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PTSA-catalyzed four-component domino reactions for the one-pot synthesis of functionalized 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-diones in PEG

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Abstract An efficient *p*-toluenesulfonic acid catalyzed synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives has been described by one-pot, four-component condensation of 2-hydroxynaphthalene-1,4-dione, *o*-phenylenediamine, aromatic aldehydes using polyethylene glycol as solvent. This domino protocol produces biologically considerable heterocycles with the formation of C–C, C=C, C–N, C=N, C–O bonds in a single operation and this efficient green process provides significant advantages such as: operational simplicity, easy work-up procedure, high yields, avoidance of hazardous or toxic catalysts and organic solvents, and is devoid of inessential derivatization and generation of hazardous substances.

Keywords Multi-component reactions (MCRs) · One-pot synthesis · 2-Hydroxynaphthalene-1 · 4-Dione · *o*-Phenylenediamine · *p*-Toluenesulfonic acid · Polyethylene glycol

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Introduction

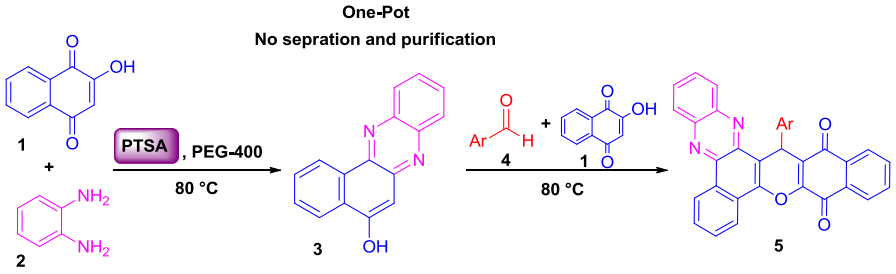
Synthesis of simple and complex bioactive heterocycles such as natural products and analogues, drugs, diagnostics, agrochemicals and any kind of material is a significant subject in modern chemistry [1–3]. Diversity-oriented synthesis (DOS) has played a critical role in the development of the design and synthesis of new diverse polycyclic heterocycles with potential medicinal and biological activity in the field of organic, combinatorial, and medicinal chemistry [4, 5]. DOS provides the synthetic means for the generation of collections of functionally and regiochemically diverse small molecules, particularly those possessing skeletons resembling those found in natural products or drug-like molecules [6]. Multicomponent reactions (MCRs) and multicomponent domino or tandem reactions are useful tools in combinatorial and DOS chemistry 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 [7–12].

Nitrogen-containing heterocyclic molecules in five- and six-membered rings constitute the largest portion of chemical entities, which are part of many natural products playing important roles in medicinal chemistry due to their pharmaceutical and biological activities [13, 14]. In this area, phenazine derivatives that are present in natural and synthetic products have attracted considerable interest due to their useful biological properties such as antimalarial [15], fungicidal [16], trypanocidal [17], antiplatelet [18], antitumor and antiparasitic [19] activities.

In addition, heterocyclic compounds containing chromene moieties are an important class of natural and synthetic compounds that have received significant attention from organic chemists because of their biological and pharmaceutical activities [20]. They are present widely in plants such as edible vegetables and fruits [21], showing a variety of biological functions, including antifungal [22], antimicrobial [23], antileishmanial [24, 25], anti-oxidant [26], antitumor [27], hypotensive [28] and antiproliferation agents [29].

Organic solvents used in most of the synthetic organic chemistry evaporate into the atmosphere with destructive effects on the environment and the ozone layer [30]. Water [31, 32], ionic liquids [33], phase-transfer catalysts [34], polyethylene glycol (PEG) [35–37], etc. can be used instead of hazardous, toxic, flammable, volatile, difficult to recycle and expensive organic solvents.

Therefore, considering our work on multi-component reactions [38–41], and in continuation of our ongoing program for the synthesis of heterocyclic compounds based on green chemistry protocols [42–45], we report here on the preparation of functionalized 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives **5** through a domino, one-pot, four-component condensation reaction between 2-hydroxynaphthalene-1,4-dione **1**, *o*-phenylenediamine **2**, aromatic aldehydes **4** in the presence of PTSA as a mild, efficient, non-toxic and inexpensive Lewis acid catalyst using PEG-400 as eco-friendly solvent system at 80 °C (Scheme 1).



