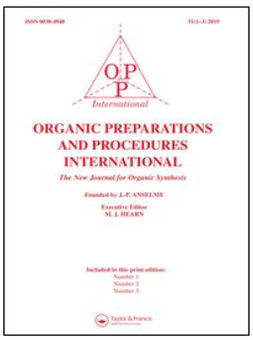

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EXPERIMENTAL PAPER

DABCO-catalyzed Five-component Domino Protocol for the Synthesis of Novel Benzo[*a*]pyrazolo[4',3':5,6]pyrano[2,3-*c*]phenazines in PEG-400 as an Efficient Green Reaction Medium

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Currently green chemistry techniques are attracting wide attention due to their environmental, health, and economic benefits. These green techniques include the use of polyethylene glycol (PEG-400), multi-component reactions (MCRs), microwave reactions, aqueous media, reusable catalysts and ionic liquids.[1–5]

In this context, multi-component domino reactions (MDRs) in which more than two components are combined in a single synthetic operation to generate the desired product, without the isolation of any intermediate, have considerable interest as parts of an efficient bond-forming strategy.[6–10] The development of novel MDRs using PEG-400 solvent medium for the design and synthesis of new bioactive heterocycles is an important topic in the drug discovery process.[11–14]

Phenazines are a large group of *N*-containing heterocycles, including more than 100 different compounds of natural origin and over 6000 synthetic compounds. Phenazine natural products are isolated as secondary metabolites from *Pseudomonas*, *Streptomyces*, and a number of other bacterial genera from soil or marine habitats.[15–18] Phenazines possess significant biological properties including antibiotic, antimicrobial, antimalarial, antiparasitic and antitumor activities.[15–18] Synthetic phenazines, such as NC-190, XR-11576 and XR-5944 (Figure 1) were reported to display antiproliferative effects against a variety of human cancer cell lines.[19–23] Pyridophenazinediones and their derivatives have also shown antitumor activity.[24,25] Fluorescent phenazine derivatives have been applied as photo-sensitizers in photodynamic therapy (PDT)[26] in which the combination of light and photo-sensitizer produces highly reactive oxygen species near the tumor to selectively destroy the targeted tissue.

Pyrazoles have become increasingly important to the pharmaceutical, chemical, and agricultural industries in recent years.[27–29] These five membered heterocycles possess antimicrobial, anticancer, analgesic, anti-inflammatory, antitubercular, antidepressant, antihelmintic, anticonvulsant, antipyretic, anti-oxidant and herbicidal properties.[30,31]

The pyran moiety embraces a number of important pharmaceuticals and natural products such as alkaloids, carbohydrates, polyether antibiotics, iridoids and

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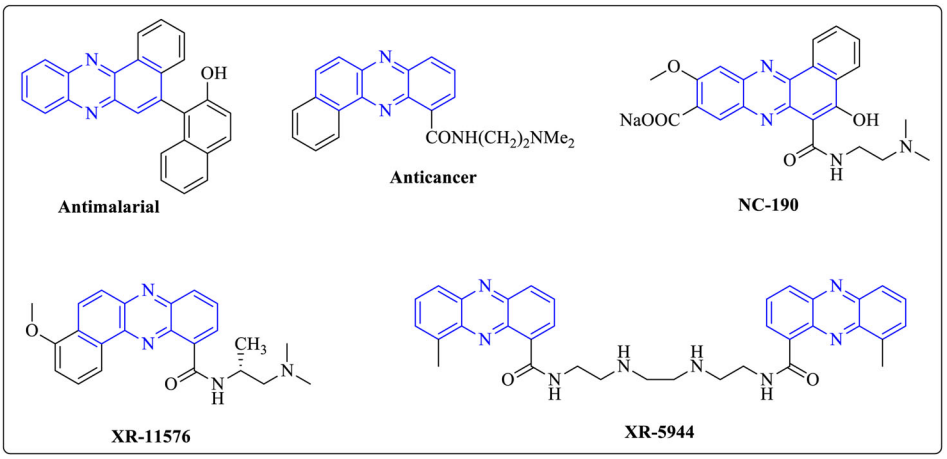


Figure 1. Biologically active phenazine derivatives.

pheromones.[32] Pyran and fused 4*H*–pyran derivatives have attracted much attention because of their antibacterial,[33] antifungal,[34] antimicrobial,[35] anticoagulant[36] and antitumor[37] activities. They could potentially be useful in the treatment of neurodegenerative diseases, including Parkinson's and Alzheimer's diseases, Down's syndrome, and AIDS-associated dementia, as well as for the treatment of schizophrenia.[38] Optical brighteners, laser dyes, fluorescence markers, cosmetics, and potent biodegradable agrochemicals[39] are well known pyrans.

Accordingly, heterocycles having benzo[*a*]phenazine, pyrazole and pyran moieties are important targets in synthetic organic chemistry. Some biologically active pyrano-fused benzophenazine and pyrazole derivatives[40–44] are shown in Figure 2.

