RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: RSC Adv., 2016, 6, 84326

Theophylline as the catalyst for the diastereoselective synthesis of *trans*-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazines in water†

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Received 23rd July 2016
Accepted 29th August 2016

DOI: 10.1039/c6ra18750a

www.rsc.org/advances

An efficient, convenient and environmentally benign procedure for the synthesis of novel 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives with high diastereoselectivity has been developed by a domino four-component condensation reaction between 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamines, aromatic aldehyde and pyridinium ylide in the presence of a catalytic amount of theophylline as an expedient, eco-friendly and reusable solid base catalyst in water. This one-pot process produces biologically and pharmacologically significant heterocycles with the formation of five new bonds (two C–C, two C=N and one C–O) and two new rings in a single operation and this effective green process provides considerable advantages such as: operational simplicity, short reaction time, high yields, reusability of catalyst, absence of any tedious workup or purification and avoiding hazardous reagents/solvents.

Introduction

Synthesis of polyfunctionalized heterocyclic compounds from readily available starting materials in a cost and time effective manner has received significant attention in organic synthesis due to their extensive applications in pharmaceuticals, agrochemicals and in materials sciences.[1–3] Benzofurans and its derivatives are an important category of oxygen-containing heterocycles owing to their wide existence in natural products, pharmaceuticals and biologically active compounds.[4–6] Benzofurans are integral to a large number of drug substances with activities including antifungal, antibacterial, antidepressant, and antitubercular properties.[7,8] Some benzofurans serve as versatile synthetic intermediates that can synthesize various useful compounds.[9–11] Also, phenazine based compounds are nitrogen-containing heterocycles that are the main core of many natural and synthetic organic materials.[12–14] Phenazines are showing a variety of biological functions, including fungicidal,[15] trypanocidal,[16] antimalarial,[17] antiplatelet[18] and antitumour[19] activities.

In this area, multi-component domino reactions (MDRs), in which more than two components are combined in a single synthetic operation, have been extensively used as a powerful strategy in the synthesis of complex heterocyclic molecules due to their advantages such as higher productivity, simple procedures, facile execution, lower costs, minimum waste production, structural diversity, shorter reaction times, environmentally friendliness, atom economy, high selectivity and allowing savings of both solvents and reagents.[20–23]

Furthermore, replacement of hazardous solvents with environmentally benign solvents[24–26] is one of the major focus areas of green chemistry. Organic solvents used in most of the synthetic organic chemistry evaporate into the atmosphere with destructive effects on the environment and ozone layer.[27] Thus, aqueous phase organic synthesis has attracted the attention of chemists as it overcomes the harmful effects associated with the organic solvents and is environmentally benign. Moreover, using water as the medium, surfactants can be used to build micelles and provide better chemical yields and shorter reaction times due to its strong hydrogen bonding ability, hydrophobic effects and high polarity.[28–30]

Xanthine is a common structural component in medicinal chemistry and new chemical entities (NCEs) development.[31] Xanthine-based lead molecules have been exploited in numerous therapeutic areas, for instance, Alzheimer's disease,[32] asthma,[33] diabetes,[34] Parkinson's disease[35] and cancer.[36] In addition, xanthine derivatives are one of the most abundant chemical classes of adenosine receptor antagonists.[37] Theophylline is a methylxanthine drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma under a variety of brand names. Theophylline has the chemical name 1,3-dimethyl-7*H*-purine-2,6-dione, and is represented by the following structural formula (Fig. 1):

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra18750a

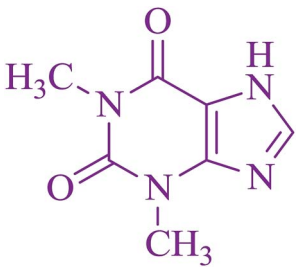
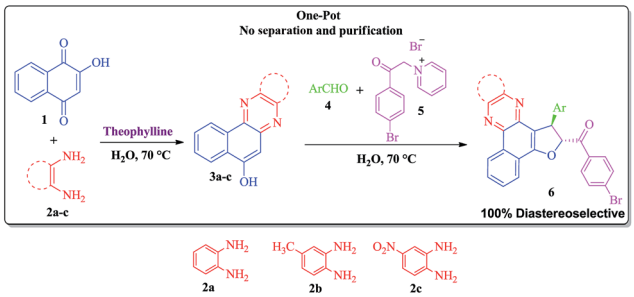


Fig. 1 The structure of theophylline.



Scheme 1 One-pot, four-component synthesis of novel 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives in the presence of theophylline.

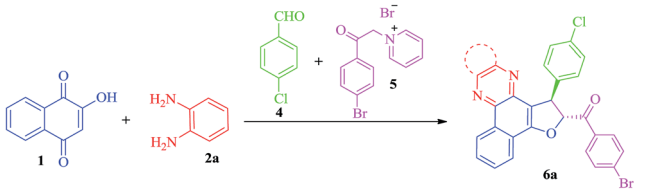
As part of our continuing interest in the development of new synthetic methods in heterocyclic compounds[38,39] and benzo[*a*]phenazin-5-ol-based multi-component reactions,[40–43] in this paper we would like to report new sequence of a one-pot, four-component condensation reaction between 2-hydroxynaphthalene-1,4-dione **1**, benzene-1,2-diamines **2**, aromatic aldehydes **4** and 1-(2-(4-bromophenyl)-2-oxoethyl) pyridinium bromide[44] **5** in the presence of theophylline as an efficient, non-toxic and inexpensive solid base catalyst for the synthesis of novel 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives **6** in aqueous medium at 70 °C (Scheme 1).

Results and discussion

The vast biological and pharmacological importance of phenazine and furan derivatives inspired us to develop a novel protocol for their efficient synthesis. In this area, theophylline is economically cost-effective and commercially available reagent, and its structure convinced us that this reagent could be used as an efficient, green and basic catalyst in the synthesis of novel 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives.

