Catalysis Letters (2020) 150:1659–1668
https://doi.org/10.1007/s10562-019-03057-2

A Convenient and Green Synthetic Approach for Benzo[*a*]pyrano[2,3-*c*] phenazines via Supramolecular Catalysis

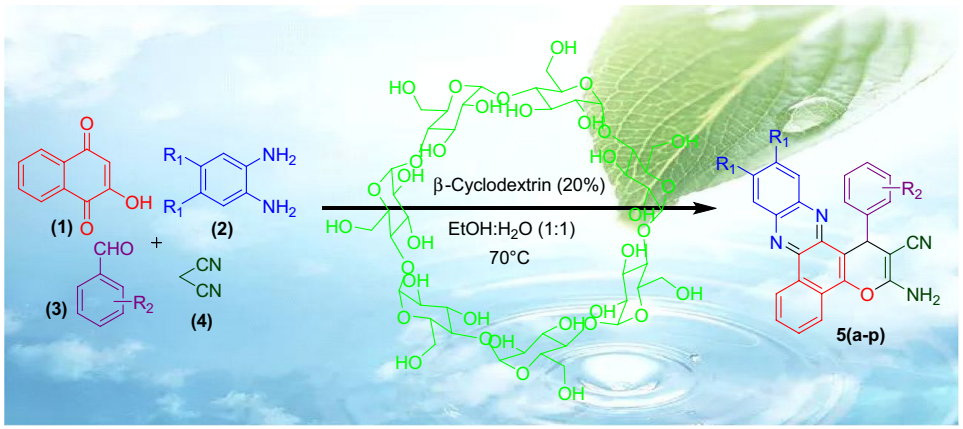
Anu Mishra[1] · Yogesh Kumar Pandey[1] · Fatima Tufail[1] · Jaya Singh[2] · Jagdamba Singh[1]

Received: 26 September 2019 / Accepted: 25 November 2019 / Published online: 11 December 2019

Abstract

A pragmatic and swift method for the synthesis of Benzo[*a*]pyrano[2,3-*c*]phenazine derivatives via one pot, multicomponent strategy by employing β-cyclodextrin in EtOH:H_2O (1:1) solvent at 70 °C has been documented here. Utilization of supramolecular catalyst β-cyclodextrin which is highly efficient, green, biodegradable and reusable catalyst augments the synthesis amazingly, is the key feature of the current pathway. The catalyst could be recovered for four successive cycles without significant loss in catalytic activity.

Graphic Abstract



Keywords Green synthesis · Supramolecular catalysis · β-cyclodextrin · EtOH:H_2O (1:1) · Benzo[*a*]pyrano[2 · 3-*c*] phenazines

1 Introduction

On the ground of environmental concerns, chemists and researchers are switching their interest towards synthetic processes which incorporate the environmentally benign reagents for the synthesis of highly privileged scaffolds and this has emerged as a phenomenally recommended platform [1–3]. Taking into account the principle of green chemistry, avoiding hazardous reaction conditions by utilization of renewable feedstocks and supramolecular chemistry has acquired prodigious significance [4–6]. Chemical reactions in the presence of a supramolecular catalyst which is

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10562-019-03057-2) contains supplementary material, which is available to authorized users.

✉ Jagdamba Singh
dr.jdsau@gmail.com

Jaya Singh
nimesh.singh@in.abb.com

[1] Environmentally Benign Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211002, India

[2] Department of Chemistry, LRPG College, Sahibabad, Uttar Pradesh, India

derived from biomass, boost the sustainability of the procedure [7–9]. Within this context, cyclodextrins (CDs), cyclic oligosaccharides of D(+)-glucopyranosyl units which are associated by α-1,4-glycosidic linkage, have noteworthy engrossment with an exclusive characteristic of hydrophilic exterior and a hydrophobic central void. Cyclodextrins, generally obtained by the enzymatic degradation of starch have characteristic cylindrical shape with a narrow and a broad end. One primary hydroxyl group is present at the narrower end where as secondary hydroxyl groups are present at the second and third carbon of the broader end of cyclodextrin [10–12]. On the basis of the number of D(+)-glucopyranosyl units, CDs are generally classified into 3 categories namely α-, β and γ-CDs having 6, 7 and 8 D(+)-glucopyranosyl units, respectively [13–16]. The diameters of hydrophobic cavities for different CDs (α-, β and γ-CDs) are in the order of 0.47–0.56, 6.0–6.5 and 7.5–8.3 nm, respectively and the heights of all CDs are around 0.78 nm [13]. The structure of cyclodextrins facilitates them to form inclusion complexes with numerous substrates via weak interactions like non-covalent bonding, H-bonding and vander waal forces of attraction and by ensnaring the substrate into their hydrophobic cavities [9, 16–18]. Among the three, β-cyclodextrin (β-CD) is the most frequently used CD. These attributes of CDs invigorated us to carry out our reaction in presence of β-cyclodextrin.

Now-a-days, atom and step economic approaches are utilized under the heading of multicomponent reactions (MCRs) for the straightforward access of diverse classes of compounds and this has emerged as a key tool for ecofriendly and sustainable protocols in organic synthesis [19–22].

Benzo[*a*]pyrano[2,3-*c*]phenazine, a nitrogen and oxygen containing heterocyclic compound, reveals tremendous biological and pharmaceutical significance. It consists of two characteristic units of important classes of heterocyclic compounds in which one is nitrogen-containing phenazine unit and the other one is oxygen containing pyran (Fig. 1). Phenazines form the core structure of various natural and synthetic products [23] and exhibit diverse biological activities as antiplatelet [24], antimalarial [25], fungicidal [26], antitumor [27], trypanocidal [28] and anti-inflammatory activities [29]. In addition, they are also used as pesticides and dyestuffs [30].

Similarly, Pyrans are also present as a key motif in various natural products and pharmaceuticals as polyether antibiotics, alkaloids and carbohydrates [31, 32]. Compounds with pyran scaffold shows astonishing biological importances such as antitumor, antifungal, antioxidant, antileishmanial, anticoagulant, anticonvulsant and antimicrobial activities. In addition, they are extensively used as potential biodegradable agrochemicals, pigments and cosmetics [33–36] (Fig. 2).

Even though, various synthetic pathways for Benzo[*a*]pyrano[2,3-*c*]phenazine and its derivatives have been reported [30, 37–47] but some of them are endured with some downsides. In view of the vast biological significance of Benzo[*a*]pyrano[2,3-*c*]phenazine and our ongoing interest in the development of new green synthetic methodologies for heterocyclic compounds [48–53], we sought to develop a straightforward and facile domino synthetic protocol for Benzo[*a*]pyrano[2,3-*c*]phenazines by using 2-hydroxynaphthalene-1,4-dione, o-phenylenediamines, aromatic aldehydes and malononitrile as reactants in presence of β-cyclodextrin in EtOH:H_2O (1:1) solvent at 70 °C (Scheme 1).