In continuing our studies on the green synthesis of heterocyclic compounds,[45,46] we now report an environmentally friendly method for the synthesis of novel benzo[*a*]pyrano[2,3-*c*]phenazine and pyrazole analogues **8** through a domino, five-component condensation reaction between 2-hydroxynaphthalene-1,4-dione **1**, aromatic 1,2-diamines **2**, hydrazine **4**, ethyl acetoacetate **5**, and benzaldehydes **7** catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) in polyethylene glycol (PEG-400) at 70 °C (Scheme 1).

To investigate the best conditions for the synthesis of our new phenazines, we carried out the five-component domino reaction between **1** (1 mmol), *o*-phenylenediamine **2a** (1 mmol), hydrazine hydrate **4a** (1.2 mmol), **5** (1 mmol) and 4-chlorobenzaldehyde **7a** (1 mmol) in EtOH as a model. To minimize the formation of byproducts, the 2-hydroxynaphthalene-1,4-dione and *o*-phenylenediamine were mixed under reflux conditions until, in less than 5 minutes, an orange solid of benzo[*a*]phenazin-5-ol **3a** was formed without using any catalyst. Separately, hydrazine hydrate and ethyl acetoacetate were mixed at 70 °C under solvent-free conditions to produce a white solid of 3-methyl-2-pyrazolin-5-one **6a** (<5 min). Eventually, the obtained 3-methyl-2-pyrazolin-5-one and 4-chlorobenzaldehyde were added into the initial reaction system and the reaction mixture was refluxed. The desired product **8a** was not obtained when the reaction was carried out under catalyst-free conditions for 90 minutes (Table 1, entry 1). However, **8a** was obtained in 71% yield when the reaction was conducted in the presence of triethylamine (20 mol%) in EtOH (Table 1, entry 2).

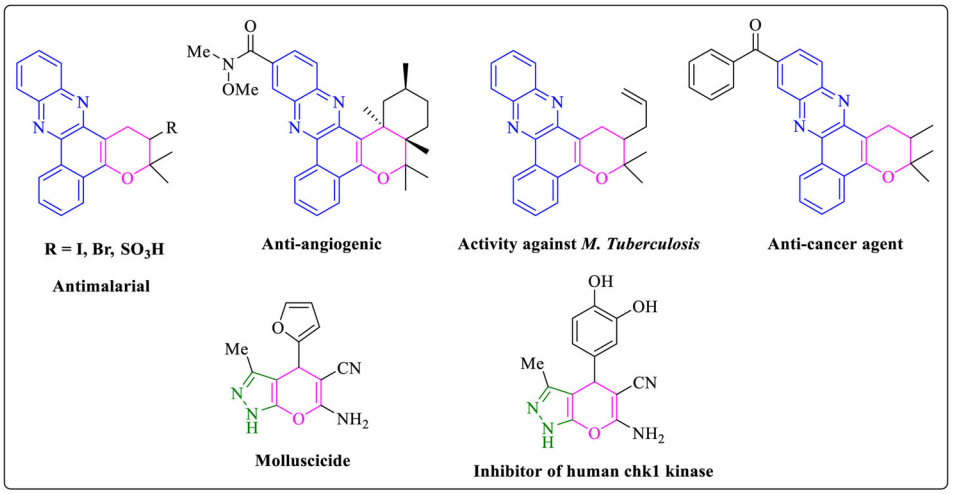
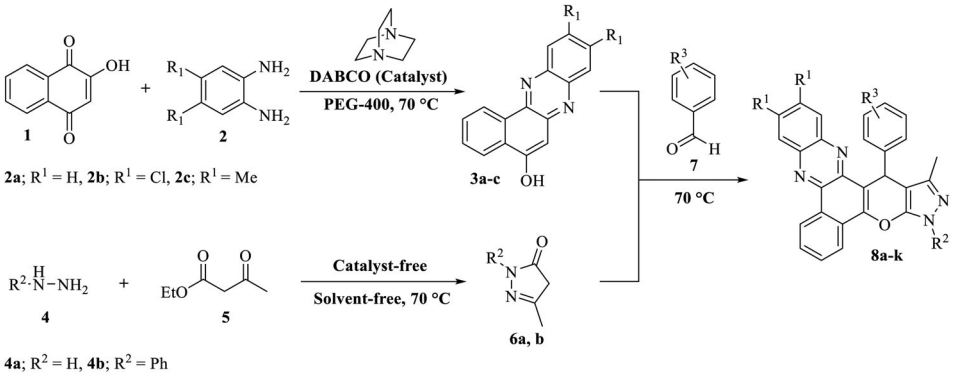


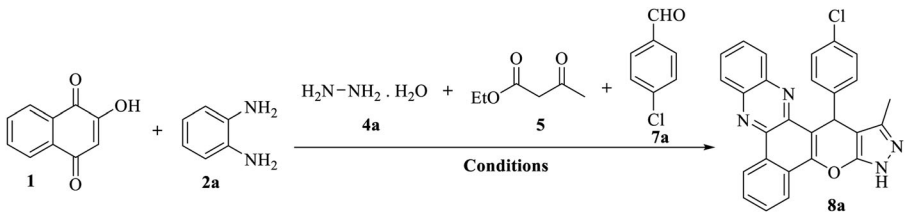
Figure 2. Biologically and pharmaceutically active pyrano-fused benzophenazine and pyrazole derivatives.