In order to investigate the optimizing reaction conditions for the synthesis of highly diastereoselective 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazines, we carried out the four-component domino reaction between 2-hydroxynaphthalene-1,4-dione **1** (1 mmol), benzene-1,2-diamine **2a** (1 mmol), 4-chlorobenzaldehyde **4** (1 mmol) and 1-(2-(4-bromophenyl)-2-oxoethyl)pyridinium bromide **5** (1 mmol) in acetonitrile as a model. We initially, to minimize the formation of byproducts, the 2-hydroxynaphthalene-1,4-dione and benzene-1,2-diamine were refluxed in acetonitrile until in less than

Table 1 Optimization of reaction conditions of compound **6a**



Entry	Cat (mol%)	Reaction conditions	Time (h)	Yield[a] (%)
1	No catalyst	CH_3CN, reflux	4	NR
2	Et_3N (20)	CH_3CN, reflux	2	76
3	Piperidine (20)	CH_3CN, reflux	2	68
4	DBU (20)	CH_3CN, reflux	2	40
5	DABCO (20)	CH_3CN, reflux	2	85
6	Imidazole (20)	CH_3CN, reflux	2	83
7	Histidine (20)	CH_3CN, reflux	2	Trace
8	Caffeine (20)	CH_3CN, reflux	2	62
9	Theophylline (20)	CH_3CN, reflux	2	81
10	Theophylline (20)	$CHCl_3$, reflux	2	64
11	Theophylline (20)	DMF, 100 °C	2	67
12	Theophylline (20)	EtOH, reflux	2	84
13	Theophylline (20)	H_2O, reflux	2	90
14	Theophylline (30)	H_2O, reflux	2	90
15	Theophylline (10)	H_2O, reflux	2	73
16	Theophylline (20)	H_2O, 70 °C	3	89
17	Theophylline (20)	H_2O, 50 °C	3	81
18	Theophylline (20)	H_2O, rt	3	Trace

[a] Isolated yields.

10 minutes an orange solid of benzo[*a*]phenazine **3a** was formed without using any catalyst. Next, 4-chlorobenzaldehyde and 1-(2-(4-bromophenyl)-2-oxoethyl)pyridinium bromide were added and the mixture was heated in acetonitrile under reflux. The desired product **6a** was not obtained when the reaction was carried out in acetonitrile for 4 h under reflux and catalyst-free conditions (Table 1, entry 1). However, **6a** was obtained in 72% yield when the reaction was conducted in the presence of triethylamine (20 mol%) in acetonitrile (Table 1, entry 2). Several bases were evaluated in the reaction as catalyst, including Et_3N, piperidine, DBU, DABCO, imidazole, histidine, caffeine and theophylline; these were all added in substoichiometric amount (20 mol%) and the reactions were carried out in acetonitrile under reflux conditions. Although the catalytic efficiency of DABCO was the highest (Table 1, entry 5) but we chose the theophylline as an effective and attractive catalyst due to features such as efficiency, non-toxicity, recoverability, and most importantly it used as drug. Different solvents were then appraised to determine the impact of the solvent on the reaction yields. Water due to its strong hydrogen bonding ability, hydrophobic effects and high polarity gave the best product yield (Table 1, entry 13). We then evaluated the amount of catalyst required for this transformation. An increase in the amount of theophylline more than 20 mol% showed no remarkable improvement in the yield, whereas the yield was reduced by decreasing the amount of theophylline to 10 mol% (Table 1, entries 13–15). Finally, the reaction was performed at different temperatures to determine the optimum reaction temperature. The reaction was conducted with

20 mol% theophylline in water at rt, 50, 70 and 100 °C, and the desired product **6a** was formed in yields of trace, 81%, 89% and 90% (Table 1, entries 13 and 16–18), respectively.

After extensive screening, we found that the optimized best yields and time profiles were obtained with 20 mol% of theophylline in H_2O at 70 °C, which furnished the corresponding (4-bromophenyl)(1-(4-chlorophenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone **6a** in 89% yield within 3 h (Table 1, entry 16).

Using these optimized conditions, we turned our attention to investigate the scope and general applicability of this methodology by carrying out the synthesis of 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazines using different benzene-1,2-diamines and various aromatic aldehydes (Table 2).

All the reactions were complete in 3–4 h and resulted in the formation of the target structures (Scheme 1, Table 2, entries 1–16) in high yields using the theophylline as environment-friendly catalyst and this domino reaction was efficiently promoted using benzene-1,2-diamine with reduced reaction times and increased yields rather than other aromatic 1,2-diamines and benzaldehydes with electron-withdrawing groups reacted rapidly and gave higher yields, while substitutions of electron-rich groups on the benzene ring required longer reaction times and got lower yields.

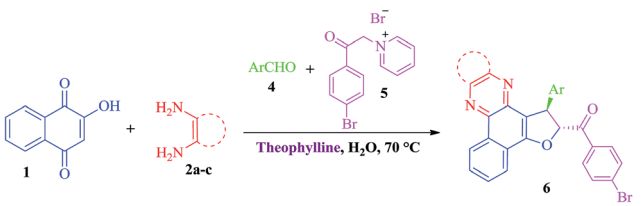
The isolated products **6** were fully characterized on the basis of IR, ^{1}H, ^{13}C NMR and MS spectroscopy and elemental analysis. In IR spectrum, stretching frequency at 1691 cm^{-1} confirmed the presence of C=O functional group of compound **6a**. In the ^{1}H NMR spectra, the two protons at 2,3-position of dihydrobenzofuran ring display two doublets at δ 5.46 and 6.10 ppm with the vicinal coupling constant J = 4.2 Hz. It has been documented that in *cis*-2,3-dihydrobenzofuran the vicinal coupling constant of the two methine protons J = 7–10 Hz, while in *trans*-2,3-dihydrobenzofuran vicinal coupling constant J = 4–7 Hz (Fig. 2).[45] So we concluded that thermodynamically stable *trans* isomer of 2,3-dihydrobenzofuran derivatives with high diastereoselectivity was formed. The ^{13}C NMR spectrum of **6a** showed twenty-six distinct resonances in agreement with the proposed structure (see Experimental section). The mass spectra of this compound displayed molecular ion peak at the appropriate *m*/*z* value at 565. Similarly, compounds **6b–p** were characterized (Table 2).

