different, with a modified technique. The first arylation of ninhydrin was carried out by stirring sterically bulky hydrocarbons such as 1,2,3-trimethoxybenzene and 1,3-dimethoxybenzene with ninhydrin in acid medium for 0.5 hr so that the reaction would stop at the monoaarylated stage of ninhydrin (Scheme II, step a). The second arylation of the monoaarylated ninhydrin 2a and 2b was carried out with sterically small hydrocarbon such as anisole (Scheme II, step b).

It was observed by us that 4-diarylmethyl-1-(2H) phthalazinones can be prepared conveniently starting from easily prepared 2,2-diaryl-1,3-indanediones such as 1 and 3 (Scheme II). We found that 2,2-diaryl-1,3-indanediones (Scheme II) react with hydrazine hydrate (99%) under refluxing conditions for about 15 min to furnish 4-diarylmethyl-1-(2H)phthalazinones 4 and 5 in very high yields. With same aryl groups phthalazinones 4, as expected, are achiral, whereas for the presence of two different aryl groups on the C-α of the phthalazinones 5 formed are potentially resolvable racemic mixture. A proposed mechanism for the reaction is depicted in Scheme III. The nucleophilic attack of hydrazine to either of the carbonyl groups of 2,2-diaryl-1,3-indanediones produce the open chain hydrazides 6, which undergo a subsequent intramolecular nucleophilic attack on the other CO, followed by dehydration to give the final products 4-diarylmethyl-1-(2H) phthalazinones 4 and 5. The proposed mechanism of the reaction has a very
interesting analogy to the deprotection step of the Gabriel synthesis.

Next we thought that it is possible to expand the scope and prospect of the reaction further. Keeping this in view we have carried out similar type of reaction with some monoarylated ninhydrin adducts. We observed that 2-hydroxy-2-aryl/naphthyl-1,3-dioxo-indanes 7a-d (Scheme IV) derived from ninhydrin, can be easily converted to 4-(α-hydroxy-α-aryl/naphthyl)methyl-1-(2H)phthalazinones 9a-d, simply by stirring in hydrazine hydrate (99%) for 7-8 hr at room temperature. In all these cases yields are high and the phthalazinones formed are potentially resolvable racemic mixture. The 2-hydroxy-2-aryl/naphthyl-1,3-
dioxindanes 7e-h, which prefer to remain in intramolecular hemiketal form. 8e-h (Scheme IV) also undergo similar type of reactions only by stirring in hydrazine hydrate (99%) for 1 hr at room temperature. However, the corresponding phthalazinones 9e-h were not possible to isolate. Interestingly, the corresponding oxidized 4-(benzoyl/naphthoyl)-1-(2H) phthalazinones, 10e-h were obtained as the final products (Scheme IV). It is observed that in general the 2-hydroxy-2-aryl/naphthyl-1,3-indanediones, 7e-h, derived from the condensation of ninhydrin with hydroxy phenols and naphthols, produce the 4-(benzoyl/naphthoyl)substituted phthalazinones.

The monoarylated ninhydrin adducts 7a-d were prepared by stirring the appropriate hydrocarbons (1,3-dimethoxybenzene, 1,4-dimethoxybenzene, 1,2,3-trimethoxybenzene and β-naphthyl methyl ether etc.) with ninhydrin in a mixture of acetic acid and conc. H$_2$SO$_4$. Since the polymethoxyaryl- and methoxynaphthyl groups are sterically bulky, the reaction would stop after monoaarylation of ninhydrin. The adducts 7c-h were prepared by the acid catalyzed condensation of hydroxyl phenols and naphthols such as α-naphthol, β-naphthol, o-cresol, p-cresol etc., with ninhydrin. In this case, it is found that the electrophilic attack of the ninhydrin carboxonium at C-2, takes place to the ortho position of −OH group. The $^1$H and $^13$C NMR spectra of the 2-hydroxy-2-(orthohydroxyphenyl/naphthyl)-1,3-indanediones 8e-h display four separate proton signals (expected as 2H (m) or 2C each)], representative of 1,2-disubstituted benzene moieties of 1,3-indanedione part. These observations were in consonance with unsymmetrical structures and adduced that they remain in intramolecular hemiketal form 8e-h (Scheme IV).
Conclusion

