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ORIGINAL ARTICLE

Multicomponent synthesis of diverse pyrano-fused benzophenazines using bifunctional thiourea-based organocatalyst in aqueous medium

Ruchi Bharti[1] · **Tasneem Parvin**[1]

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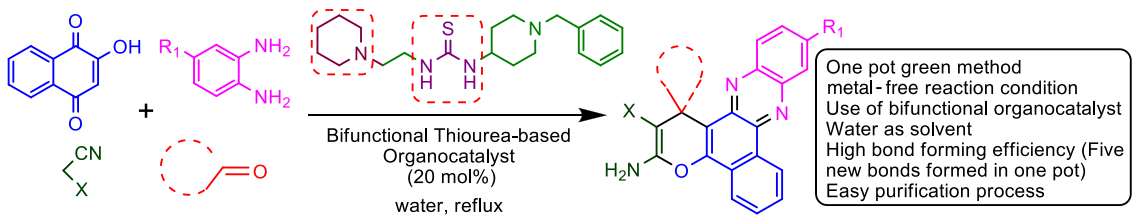
Abstract A series of pyrano-fused benzophenazines were synthesized using a bifunctional thiourea-based organocatalyst from the one-pot four-component reaction of 2-hydroxy-1,4-naphthoquinone, benzene-1,2-diamines, malononitrile or its derivatives and isatins or aromatic aldehydes in aqueous medium. Metal-free reaction condition, water as solvent, high bond forming efficiency (five new bonds formed in one step), good yields and easy purification process are the notable features of this methodology.

Graphical Abstract



Keywords Multicomponent reactions · MCRs · Thiourea-based organocatalysts · Pyrano-fused benzophenazines · Aqueous medium

Introduction

Organocatalysis has emerged as a powerful tool in organic synthesis, especially for the synthesis of various biologically active heterocyclic compounds [1–6] due to their improved stability, lesser toxicity and metal-free reaction conditions. Among organocatalysts, thiourea-based organocatalysts [7,8] have numerous applications in organic synthesis due to their ability to activate carbonyl compounds by double hydrogen bonding. Jacobsen [9], Schreiner [10] and Takemoto [11] catalysts are some of the most well-explored thiourea-based organocatalysts. Bifunctional organocatalysts bearing a thiourea moiety and an amine group exhibit better catalytic activity [12–14] due to their dual activation of both electrophile and nucleophile by double-hydrogen-bonding interactions of the thiourea moiety and the basic amine moiety (Fig. 1).

Multicomponent reactions (MCRs) have gained considerable attention in recent years for the easy access of diverse classes of compounds. They are considered ecofriendly and cost-effective tools because of their pot, atom and step economic approach [15–19]. Therefore, the design of novel MCRs for the synthesis of diverse heterocycles has remained as an important topic for medicinal and organic chemists. Heterocyclic compounds, especially functionalized nitrogen

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✉ Tasneem Parvin
tasneem@nitp.ac.in

[1] Department of Chemistry, National Institute of Technology Patna, Ashok Rajpath, Patna 800005, India

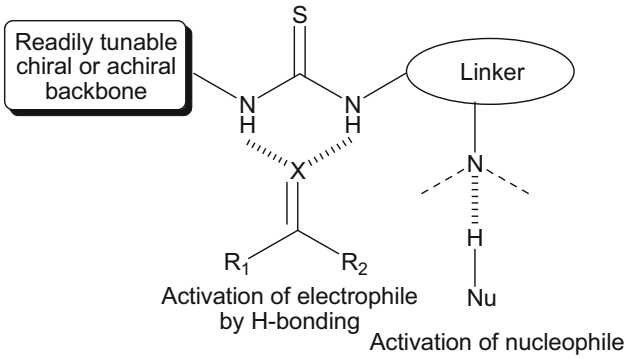


Fig. 1 Bifunctional organocatalysts bearing a thiourea moiety and a basic amine moiety

and oxygen heterocycles, play important roles in medicinal chemistry [20,21]. Benzo[*a*]phenazines and pyrans are structural subunits in a variety of important natural products and show a variety of pharmaceutical activities, such as antimalarial, anticancer activities and are also employed as useful substrates to prepare dyestuffs, pesticides, antibiotics and antitumor agents [22–30]. Some of the pharmaceutical active pyrano-fused benzophenazine derivatives [31–33] are shown in Fig. 2.