Scheme 1. DABCO-catalyzed domino synthesis of 1-methyl-15-aryl-3,15-dihydrobenzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazines (**8a-k**) using PEG-400 medium.

Several catalysts were subsequently evaluated in the reaction, including triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), L-proline, *p*-toluenesulfonic acid (PTSA) and DABCO; these were all added in substoichiometric amounts (20 mol%) and the reactions were carried out in ethanol under reflux conditions. The reaction went smoothly in the presence of DABCO affording higher yield (75%) within 60 min (Table 1, entry 6). To select the best solvent for the reaction, the synthesis of compound **8a** was examined in water and PEG-400 (Table 1, entries 7 and 8). Higher yields were obtained when the reaction was carried out in PEG-400 (Table 1, entry 8). The reaction was performed at different temperatures to determine the optimum reaction temperature. The reaction was conducted with 20 mol% DABCO in PEG-400 at 90, 70 and 50 °C, and the desired product **8a** was formed in yields of 82%, 80% and 73%, respectively (Table 1, entries 8-10). Finally, the loading of DABCO was selected, and 10 mol% of DABCO was the optimal (Table 1, entries 9, 11, 12).

Table 1. Optimization of reaction conditions for the synthesis of compound **8a**[a].



Entry	Catalyst	Reaction conditions	Time (min)	Yield (%)[b]
1	No catalyst	EtOH, Reflux	90	NR
2	Et_3N (20 mol%)	EtOH, Reflux	60	71
3	DBU (20 mol%)	EtOH, Reflux	60	53
4	L-Proline (20 mol%)	EtOH, Reflux	60	58
5	PTSA (20 mol%)	EtOH, Reflux	60	64
6	DABCO (20 mol%)	EtOH, Reflux	60	75
7	DABCO (20 mol%)	H_2O, Reflux	60	62
8	DABCO (20 mol%)	PEG-400, 90 °C	60	82
9	DABCO (20 mol%)	PEG-400, 70 °C	60	80
10	DABCO (20 mol%)	PEG-400, 50 °C	90	73
11	DABCO (10 mol%)	PEG-400, 70 °C	90	82
12	DABCO (5 mol%)	PEG-400, 70 °C	90	67

[a]Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), *o*-phenylenediamine (1 mmol), hydrazine hydrate (1.2 mmol), ethyl acetoacetate (1 mmol) and 4-chlorobenzaldehyde (1 mmol) in the presence of different catalytic systems under various conditions.
[b]Isolated yields.

After extensive screening, we thus found that the optimized best yields and time profiles were obtained with 10 mol% of DABCO in PEG-400 at 70 °C, which furnished **8a** in 82% yield within 90 minutes (Table 1, entry 11).

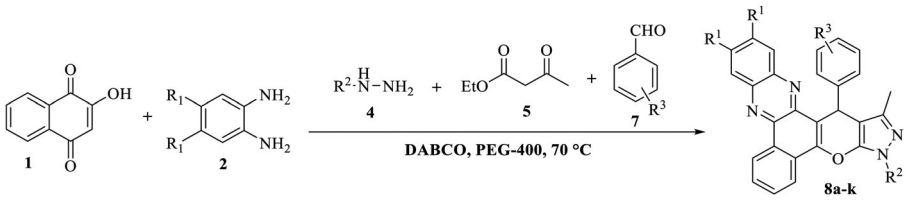
To explore the scope of the reaction further, the study was extended to various benzene-1,2-diamines, hydrazines and different aromatic aldehydes using the optimized conditions, and the results are presented in Table 2. All the reactions were complete in 90-120 minutes and resulted in the formation of the target structures in good yields (mean 78%).

The structures of all the newly synthesized benzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazines were deduced by their satisfactory IR, ^{1}H, ^{13}C NMR, and elemental analysis data. The mass spectra of these compounds further displayed molecular ion peaks at the appropriate *m/z* values.

For example, the ^{1}H NMR spectrum of **8a** exhibited one single sharp line at δ 1.87, characteristic for the methyl group; the CH proton (methine group) was observed at δ 5.42 as a singlet. The aromatic protons appeared as a mixture of doublets and multiplets around δ 7.02–9.26 and one singlet was observed for the NH group at δ 12.01. The ^{13}C NMR spectrum of **8a** showed the characteristic signals due to the methyl and methine carbons at δ 10.4 and 42.3 and the carbons of the olefinic and aromatic groups resonated at δ 111.5–160.2. The structural assignment of compound **8a** was supported by its IR spectrum. The NH, aliphatic, C=N and aromatic groups exhibited strong absorption bands at 3137, 2930, 1623, 1591 and 1479 cm^{-1}.