Recovery of the catalysts is important in green organic synthesis. Thus, we also for recyclability of the catalyst, investigated the recycling of the theophylline in aqueous medium at 70 °C using a selected model reaction of 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamine, 4-chlorobenzaldehyde and 1-(2-(4-bromophenyl)-2-oxoethyl)pyridinium bromide in the presence of theophylline as homogeneous catalyst (Table 2, entry 1). After completion of the reaction, then reaction mixture was cooled to room temperature. Then, 5 mL of water was added to the mixture. The theophylline was dissolved in water and filtered for separation of the crude product. The separated product was washed twice with water (2 × 5 mL). The resulting product subsequently recrystallized from hot ethanol to give the pure solid. In order to recover the catalyst, since theophylline is soluble in water, the filtrate was extracted with diethyl ether. The aqueous layer (including theophylline) was separated, and its solvent was evaporated under reduced pressure and theophylline was recovered and reused.

As shown in Fig. 3, the recovered catalyst works with the same performance up to 2nd run, while in the 3rd, 4th and 5th runs product yield gets reduced slightly that may be due to little weight loss of catalyst during each recovery process.

In order to determine the catalytic behavior of theophylline, the suggested mechanism for the formation of the products is shown in Scheme 2 according to the literature.[45a,b] On the basis of this mechanism, at first, 2-hydroxynaphthalene-1,4-dione **1** tautomerizes to intermediate **7**. The primary condensation of 4-hydroxy-1,2-naphthoquinone **7** with benzene-1,2-diamine **2**

Table 2 Domino one-pot four-component synthesis of 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives by using theophylline (20 mol%) as catalyst in water at 70 °C



Entry	Diamine	Ar	Product	Time (h)	Yield[a] (%)
1	**1a**	4-ClC_6H_4	**6a**	3	89
2	**1a**	2-ClC_6H_4	**6b**	3	87
3	**1a**	2,4-$Cl_2C_6H_3$	**6c**	3	89
4	**1a**	4-$NO_2C_6H_4$	**6d**	3	90
5	**1a**	2-OH-5-$NO_2C_6H_4$	**6e**	4	85
6	**1a**	2-Thienyl	**6f**	4	80
7	**1a**	4-MeC_6H_4	**6g**	4	81
8	**1a**	4-OMeC_6H_4	**6h**	4	83
9	**1a**	3,4-$(OMe)_2C_6H_3$	**6i**	4	78
10	**1a**	2-OH-3-OMeC_6H_4	**6j**	4	79
11	**1b**	4-ClC_6H_4	**6k**	3	87
12	**1b**	4-$NO_2C_6H_4$	**6l**	3	87
13	**1b**	4-MeC_6H_4	**6m**	4	80
14	**1c**	4-ClC_6H_4	**6n**	3	85
15	**1c**	4-$NO_2C_6H_4$	**6o**	3	88
16	**1c**	2-ClC_6H_4	**6p**	3	85

[a] Isolated yields.

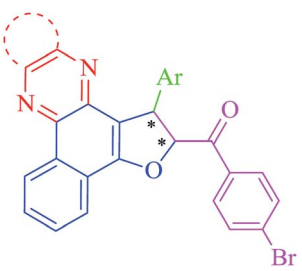


Fig. 2 Stereogenic centers on the structure of 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazines.

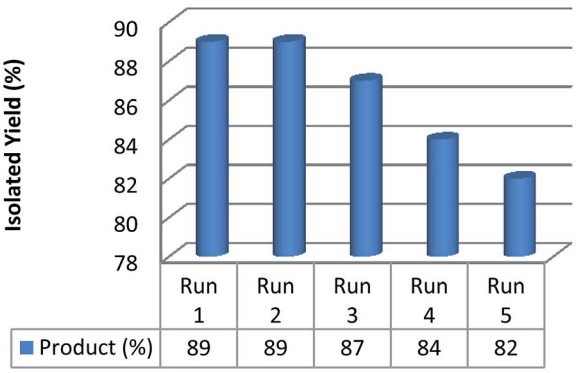
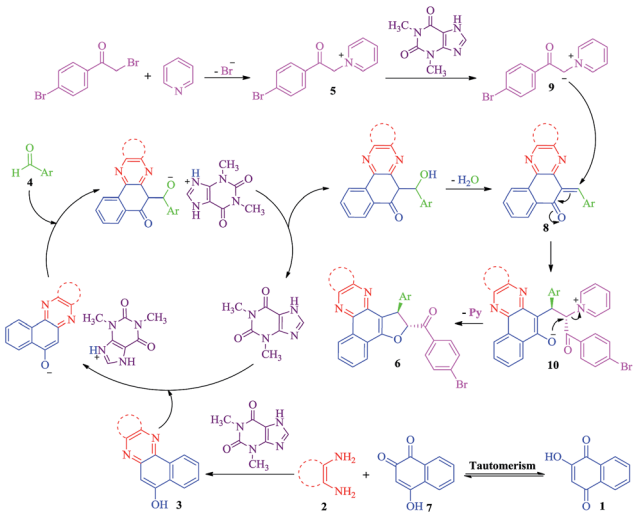


Fig. 3 The reusability of the catalyst (100 mg) in the synthesis of (4-bromophenyl)(1-(4-chlorophenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone in water at 70 °C (3 h).