Considering the importance of benzophenazine and pyran derivatives, only very few methods [34–38] are known in the literature for the synthesis of pyrano-fused benzophenazines. In continuation of our research on MCRs for the synthesis of biologically important heterocycles [39–44], we wish to report the synthesis of some thiourea-based organocatalysts and their application in the synthesis of pyrano-fused benzophenazines via the one-pot four-component reaction of 2-hydroxy-1,4-naphthoquinone, *o*-phenylenediamines, malononitriles and substituted isatins or aldehydes under reflux condition in aqueous medium (Scheme 1).

Results and discussion

We recently reported the three-component reaction of aldehydes, 1,3-dimethyl-6-aminouracil and 2-hydroxy-1,4-naphthoquinone/4-hydroxycoumarin for the synthesis of tri-substituted methane derivatives in the presence of a bifunctional thiourea-based organocatalyst in aqueous medium [39]. In continuation of our research on multicomponent reactions using thiourea-based organocatalyst, we initially prepared organocatalysts **I–IV** (Fig. 3) by the reaction of 2-piperidinoethyl isothiocyanate and the corresponding primary amines in DCM at room temperature.

Next, we screened these thiourea-based organocatalysts **I–IV** for the synthesis of pyrano benzophenazine-fused spirooxindoles **5**. To find the best reaction conditions, we studied the reaction of 2-hydroxy-1,4-naphthoquinone **1**, 1,2-diamines **2**, malononitrile **3** and 5-chloroisatin **4a** as our model reaction in the presence of some readily available organocatalysts as well as with our synthesized organocatalysts **I–IV**, and the results are summarized in Table 1.

Among them, organocatalyst **IV** gave the best results in terms of reaction time and yield obtained (92 %, entry 9). Next, the same reaction was performed in the presence of various amounts (5, 10, 15, 20, 30 mol%) of organocatalyst **IV** (entries 9–13), and the best result was obtained using 20 mol% of **IV** (Table 1, entry 9).

Then, various solvents, such as DMSO, H_2O, EtOH, CH_3CN, THF, DMF and DCM (Table 2, entries 1–7), were screened, and water was found to be the best solvent for the reaction in terms of yield and reaction time (92 %, entry 3).

Next, a variety of pyrano benzophenazine-fused spirooxindoles **5** were synthesized by varying 1,2-diamines **2**, malononitrile derivatives **3** and isatin derivatives **4** under the optimized reaction conditions, and the results are shown in Table 3. All the reactions proceeded smoothly to yield the corresponding products (**5a–o**) in good yields (75–92 %).

Considering the importance of the molecular skeleton having benzophenazine and pyran moieties, the scope of the reaction was explored using a variety of aldehydes in place of isatin derivatives under the optimized reaction conditions to afford the corresponding products, and the results are summarized in Table 4.