Scheme 1 Synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives in the presence of PTSA as solid acid catalyst

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 Heraeus CHN-O-Rapid analyzer at the Iranian Central Research of Petroleum Company. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on Bruker DRX-400 Advance instrument with dimethyl sulfoxide (DMSO) as solvent. Thin-layer chromatography (TLC) was performed on silica-gel Polygram SILG/UV 254 plates. All reagents and solvents were purchased from Merck and Aldrich and used without further purification.

General experimental procedure for the synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives (5a–k)

At the first step, 2-hydroxynaphthalene-1,4-dione **1** (1 mmol), *o*-phenylenediamine **2** (1 mmol) and PTSA (20 mol% or 0.2 mmol) and 5 mL of PEG-400 were mixed in a 50-mL round-bottomed flask and the contents were stirred magnetically in an oil-bath maintained at 80 °C until in <30 min an orange solid of benzo[*a*]phenazine **3** was formed. Then, aryl aldehyde **4** (1 mmol) and 2-hydroxynaphthalene-1,4-dione **1** (1 mmol) were added to the above reaction mixture which was heated further for the times reported in Table 2. Upon completion of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature and was quenched with H_2O (5 mL). The precipitate formed was collected by filtration at pump, then the separated product was washed with water. The resulting product subsequently recrystallized from hot ethanol to give the pure solid **5**. The spectral and analytical data are presented below.

*17-(4-Nitrophenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5a**)*

Yellow solid; yield 93 %, 0.497 g; mp 273–275 °C; IR (KBr) (ν_{max}, cm^{-1}): 2920, 1693, 1662, 1635, 1585, 1512, 1340, 1289, 1168, 1054, 758; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 5.93 (s, 1H, CH), 7.75–7.79 (m, 1H, Ar–H), 7.78 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.85–7.94 (m, 5H, Ar–H), 7.97 (d, 2H, $J = 9.2$ Hz, Ar–H), 8.04 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.17 (t, 2H, $J = 8.8$ Hz, Ar–H), 8.40 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.62 (d, 1H, $J = 8.0$ Hz, Ar–H), 9.12 (d, 1H, $J = 8.0$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 32.1, 111.5, 113.8, 114.2, 118.0, 121.5, 122.6, 122.8, 122.9, 124.7, 128.0, 128.5, 128.7, 129.2, 130.0, 130.2, 130.6, 132.6, 133.7, 134.5, 136.1, 137.2, 134.5, 136.1, 137.2, 138.7, 140.3, 144.1, 144.9, 145.6, 147.6, 154.5, 177.1, 178.6; MS (*m/z*, %): 535 (M^+, 6); Anal. Calcd for $C_{33}H_{17}N_3O_5$: C, 74.01; H, 3.20; N, 7.85 %. Found: C, 74.15; H, 3.36; N, 7.92 %.

*17-(4-Chlorophenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5b**)*

Orange solid; yield 91 %, 0.476 g; mp 324–326 °C; IR (KBr) (ν_{max}, cm^{-1}): 3035, 1688, 1651, 1632, 1590, 1483, 1352, 1286, 1164, 1049, 757; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 5.98 (s, 1H, CH), 7.19 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.56 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.77 (td, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.6$ Hz, Ar–H), 7.93–7.98 (m, 3H, Ar–H), 8.00 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.2$ Hz, Ar–H), 8.04 (t, 2H, $J = 6.7$ Hz, Ar–H), 8.25–8.27 (m, 2H, Ar–H), 8.46 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.70 (d, 1H, $J = 7.6$ Hz, Ar–H), 9.22 (d, 1H, $J = 7.6$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 33.3, 113.5, 116.6, 117.5, 120.7, 121.7, 122.4, 124.7, 127.8, 128.6, 128.8, 129.1, 129.3, 130.6, 130.8, 130.9, 131.0, 131.6, 135.2, 138.5, 140.3, 140.8, 141.6, 142.3, 144.9, 149.9, 154.4, 156.2, 176.8, 178.1; MS (*m/z*, %): 524 (M^+, 11); Anal. Calcd for $C_{33}H_{17}ClN_2O_3$: C, 75.50; H, 3.26; N, 5.34 %. Found: C, 75.64; H, 3.19; N, 5.46 %.