Scheme 2 Plausible mechanism for the synthesis of 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives.

obtain benzo[*a*]phenazin-5-ol **3**. On this mechanism, theophylline is an efficient catalyst to form the 6-benzylidenebenzo[*a*]phenazin-5(6*H*)-one **8**, which easily prepares *in situ* from Knoevenagel condensation of benzo[*a*]phenazin-5-ol **3** with carbonyl group of aldehyde **4**. On the other hand, the pyridinium ylide **9**, which forms from the reaction of 1-(2-(4-bromophenyl)-2-oxoethyl)pyridinium **5** with theophylline undergoes Michael addition to intermediate **8** to afford the enolate intermediate **10**. Eventually, the enolate **10** eliminates pyridine (intramolecular S_N2) and cyclizes instantly to produce novel 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives **6**.

Experimental

General

All melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a shimadzu IR-470 spectrometer. Elemental analyses for C, H, and N were performed using a Costech ECS 4010 CHNS-O analyser at the analytical laboratory of Islamic Azad University Yazd branch. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. 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. Thin-layer chromatography (TLC) was performed on silica-gel Polygram SILG/UV 254 plates. All reagents and solvent were purchased from Merck and Aldrich and used without further purification.

General procedure for the synthesis of novel 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives (6a–p)

Initially, a mixture of 2-hydroxynaphthalene-1,4-dione **1** (1 mmol), benzene-1,2-diamine **2** (1 mmol), theophylline (20 mol%) and water (10 mL) was placed in a 50 mL round-bottomed flask mounted over a magnetic stirrer. The contents were stirred magnetically in an oil-bath maintained at 70 °C until in less than 10 minutes benzo[*a*]phenazin-5-ol **3** was formed. Then, aryl aldehyde **4** (1 mmol) and 1-(2-(4-bromophenyl)-2-oxoethyl) pyridinium bromide **5** (1 mmol) were added to the above reaction mixture which was heated further at same temperature for an appropriate time as shown in Table 2. Upon completion of the reaction, monitored by TLC, the reaction mixture was allowed to cool to room temperature. Then, 5 mL of water was added to the mixture and filtered for separation of the crude product. The separated product was washed twice with water (2 × 5 mL). The solid crude product subsequently recrystallized from hot ethanol to give the pure product **6**.

The spectral and analytical data of all the compounds are given as follows.

(4-Bromophenyl)(1-(4-chlorophenyl)-1,2-dihydrobenzo[*a*]furo-[2,3-*c*]phenazin-2-yl)methanone (6a). Yellow powder; yield 0.502 g (89%), mp 279–281 °C; IR (KBr): ν_{max} = 3045, 2900, 1691, 1627, 1591, 1535, 1499, 1415, 1386, 1332, 1224, 1131, 1045, 978, 800, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.46 (d, 1H, J = 4.2 Hz, CH), 6.10 (d, 1H, J = 4.2 Hz, CH), 7.22 (d, 2H, J = 8.4 Hz, Ar-H), 7.32 (d, 2H, J = 8.4 Hz, Ar-H), 7.59–7.67 (m, 4H, Ar-H), 7.78–7.83 (m, 4H, Ar-H), 7.89–7.92 (m, 1H, Ar-H), 8.15–8.20 (m, 2H, Ar-H), 9.32–9.35 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.1 and 91.9 (2CH), 115.4, 122.6, 123.9, 126.1, 128.6, 128.8, 128.9, 129.0, 129.2, 129.5, 129.7, 129.9, 130.0, 130.6, 132.3, 132.5, 133.2, 140.2, 140.4, 141.3, 141.5, 142.5 and 157.9 ($C_{olefinic}$ and C_{arom}), 192.7 (C=O) ppm; MS (*m*/*z*, %): 565 (M^+, 1), 448 (1), 381 (100), 246 (91), 185 (15), 43 (76); anal. calcd for $C_{31}H_{18}BrClN_2O_2$: C, 65.80; H, 3.21; N, 4.95%. Found: C, 66.03; H, 3.46; N, 4.87%.

(4-Bromophenyl)(1-(2-chlorophenyl)-1,2-dihydrobenzo[*a*]furo-[2,3-*c*]phenazin-2-yl)methanone (6b). Orange powder; yield 0.492 g (87%), mp 243–245 °C; IR (KBr): ν_{max} = 3035, 2895, 1692, 1626, 1594, 1534, 1498, 1414, 1386, 1332, 1223, 1129, 1045, 978, 800, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (s, 2H, 2CH), 6.99–7.14 (m, 3H, Ar-H), 7.39 (d, 1H, J = 7.8 Hz, Ar-H), 7.60 (d, 2H, J = 8.7 Hz, Ar-H), 7.64–7.67 (m, 2H, Ar-H), 7.73–7.82 (m, 2H, Ar-H), 7.88 (d, 2H, J = 8.4 Hz, Ar-H), 7.93–7.96 (m, 1H, Ar-H), 8.08–8.11 (m, 1H, Ar-H), 8.17–8.21 (m, 1H, Ar-H), 9.33–9.36 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.6 and 90.9 (2CH), 115.3,

122.5, 124.0, 125.7, 126.1, 127.3, 128.5, 128.6, 128.8, 129.1, 129.3, 129.6, 129.7, 129.8, 129.9, 130.8, 131.4, 131.9, 132.2, 132.5, 132.9, 133.5, 139.3, 140.3, 141.2, 141.7, 142.7 and 158.1 ($C_{olefinic}$ and C_{arom}), 191.9 (C=O) ppm; MS (*m*/*z*, %): 565 (M^+, 1), 529 (1), 381 (100), 246 (9), 183 (11), 76 (4); anal. calcd for $C_{31}H_{18}BrClN_2O_2$: C, 65.80; H, 3.21; N, 4.95%. Found: C, 65.93; H, 3.51; N, 5.10%.