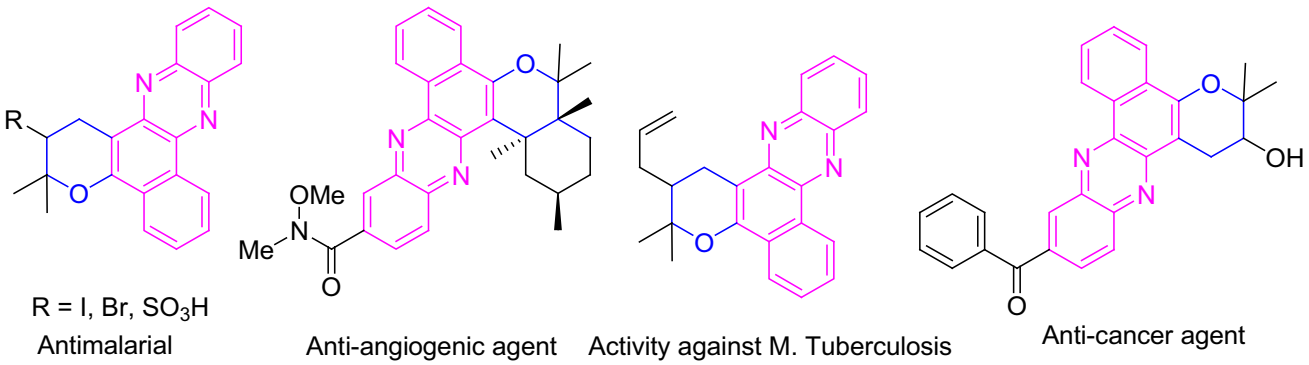
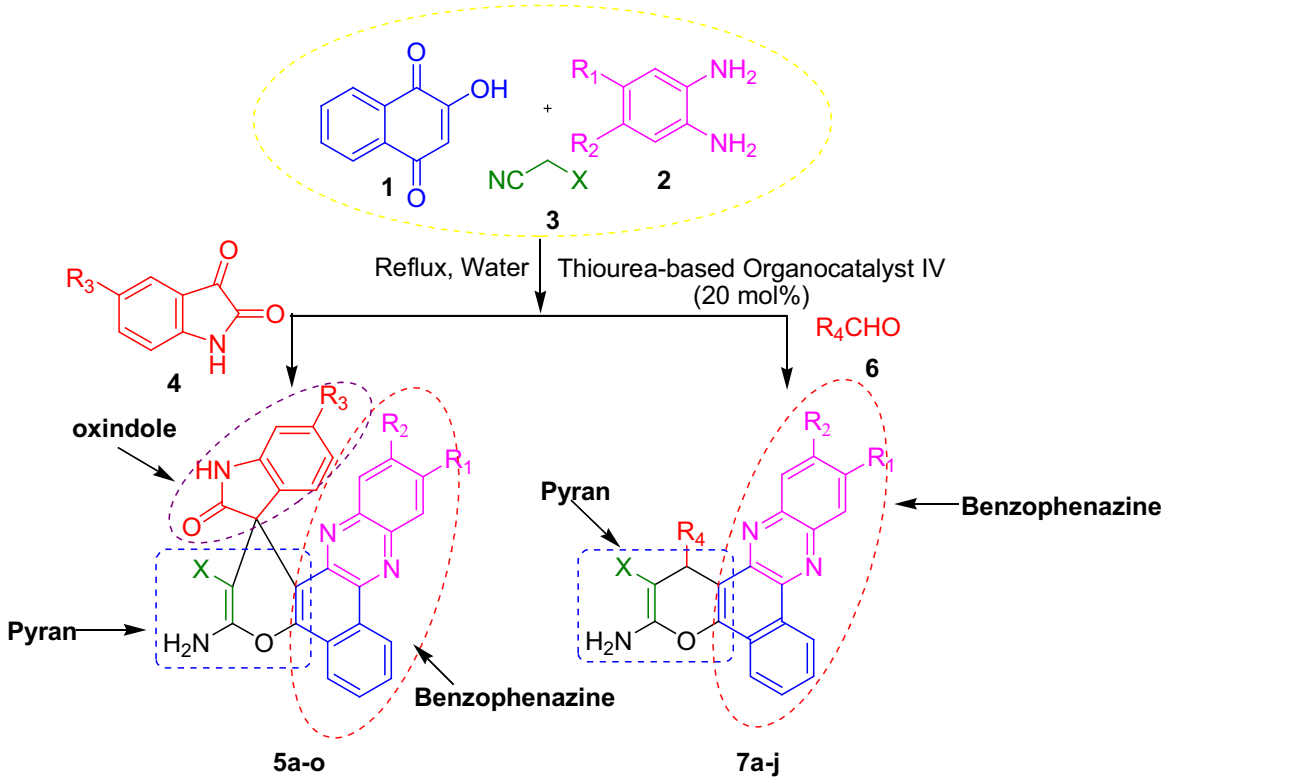


Fig. 2 Pharmaceutically active pyrano-fused phenazine derivatives



Scheme 1 Synthesis of pyrano-fused phenazine derivatives

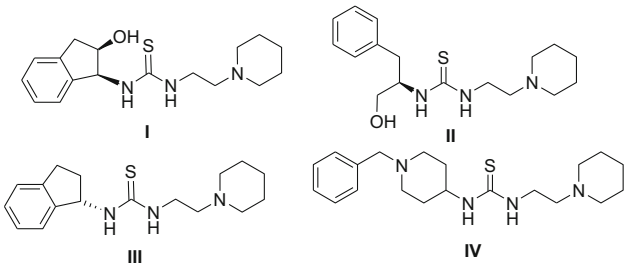


Fig. 3 Thiourea-based organocatalysts synthesized in this study

The proposed mechanism for the synthesis of pyrano-fused benzophenazines in the presence of organocatalyst **IV** is shown in Scheme 2. Based on literature reports [34–38], we believe that the condensation reaction between 2-hydroxy-1,4-naphthoquinone and the benzene 1,2-diamine leading to the corresponding benzo[a]phenazin-5-ol **A** does not need any catalyst. However, our organocatalyst plays significant role in other steps, and it activates both the electrophile and nucleophile through its thiourea moiety and basic amine moiety, respectively. The Knoevenagel condensation of isatin or aldehyde with malononitrile affords **B,** which undergoes a Michael addition with **A** to form intermediate **C** in the presence of organocatalyst **IV**. A subsequent cyclization leads to the formation of **D** which undergoes tautomerization to form the corresponding final product 5 or 7.