*17-(3-Nitrophenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5c**)*

Orange solid; yield 90 %, 0.481 g; mp 368–370 °C; IR (KBr) (ν_{max}, cm^{-1}): 3020, 1686, 1660, 1636, 1590, 1524, 1339, 1286, 1166, 1049, 759; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.16 (s, 1H, CH), 7.46 (t, 1H, $J = 7.6$ Hz, Ar–H), 7.57 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.79–8.12 (m, 9H, Ar–H), 8.27–8.30 (m, 1H, Ar–H), 8.45 (s, 1H, Ar–H), 8.54–8.56 (m, 1H, Ar–H), 8.81 (d, 1H, $J = 8.0$ Hz, Ar–H), 9.26 (t, 1H, $J = 8.0$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 31.5, 113.0, 114.8, 119.4, 120.2, 120.6, 121.0, 123.0, 125.5, 125.7, 125.8, 128.1, 128.9, 129.0, 129.8, 130.7, 134.4, 138.3, 139.6, 140.1, 140.5, 144.9, 146.4, 153.5, 154.9, 175.4, 178.1; MS (*m/z*, %): 535 (M^+, 3); Anal. Calcd for $C_{33}H_{17}N_3O_5$: C, 74.01; H, 3.20; N, 7.85 %. Found: C, 74.12; H, 3.33; N, 7.73 %.

*17-(2-Nitrophenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5d**)*

Brown solid; yield 90 %, 0.481 g; mp 293–295 °C; IR (KBr) (ν_{max}, cm^{-1}): 3035, 1688, 1655, 1630, 1590, 1526, 1341, 1286, 1171, 1048, 761; ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.14 (s, 1H, CH), 7.39–7.44 (m, 1H, Ar–H), 7.53 (t, 1H, $J = 7.6$ Hz, Ar–H), 7.61–7.66 (m, 1H, Ar–H), 7.73 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.85–8.11 (m, 8H, Ar–H), 8.24 (d, 1H, $J = 8.0$ Hz, Ar–H), 8.49 (t, 1H, $J = 7.2$ Hz, Ar–H), 8.71 (d, 1H, $J = 8.4$ Hz, Ar–H), 9.18 (t, 1H, $J = 7.6$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 32.6, 114.1, 115.0, 116.1, 119.0, 120.0, 121.0, 122.8, 126.2, 126.3, 126.4, 127.3, 129.2, 130.2, 130.5, 130.7, 131.1, 131.4, 132.3, 133.7, 135.2, 139.6, 140.5, 143.7, 145.5, 146.9, 155.1, 156.5, 177.4, 178.3; MS (*m/z*, %): 535 (M^+, 7); Anal. Calcd for $C_{33}H_{17}N_3O_5$: C, 74.01; H, 3.20; N, 7.85 %. Found: C, 74.11; H, 3.38; N, 8.02 %.

*17-(2-Chlorophenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5e**)*

Orange solid; yield 89 %, 0.466 g; mp 336–338 °C; IR (KBr) (ν_{max}, cm^{-1}): 3035, 1687, 1657, 1635, 1585, 1493, 1349, 1286, 1165, 1048, 757; ^1H NMR (400 MHz, DMSO-d_6): δ_H 5.49 (s, 1H, CH), 7.04 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.20 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.36–7.49 (m, 2H, Ar–H), 7.73–8.28 (m, 10H, Ar–H), 8.54 (d, 1H, $J = 8.0$ Hz, Ar–H), 9.23–8.28 (m, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 32.0, 114.0, 114.4, 115.1, 121.6, 122.5, 123.1, 128.6, 129.0, 129.3, 129.4, 131.4, 131.8, 131.9, 132.7, 133.4, 133.9, 134.0, 134.3, 134.7, 139.0, 139.6, 140.3, 143.5, 144.1, 146.7, 148.3, 156.2, 175.9, 176.8; MS (*m/z*, %): 524 (M^+, 10); Anal. Calcd for $C_{33}H_{17}ClN_2O_3$: C, 75.50; H, 3.26; N, 5.34 %. Found: C, 75.42; H, 3.34; N, 5.47 %.