In summary, we have developed a novel two-step synthetic pathway for various potentially bio-active 4-diaryl-methyl-, 4-(α-hydroxy-α-arylnaphthyl)methyl- and 4-(benzoyl/naphthanoyl)-1(2H)phthalizinones starting from ninhydrin. This paper describes the conversion of a series of C-2 arylated ninhydrin derivatives to ring-expanded 4-substituted phthalalazines through reaction with hydrazine. The advantages of this procedure reside in a short synthetic sequence, in the high chemical yields, in easier operating conditions, and in the commercial availability of ninhydrin and aromatic hydrocarbons.

Experimental Section

In this report all the mps are uncorrected and the yields refer to pure isolated product.

General procedure for preparation of 2,2-diaryl-1,3-indanediones 1a-g. The ninhydrin adducts 2,2-diaryl-1,3-indanediones 1a-e were prepared from ninhydrin following the reported procedure.15

Preparation of 1f and 1g. The appropriate substrate (Ar-H, anisole or 1,3-dimethoxy benzene, 4.2 mmole), was added to a solution of ninhydrin (0.25 g, 1.4 mmole) in a mixture of acetic acid (10 mL) and conc. H2SO4 (0.5 to 1.0 mL). The whole reaction mixture was stirred at room temperature for 1 hr. The solid product was filtered out and washed thoroughly with acetic acid and then with water. The product was purified by silica-gel column chromatography using acetone as the eluent (yield-85%).

For the 2nd arylation of 2a and 2b, the hydrocarbon Ar-H, anisole (4.2 mmole) was added to a solution of monooarylated ninhydrin adducts 2a and 2b (1.4 mmole) in a mixture of acetic acid (10 mL) and conc. H2SO4 (3-4 mL). The mixture was stirred at 25°C for 6 hr and then poured over ice. The product was extracted into CHCl3 and the organic phase was washed twice with water, twice with brine, further washed with water, dried over Na2SO4, and concentrated in vacuo. The resulting solid was further purified by crystallization from CHCl3.

2-(2,3,4-Tri-methoxyphenyl)-2-(4-methoxyphenyl)-1,3-indanediones 3a-c. White solid, yield 70%; mp 159-60°C; IR(KBr): 1709 cm⁻¹; 1H NMR (300 MHz in CDCl3): δ 8.01 (m, 2H), 7.80 (m, 2H), 7.46 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 8.7 Hz, 1H), 6.34 (d, J = 8.7 Hz, 1H), 3.80 (s, OCH3), 3.77 (s, OCH3), 3.54 (s, OCH3); 13C NMR (75 MHz in CDCl3): δ 200.2, 159.7, 154.6, 150.3, 141.4, 140.9, 135.1 (d, 2C), 130.3 (d, 2C), 127.0, 126.0 (d), 125.9, 123.4 (d, 2C), 114.5 (d, 2C), 106.7 (d), 65.6, 60.5 (q), 59.5 (q), 56.0 (q), 55.2 (q); Anal. Caled for C32H20O6: C, 71.76; H, 5.06. Found: C, 71.62; H, 5.17%.