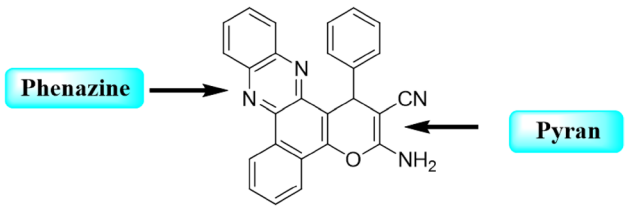
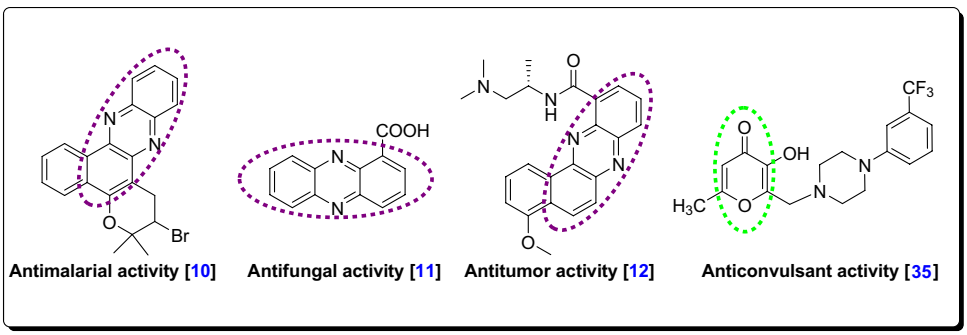
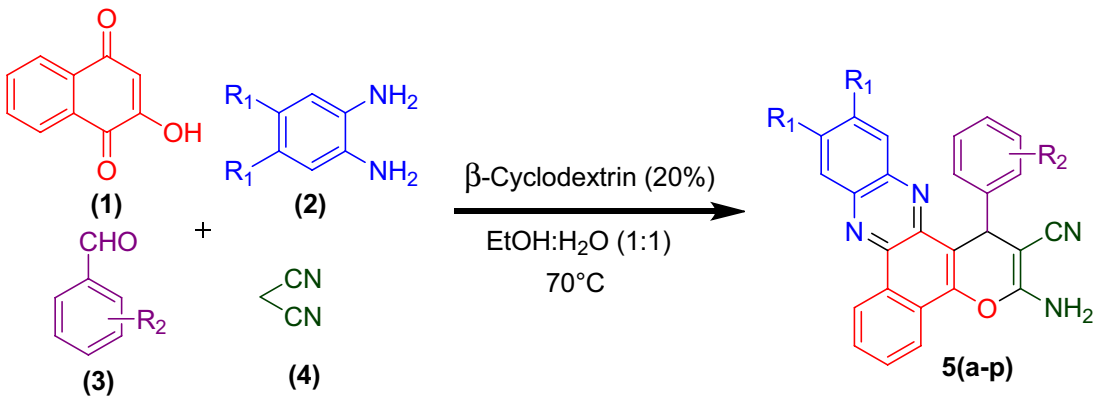


Fig. 1 Structure of Benzo[*a*]pyrano[2,3-*c*]phenazine showing Phenazine and Pyran unit

Fig. 2 Some biologically active derivatives of Phenazines and Pyran





Scheme 1 Synthesis of Benzo[*a*]pyrano[2,3-*c*]phenazines

2 Experimental

2.1 General Information

Reagents were obtained from commercial suppliers and used without further purification unless otherwise specified by a reference. All reactions were performed using oven-dried glass wares. Organic solutions were concentrated using a Buchi rotary evaporator. TLC was performed using silica gel GF254 (Merck) plates. Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer, ^{1}HNMR and ^{13}C NMR spectra were recorded on a Bruker AVII 400 and 100 MHz spectrometer in DMSO-d_6 using TMS as internal reference with chemical shift value being reported in ppm. All coupling constants (J) have been reported in Hertz (Hz).

2.2 General Method for the Synthesis of Benzo[*a*]pyrano[2,3-*c*]phenazine Derivatives (5a-p)

To a homogeneous solution of β-cyclodextrin (20 mol%) in 15 ml of ethanol:water (1:1) at 70 °C, 1.0 mmol of 2-hydroxynaphthalene-1,4-dione (**1**), o-phenylenediamine (**2**), aromatic aldehyde (**3**) and malononitrile (**4**) were added and stirred until the completion of reaction (monitored by TLC) then water (10 ml) was added. Product was precipitated out which was filtered off by using Whatman filter paper. The crude product was purified by column chromatography by using ethyl acetate and hexane as eluent. All the desired products were known and were characterized by the comparison of their spectra and melting points with those reported in the literature [37–47].

2.3 Spectral Data of Compounds

2.3.1 3-Amino-1-phenyl-1H-benzo[a]pyrano[2,3-c] phenazine-2-carbonitrile (5a)

Yellow solid, M.P.: 297–299 °C; IR (KBr) ν (cm^{-1}): 3440, 3315, 3171, 2183, 1652, 1626, 1595, 1544, 1491, 1477, 1400, 1381, 1353, 1322, 1263, 1165, 1121, 1048, 1021, 759, 731, 704; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.15 (d, 1H, J = 7.6 Hz), 8.40 (d, 1H, J = 8.0 Hz), 8.23–8.20 (m, 1H), 8.10–8.07 (m, 1H), 8.01–7.91 (m, 4H), 7.42–7.38 (m, 4H), 7.22 (t, 2H, J = 7.6 Hz), 7.10–7.06 (m, 1H), 5.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.6, 146.5, 145.2, 141.2, 140.2, 140.1, 139.5, 130.5, 130.3, 130.1, 129.7, 129.2, 129.0, 128.4, 128.1, 127.3, 126.3, 125.2, 124.4, 122.0, 120.3, 113.6, 58.0, 37.1; MS (ESI) *m/z*: 400.

2.3.2 3-Amino-1-(4-chloro-phenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5b)

Yellow solid, M.P.: 286–289 °C; IR (KBr) ν (cm^{-1}): 3449, 3304, 3170, 2181, 1658, 1621, 1590, 1483, 1470, 1400, 1381, 1345, 1322, 1288, 1262, 1160, 1101, 1081, 1049, 1012, 843, 756, 747; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29–9.27 (d, 1H, J = 8.76 Hz), 8.49–8.47 (d, 1H, J = 8.6 Hz), 8.33–8.31 (m, 1H), 8.21–8.18 (m, 1H), 8.05–7.94 (m, 4H), 7.47–7.45 (m, 4H), 7.31–7.28 (m, 2H), 5.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.6, 152.0, 144.1, 140.3, 139.6, 131.1, 130.6, 130.2, 130.1, 130.0, 129.3, 129.1, 128.4, 128.0,125.3, 124.4, 122.0, 120.1, 113.1, 57.3; MS (ESI) *m/z*: 434.