(4-Bromophenyl)(1-(2,4-dichlorophenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6c). Yellow powder; yield 0.534 g (89%), mp 256–257 °C; IR (KBr): ν_{max} = 3110, 2905, 1683, 1626, 1591, 1534, 1500, 1412, 1380, 1351, 1221, 1134, 1065, 978, 800, 761 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 5.92 (d, 1H, J = 3.9 Hz, CH), 6.74 (d, 1H, J = 3.9 Hz, CH), 7.16 (d, 1H, J = 8.4 Hz, Ar-H), 7.25 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.1 Hz, Ar-H), 7.73 (d, 1H, J = 2.1 Hz, Ar-H), 7.84–7.89 (m, 4H, Ar-H), 7.94–8.02 (m, 3H, Ar-H), 8.05 (d, 2H, J = 8.7 Hz, Ar-H), 8.13–8.16 (m, 1H, Ar-H), 8.28–8.32 (m, 1H, Ar-H), 9.31–9.34 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.3 and 90.4 (2CH), 114.9, 122.9, 123.7, 126.1, 128.3, 128.8, 129.0, 129.3, 129.8, 131.1, 131.2, 131.7, 132.1, 132.6, 133.0, 133.2, 134.0, 138.2, 140.0, 140.9, 141.5, 142.3 and 158.5 ($C_{olefinic}$ and C_{arom}), 193.2 (C=O) ppm; MS (*m*/*z*, %): 600 (M^+, 1), 523 (1), 415 (100), 352 (16), 182 (20), 57 (14); anal. calcd for $C_{31}H_{17}BrCl_2N_2O_2$: C, 62.03; H, 2.85; N, 4.67%. Found: C, 62.27; H, 2.64; N, 4.76%.

(4-Bromophenyl)(1-(4-nitrophenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6d). Yellow powder; yield 0.516 g (90%), mp 283–285 °C; IR (KBr): ν_{max} = 3025, 2905, 1689, 1624, 1593, 1532, 1507, 1447, 1393, 1336, 1223, 1132, 1046, 941, 803, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.72 (d, 1H, J = 4.8 Hz, CH), 6.10 (d, 1H, J = 4.8 Hz, CH), 7.56–7.70 (m, 7H, Ar-H), 7.78–7.83 (m, 2H, Ar-H), 7.86–7.89 (m, 3H, Ar-H), 8.11–8.14 (m, 3H, Ar-H), 9.34–9.37 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.5 and 90.6 (2CH), 115.3, 122.3, 124.0, 125.5, 127.3, 128.0, 128.5, 128.7, 129.1, 129.5, 129.7, 130.0, 130.1, 130.2, 130.3, 131.6, 132.5, 132.9, 133.5, 139.3, 140.3, 141.4, 141.5, 142.5, and 157.5 ($C_{olefinic}$ and C_{arom}), 192.6 (C=O) ppm; MS (*m*/*z*, %): 576 (M^+, 1), 530 (1), 384 (2), 344 (48), 271 (68), 57 (100); anal. calcd for $C_{31}H_{18}BrN_3O_4$: C, 64.60; H, 3.15; N, 7.29%. Found: C, 64.48; H, 3.37; N, 7.53%.

(4-Bromophenyl)(1-(2-hydroxy-5-nitrophenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6e). Green powder; yield 0.503 g (85%), mp 156–157 °C; IR (KBr): ν_{max} = 3050, 2910, 1688, 1632, 1591, 1527, 1500, 1415, 1386, 1336, 1224, 1152, 1063, 948, 811, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.74 (d, 1H, J = 4.8 Hz, CH), 6.13 (d, 1H, J = 4.5 Hz, CH), 7.43 (t, 1H, J = 7.8 Hz, Ar-H), 7.60–7.67 (m, 3H, Ar-H), 7.75–7.84 (m, 3H, Ar-H), 7.86–7.90 (m, 3H, Ar-H), 8.03–8.06 (m, 1H, Ar-H), 8.12–8.19 (m, 2H, Ar-H), 8.30 (t, 1H, J = 2.1 Hz, Ar-H), 9.32–9.35 (m, 1H, Ar-H), 10.80 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.7 and 91.6 (2CH), 114.8, 122.5, 122.7, 123.1, 126.1, 128.7, 129.1, 129.7, 129.8, 130.0, 130.7, 130.9, 131.2, 131.5, 131.6, 132.3, 132.6, 134.2, 137.2, 138.5, 140.2, 141.4, 141.9, 143.9 and 157.8 ($C_{olefinic}$ and C_{arom}), 192.4 (C=O) ppm; MS (*m*/*z*, %): 592 (M^+, 1), 575 (2), 415 (100), 345 (22), 182 (49), 57 (92); anal. calcd for $C_{31}H_{18}BrN_3O_5$: C, 62.85; H, 3.06; N, 7.09%. Found: C, 62.63; H, 3.15; N, 7.26%.

(4-Bromophenyl)(1-(thiophen-2-yl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6f). Brown powder; yield 0.431 g (80%), mp 160 °C; IR (KBr): ν_{max} = 3050, 2895, 1687, 1629, 1579, 1524, 1489, 1412, 1386, 1330, 1219, 1133, 1063, 973, 834, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 (d, 1H, J = 3.9 Hz, CH), 6.21 (d, 1H, J = 3.9 Hz, CH), 7.87–8.89 (m, 1H, Ar-H), 7.05 (d, 1H, J = 3.3 Hz, Ar-H), 7.11 (d, 1H, J = 4.8 Hz, Ar-H), 7.60–7.68 (m, 5H, Ar-H), 7.76–8.79 (m, 2H, Ar-H), 7.89 (d, 1H, J = 8.4 Hz, Ar-H), 7.95–7.98 (m, 1H, Ar-H), 8.14–8.19 (m, 2H, Ar-H), 9.30–9.34 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.6 and 91.8 (2CH), 115.0, 122.7, 123.9, 124.7, 125.4, 126.0, 127.1, 128.5, 128.8, 128.9, 129.5, 129.6, 129.7, 129.8, 129.9, 130.7, 132.0, 132.3, 132.5, 132.6, 140.2, 141.3, 141.6, 142.5, 145.0, and 157.8 ($C_{olefinic}$ and C_{arom}), 192.5 (C=O) ppm; MS (*m*/*z*, %): 537 (M^+, 1), 426 (2), 353 (100), 246 (18), 183 (14), 76 (5); anal. calcd for $C_{29}H_{17}BrN_2O_2S$: C, 64.81; H, 3.19; N, 5.21; S, 5.97%. Found: C, 65.06; H, 3.26; N, 5.30; S, 5.82%.