2-(2,3,4-Di-methoxyphenyl)-1,3-indanediones 3d-f. White solid, yield 75%; mp 219-20°C; IR(KBr): 1710 cm⁻¹; 1H NMR (300 MHz in CDCl3): δ 8.01 (m, 2H), 7.87 (m, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.55 (dd, J = 8.8, 2.4 Hz, 1H), 6.28 (d, J = 8.8 Hz, 1H), 3.72 (s, OCH3), 3.43 (s, OCH3), 3.41 (s, OCH3); 13C NMR (75 MHz in CDCl3): δ 199.8, 158.1, 156.9, 140.8, 135.7 (d), 134.9, 134.2 (d), 132.8 (d), 130.1 (d), 123.3 (d), 123.0 (d), 114.3 (d), 105.9, 99.7, 96.5, 56.6 (q), 55.4 (q); Anal. Caled for C33H18O6...
General procedure for preparation of 3-diarylmethyl-1-(2H)phthalazinones 4a-g, 5a and 5b. The appropriate substrate 1a-g, 3a and 3b (1.4 mmole) was added to hydrazine hydrate (10 mL, 99%) and the mixture refluxed for about 15 min. The cooled reaction mixture was acidified with 6M HCl to pH 6. The solid product separated was extracted with CHCl₃ and worked-up as usual. The residue from the CHCl₃ layer was purified by column chromatography over silica gel and CHCl₃ eluate fractions afforded pure solid products 4a-g, 5a and 5b which were crystallized from CHCl₃-light-petroleum.

4-Diphenylmethylnaphthalalazine 4a. White solid, yield 92%; mp 220-21°C; IR (KBr): 1652, 3170 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 10.8 (s, NH), 8.46 (m, 1H), 7.72 (m, 3H), 7.34-7.20 (m, 10H), 5.97 (s, H-α); Anal. Caled for C₃₂H₂₆N₂O: C, 80.74; H, 5.16; N, 8.97. Found: C, 80.84; H, 5.07; N, 8.81%.

4-[(2,3,4-tri-methoxyphenyl)-(4-methoxyphenyl)]-1-(2H)phthalazinone 4c. White solid, yield 94%; mp 228-29°C; IR (KBr): 1643, 3151 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 10.61 (s, NH), 8.47 (m, 1H), 7.81 (m, 1H), 7.70 (m, 2H), 7.18 (s, 8H), 5.93 (s, H-α), 3.33 (s, CH₃ × 2); ¹³C NMR (75 MHz in CDCl₃): δ 160.0, 148.4, 138.2, 136.4, 133.3 (d), 131.0 (d), 130.1, 129.2 (d), 128.4, 127.0 (d), 125.2 (d), 52.5 (d), 29.9 (q); Anal. Caled for C₂₂H₂₂N₂O: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.10; H, 6.08; N, 8.38%.

4-[(2,3,4-tri-methoxyphenyl)-(4-methoxyphenyl)]-1-(2H)phthalalazine 4d. White solid, yield 93%; mp 254-55°C; IR (KBr): 1659, 3170 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 10.8 (s, NH), 8.46 (m, 1H), 7.73 (m, 3H), 7.28 (apparent d, J = 8.6 Hz, 4H), 7.13 (apparent d, J = 8.6 Hz, 4H), 5.90 (s, H-α); ¹³C NMR (75 MHz in CDCl₃): δ 159.9, 147.2, 139.1, 133.6 (d), 133.2, 131.5 (d), 130.6 (d), 129.7, 128.9 (d), 128.5, 127.3 (d), 124.8 (d), 52.0 (d); Anal. Caled for C₂₂H₂₂Cl₂Cl₃N₂O: C, 66.15; H, 3.70; Cl, 18.60; N, 7.35. Found: C, 66.06; H, 3.78; Cl, 18.52; N, 7.29%.

4-Di-para-iodophenylmethyl-1-(2H)phthalalazine 4e. White solid, yield 91%; mp 279-80°C; IR (KBr): 1649, 3172 cm⁻¹.

4-Di-para-methoxyphenylmethyl-1-(2H)phthalalazine 4f. White solid, yield 92%; mp 226-27°C; IR (KBr): 1667, 3176 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 10.4 (br, NH), 8.45 (m, 1H), 7.79 (m, 1H), 7.71 (m, J = 8.6 Hz, 2H), 7.12 (apparent d, J = 8.7 Hz, 4H), 6.84 (apparent d, J = 8.7 Hz, 4H), 5.88 (s, H-α), 3.77 (s, 2 × OCH₃); ¹³C NMR (75 MHz in CDCl₃): δ 159.9, 158.6, 148.6, 133.4 (d), 133.3, 131.1 (d), 130.2, 130.1 (d), 128.5, 127.1 (d), 125.2 (d), 114.1 (d), 55.2 (d), 51.7 (q); Anal. Caled for C₂₂H₂₂N₂O₃: C, 74.17; H, 5.41; N, 7.52. Found: C, 74.14; H, 5.37; N, 7.48%.