*17-(p-tolyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5f**)*

Orange solid; yield 87 %, 0.438 g; mp 333–335 °C; IR (KBr) (ν_{max}, cm^{-1}): 2895, 1687, 1655, 1635, 1588, 1493, 1350, 1285, 1162, 1048, 752; ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.20 (s, 3H, CH_3), 5.08 (s, 1H, CH), 6.98 (t, 1H, $J = 7.6$ Hz, Ar–H), 7.06 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.32 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.46–7.52 (m, 1H, Ar–H), 7.74 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.88–8.13 (m, 6H, Ar–H), 8.35 (t, 1H, $J = 8.0$ Hz, Ar–H), 8.54–8.59 (m, 1H, Ar–H), 9.31 (t, 1H, $J = 8.0$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 20.6, 33.8, 112.5, 114.2, 115.3, 115.7, 120.7, 121.6, 122.3, 123.4, 125.9, 128.4, 128.7, 128.8, 128.9, 129.0, 129.9, 130.3, 131.2, 131.7, 132.8, 134.7, 136.4, 138.9, 139.6, 140.3, 140.7, 144.6, 155.1, 155.5, 177.2, 178.1; MS (*m/z*, %): 504 (M^+, 6); Anal. Calcd for $C_{34}H_{20}N_2O_3$: C, 80.94; H, 4.00; N, 5.55 %. Found: C, 81.09; H, 4.14; N, 5.39 %.

*17-(2,4-Dichlorophenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16 (17H)-dione (**5g**)*

Orange solid; yield 85 %, 0.474 g; mp 330–332 °C; IR (KBr) (ν_{max}, cm^{-1}): 3040, 1686, 1655, 1640, 1588, 1493, 1351, 1286, 1166, 1048, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 5.43 (s, 1H, CH), 7.08 (d, 1H, $J = 9.2$ Hz, Ar–H), 7.26 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.39–7.43 (m, 1H, Ar–H), 7.46 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.72–8.23 (m, 8H, Ar–H), 8.44 (d, 1H, $J = 7.2$ Hz, Ar–H), 8.69 (d, 1H, $J = 8.0$ Hz, Ar–H), 9.18 (d, 1H, $J = 8.4$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 32.4, 110.3, 114.7, 115.7, 116.2, 118.5, 120.3, 122.5, 124.7, 124.8, 126.1, 127.1, 127.2, 128.0, 128.6, 129.4, 130.7, 131.8, 135.4, 137.4, 138.9, 140.5, 141.2, 141.7, 146.7, 147.5, 149.3, 154.6, 155.1, 174.9, 175.4; MS (*m/z*, %): 558 (M^+, 8); Anal. Calcd for $C_{33}H_{16}Cl_2N_2O_3$: C, 70.85; H, 2.88; N, 5.01 %. Found: C, 70.77; H, 3.03; N, 5.14 %.

*17-(4-Methoxyphenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16 (17H)-dione (**5h**)*