(4-Bromophenyl)(1-(*p*-tolyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6g). Green powder; yield 0.441 g (81%), mp 260–263 °C; IR (KBr): ν_{max} = 3045, 2900, 1684, 1633, 1594, 1533, 1500, 1416, 1382, 1331, 1222, 1130, 1063, 978, 828, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 5.37 (d, 1H, J = 3.9 Hz, CH), 6.15 (d, 1H, J = 4.2 Hz, CH), 7.06 (d, 2H, J = 7.8 Hz, Ar-H), 7.29 (d, 2H, J = 7.8 Hz, Ar-H), 7.58–7.66 (m, 4H, Ar-H), 7.77–7.82 (m, 4H, Ar-H), 7.89–7.94 (m, 1H, Ar-H), 8.15–8.22 (m, 2H, Ar-H), 9.32–9.35 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1 (CH_3), 50.6 and 92.2 (2CH), 116.0, 122.6, 124.1, 126.0, 127.7, 128.4, 128.7, 128.8, 129.3, 129.6, 129.7, 129.8, 129.9, 130.6, 132.2, 132.5, 132.6, 137.1, 138.9, 140.2, 141.3, 141.8, 142.5 and 157.9 ($C_{olefinic}$ and C_{arom}), 192.9 (C=O) ppm; MS (*m*/*z*, %): 545 (M^+, 1), 466 (2), 361 (100), 270 (5), 183 (9), 57 (3); anal. calcd for $C_{32}H_{21}BrN_2O_2$: C, 70.47; H, 3.88; N, 5.14%. Found: C, 70.71; H, 3.69; N, 5.22%.

(4-Bromophenyl)(1-(4-methoxyphenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6h). Brown powder; yield 0.566 g (83%), mp 180–181 °C; IR (KBr): ν_{max} = 3025, 2895, 1688, 1628, 1583, 1531, 1507, 1410, 1390, 1330, 1223, 1133, 1061, 948, 820, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3), 5.35 (d, 1H, J = 3.9 Hz, CH), 6.12 (d, 1H, J = 4.2 Hz, CH), 6.77 (d, 2H, J = 8.4 Hz, Ar-H), 7.30 (d, 2H, J = 8.7 Hz, Ar-H), 7.53–7.62 (m, 4H, Ar-H), 7.67–7.80 (m, 5H, Ar-H), 8.12–8.19 (m, 2H, Ar-H), 9.29–9.32 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.3 (CH), 55.2 (OCH_3), 92.2 (CH), 114.2, 116.0, 122.6, 124.0, 126.0, 128.4, 128.7, 128.8, 128.9, 129.3, 129.6, 129.7, 129.9, 130.6, 132.2, 132.4, 132.5, 134.0, 140.1, 141.3, 141.8, 142.5 and 158.8 ($C_{olefinic}$ and C_{arom}), 193.0 (C=O) ppm; MS (*m*/*z*, %): 561 (M^+, 1), 425 (1), 377 (100), 246 (20), 183 (12), 76 (4); anal. calcd for $C_{32}H_{21}BrN_2O_3$: C, 68.46; H, 3.77; N, 4.99%. Found: C, 68.57; H, 3.96; N, 5.18%.

(4-Bromophenyl)(1-(3,4-dimethoxyphenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6i). Brown powder; yield 0.460 g (78%), mp 162–164 °C; IR (KBr): ν_{max} = 3040, 2910, 1688, 1629, 1594, 1551, 1512, 1415, 1386, 1331, 1223, 1137, 1048, 948, 800, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.37 (d, 1H, J = 4.2 Hz, CH), 6.18 (d, 1H, J = 4.2 Hz, CH), 6.73 (d, 1H, J = 8.4 Hz, Ar-H), 6.91 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.8 Hz, Ar-H), 6.99 (d, 1H, J = 1.8 Hz, Ar-H), 7.58–7.67 (m, 4H, Ar-H), 7.77–8.84 (m, 4H, Ar-H), 7.89–7.93 (m, 1H, Ar-H), 8.16–8.21 (m, 2H, Ar-H), 9.32–9.35 (m, 1H, Ar-H)

ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.6 (CH), 55.8 and 56.0 ($2OCH_3$), 92.1 (CH), 111.4, 111.5, 115.8, 119.7, 122.6, 124.0, 126.0, 128.4, 128.7, 129.4, 129.7, 129.8, 129.9, 130.6, 131.7, 131.9, 132.2, 132.4, 132.5, 134.4, 140.1, 141.3, 141.8, 142.5, 148.3, 149.0 and 157.8 ($C_{olefinic}$ and C_{arom}), 193.0 (C=O) ppm; MS (*m*/*z*, %): 591 (M^+, 1), 454 (1), 407 (100), 345 (13), 182 (23), 57 (11); anal. calcd for $C_{33}H_{23}BrN_2O_4$: C, 67.01; H, 3.92; N, 4.74%. Found: C, 67.19; H, 3.85; N, 4.90%.