Since polyethylene glycol (PEG-400) has emerged as a green reaction medium with unique properties, we were able to use PEG-400 as a recyclable medium instead of

Table 2. Domino five-component synthesis of benzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazine derivatives[a].



Entry	R^1	R^2	R^3	Product	Time (min)	Yield[b] (%)
1	H	H	4-Cl	**8a**	90	82
2	H	H	4-NO_2	**8b**	90	84
3	H	H	4-CN	**8c**	90	79
4	H	H	4-Me	**8d**	120	81
5	H	H	4-OMe	**8e**	120	75
6	H	Ph	4-Cl	**8f**	120	77
7	H	Ph	4-Me	**8g**	120	72
8	Cl	H	4-Cl	**8h**	120	78
9	Cl	H	4-Me	**8i**	120	75
10	Me	Ph	4-Cl	**8j**	120	79
11	Me	H	4-NO_2	**8k**	90	81

[a]Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), hydrazine (1.2 mmol), ethyl acetoacetate (1 mmol), benzaldehydes (1 mmol) and DABCO (10 mol%) in PEG-400 at 70 °C.
[b]Isolated yields.

volatile organic solvents and we did this without the addition of any organic co-solvent. We have also examined the recyclability of the PEG-400 during the synthesis of **8a**. After completion of the reaction, the reaction mixture was quenched with water and filtered for separation of the crude product. The aqueous filtrate was extracted with diethyl ether to remove any organic impurities. The aqueous layer was distilled at 90 °C for 2 h to remove water and the separated PEG-400 was reused directly for the next run. As shown in Figure 3, only a small loss in the yield of the products was observed through the first four runs (Figure 3).

A detailed reaction mechanism for the domino cyclocondensation of benzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazines **8** using DABCO is outlined in Scheme 2. The primary condensation of 2-hydroxynaphthalene-1,4-dione **1** with benzene-1,2-diamine **2** in the presence of DABCO gives benzo[*a*]phenazin-5-ol **3**. Then, hydrazine **4** condenses with ethyl acetoacetate **5** to generate the pyrazolone ring **6**, which is then isomerized to intermediate **9**. In this mechanism, DABCO is a catalyst to form the olefin **10**, which is readily formed *in situ* from the Knoevenagel condensation of aromatic aldehyde **7** with pyrazole **9**. In the presence of DABCO, benzo[*a*]phenazin-5-ol **3** converts to its corresponding enolate form **11**, to react easily with olefin **10** (Michael addition) and give intermediate **12**, which then produces **8**.

To conclude, we have introduced an environmentally benign approach for the efficient synthesis of novel benzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazines in high yields via a five-component domino protocol by using DABCO as a mild, effective, non-toxic and inexpensive solid base catalyst and PEG-400 as a recyclable medium without the addition of any organic co-solvent. The promising points for the presented methodology are environmental acceptability, economic viability, and compliance with

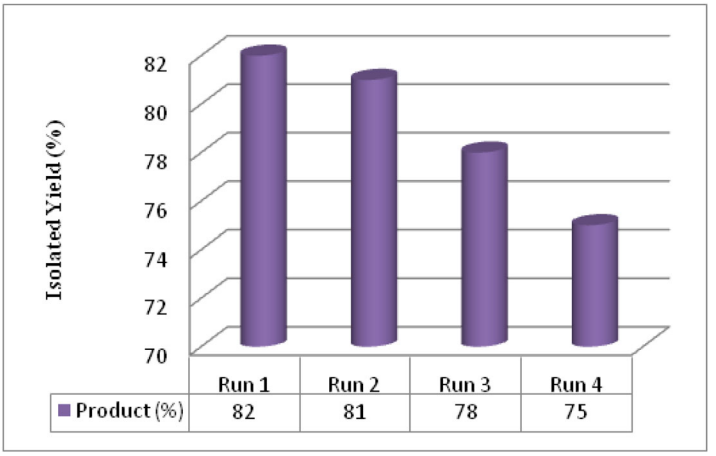


Figure 3. Recycling and reuse of PEG-400.