Orange solid; yield 86 %, 0.447 g; mp 341–342 °C; IR (KBr) (ν_{max}, cm^{-1}): 3025, 1688, 1651, 1640, 1590, 1500, 1352, 1285, 1163, 1027, 752; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.56 (s, 3H, OCH_3), 5.05 (s, 1H, CH), 6.72 (d, 1H, $J = 8.8$ Hz, Ar–H), 6.81 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.34 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.48 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.71–8.10 (m, 8H, Ar–H), 8.33 (t, 1H, $J = 8.4$ Hz, Ar–H), 8.52 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.78 (d, 1H, $J = 7.6$ Hz, Ar–H), 9.29 (t, 1H, $J = 8.4$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 33.5, 55.8, 113.6, 113.8, 114.5, 117.7, 120.9, 121.8, 124.6, 125.9, 126.8, 129.1, 129.6, 130.0, 130.3, 131.2, 131.3, 131.7, 135.5, 139.5, 140.0, 141.0, 141.6, 142.9, 146.9, 153.2, 153.6, 156.9, 176.5, 178.3; MS (*m/z*, %): 520 (M^+, 5); Anal. Calcd for $C_{34}H_{20}N_2O_4$: C, 78.45; H, 3.87; N, 5.38 %. Found: C, 78.60; H, 4.01; N, 5.25 %.

*3-(11,16-Dioxo-16,17-dihydro-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazin-17-yl)benzonitrile (**5i**)*

Brown solid; yield 89 %, 0.458 g; mp 289–291 °C; IR (KBr) (ν_{max}, cm^{-1}): 2935, 2260, 1689, 1660, 1643, 1591, 1496, 1347, 1287, 1165, 1049, 754; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 5.89 (s, 1H, CH), 7.35 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.47 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.75 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.74–8.19 (m, 10H, Ar–H), 8.37 (t, 1H, $J = 8.0$ Hz, Ar–H), 8.56–8.64 (m, 1H, Ar–H), 9.08 (t, 1H, $J = 8.0$ Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 33.5, 113.9, 115.1, 116.6, 118.4, 121.6, 122.8, 125.2, 129.0, 129.4, 129.5, 129.6, 130.4, 130.9, 131.0, 131.1, 131.2, 131.3, 131.8, 132.0, 133.1, 134.8, 140.2, 140.3, 141.8, 143.5, 146.0, 155.9, 158.9, 175.9, 177.4; MS (*m/z*, %): 515 (M^+, 12); Anal. Calcd for $C_{34}H_{17}N_3O_3$: C, 79.21; H, 3.32; N, 8.15 %. Found: C, 79.18; H, 3.44; N, 8.31 %.

*17-(5-Bromo-2-hydroxyphenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5j**)*

Brown solid; yield 86 %, 0.502 g; mp 359–361 °C; IR (KBr) (ν_{max}, cm^{-1}): 3030, 1689, 1645, 1615, 1582, 1519, 1331, 1284, 1122, 1075, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 5.68 (s, 1H, CH), 7.11 (d, 1H, $J = 7.6$ Hz, Ar–H), 7.47 (d, 1H, $J = 8.4$ Hz, Ar–H), 8.00–8.14 (m, 8H, Ar–H), 8.33–8.37 (m, 3H, Ar–H), 8.86 (d, 1H, $J = 8.0$ Hz, Ar–H), 9.33 (d, 1H, $J = 7.6$ Hz, Ar–H), 10.62 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 32.6, 115.9, 116.9, 117.2, 120.0, 121.8, 123.7, 124.2, 125.4, 127.3, 129.3, 129.4, 129.6, 130.5, 130.8, 131.2, 131.7, 132.1, 134.2, 136.0, 140.1, 140.6, 141.4, 145.4, 148.7, 152.5, 154.1, 156.5, 176.0, 177.4; MS (*m/z*, %): 584 (M^+, 9); Anal. Calcd for $C_{33}H_{17}BrN_2O_4$: C, 67.71; H, 2.93; N, 4.79 %. Found: C, 67.83; H, 284; N, 4.68 %.

*17-(2-Hydroxy-5-nitrophenyl)-11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione (**5k**)*