2.3.3 3-Amino-1-(2-chlorophenyl)-1H-benzo[c] pyrano[2,3-c]phenazine-2-carbonitrile (5c)

Yellow solid, M.P.: 300–302 °C; IR (KBr) ν (cm^{-1}): 3331, 3237, 3144, 2981, 1653, 1581, 1472, 1383, 1271, 1153,

1038, 950, 831, 755; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (d, 1H, J = 8.0 Hz), 8.48 (d, 1H, J = 8.0 Hz), 8.30–8.27 (m, 1H), 8.04–7.93 (m, 3H), 7.93–7.90 (m, 2H), 7.42–7.40 (m, 1H), 7.34 (s, 2H), 7.23–7.21 (m, 1H), 7.13–7.09 (m, 2H), 6.01 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.1, 159.1, 146.3, 142.3, 141.2, 140.3, 140.0, 139.6, 132.0, 130.6, 130.3, 130.1, 130.0, 129.2, 129.1, 129.0, 128.3, 128.0, 127.1, 125.2, 124.5, 122.1, 119.2, 112.7, 56.6, 36.5; MS (ESI) *m/z*: 434.

2.3.4 3-Amino-1-(2,4-dichlorophenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5d)

Brown solid, M.P.: 305–308 °C; IR (KBr) ν (cm^{-1}): 3471, 3310, 3162, 3063, 2181, 1653, 1620, 1584, 1463, 1400, 1381; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.17 (d, 1H, J = 8.0 Hz), 8.40 (d, 1H, J = 8.0 Hz), 8.19–8.21 (m, 1H), 7.86–8.02 (m, 5H), 7.51 (s, 1H), 7.38 (s, 2H), 7.18 (d, 1H, J = 8.0 Hz), 7.11 (d, 1H, J = 8.0 Hz), 5.82 (s, 1H); MS (ESI) *m/z*: 469.

2.3.5 3-Amino-1-(4-bromo-phenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5e)

Yellow solid, M.P.: 281–283 °C; IR (KBr) ν (cm^{-1}): 3464, 3311, 3171, 2184, 1657, 1621, 1588, 1400, 1381, 1346, 1327, 1289, 1219, 1161, 1101, 1051, 1007, 841, 753, 676; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.25-9.21 (m, 1H), 8.46–8.44 (m, 1H), 8.30–8.27 (m, 1H), 8.18–8.13 (m, 1H), 8.03–7.91 (m, 4H), 7.44–7.40 (m, 4H), 7.37–7.35 (m, 2H), 5.50 (s, 1H); MS (ESI) *m/z*: 479.

2.3.6 3-Amino-1-(3-bromophenyl)-1H-benzo[a] pyrano[2,3-c] Phenazine-2-carbonitrile (5f)

Brown solid, M.P.: 266–268 °C; IR (KBr) ν (cm^{-1}): 3481, 3300, 3165, 3057, 2191, 1658, 1622, 1587, 1467, 1381; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.20–9.24 (m, 1H), 8.41–8.46 (m, 1H), 8.26–8.30 (m, 1H), 8.12–8.15 (m, 1H), 7.93–8.00 (m, 4H), 7.60–7.62 (m, 1H), 7.45–7.48 (m, 2H), 7.39–7.43 (m, 1H), 7.27–7.31 (m, 1H), 7.17–7.21 (m, 1H), 5.49 (s, 1H); MS (ESI) *m/z*: 479.

2.3.7 3-Amino-1-(4-methoxyphenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5 g)

Yellow solid, M.P.: 268–270 °C; IR (KBr) ν (cm^{-1}): 3428, 3311, 3191, 3041, 2190, 1661, 1592, 1503, 1381; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.25 (d, 1H, J = 8.0 Hz), 8.44 (d, 1H, J = 8.0 Hz), 8.28–8.30 (m, 1H), 8.19–8.21 (m, 1H), 7.93–7.98 (m, 4H), 7.31 (d, 2H, J = 8.0 Hz), 7.17–7.19 (m, 2H), 6.75 (d, 2H, J = 8.0 Hz), 5.48 (s, 1H), 3.60 (s, 3H); MS (ESI) *m/z*: 430.

2.3.8 3-Amino-1-(2-methoxy-phenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5 h)

Yellow solid, M.P.: 268–270 °C; IR (KBr) ν (cm^{-1}): 3309, 3169, 3051, 2827, 2181, 1652, 1621, 1591, 1484, 1471, 1452, 1395, 1381, 1347, 1327, 1287, 1247, 1161, 1100, 1048, 1021, 829, 751; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.25–9.23 (m, 1H), 8.47–8.45 (m, 1H), 8.28–8.24 (m, 1H), 8.05–7.88 (m, 5H), 7.20 (s, 2H), 7.11-7.04 (m, 2H), 6.94 (d, 1H, J = 7.6 Hz), 6.75–6.71 (m, 1H), 5.84 (s, 1H), 3.85 (s, 3H); MS (ESI) *m/z*: 430.

2.3.9 3-Amino-1-(3-methoxyphenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5i)

Yellow solid, M.P.: 236–241 °C; IR (KBr) ν (cm^{-1}): 3416, 3336, 3211, 2189, 1661, 1591, 1487, 1381; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.20 (d, 1H, J = 8.0 Hz), 8.41 (d, 1H, J = 8.0 Hz), 8.23–8.26 (m, 1H), 8.13–8.16 (m, 1H), 7.97 (t, 2H, J = 8.0 Hz), 7.91–7.92 (m, 2H), 7.39 (s, 2H), 7.11 (t, 1H, J = 8.0 Hz), 7.00 (s, 1H), 6.90 (d, 1H, J = 8.0 Hz), 6.65 (d, 1H, J = 8.0 Hz), 5.46 (s, 1H), 3.65 (s, 3H); MS (ESI) *m/z*: 430.