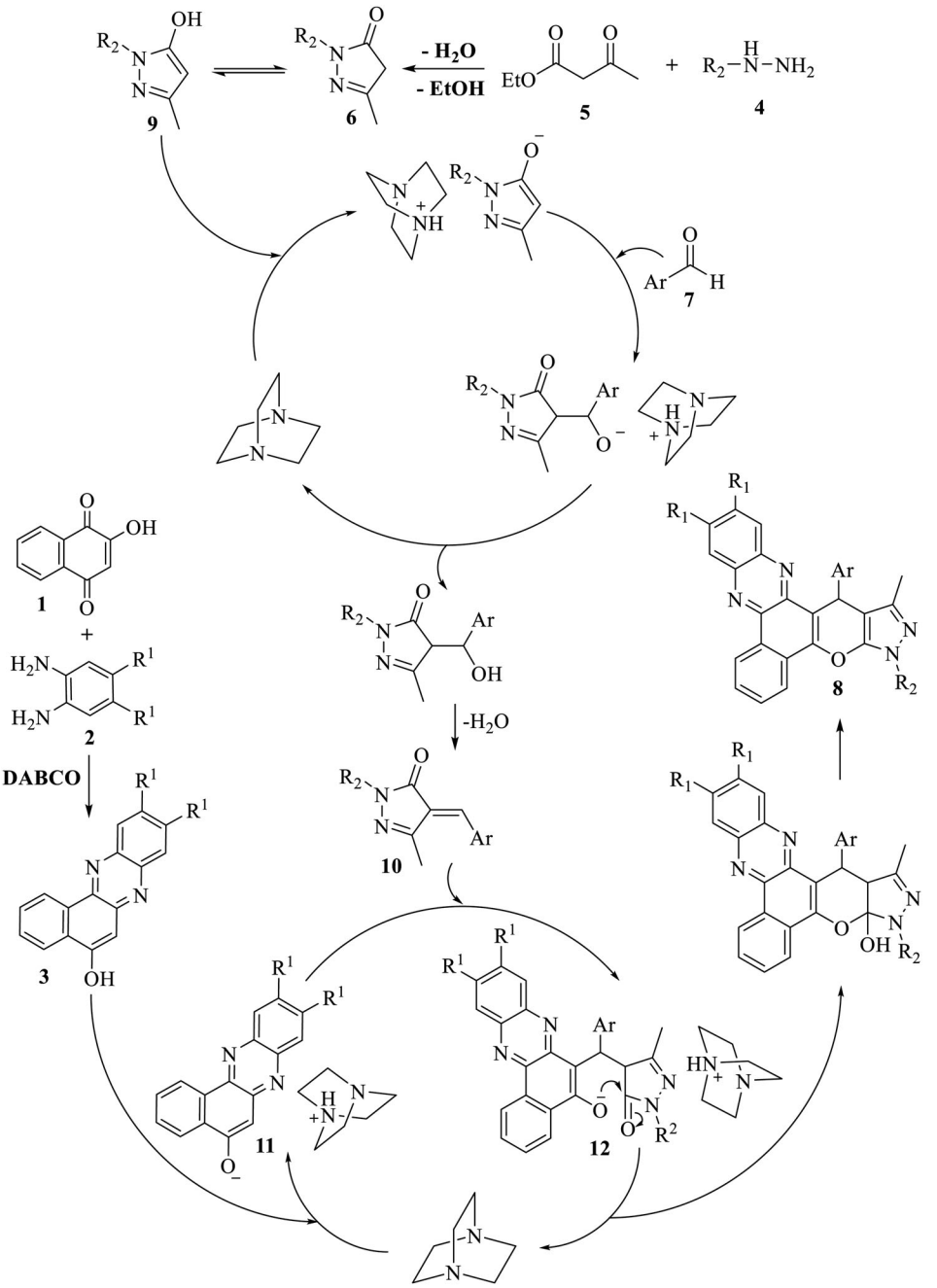
green chemistry protocols. Our new compounds are likely to have biological activities, which will be reported in due course.

Experimental section

All reagents and solvents were purchased from Merck or Aldrich and used without further purification. Melting points and IR spectra of all compounds were determined on an Electrothermal 9100 apparatus and Shimadzu IR-470 spectrometer. The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-300 spectrometer operating at 300 MHz for ^{1}H analysis and 75 MHz for ^{13}C analysis using TMS as an internal standard. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer at the Central Research Facility of the Iranian Petroleum Company. Thin-layer chromatography (TLC) was performed on silica-gel Polygram SILG/UV 254 plates and the solvent for TLC was *n*-hexane/ethyl acetate, 2:1. An approximate R_f value for a typical product was 0.6.

General procedure for the synthesis of novel benzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazine derivatives (8a-k)

2-Hydroxynaphthalene-1,4-dione **1** (1 mmol), benzene-1,2-diamine **2** (1 mmol) and DABCO (10 mol%) were mixed in a 50 mL round-bottomed flask containing 5 mL of PEG-400 and the contents were stirred magnetically in an oil-bath maintained at 70 °C until, in less than 5 minutes, an orange solid of benzo[*a*]phenazin-5-ol **3** was formed. Separately, hydrazine **4** and ethyl acetoacetate **5** were mixed at 70 °C under solvent-free conditions to produce a white solid of pyrazolone **6** (< 5 min). Finally, the obtained pyrazolone **6** and aryl aldehydes were added into the initial reaction system containing **3**. The reaction mixture was heated further for the appropriate time (Table 2). Upon the completion of the reaction, monitored by TLC analysis, the reaction mixture was cooled



Scheme 2. Proposed mechanism for the synthesis of benzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazine derivatives.

to room temperature and was quenched with H_2O (5 mL). The precipitate formed was collected by filtration at the pump, then the separated product was washed with water. The resulting compound was subsequently recrystallized from hot EtOH to give the pure product **8**. The spectral and analytical data are presented below.