4-Di-para-dimethoxyphenylmethyl-1-(2H)phthalalazine 4g. White solid, yield 90%; mp 222-23°C; IR (KBr): 1647, 3153 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 9.79(s, NH), 8.41 (m, 1H), 7.71 (m, 3H), 6.84 (d, J = 7.1 Hz, 2H), 6.47 (dd, J = 2.1 Hz, J = 9.9 Hz, 2H), 6.38 (d, J = 2.4 Hz, 2H), 6.36 (s, H-α), 3.77 (s, 2 × OCH₃), 3.74 (s, 2 × OCH₃); ¹³C NMR (75 MHz in CDCl₃): δ 160.0, 157.7, 149.8, 133.3 (d), 130.8 (d), 130.4 (d), 126.8 (d), 125.3 (d), 121.9, 104.2 (d), 99.1 (d), 55.7 (d), 55.5 (q), 55.3 (q); Anal. Caled for C₂₂H₂₂N₂O₃: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.51; H, 5.67; N, 6.59%.

4-(2,3,4-tri-methoxyphenyl)-(4-methoxyphenyl)methyl-1-(2H)phthalalazine 5a. White solid, yield 75%; mp 271-72°C; IR (KBr): 1648, 3148 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 10.39 (s, NH), 8.38 (m, 1H), 7.80 (m, 3H), 7.11 (d, J = 7.4 Hz, 2H), 6.81 (d, J = 7.4 Hz, 2H), 6.59 (d, J = 8.7 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 6.17 (s, H-α), 3.82 (s, OCH₃), 3.78 (s, OCH₃), 3.71 (s, OCH₃), 3.59 (s, OCH₃); ¹³C NMR (75 MHz in CDCl₃): δ 160.1, 158.6, 152.8, 151.0, 149.1, 142.4, 133.3 (d), 132.6, 131.0 (d), 130.4 (d), 130.0, 128.4, 127.9 (d), 126.9 (d), 125.1 (d), 124.1 (d), 114.0 (d), 106.9, 60.9 (q), 56.8 (q), 56.6 (d), 56.1 (q), 45.4 (q); Anal. Caled for C₂₂H₂₂N₂O₃: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.59; H, 5.67; N, 6.55%.

General procedure for preparation of 2-hydroxy-2-arylnaphthalalazine 7a-d. The appropriate substrate (Ar-H, 1,3-dimethoxybenzene, 1,4-dimethoxybenzene, 1,2,3-tri-methoxybenzene, β-naphthyl methyl ether etc., 4.2 mmole), was added to a solution of ninhydrin (0.25 g, 1.4 mmole) in a mixture of acetic acid (10 mL) and conc. H₂SO₄ (0.5 to 1.0 mL). The whole reaction mixture was stirred at room temperature for 0.5 hr. The solid product separ-
rated was filtered out and washed thoroughly with water. The product was purified by silica-gel column chromatography using aceton as the eluent.

2-Hydroxy-2-(2,4-dimethoxyphenyl)-1,3-indanedione 7a. Reddish solid, yield 84%; mp 149-50°C; IR (KBr): 1706, 3430 cm⁻¹; ¹H NMR (300 MHz in acetone-d₆): δ 7.98 (s, 4H), 7.70 (d, J = 8.5 Hz, 1H), 6.60 (dd, J = 8.5 Hz, 2.3Hz, 1H), 6.39 (d, J = 2.3 Hz, 1H), 3.50 (s, 2 × OCH₃); ¹³C NMR (75 MHz in acetone-d₆): δ 200.2, 162.0, 156.9, 141.2, 136.8 (d, 2C), 129.4 (d), 124.0 (d, 2C), 120.0, 105.9 (d), 98.9 (d), 76.6, 55.6 (q), 55.4 (q); Anal. Caled for C₂₉H₂₀O₄: C, 75.12; H, 4.97. Found: C, 74.87; H, 4.80%