2.3.10 3-Amino-1-p-tolyl-1H-benzo[a]pyrano[2,3-c] phenazine-2-carbonitrile (5j)

Yellow solid, M.P.: 291–293 °C; IR (KBr) ν (cm^{-1}): 3439, 3307, 3171, 2183, 1657, 1621, 1591, 1492, 1471, 1394, 1380, 1346, 1322, 1286, 1261, 1219, 1157, 1101, 1051, 1018, 826, 753, 741; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (d, 1H, J = 8.0 Hz), 8.43–8.42 (m, 1H), 8.27–8.24 (m, 1H), 8.16–8.13 (m, 1H), 8.01–7.90 (m, 4H), 7.32–7.26 (m, 4H), 7.01 (d, 2H, J = 8.0 Hz), 5.45 (s, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.0, 164.1, 159.5, 150.1, 146.2, 141.3, 140.0, 135.3, 130.6, 129.9, 129.3, 129.0, 128.7, 127.4, 125.5, 123.4, 122.0, 118.1, 58.1, 36.9, 20.3; MS (ESI) *m/z*: 414.

2.3.11 3-Amino-1-(4-nitro-phenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5 k)

Yellow solid, M.P.: 280–282 °C; IR (KBr) ν (cm^{-1}): 3327, 3311, 3249, 3195, 2194, 1671, 1588, 1510, 1471, 1399, 1381, 1341, 1289, 1261, 1215, 1162, 1103, 1049, 1021, 823, 768, 741; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.26 (d, 1H, J = 7.6 Hz), 8.48 (d, 1H, J = 8.0 Hz), 8.30-8.28 (m, 1H), 8.15–8.13 (m, 1H), 8.10 (d, 2H, J = 8.4 Hz), 8.05–7.91 (m, 4H), 7.70 (d, 2H, J = 8.8 Hz), 7.54 (s, 2H), 5.66 (s, 1H); MS (ESI) *m/z*: 445.

2.3.12 3-Amino-1-(3-nitro-phenyl)-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5 l)

Yellow solid, M.P.: 276–278 °C; IR (KBr) ν (cm^{-1}): 3421, 3333, 3194, 2187, 1661, 1625, 1591, 1521, 1492, 1471, 1397, 1384, 1341, 1288, 1261, 1161, 1102, 1049, 1022, 808, 758, 726, 692; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.11 (d, 1H, J = 7.6 Hz), 8.40 (d, 1H, J = 8.0 Hz), 8.28 (s, 1H), 8.20–8.12 (m, 1H), 8.05–8.03 (m, 1H), 7.98–7.95 (m, 2H), 7.90–7.86 (m, 4H), 7.53–7.51 (m, 3H), 5.57 (s, 1H); MS (ESI) *m/z*: 445.

2.3.13 3-Amino-11,12-dimethyl-1-phenyl-1H-benzo[a] pyrano[2,3-c]phenazine-2-carbonitrile (5 m)

Yellow solid, M.P.: 295–297 °C; IR (KBr) ν (cm^{-1}): 3471, 3291, 3174, 3023, 2186, 1659, 1631, 1593, 1491, 1385, 1338, 1291, 1262, 1203, 1162, 1105, 1054, 1023, 997, 861, 762; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.11 (d, 1H, J = 8.0 Hz), 8.39 (d, 1H, J = 8.0 Hz), 7.97–7.85 (m, 3H), 7.69 (s, 1H), 7.37–7.34 (m, 4H), 7.21 (t, 2H, J = 7.6 Hz), 7.07 (t, 1H, J = 7.6 Hz), 5.41 (s, 1H), 2.42 (s, 6H); MS (ESI) *m/z*: 428.

2.3.14 3-Amino-11,12-dimethyl-1-(4-nitro-phenyl)-1H-ben zo[a]pyrano[2,3-c]phenazine-2-carbonitrile (5n)

Yellow solid, M.P.: 296–298 °C; IR (KBr) ν (cm^{-1}): 3491, 3319, 3163, 2185, 1656, 1629, 1587, 1509, 1469, 1382, 1341, 1294, 1205, 1165, 1105, 1053, 1021, 853, 824, 756, 711; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.10 (dd, 1H, J = 0.8 Hz, 8.0 Hz), 8.40 (dd, 1H, J = 1.2 Hz, 8.0 Hz), 8.10–8.06 (m, 2H), 8.00–7.90 (m, 2H), 7.84 (s, 1H), 7.63–7.59 (m, 3H), 7.53 (s, 2H), 5.47 (s, 1H), 2.45 (s, 3H), 2.43 (s, 3H); MS (ESI) *m/z*: 473.

2.3.15 3-Amino-11,12-dimethyl-1-(4-bromo-phenyl)-1H-b enzo[a]pyrano[2,3-c]phenazine-2-carbonitrile (5o)

Yellow solid, M.P.: 293–295 °C; IR (KBr) ν (cm^{-1}): 3471, 3361, 3173, 2181, 1657, 1616, 1591, 1480, 1403, 1383, 1341, 1292, 1261, 1204, 1161, 1103, 1055, 1008, 858, 824, 759; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.20–9.18 (m, 1H), 8.44–8.42 (m, 1H), 8.00–7.91 (m, 3H), 7.83 (s, 1H), 7.41–7.38 (m, 4H), 7.35–7.31 (m, 2H), 5.45 (s, 1H), 2.48 (s, 3H), 2.49 (s, 3H); MS (ESI) *m/z*: 507.

2.3.16 3-Amino-11,12-dimethyl-1-(3-nitro-phenyl)-1H-ben zo[a]pyrano[2,3-c]phenazine-2-carbonitrile (5p)

Yellow solid, M.P.: 275–277 °C; IR (KBr) ν (cm^{-1}): 3472, 3329, 3201, 2198, 1711, 1662, 1627, 1590, 1525, 1470, 1387, 1341, 1293, 1264, 1203, 1163, 1100, 1049, 871, 763, 722; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22–9.20 (m, 1H), 8.47–8.45 (m, 1H), 8.25 (t, 1H, J = 2.0 Hz), 8.03–7.91 (m, 5H), 7.87 (s, 1H), 7.56 (d, 1H, J = 8.0 Hz), 7.53 (s, 2H), 5.69 (s, 1H), 2.53 (s, 3H), 2.51 (s, 3H); MS (ESI) *m/z*: 473.