15-(4-Chlorophenyl)-1-methyl-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazine (8a)

Yellow powder; yield 0.367 g (82%), mp 293-295 °C; IR (KBr): ν_{max} = 3337, 2930, 1623, 1591, 1479, 1406, 1385, 1350, 1290, 1165, 1076, 968, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 3H, CH_3), 5.42 (s, 1H, CH), 7.03 (d, 2H, J = 7.8 Hz, Ar-H), 7.18 (d, 2H, J = 7.8 Hz, Ar-H), 7.54-7.58 (m, 2H, Ar-H), 7.82-7.86 (m, 3H, Ar-H), 8.11-8.13 (m, 2H, Ar-H), 9.23-9.26 (m, 1H, Ar-H), 12.01 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4 (CH_3), 42.3 (CH), 111.5, 116.4, 123.5, 124.6, 126.1, 126.6, 127.4, 128.7, 129.0, 129.2, 129.6, 129.8, 130.2, 131.2, 132.7, 140.1, 141.3, 141.7, 142.8, 145.5, 146.8, 157.4 and 160.2 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 448 (M^+, 4).

Anal. Calcd for $C_{27}H_{17}ClN_4O$: C, 72.24; H, 3.82; N, 12.48. Found: C, 72.51; H, 4.06; N, 12.80.

1-Methyl-15-(4-nitrophenyl)-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazine (8b)

Yellow powder; yield 0.386 g (84%), mp 281-282 °C; IR (KBr): ν_{max} = 3345, 2932, 1628, 1583, 1483, 1401, 1388, 1348, 1293, 1165, 1057, 961, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.89 (s, 3H, CH_3), 5.48 (s, 1H, CH), 6.87 (d, 2H, J = 8.1 Hz, Ar-H), 7.06 (d, 2H, J = 8.1 Hz, Ar-H), 7.38-7.43 (m, 3H, Ar-H), 7.69-7.71 (m, 2H, Ar-H), 8.05-8.09 (m, 1H, Ar-H), 8.24-8.26 (m, 1H, Ar-H), 9.28-9.31 (m, 1H, Ar-H), 12.19 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7 (CH_3), 43.4 (CH), 110.4, 118.6, 122.7, 123.5, 125.1, 126.8, 127.2, 128.4, 129.1, 129.5, 129.9, 130.0, 130.3, 131.1, 132.2, 140.3, 140.8, 141.3, 142.8, 145.3, 146.5, 157.5 and 160.7 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 459 (M^+, 1).

Anal. Calcd for $C_{27}H_{17}N_5O_3$: C, 70.58; H, 3.73; N, 15.24. Found: C, 70.92; H, 3.86; N, 15.45.

4-(1-Methyl-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazin-15-yl)benzonitrile (8c)

Yellow powder; yield 0.347 g (79%), mp 287-289 °C; IR (KBr): ν_{max} = 3327, 2928, 2187, 1625, 1592, 1458, 1402, 1384, 1350, 1292, 1167, 1053, 972, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 3H, CH_3), 5.54 (s, 1H, CH), 7.27-7.29 (m, 2H, Ar-H), 7.41-7.43 (m, 4H, Ar-H), 7.89-8.01 (m, 4H, Ar-H), 8.22-8.24 (m, 1H, Ar-H), 9.16-9.18 (m, 1H, Ar-H), 12.10 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.1 (CH_3), 42.6 (CH), 113.4, 116.7, 119.5, 123.2, 125.7, 126.2, 126.4, 128.2, 128.8, 129.1, 129.3, 129.5, 129.9, 130.2, 131.4, 132.5, 140.4, 141.5, 141.8, 142.4, 145.5, 147.0, 157.8 and 161.1 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 439 (M^+, 7).

Anal. Calcd for $C_{28}H_{17}N_5O$: C, 76.52; H, 3.90; N, 15.94. Found: C, 76.77; H, 4.08; N, 15.73.

1-Methyl-15-(p-tolyl)-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazine (8d)

Yellow powder; yield 0.347 g (81%), mp 299-301 °C; IR (KBr): ν_{max} = 3335, 2930, 1630, 1587, 1474, 1399, 1385, 1351, 1290, 1161, 1053, 975, 754 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$): δ 1.77 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 5.38 (s, 1H, CH), 7.07 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.20 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.48-7.53 (m, 3H, Ar-H), 7.94-8.00 (m, 3H, Ar-H), 8.16-8.19 (m, 1H, Ar-H), 9.26-9.29 (m, 1H, Ar-H), 11.86 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.8, 20.52 ($2CH_3$), 43.1 (CH), 113.8, 121.4, 123.7, 125.2, 125.7, 127.3, 128.7, 129.1, 129.4, 129.6, 129.8, 130.1, 131.4, 132.5, 133.3, 140.4, 141.3, 141.8, 142.4, 145.5, 146.7, 157.0 and 160.6 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 428 (M^+, 5).