Brown solid; yield 88 %, 0.484 g; mp 364–366 °C; IR (KBr) (ν_{max}, cm^{-1}): 3035, 1685, 1658, 1640, 1587, 1524, 1340, 1270, 1165, 1049, 759; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 5.24 (s, 1H, CH), 7.46 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.57 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.73–7.81 (m, 1H, Ar–H), 7.87–8.13 (m, 8H, Ar–H), 8.27 (s, 1H, Ar–H), 8.52 (d, 1H, $J = 8.0$ Hz, Ar–H), 8.77 (d, 1H, $J = 8.0$ Hz, Ar–H), 9.23 (t, 1H, $J = 8.0$ Hz, Ar–H), 10.15 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 33.2, 112.8, 116.4, 118.5, 119.6, 121.0, 121.9, 123.8, 125.7, 125.8, 125.9, 128.4, 129.3, 129.6, 130.1, 130.5, 130.8, 131.5, 131.6, 134.1, 134.4, 135.9, 138.6, 140.1, 140.6, 142.0, 147.0, 154.3, 157.9, 176.1, 177.9; MS (*m/z*, %): 551 (M^+, 4); Anal. Calcd for $C_{33}H_{17}N_3O_6$: C, 71.87; H, 3.11; N, 7.62 %. Found: C, 71.80; H, 3.28; N, 7.74 %.

Results and discussion

The strategy provided C–C, C=C, C–N, C=N, and C–O bonds in a single operation through condensation/Knoevenagel/Michael/annulation sequences. In order to investigate the reaction conditions for the synthesis of 11*H*-benzo[*a*]benzo[6,7]-chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives, we carried out the reaction between 2-hydroxynaphthalene-1,4-dione (2 mmol), *o*-phenylenediamine (1 mmol) and 4-nitrobenzaldehyde (1 mmol) as a model. Initially, we began this domino one-pot four-component reaction in the absence of a catalyst in EtOH under reflux and the product was obtained in very low yield after a long time.

Thus, our efforts were focused on the search for a suitable catalyst. At first, Lewis acids such as $ZnCl_2$ and $FeCl_3$ (20 mol%) were chosen as a catalyst to perform this reaction. As a result, low yields were obtained after a prolonged time (Table 1, entries 2, 3). Attempts with HCl and H_2SO_4 as a catalyst were successful, which afforded the corresponding products in 3 h with 78 and 83 % yield, respectively (Table 1, entries 4, 5). Eventually, we discovered that PTSA showed excellent

Table 1 Optimization of reaction conditions to domino one-pot four-component synthesis of compound **5a** from 2-hydroxynaphthalene-1,4-dione (2 mmol), *o*-phenylenediamine (1 mmol) and 4-nitrobenzaldehyde (1 mmol) under various conditions

Entry	Catalyst (mol%)	Reaction conditions	Time (h)	Yield (%)[a]
1	No catalyst	EtOH, reflux	8	Trace
2	$ZnCl_2$ (20 mol%)	EtOH, reflux	6	45
3	$FeCl_3$ (20 mol%)	EtOH, reflux	6	40
4	HCl (20 mol%)	EtOH, reflux	3	78
5	H_2SO_4 (20 mol%)	EtOH, reflux	3	83
6	PTSA (20 mol%)	EtOH, reflux	3	88
7	PTSA (20 mol%)	H_2O, reflux	3	71
8	PTSA (20 mol%)	Toluene, 100 °C	3	62
9	PTSA (20 mol%)	THF, reflux	3	70
10	PTSA (20 mol%)	CH_3CN, reflux	3	75
11	PTSA (20 mol%)	DMF, 100 °C	3	64
12	PTSA (20 mol%)	PEG-400, rt	8	Trace
13	PTSA (20 mol%)	PEG-400, 70 °C	3	91
14	PTSA (20 mol%)	PEG-400, 80 °C	2	93
15	PTSA (20 mol%)	PEG-400, 100 °C	1	91
16	PTSA (20 mol%)	PEG-400, 100 °C	6	94
17	PTSA (30 mol%)	PEG-400, 80 °C	2	93
18	PTSA (10 mol%)	PEG-400, 80 °C	2	87