3 Results and Discussion

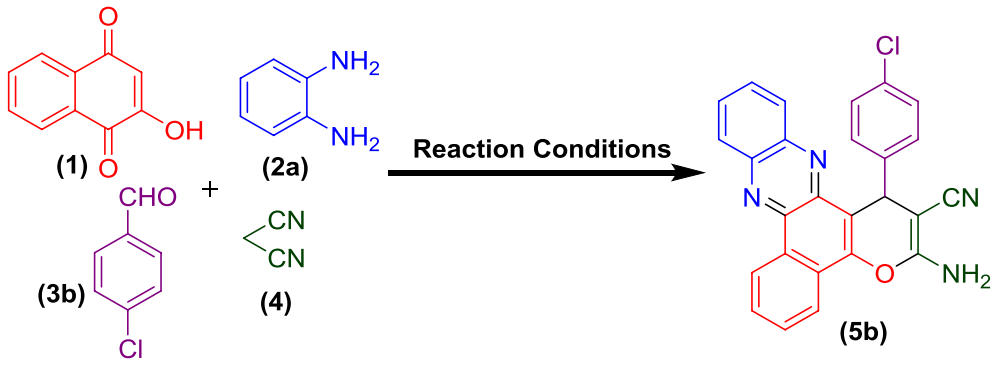
In our initial quest for the optimization of the reaction conditions, we chose 2-hydroxynaphthalene-1,4-dione (**1**), o-phenylenediamine (**2a**), 4-Chlorobenzaldehyde (**3b**) and malononitrile (**4**) as model substrates for the synthesis of Benzo[*a*]pyrano[2,3-*c*]phenazine (**5a**). Initially, due to environmental concerns we chose water in place of widely used organic solvents as reaction medium. Throughout optimization studies, we scrutinized the effect of different catalysts, solvents and temperature on our model reaction. The results have been recapitulated in (Table 1).

In our preliminary pursuit, we took 2-hydroxynaphthalene-1,4-dione (**1**, 1.0 mmol) and o-phenylenediamine (**2a**, 1.0 mmol) in the absence of catalyst at room temperature using water as a solvent and found that product was not formed even after 24 h of stirring (Table 1, entry 1). After this, we attempted the same reaction at 70 °C, yet again formation of product did not take place effectively (Table 1, entry 2). In our next endeavour we used some phase transfer catalysts like cetyltrimethylammonium bromide (CTAB), tetradecyltrimethylammonium bromide (TTAB) and sodium dodecylsulfate (SDS) and observed that the product was formed in very small amount after 12 h of stirring (Table 1, entries 3–5). After that we tried our reaction with cyclodextrins (Table 1, entries 6–8) and observed that β-cyclodextrin in presence of water as a solvent at 70 °C gave the best result with 82% yield of the product within 1 h (Table 1, entry 7).

Once an apposite green catalyst had been recognized for fostering this reaction, we carried out a batch of experiments in presence of different solvents at 70 °C in order to inspect the effect of different solvents on the course of the reaction (Table 1, entries 9–15) and found that EtOH:H_2O (1:1) as a solvent is the most appropriate for our proposed pathway (Table 1, entry 10). Subsequently, we performed a set of reactions with different concentrations of β-cyclodextrin (Table 1, entries 10 and 16–18) and concluded that 20 mol% of β-cyclodextrin is relevant for the present strategy which afforded a 91% yield of product (Table 1, entry 10).

Further, our ensuing effort involved the optimization of temperature for the current protocol (Table 1, entries 10 and 19–21). At first, we carried out the reaction at room temperature which gave only 25% yield of product in 12 h (Table 1, entry 19). Further we carried out the present protocol with 50 °C, 70 °C and 80 °C and the yield of product clearly demonstrated that 70 °C is the most suitable temperature for our synthetic strategy (Table 1, entry 10).

Table 1 Optimization of reaction conditions



Entry	Solvent	Catalyst	Concentration (mol %)	Time (h)	Yield (%)[a]
1	Water	–[b,c]	–	24	–[d]
2	Water	–[b]	–	24	Trace
3	Water	Cetyltrimethylammonium bromide	20	12	34
4	Water	Tetradecyltrimethylammonium bromide	20	12	12
5	Water	Sodium dodecylsulfate	20	12	10
6	Water	α-Cyclodextrin	20	6	42
7	Water	β-Cyclodextrin	20	1	82
8	Water	γ-Cyclodextrin	20	6	40
9	EtOH	β-Cyclodextrin	20	1	72
10	**EtOH:H_2O (1:1)**	**β-Cyclodextrin**	**20**	**1**	**91**
11	EtOH:H_2O (2:1)	β-Cyclodextrin	20	1	80
12	EtOH:H_2O (3:1)	β-Cyclodextrin	20	1	77
13	MeOH	β-Cyclodextrin	20	12	59
14	CH_3CN	β-Cyclodextrin	20	12	37
15	DMF	β-Cyclodextrin	20	12	29
16	EtOH:H_2O (1:1)	β-Cyclodextrin	10	1	78
17	EtOH:H_2O (1:1)	β-Cyclodextrin	30	1	91
18	EtOH:H_2O (1:1)	β-Cyclodextrin	40	1	91
19	EtOH:H_2O (1:1)	β-Cyclodextrin[c]	20	12	25
20	EtOH:H_2O (1:1)	β-Cyclodextrin[e]	20	1	67
21	EtOH:H_2O (1:1)	β-Cyclodextrin[f]	20	1	91

Bold indicates the most suitable reaction condition for our proposed pathway

All reactions were carried out stirring with **1** (1.0 mmol) **2a** (1.0 mmol) **3a** (1.0 mmol) and **4** (1.0 mmol) using different solvent and catalyst under air at 70 °C