2-Hydroxy-2-(2,5-dimethoxyphenyl)-1,3-indanedione 7b. Green solid, yield 71%; mp 147-48°C; IR (KBr): 1705, 3369 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 8.01 (m, 2H), 7.87 (m, 2H), 7.34 (d, J = 3.0 Hz, 1H), 6.78 (dd, J = 8.7 Hz, 3.0Hz, 1H), 6.64 (d, J = 8.7 Hz, 1H), 3.88 (s, 1H), 3.75 (s, OCH₃), 3.26 (s, OCH₃); ¹³C NMR (75 MHz in CDCl₃): δ 198.4, 154.8, 149.4, 140.8, 135.9 (d, 2C), 127.3, 128.3 (d, 2C), 115.3 (d), 113.8 (d), 112.7 (d), 55.9 (q, 2C); Anal. Caled for C₂₉H₂₀O₄: C, 74.99; H, 3.97. Found: C, 74.87; H, 4.10%

2-Hydroxy-2-(2,3,4-trimethoxyphenyl)-1,3-indanedione 7c. White solid, yield 86%; mp 174-75°C; IR (KBr): 1706, 3330 cm⁻¹; ¹H NMR (300 MHz in acetone-d₆): δ 8.01 (s, 4H), 7.49 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 3.82 (s, OCH₃), 3.64 (s, OCH₃), 1.25 (s, OCH₃); ¹³C NMR (75 MHz in acetone-d₆): δ 198.9, 155.0, 149.6, 141.7, 141.3, 136.7 (d, 2C), 125.0, 124.2 (d, 2C), 123.2 (d), 108.0 (d), 76.7, 60.0 (q), 59.8 (q), 56.3 (q); Anal. Caled for C₂₉H₂₀O₄: C, 65.85; H, 4.91. Found: C, 65.75; H, 4.80%

2-Hydroxy-2-(2-methoxy-1-naphthyl)-1,3-indanedione 7d. Yellow solid, yield 80%; mp 219-20°C; IR (KBr): 1712, 3489 cm⁻¹; ¹H NMR (300 MHz in acetone-d₆): δ 9.43 (d, J = 9.0 Hz, 1H), 8.00 (m, 4H), 7.86 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.48 (m, 1H), 7.38 (m, 1H), 7.23 (d, J = 9.0 Hz, 1H), 6.26 (s, 1H), 4.05 (br. s, 1H), 3.49 (s, OCH₃); ¹³C NMR (75 MHz in acetone-d₆): δ 198.3, 154.7, 141.4, 136.9 (d, 2C), 135.2, 132.3 (d, 1H), 129.1 (d), 128.7 (d), 128.6, 124.8 (d, 2C), 115.4 (d), 80.6, 56.9 (q); Anal. Caled for C₂₉H₂₀O₄: C, 75.46; H, 4.43. Found: C, 75.56; H, 4.54%

General procedure for the preparation of 2-hydroxy-2-aryl/naphthyl-1,3-indanediones 8e-h (intramolecular hemi-ketal form). The appropriate substrate (α-naphthol, β-naphthol, p-cresol, p-cresol etc., 4.2 mmole) was added to a solution of ninhydrin (0.25 g, 1.4 mmole) in acetic acid (10 ml). The reaction mixture was stirred at room temperature for 0.5 hr. The solid product separated was filtered out and washed thoroughly with acetic acid and then with water. The product was purified by silica-gel column chromatography using aceton as the eluent.