(4-Bromophenyl)(1-(2-hydroxy-3-methoxyphenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6j). Orange powder; yield 0.458 g (79%), mp 251–252 °C; IR (KBr): ν_{max} = 3025, 2900, 1674, 1620, 1581, 1524, 1468, 1416, 1392, 1337, 1220, 1133, 1063, 979, 809, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.67 (d, 1H, J = 3.0 Hz, CH), 6.55 (d, 1H, J = 3.0 Hz, CH), 6.74–6.77 (m, 1H, Ar-H), 6.85 (t, 1H, J = 7.8 Hz, Ar-H), 7.07 (d, 1H, J = 6.9 Hz, Ar-H), 7.55 (d, 2H, J = 8.4 Hz, Ar-H), 7.66–7.82 (m, 6H, Ar-H), 8.15–8.21 (m, 3H, Ar-H), 9.25–9.28 (m, 1H, Ar-H), 10.12 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.0 (CH), 56.0 (OCH_3), 90.3 (CH), 111.0, 116.1, 118.1, 121.5, 122.7, 124.1, 126.0, 127.5, 128.7, 129.0, 129.4, 129.8, 129.9, 130.2, 130.3, 130.7, 131.8, 132.1, 132.4, 140.3, 140.6, 141.9, 143.8, 150.5 and 158.5 ($C_{olefinic}$ and C_{arom}), 192.4 (C=O) ppm; MS (*m*/*z*, %): 577 (M^+, 1), 407 (1), 358 (96), 285 (100), 142 (6), 89 (4); anal. calcd for $C_{32}H_{21}BrN_2O_4$: C, 66.56; H, 3.67; N, 4.85%. Found: C, 66.78; H, 3.90; N, 4.89%.

(4-Bromophenyl)(1-(4-chlorophenyl)-11-methyl-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6k). Yellow powder; yield 0.504 g (87%), mp 307–309 °C; IR (KBr): ν_{max} = 3025, 2910, 1690, 1624, 1593, 1530, 1501, 1405, 1352, 1315, 1225, 1132, 1047, 1003, 817, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H, CH_3), 5.45 (d, 1H, J = 4.2 Hz, CH), 6.08 (d, 1H, J = 4.2 Hz, CH), 7.22 (d, 2H, J = 8.4 Hz, Ar-H), 7.32 (d, 2H, J = 8.4 Hz, Ar-H), 7.49 (dd, 1H, J_1 = 8.7 Hz, J_2 = 1.8 Hz, Ar-H), 7.61 (d, 2H, J = 8.4 Hz, Ar-H), 7.76–7.83 (m, 5H, Ar-H), 7.95 (s, 1H, Ar-H), 8.14–8.17 (m, 1H, Ar-H), 9.29–9.33 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 (CH_3), 50.1 and 91.9 (2CH), 115.4, 122.6, 126.0, 128.2, 128.3, 128.4, 128.7, 129.0, 129.2, 129.4, 129.8, 130.6, 131.1, 132.3, 132.5, 132.6, 133.2, 135.0, 137.1, 137.2, 139.2, 140.5, 141.0, 157.4 and 157.7 ($C_{olefinic}$ and C_{arom}), 192.8 (C=O) ppm; MS (*m*/*z*, %): 579 (M^+, 1), 439 (1), 395 (27), 260 (100), 130 (12), 57 (14); anal. calcd for $C_{32}H_{20}BrClN_2O_2$: C, 66.28; H, 3.48; N, 4.83%. Found: C, 66.45; H, 3.51; N, 4.98%.

(4-Bromophenyl)(11-methyl-1-(4-nitrophenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6l). Yellow powder; yield 0.511 g (87%), mp 296–297 °C; IR (KBr): ν_{max} = 3045, 2900, 1690, 1629, 1594, 1563, 1508, 1480, 1391, 1330, 1226, 1144, 1062, 943, 820, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3), 5.72 (d, 1H, J = 4.5 Hz, CH), 6.07 (d, 1H, J = 4.5 Hz, CH), 7.49–7.64 (m, 6H, Ar-H), 7.76–7.88 (m, 5H, Ar-H), 8.09–8.13 (m, 3H, Ar-H), 9.32–9.35 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7 (CH_3), 51.2 and 90.4 (2CH), 110.9, 115.9, 118.1, 121.5, 122.8, 124.1, 126.1, 127.4, 128.8, 129.0, 129.4, 129.7, 129.9, 130.2, 130.4, 130.6, 131.8, 132.0, 132.4, 140.2, 140.6, 141.8, 143.9, 150.6 and 158.4 ($C_{olefinic}$ and C_{arom}), 192.3 (C=O) ppm; MS (*m*/*z*, %): 590 (M^+, 1), 406 (100), 360 (20), 284 (7), 184 (16), 57 (20); anal. calcd for $C_{32}H_{20}BrN_3O_4$: C, 65.10; H, 3.41; N, 7.12%. Found: C, 65.33; H, 3.52; N, 7.01%.

(4-Bromophenyl)(11-methyl-1-(*p*-tolyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6m). Brown powder; yield 0.449 g (80%), mp 205–207 °C; IR (KBr): ν_{max} = 2995, 2910, 1692, 1631, 1595, 1532, 1502, 1479, 1396, 1331, 1223, 1147, 1049, 950, 820, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 5.48 (d, 1H, J = 4.2 Hz, CH), 6.23 (d, 1H, J = 3.9 Hz, CH), 7.16 (d, 2H, J = 7.2 Hz, Ar-H), 7.38 (d, 2H, J = 7.8 Hz, Ar-H), 7.53–7.58 (m, 2H, Ar-H), 7.68 (d, 2H, J = 8.4 Hz, Ar-H), 7.82–8.82 (m, 5H, Ar-H), 8.27–8.30 (m, 1H, Ar-H), 9.37–9.41 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1 and 21.9 ($2CH_3$), 50.6 and 92.1 (2CH), 116.0, 122.5, 123.8, 125.8, 125.9, 127.4, 127.7, 128.1, 128.3, 128.5, 128.6, 129.1, 129.3, 129.6, 129.7, 130.6, 131.0, 132.2, 132.3, 132.5, 137.0, 138.8, 139.0, 140.3, 141.1, 142.6, 157.4 and 157.7 ($C_{olefinic}$ and C_{arom}), 193.0 (C=O) ppm; MS (*m*/*z*, %): 559 (M^+, 1), 440 (2), 375 (100), 260 (20), 183 (10), 57 (3); anal. calcd for $C_{33}H_{23}BrN_2O_2$: C, 70.85; H, 4.14; N, 5.01%. Found: C, 70.77; H, 3.37; N, 5.25%.