[a]Isolated yields

[b]absence of catalyst

[c]at rt

[d]not detected

[e]at 50 °C

[f]at 80 °C

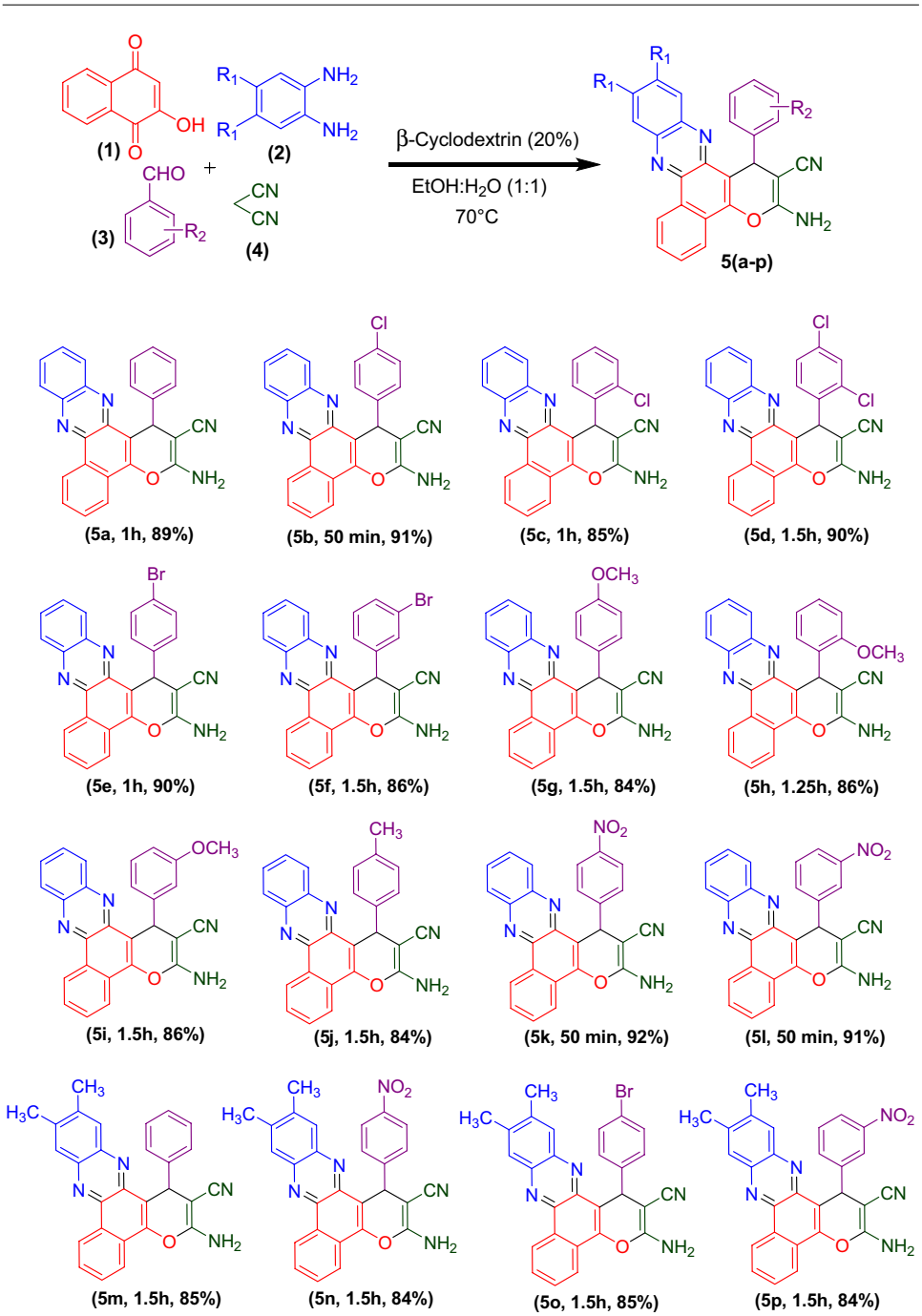
Consequently we managed to identify the optimized reaction conditions for the present transformation. Our reaction works well by using 20 mol% of β-cyclodextrin in EtOH:H_2O (1:1) solvent at 70 °C, affording 91% yield of the product within 1 h with our model substrates.

Once the perfect reaction conditions had been identified, in order to ensure the versatility and generality of the

proposed synthesis, the scope of the reported synthetic strategy was successfully evaluated (Scheme 2). We used different derivatives of o-phenylenediamine (**2**) and aromatic aldehydes (**3**) to achieve the illustrated pathway for the formation of target product (**5a-p**) in good to excellent yields. To our gratification, aromatic aldehydes (**3**) having both an electron withdrawing group and an electron donating group were well endured and afforded a significant yield of the product in all the instances.

3.1 Practicability of the Reaction

To set up the feasibility of the current protocol, we carried out the experiment on a large scale. For this we took our model substrates in a round bottom flask in presence of β-cyclodextrin in EtOH:H_2O (1:1) solvent at 70 °C. 2-hydroxynaphthalene-1,4-dione (**1**, 10 mmol, 1.7415 g), o-phenylenediamine (**2a**, 10 mmol, 1.081 g), 4-chlorobenzaldehyde (**3a,** 10 mmol, 1.40 g) and malononitrile (**4,**



Scheme 2 Substrate scope for 5. All reactions were carried out stirring with 1 (1.0 mmol), 2 (1.0 mmol), 3 (1.0 mmol) and 4 (1.0 mmol) using 20 mol% β-Cyclodextrin as catalyst in EtOH:H2O (1:1) solvent under air at 70 °C.

10 mmol) were reacted to obtain the dihydropyrano[2,3-c] pyrazole (**5b**) in 91% yield in about 50 min by using common laboratory glasswares at 70 °C (Scheme 3).

3.2 Recyclability of β-CD

The reusability of catalyst was explored by investigating it's activity in six cycles in which the initial use of fresh catalyst for the synthesis of Benzo[*a*]pyrano[2,3-*c*]phenazine was also taken into account. In each cycle, the catalyst was almost quantitatively recovered and even after third and fourth use there was a negligible decrease in the quantity and in the effectiveness of the catalyst but after fourth cycle there was appreciable decrease in the quantity and in the effectiveness of the catalyst (Fig. 3).

3.3 Mechanism

A plausible reaction mechanism reconcilable with the above results is depicted in Scheme 4. The desired product is expected to form by the Knoevenagel condensation followed by Michael addition and at last cyclization within the cavity of β-CD where it is anticipated that seven free primary –OH groups of β-CD execute synergistically as a proficient host and supramolecular catalyst [54, 55]. Reactants may form reversible non covalent supramolecular complexes within the cavity in order to increase the localized concentration that results in the dissolution of reactants in the aqueous medium. Initially, the condensation of 2-hydroxynaphthalene-1,4-dione (**1**) and diamine (**2**) takes place to afford the intermediate A. Similar condensation of aldehyde (**3**) and malanonitrile (**4**) occurs to form the intermediate B. After that, intermediate A reacts with intermediate B via Michael addition to yield an intermediate C. Finally, intermediate C undergo cyclization to afford the desired product 5.

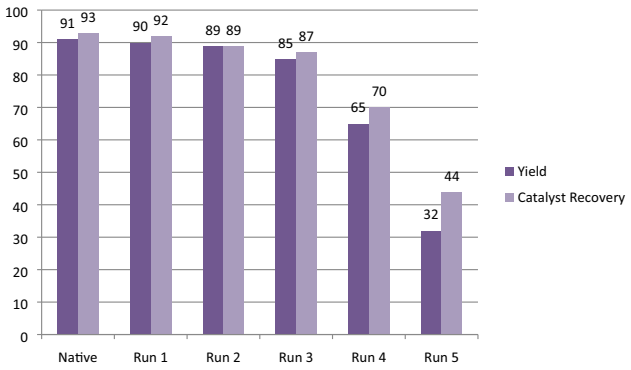
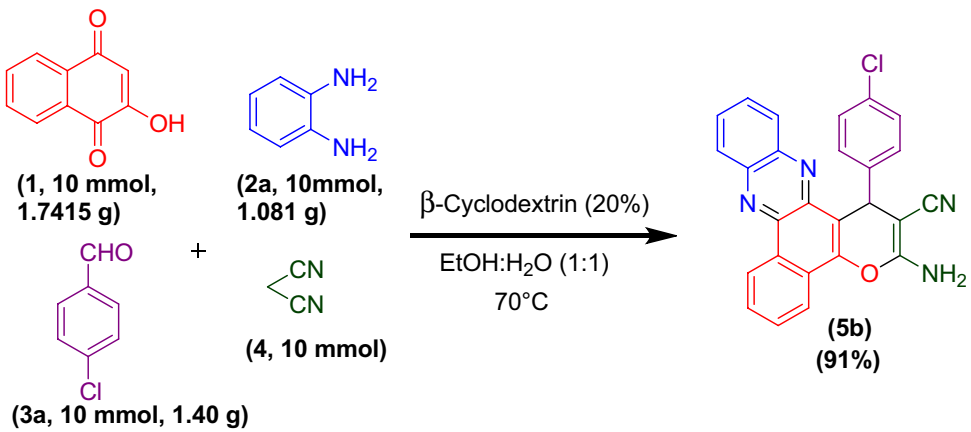