2-Hydroxy-2-(1-hydroxy-2-naphthyl)-1,3-indanedione 8e. Yellow solid, yield 75%; mp 216-17°C; IR (KBr): 1709, 3370 cm⁻¹; ¹H NMR (300 MHz in acetone-d₆): δ 8.09 (d, J = 6.6 Hz, 1H), 7.95 (apparent d, J = 5.4 Hz, 1H), 7.84-7.79 (m, 2H), 7.72 (d, J = 6.6 Hz, 1H), 7.55 (m, 2H), 7.44 (m, 3H); ¹³C NMR (75 MHz in acetone-d₆): δ 197.6, 155.2, 150.9, 138.3 (d), 137.6, 136.6, 132.9 (d), 130.0 (d), 129.1 (d), 127.7 (d), 124.9 (d), 123.8 (d), 123.4 (d), 123.3 (d), 122.4, 120.4, 85.5; Anal. Caled for C₂₉H₂₀O₄: C, 74.99; H, 3.97. Found: C, 75.12; H, 4.10%

2-Hydroxy-2-(2-hydroxy-1-naphthyl)-1,3-indanedione 8f. Yellow solid, yield 78%; mp 225-26°C; IR (KBr): 1712, 3489 cm⁻¹; ¹H NMR (300 MHz in acetone-d₆): δ 8.60 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.84 (t, J = 7.3 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.56 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 8.9 Hz, 1H), 3.30 (br. s, 2 × OH); ¹³C NMR (75 MHz in acetone-d₆): δ 199.9, 157.4, 150.5, 138.4 (d), 136.7, 134.8 (d), 132.9 (d), 131.8 (d), 130.4, 129.1 (d), 127.0 (d), 126.1 (d), 125.5 (d), 125.0 (d), 117.8, 114.2 (d), 112.0, 87.1; Anal. Caled for C₂₉H₂₀O₄: C, 74.99; H, 3.97. Found: C, 74.87; H, 4.13%

8g and 8h were also prepared from ninhydrin following the reported procedure.¹⁶a

General procedure for the preparation of 4-(α-hydroxy-α-aryl/naphthyl)methyl-1-(2H)phthalazinones 9a-d. The appropriate substrate 7a-d (1.4 mmole) was added to hydrazine hydrate (10 mL, 99%) and the mixture was stirred for 7-8 hr at room temp. Then the reaction mixture was acidified with 6N HCl to pH 6. The solid product separated was filtered and washed thoroughly with water. Crystallization of the crude products from EtOH afforded the pure solid products 9a-d.

4-(α-Hydroxy-α-aryl/naphthyl)methyl-1-(2H)phthalazinone 9a. White solid, yield 86%; mp 208-09°C; IR (KBr): 1659, 3178 cm⁻¹; ¹H NMR (300 MHz in DMSO-d₆): δ 12.44 (s, NH), 8.22-8.11 (m,
4-(α-Hydroxy-α-2,5-dimethoxyphenyl)methyl-1-(2H)phthalazinone 9b. White solid, yield 84%; mp 216-17°C; IR (KBr): 1673, 3061, 3180 cm⁻¹; ¹H NMR (300 MHz in DMSO-d₆): δ 12.14 (s, NH), 8.22 (br. s, 2H), 7.90 (apparent d, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.40 (br. s, H-α), 6.34 (m, 1H), 5.56 (d, J = 7.5 Hz, H-α), 5.28 (d, J = 7.2 Hz, H-α), 3.69(s, OCH₃), 3.34 (s, OCH₃); Anal. Calcd for C₁₇H₁₆N₂O₄: C, 63.15; H, 5.28; Found: C, 63.54; H, 5.22; N, 8.87%.

4-(α-Hydroxy-α-2,3,4-tri-methoxyphenyl)methyl-1-(2H)phthalazinone 10e. Yellow solid, yield 86%; mp 178-79°C; IR (KBr): 1695, 3285 cm⁻¹; ¹H NMR (300 MHz in CDCl₃): δ 12.04 (s, NH), 8.39 (d, J = 9.0 Hz, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.94-7.76 (m, 4H), 7.62-7.52 (m, 2H), 7.38 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H); Anal. Calcd for C₁₉H₁₂N₂O₄: C, 68.65; H, 4.27; N, 9.99; Found: C, 68.65; H, 4.27; N, 10.08%.

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References