(4-Bromophenyl)(1-(4-chlorophenyl)-10-nitro-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6n). Yellow powder; yield 0.518 g (85%), mp 275–277 °C; IR (KBr): ν_{max} = 3055, 2900, 1684, 1625, 1590, 1551, 1514, 1415, 1388, 1332, 1220, 1125, 1046, 1005, 818, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.43 (d, 1H, J = 4.5 Hz, CH), 6.16 (d, 1H, J = 4.5 Hz, CH), 7.23–7.35 (m, 4H, Ar-H), 7.63 (d, 2H, J = 8.7 Hz, Ar-H), 7.80–7.88 (m, 4H, Ar-H), 8.00 (d, 1H, J = 9.3 Hz, Ar-H), 8.19–8.22 (m, 1H, Ar-H), 8.40 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.4 Hz, Ar-H), 9.11 (d, 1H, J = 2.4 Hz, Ar-H), 9.31–9.35 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.8 and 92.2 (2CH), 115.6, 122.9, 123.1, 126.4, 126.5, 128.6, 128.8, 128.9, 129.0, 129.1, 129.2, 129.8, 130.2, 130.6, 131.0, 132.4, 132.5, 139.8, 140.4, 141.3, 141.5, 142.5 and 157.9 ($C_{olefinic}$ and C_{arom}), 192.2 (C=O) ppm; MS (*m*/*z*, %): 610 (M^+, 1), 551 (1), 426 (53), 291 (100), 182 (23), 43 (44); anal. calcd for $C_{31}H_{17}BrClN_3O_4$: C, 60.95; H, 2.81; N, 6.88%. Found: C, 70.19; H, 2.88; N, 6.98%.

(4-Bromophenyl)(10-nitro-1-(4-nitrophenyl)-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6o). Yellow powder; yield 0.544 g (88%), mp 312–314 °C; IR (KBr): ν_{max} = 3070, 2910, 1688, 1629, 1589, 1552, 1510, 1412, 1386, 1337, 1225, 1141, 1046, 979, 822, 762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.69 (d, 1H, J = 4.5 Hz, CH), 6.16 (d, 1H, J = 4.5 Hz, CH), 7.53–7.59 (m, 2H, Ar-H), 7.65 (d, 2H, J = 8.7 Hz, Ar-H), 7.88–7.89 (m, 4H, Ar-H), 8.13–8.20 (m, 3H, Ar-H), 8.33 (d, 1H, J = 9.3 Hz, Ar-H), 8.42 (dd, 1H, J_1 = 9.3 Hz, J_2 = 2.4 Hz, Ar-H), 8.80 (d, 1H, J = 2.4 Hz, Ar-H), 9.34–9.37 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.1 and 90.5 (2CH), 113.8, 115.8, 122.2, 123.4, 125.3, 125.5, 127.1, 128.1, 129.2, 130.3, 130.4, 130.9, 131.0, 132.2, 133.0, 133.5, 137.3, 139.9, 140.2, 141.1, 141.7, 143.0 and 157.3 ($C_{olefinic}$ and C_{arom}), 191.7 (C=O) ppm; MS (*m*/*z*, %): 621 (M^+, 1), 577 (2), 437 (17), 375 (65), 184 (33), 43 (100); anal. calcd for $C_{31}H_{17}BrN_4O_6$: C, 59.92; H, 2.76; N, 9.02%. Found: C, 60.11; H, 2.59; N, 8.90%.

(4-Bromophenyl)(1-(2-chlorophenyl)-10-nitro-1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)methanone (6p). Yellow powder; yield 0.521 g (85%), mp 300 °C; IR (KBr): ν_{max} = 3030, 2900, 1686, 1627, 1583, 1526, 1493, 1409, 1386, 1333, 1223, 1145, 1048, 1004, 808, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 (d, 1H, J = 4.2 Hz, CH), 6.18 (d, 1H, J = 4.2 Hz, CH), 7.06–7.14 (m, 3H, Ar-

H), 7.34 (d, 1H, $J = 7.8$ Hz, Ar-H), 7.62 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.83–7.88 (m, 4H, Ar-H), 8.14–8.17 (m, 1H, Ar-H), 8.32 (d, 1H, $J = 9.3$ Hz, Ar-H), 8.40 (dd, 1H, $J_1 = 9.3$ Hz, $J_2 = 2.4$ Hz, Ar-H), 8.83 (d, 1H, $J = 2.4$ Hz, Ar-H), 9.34–9.37 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.3 and 91.3 (2CH), 113.9, 122.9, 125.2, 125.3, 127.1, 127.2, 128.1, 128.2, 128.9, 129.0, 129.1, 129.6, 129.7, 129.9, 131.6, 132.2, 132.8, 132.9, 140.1, 140.5, 141.4, 141.5, 142.8 and 156.9 ($C_{olefinic}$ and C_{arom}), 192.5 (C=O) ppm; MS (*m*/*z*, %): 610 (M^+, 1), 572 (1), 426 (100), 316 (20), 182 (20), 76 (6); anal. calcd for $C_{31}H_{17}BrClN_3O_4$: C, 60.95; H, 2.81; N, 6.88%. Found: C, 61.12; H, 2.94; N, 6.71%.

Conclusions

In summary, we have described a novel domino four-component coupling reaction leading to selective and high-yielding 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives from readily available starting materials in aqueous medium. The strategy provided two C–C, two C=N, one C–O bonds and two new rings in a single operation through condensation/Knoevenagel/Michael/annulation sequences. This protocol also offers several advantages such as convenient one-pot operation, high atom economy, easy work-up, short reaction time, use of theophylline as a non-toxic, inexpensive and easily obtained catalyst and avoidance of conventional volatile organic solvents that make it a green, economically cost-effective and attractive process for the synthesis of these heterocycles. Furthermore, our work is expected to exhibit interesting pharmacology activities and may act as potential drug candidates, since phenazine and furan motifs have a vast range of biological activities.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the Islamic Azad University of Yazd and University of Sistan and Baluchestan.

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