Fig. 3 Reuse and recovery of β-CD and its consequence on yield

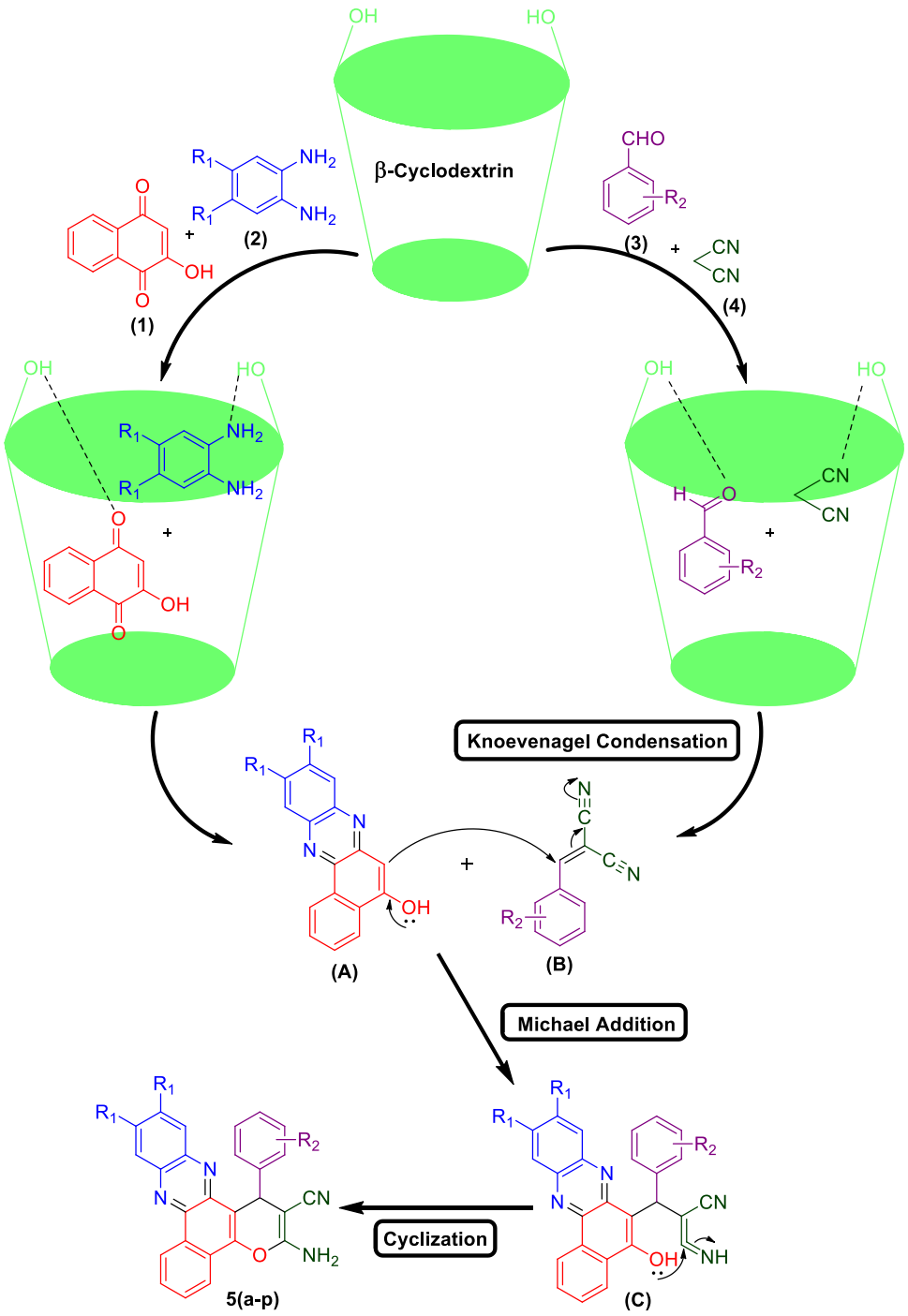
4 Conclusion

In conclusion, we have reported a facile and convenient new pathway for the one-pot, multicomponent, sustainable green synthesis of highly functionalized and efficacious biologically significant scaffold Benzo[*a*]pyrano[2,3-*c*]phenazine and its derivatives in ethanol:water solvent at 70 °C in the catalytic activity of β-cyclodextrin. To the best of our knowledge this is the first synthesis of the title compound. The utilization of biodegradable, environmentally benign supramolecular catalyst as a recyclable catalyst and EtOH:H_2O mixed green solvent system has engrossed substantial attention and has emerged as a hallmark of this transformation. The other key attributes of the disclosed protocol are operational feasibility, short reaction time, simple workup procedure, good to excellent yields of the product and easy recovery plus reusability of the catalyst. All these traits ascertain the disclosed methodology as superior to the previously reported methods.

Scheme 3 Practicability of the Present methodology



Scheme 4 Plausible mechanism for Benzo[*a*]pyrano[2,3-*c*] phenazine derivatives **(5a-p)**



Acknowledgements The authors are thankful to SAIF, Punjab University, Chandigarh, India for providing spectral data. Authors A. Mishra, Y. K. Pandey and F. Tufail are thankful to UGC and CSIR, New Delhi, for the award of Senior Research Fellowship (SRF). Prof. J. Singh thankful to UGC for UGC BSR fellowship.