Anal. Calcd for $C_{28}H_{20}N_4O$: C, 78.49; H, 4.70; N, 13.08. Found: C, 78.31; H, 4.88; N, 12.96.

15-(4-Methoxyphenyl)-1-methyl-3,15-dihydrobenzo[a]pyrazolo[4',3':5,6]pyrano [2,3-c]phenazine (8e)

Yellow powder; yield 0.333 g (75%), mp 274-276 °C; IR (KBr): ν_{max} = 3353, 2935, 1632, 1595, 1458, 1422, 1383, 1328, 1269, 1168, 1053, 986, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.56 (s, 1H, CH), 7.41-7.44 (m, 5H, Ar-H), 7.90-8.02 (m, 4H, Ar-H), 8.09-8.12 (m, 1H, Ar-H), 8.40-8.43 (m, 1H, Ar-H), 9.17-9.19 (m, 1H, Ar-H), 12.23 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2 (CH_3), 57.3 (OCH_3), 44.1 (CH), 112.6, 117.2, 123.8, 124.5, 126.1, 126.4, 127.3, 128.2, 129.4, 129.6, 129.9, 130.2, 131.4, 132.2, 132.9, 140.5, 141.3, 142.1, 142.8, 145.7, 146.4, 157.8 and 161.1 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 444 (M^+, 3).

Anal. Calcd for $C_{28}H_{20}N_4O_2$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.87; H, 4.62; N, 12.34.

15-(4-Chlorophenyl)-1-methyl-3-phenyl-3,15-dihydrobenzo[a]pyrazolo[4',3':5,6] pyrano[2,3-c]phenazine (8f)

Yellow powder; yield 0.404 g (77%), mp 243-245 °C; IR (KBr): ν_{max} = 2931, 1628, 1591, 1467, 1410, 1392, 1335, 1277, 1151, 1069, 975, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 3H, CH_3), 5.64 (s, 1H, CH), 7.05 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.15 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.48-7.54 (m, 5H, Ar-H), 7.79-7.84 (m, 3H, Ar-H), 8.03-8.06 (m, 2H, Ar-H), 8.21-8.23 (m, 1H, Ar-H), 8.49-8.52 (m, 1H, Ar-H), 9.29-9.32 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.3 (CH_3), 44.1 (CH), 115.4, 117.8, 121.4, 122.5, 123.2 124.1, 126.4, 127.1, 127.4, 128.2, 128.4, 129.2, 129.4, 129.7, 129.8, 130.1, 130.6, 131.4, 132.7, 133.8, 140.2, 141.4, 141.8, 142.5, 145.2, 145.9, 152.8 and 158.1 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 525 (M^+, 6).

Anal. Calcd for $C_{33}H_{21}ClN_4O$: C, 75.50; H, 4.03; N, 10.67. Found: C, 75.76; H, 3.93; N, 10.94.

1-Methyl-3-phenyl-15-(p-tolyl)-3,15-dihydrobenzo[a]pyrazolo[4',3':5,6]pyrano [2,3-c]phenazine (8g)

Yellow powder; yield 0.363 g (72%), mp 259-260 °C; IR (KBr): ν_{max} = 2930, 1623, 1587, 1471, 1407, 1385, 1332, 1258, 1150, 1065, 988, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 5.59 (s, 1H, CH), 6.81-6.83 (m, 2H, Ar-H), 6.98-

7.01 (m, 2H, Ar-H), 7.56-7.60 (m, 4H, Ar-H), 7.90-8.04 (m, 5H, Ar-H), 8.26-8.29 (m, 2H, Ar-H), 8.49 (d, 1H, $J = 7.5$ Hz, Ar-H), 9.27-9.30 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.0, 20.78 ($2CH_3$), 43.6 (CH), 116.2, 117.5, 120.2, 121.6, 123.4 124.6, 125.2, 127.5, 127.9, 128.1, 128.6, 129.1, 129.4, 129.7, 129.9, 130.1, 130.4, 131.2, 132.6, 132.9, 140.3, 141.2, 141.5, 142.8, 145.3, 146.1, 152.4 and 157.4 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 504 (M^+, 1).

Anal. Calcd for $C_{34}H_{24}N_4O$: C, 80.93; H, 4.79; N, 11.10. Found: C, 81.19; H, 4.85; N, 11.31.

11,12-Dichloro-15-(4-chlorophenyl)-1-methyl-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazine (8h)

Yellow powder; yield 0.403 g (78%), mp 307-309 °C; IR (KBr): ν_{max} = 3320, 2928, 1627, 1591, 1469, 1408, 1372, 1335, 1290, 1162, 1070, 976, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H, CH_3), 5.40 (s, 1H, CH), 6.98 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.12 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.41-7.44 (m, 2H, Ar-H), 7.62 (s, 1H, Ar-H), 7.82-7.85 (m, 1H, Ar-H), 8.12-8.14 (m, 1H, Ar-H), 9.25-9.28 (m, 1H, Ar-H), 12.11 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.6 (CH_3), 42.8 (CH), 112.6, 117.3, 123.5, 125.2, 126.3, 127.1, 128.5, 129.1, 129.4, 129.6, 129.9, 130.2, 131.6, 132.8, 137.2, 140.6, 141.7, 142.5, 145.4, 147.6, 148.6, 158.3 and 160.4 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 517 (M^+, 5).