[a] Isolated yields

catalytic activity in terms of reaction time as well as yield of the product. We then examined the effect of different solvents on the model reaction. As Table 1 indicates, the best results were obtained by heating the reaction mixture in PEG-400 at 80 °C (Table 1, entry 14) and also other protic solvents showed much better performance relative to aprotic solvents. The effect of amount of catalyst on the conversion and rate of the reaction was evaluated by varying the amount of PTSA in PEG-400 at 80 °C (Table 1, entries 14, 17, 18). It turned out that 20 mol% of PTSA was enough to carry out the reaction smoothly (Table 1, entry 14). An increase in the amount of PTSA more than 20 mol% showed no remarkable improvement in the yield, whereas the yield was reduced by decreasing the amount of PTSA to 10 mol%. So, a domino one-pot reaction of 2-hydroxynaphthalene-1,4-dione (2 mmol), *o*-phenylenediamine (1 mmol) and aldehyde (1 mmol) using 20 mol% of PTSA as catalyst in PEG-400 at 80 °C proved to be the optimum conditions. This two-step process allows the one-pot four-component domino or tandem reaction to be controlled, avoiding the separation of intermediates, as well as time-consuming and costly purification processes [46].

We next realized the generality and versatility of the PTSA as a catalyst using these optimized conditions, the reaction scope was studied by using different aromatic aldehydes. All the reactions were complete in 2–3 h and resulted in the formation of the target structures (Scheme 1; Table 2, entries 1–11) in high yields

Table 2 Domino one-pot four-component synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives in the presence of PTSA (20 mol%) as catalyst in PEG-400 at 80 °C

Entry	Aldehydes	Product	Time (h)	Yield (%)[a]
1	4-$NO_2C_6H_4$	**5a**	2	93
2	4-ClC_6H_4	**5b**	2	91
3	3-$NO_2C_6H_4$	**5c**	2	90
4	2-$NO_2C_6H_4$	**5d**	2	90
5	2-ClC_6H_4	**5e**	2	89
6	4-$CH_3C_6H_4$	**5f**	2	87
7	2,4-$Cl_2C_6H_3$	**5g**	3	85
8	4-$CH_3OC_6H_3$	**5h**	3	86
9	3-CNC_6H_4	**5i**	3	89
10	5-Br-2-OHC_6H_3	**5j**	3	86
11	2-OH-5-$NO_2C_6H_3$	**5k**	3	88
12	*n*-Heptanal	–	8	–
13	*n*-Octanal	–	8	–

[a] Isolated yields

and no clear electronic effects of the aldehyde were observed. In the presence of aliphatic aldehydes such as *n*-heptanal and *n*-octanal, the expected product was not obtained in these reaction conditions even after 8 h (Table 2, entries 12, 13).

The structures of all 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives **5a–k** are in complete agreement with IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values.

Since hazardous organic solvents are a significant challenge in synthetic chemistry, we used polyethylene glycol (PEG-400) as a recyclable medium instead of volatile organic solvents without the addition of an organic co-solvent. We also, for recyclability of the solvent, investigated the recycling of PEG-400 at 80 °C using a selected model reaction of 2-hydroxynaphthalene-1,4-dione, *o*-phenylenediamine and 4-nitrobenzaldehyde (Table 2, entry 1). After completion of the reaction, the reaction mixture was quenched with water and filtered for separation of the crude product. The filtrate containing polyethylene glycol was rinsed with diethyl ether and further vacuumed to dryness at 90 °C for 2 h to remove any trapped water, which afforded PEG-400 which was reused directly for the next run. As shown in Fig. 1, the reaction media could be successfully recycled for up to four runs with limited loss of activity (the yield decreased from 93 to 82 % after four runs; Fig. 1).

The plausible mechanism of this domino reaction consistent with the above results is depicted in Scheme 2. Initially, in this mechanism, 2-hydroxynaphthalene-1,4-dione **1** tautomrizes to intermediate **6**. The primary condensation of **6** with *o*-phenylenediamine **2** obtains 6*H*-benzo[*a*]phenazin- 5-one **7**, which in tautomerism equilibrium prepares benzo[*a*]phenazin-5-ol **3**. The catalyst PTSA appears to play a key role as acid in the reaction to form (6-benzylidenebenzo[*a*]phenazin-5(6*H*)-