References

1. Anastas PT, Warner JC (1998) Green chemistry: theory and practice. Oxford University Press, New York
2. Horvath IT (2002) Acc Chem Res 35:685
3. Madhumitha G, Roopan SM (2013) J Nanomater 2013:1
4. Maity A, Chakraborty D, Hazra A, Bharitkar YP, Kundu S, Maulik PR, Mondal NB (2014) Tetrahedron Lett 55:3059–3063
5. Srivastava M, Singh J, Singh SB, Tiwari K, Pathak VK, Singh J (2012) Green Chem 14:901–905
6. Chaudhari MA, Gujar JB, Kawade DS, Shinde PV, Shingare MS (2015) Res Chem Intermed 41:10027–10035
7. Sun T, Wang Q, Bi Y, Chen X, Liu L, Ruan C, Zhao Z, Jiang C (2017) J Mater Chem B5:2644–2654
8. Ao M, Gan C, Shao W, Xing Z, Yong C (2016) Eur J Pharm Sci 91:183–189

9. Mishra NP, Mohapatra S, Pravati P, Nayak S (2018) Curr Org Chem 22:1956–1982
10. Abbasi M (2017) J Chin Chem Soc 64:896–917
11. Rekharsky MV, Inoue Y (1998) Chem Rev 98:1875–1917
12. Connors KA (1997) Chem Rev 97:1325–1358
13. Valle EMD (2004) Biochem 39:1033–1046
14. Bender ML, Komiyama M (2012) Cyclodextin chemistry. Springer Science & Business Media, Berlin
15. Seidi F, Ahmad AS, Mojtaba A, Meisam S, Daniel C (2019) Polym Chem 10:3674–3711
16. Kumar AR, Ashok K, Brahmaiah B, Sreekanth N, Baburao C (2013) IJPRBS 2(2):291–304
17. Rutenberg R, Leitus G, Fallik E, Poverenov E (2016) Chem Commun 52:2565–2568
18. Szejtli J (1998) Chem Rev 98:1743–1754
19. Ramón DJ, Yus M (2005) Angew Chem Int Ed 44:1602–1634
20. Voigt B, Linke M, Mahrwald R (2015) Org Lett 17:2606–2609
21. Toure BB, Hall DG (2009) Chem Rev 109:4439–4486
22. Alvim HGO, Silva JE, Neto BAD (2014) RSC Adv 4:54282–54299
23. Barreiros ALBS, David JM, David JP (2006) Quim Nova 29:113–123
24. Muller M, Sorrell T (1995) Prostaglandins 50:301–311
25. Andrade-Nieto V, Goulart M, da Silva JF, da Silva MJ, Pinto M, Pinto A, Zalis M, Carvalho L, Krettli A (2004) Bioorg Med Chem Lett 14:1145–1149
26. Ligon J, Dwight S, Hammer P, Torkewitz N, Hofmann D, Kempf H, Pee K (2000) Pest Manage Sci 56:688–695
27. Vickr N, Burgess L, Chuckowree IS, Dodd R, Folkes AJ, Hardick DJ, Hancox TC, Miller WH, Milton J, Sohal S, Wang S, Wren SP, Charlton PA, Dangerefield W, Liddle C, Mistry P, Stewart AJ, Denny WA (2002) J Med Chem 45:721–739
28. Neves-Pinto C, Malta V, Pinto M, Santos R, Castro S, Pinto A (2002) J Med Chem 45:740–743
29. Kondratyuk TP, Park EJ, Yu R, Van BRB, Asolkar RN, Murphy BT, Fenical W, Pezzuto JM (2012) Mar Drugs 10:451–464
30. Esmaeilpour M, Sardarian AR, Firouzabadi H (2018) ChemistrySelect 3:9236–9248
31. Chaniyara R, Thakrar S, Kakadiya R, Marvania B, Detroja D, Vekariya N, Upadhyay K, Manvar A, Shah A (2014) J Hetercyclic Chem 51:466–474
32. Magedov IV, Manpadi M, Ogasawara MA, Dhawan AS, Rogelj S, Van Slambrouck S, Steelant WFA, Evdokimov NM, Uglinskii PY, Elias EM, Knee EJ, Tongwa P, Antipin MY, Kornienko A (2008) J Med Chem 51:2561–2570
33. Narender T, Gupta S (2004) Bioorg Med Chem Lett 14:3913–3916
34. Evidente A, Cabras A, Maddau L, Serra S, Andolfi A, Motta AJ (2003) Agr Food Chem 51:6957–6960
35. Aytemir MD, Calis U, Ozalp M (2004) Arch Pharm Pharm Med Chem 337:281–288
36. Esmaeilpour M, Javidi J, Dehghani F, Dodeji FN (2015) RSC Adv 5:26625–26633
37. Wang SL, Wu FY, Cheng C, Zhang G, Liu YP, Jiang B, Shi F, Tu SJ (2011) ACS Comb Sci 13:135–139
38. Shaterian HR, Moradi F, Mohammadnia M (2012) C R Chim 15:1055–1059
39. Shaterian HR, Mohammadnia M (2013) J Mol Liq 177:162–166
40. Bharti R, Parvin T (2016) Mol Divers 20:867–876
41. Hasaninejad A, Firoozi S (2013) Mol Divers 17:499–513
42. Choghamarani AG, Sahraei R, Taherinia Z (2019) Res Chem Intermed 45(5):3199–3214
43. Yazdani-Elah-Abadi A, Maghsoodlou MT, Mohebat R, Heydari R (2017) Chin Chem Lett 28(2):446–452
44. Gao J, Chen M, Tong X, Zhu H, Yan H, Liu D, Li W, Qi S, Xiao D, Wang Y, Lu Y, Jiang F (2015) Comb Chem High Throughput Screen 18(10):960–974
45. Zarabi MF, Naeimi H (2019) Polycycl Aromat Compd. https://doi.org/10.1080/10406638.2019.1672202
46. Choghamarani AG, Mohammadi M, Shiri L, Taherinia Z (2019) Res Chem Intermed 45:5705–5723
47. Naeimi H, Zarabi MF (2019) RSC Adv 9:7400–7410
48. Rai P, Srivastava M, Yadav S, Singh J, Singh J (2015) Catal Lett 145:2020–2028
49. Mishra A, Srivastava M, Rai P, Yadav S, Tripathi BP, Singh J, Singh J (2016) RSC Adv 6:49164–49172
50. Mishra A, Rai P, Srivastava M, Tripathi BP, Yadav S, Singh J, Singh J (2017) Catal Lett 147:2600–2611
51. Tripathi BP, Mishra A, Rai P, Pandey YK, Srivastava M, Yadav S, Singh J, Singh J (2017) New J Chem 41:11148–11154
52. Mishra A, Rai P, Singh J, Singh J (2018) ChemistrySelect 3:8408–8414
53. Mishra A, Rai P, Pandey YK, Singh J, Singh J (2017) ChemistrySelect 2:10979–10983
54. Tayade YA, Dalal DS (2017) Catal Lett 147:1411–1421
55. Ghorad A, Mahalle S, Khillare LD, Sangshetti JN, Bhosle MR (2017) Catal Lett 147:640–648