Anal. Calcd for $C_{27}H_{15}Cl_3N_4O$: C, 62.63; H, 2.92; N, 10.82. Found: C, 62.50; H, 3.09; N, 10.98.

11,12-Dichloro-1-methyl-15-(p-tolyl)-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazine (8i)

Yellow powder; yield 0.373 g (75%), mp 269-271 °C; IR (KBr): ν_{max} = 3357, 2926, 1625, 1594, 1438, 1412, 1358, 1333, 1268, 1145, 1069, 972, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 5.47 (s, 1H, CH), 7.47-7.52 (m, 4H, Ar-H), 7.97-8.01 (m, 1H, Ar-H), 8.04-8.08 (m, 1H, Ar-H), 8.46-8.48 (m, 1H, Ar-H), 8.53 (s, 1H, Ar-H), 8.59 (s, 1H, Ar-H), 9.31-9.34 (m, 1H, Ar-H), 12.08 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.6, 20.50 ($2CH_3$), 42.6 (CH), 114.2, 117.6, 122.2, 124.9, 126.6, 127.3, 128.4, 129.2, 129.4, 129.7, 129.9, 130.1, 131.4, 132.6, 138.1, 140.0, 141.5, 142.3, 145.2, 147.3, 148.7, 158.0 and 161.1 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 497 (M^+, 7).

Anal. Calcd for $C_{28}H_{18}Cl_2N_4O$: C, 67.61; H, 3.65; N, 11.26. Found: C, 67.83; H, 3.74; N, 11.50.

15-(4-Chlorophenyl)-1,11,12-trimethyl-3-phenyl-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6]pyrano[2,3-c]phenazine (8j)

Yellow powder; yield 0.437 g (79%), mp 252-253 °C; IR (KBr): ν_{max} = 2930, 1630, 1594, 1482, 1407, 1389, 1346, 1295, 1164, 1058, 972, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (s, 3H, CH_3), 2.53 (s, 6H, $2CH_3$), 5.38 (s, 1H, CH), 6.85 (d, 2H, $J = 7.8$ Hz, Ar-H),

7.03 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.44-7.47 (m, 4H, Ar-H), 7.86 (s, 1H, Ar-H), 7.93-8.02 (m, 3H, Ar-H), 8.44-8.46 (m, 2H, Ar-H), 9.18-9.20 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 20.2, 20.3 ($3CH_3$), 44.1 (CH), 117.2, 118.4, 121.2, 122.3, 122.8, 124.2, 125.1, 125.5, 126.2, 128.1, 129.1, 129.2, 129.4, 129.6, 130.2, 131.3, 132.5, 138.1, 140.4, 140.8, 141.4, 142.8, 145.4, 146.1, 147.2, 153.6 and 158.3 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 553 (M^+, 4).

Anal. Calcd for $C_{35}H_{25}ClN_4O$: C, 76.01; H, 4.56; N, 10.13. Found: C, 76.25; H, 4.38; N, 10.21.

1,11,12-Trimethyl-15-(4-nitrophenyl)-3,15-dihydrobenzo[a]pyrazolo[4′,3′:5,6] pyrano[2,3-c]phenazine (8k)

Yellow powder; yield 0.394 g (81%), mp 315-317 °C; IR (KBr): ν_{max} = 3345, 2935, 1632, 1590, 1475, 1406, 1387, 1345, 1297, 1172, 1070, 969, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85, 247, 2.49 (s, 9H, $3CH_3$), 5.47 (s, 1H, CH), 7.02 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.17 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.59-7.62 (m, 2H, Ar-H), 7.86 (s, 1H, Ar-H), 8.02-8.04 (m, 1H, Ar-H), 8.42 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.8 Hz, Ar-H), 9.24-9.27 (m, 1H, Ar-H), 11.92 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.9, 20.3, 20.5 ($3CH_3$), 43.6 (CH), 118.1, 122.4, 124.1, 125.2, 126.5, 127.2, 128.6, 128.9, 129.2, 129.5, 129.8, 130.1, 130.3, 131.5, 132.2, 140.4, 140.8, 141.5, 144.1, 145.6, 146.2, 157.8 and 160.9 ($C_{olefinic}$ and C_{arom}) ppm; MS (*m/z*, %): 487 (M^+, 2).

Anal. Calcd for $C_{29}H_{21}N_5O_3$: C, 71.45; H, 4.34; N, 14.37. Found: C, 71.67; H, 4.41; N, 14.54.

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