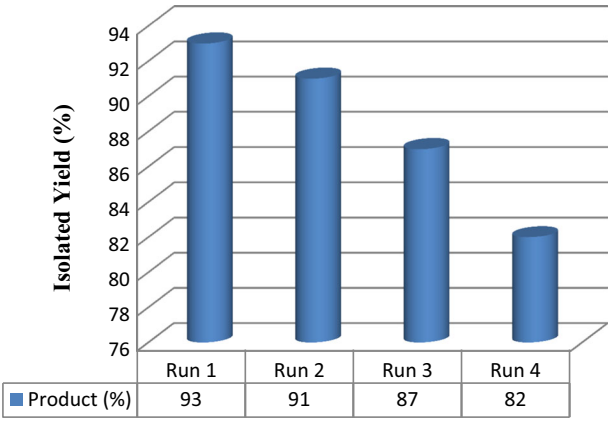
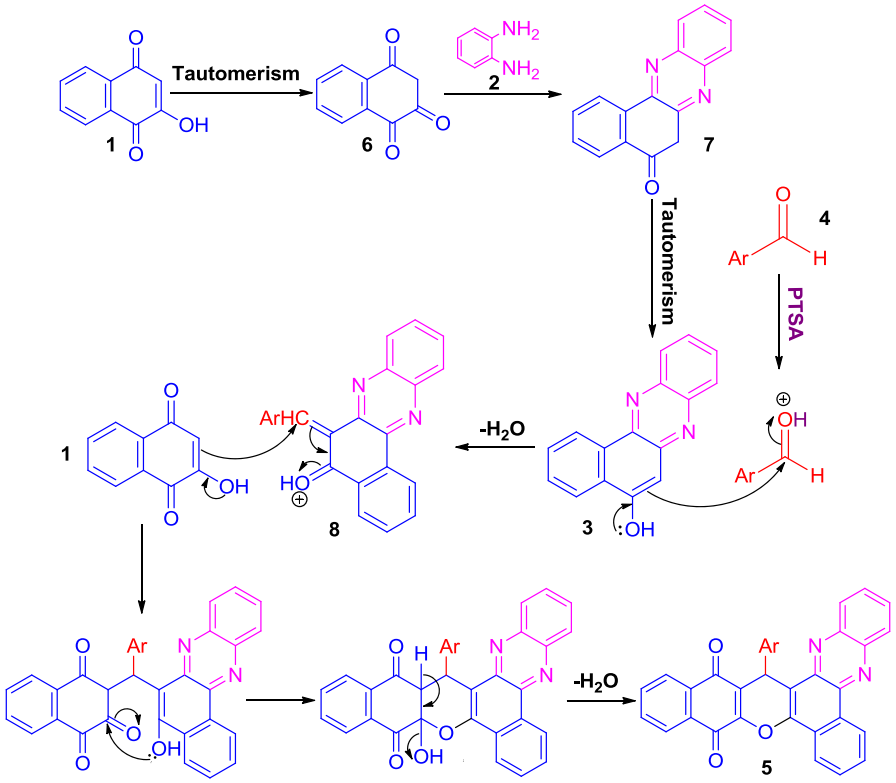


Fig. 1 Recycling and reuse of PEG-400



Scheme 2 Proposed mechanism for the synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives

ylidene)oxonium **8**, which prepares in situ from condensation of aldehyde **4** with benzo[*a*]phenazin-5-ol **3**. Subsequent Michael addition of 2-hydroxynaphthalene-1,4-dione **1** with (6-benzylidenebenzo[*a*]phenazin-5(6*H*)-ylidene)oxonium **8**, followed by cyclization and dehydration, leads to the formation of the desired product **5**.

Conclusions

In this context, we demonstrated a green and straightforward procedure for the efficient synthesis of novel 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives in high yields via one-pot, four-component domino protocol by using PTSA as a mild, effective, non-toxic and inexpensive solid acid catalyst and PEG-400 as a recyclable medium without the addition of organic co-solvent. The operational simplicity, easy work-up, high atom economy, high yields and environmentally friendly are the advantages of this protocol. In all these cases, our work has introduced green and economically cost-effective. Furthermore, our work is expected to exhibit interesting pharmacology activities and may act as potential drug candidates, since phenazine and chromene motifs have a vast range of biological activities.

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