Conclusions

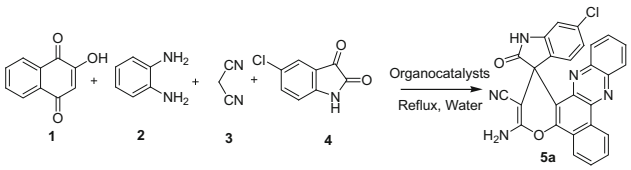
We have synthesized a series of pyrano-fused benzophenazines in the presence of thiourea-based organocatalysts by the one-pot four-component reaction of 2-hydroxy-1,4-naphthoquinone, benzene-1,2-diamines, malononitriles and isatin/aldehydes in aqueous medium. The attractive features of this methodology are metal-free reaction conditions, use of a bifunctional organocatalyst, water as solvent, easy purification and good yields.

Experimental

General

Starting materials and solvents are commercially available and used without further purification. The purity of the synthesized compounds were ascertained by thin-layer chro-

Table 1 Screening of organocatalysts

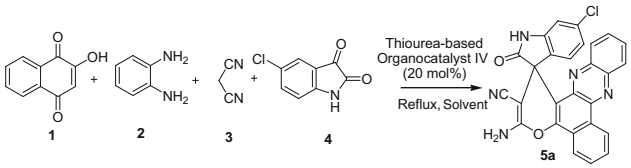


Entry	Catalysts	Mol (%)	Time (h)	Yield[a] (%)
1	Et_3N	20	9	53
2	Imidazole	20	10	46
3	Piperidine	20	12	43
4	Thiourea + Et_3N	10 + 10	7	78
5	Thiourea	20	9	70
6	I	20	10	46
7	II	20	12	54
8	III	20	7	67
9	IV	20	3	92
10	IV	5	10	68
11	IV	10	8	75
12	IV	15	8	80
13	IV	30	12	71

All reactions were carried out using 2-hydroxy-1,4-naphthoquinone (1 mmol), 1,2-benzenediamine (1 mmol), malononitrile (1mmol) and 5-chloroisatin (1 mmol) in the presence of water (3.0 mL) and different catalysts

[a] Isolated yield

Table 2 Screening of solvents



Entry	Catalyst	Solvent	Time (h)	Yield[a] (%)
1	IV (20 mol%)	DMSO	8	59
2	IV (20 mol%)	EtOH	2	75
3	IV (20 mol%)	H_2O	3	92
4	IV (20 mol%)	CH_3CN	8	62
5	IV (20 mol%)	THF	15	≤30
6	IV (20 mol%)	DMF	10	27
7	IV (20 mol%)	DCM	12	≥20

All reactions were carried out using 2-hydroxy-1,4-naphthaquinone (1 mmol), 1,2-benzenediamine (1 mmol), malononitrile (1mmol) and 5-chloroisatin (1 mmol) in the presence of 20 mol% of thiourea-based organocatalyst IV in different solvents (3.0 mL)

[a] Isolated yield

matography on silica gel GF 254 in ethyl acetate using iodine vapours as the developing agent. Melting points were determined by the melting point apparatus using capillary tube method and uncorrected. IR spectra were recorded on a Shimadzu FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 and were expressed in parts per million (δ, ppm) downfield using Me_4Si as internal standard on a Bruker Avance II 400 MHz spectrophotometer. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as brs (broad singlet). Coupling constants (J) are given in hertz. Elemental analyses were carried out in a Perkin Elmer 2400 automatic carbon, hydrogen, nitrogen analyzer. Optical rotation was measured on a Jasco P-2000 digital polarimeter with $[\alpha]_D$ values reported in degrees; concentration (c) is in g/100 mL.

General procedure for the synthesis of thiourea-based organocatalysts (I–IV)

First, amines (0.5 mmol) were dissolved in DCM and allowed to cool at 0 °C. Then, 2-piperidinoethyl isothiocyanate (0.5 mmol, 0.082 mL) was added to the reaction mixture and stirred at room temperature until the reaction was complete as determined by TLC. The reaction mixture was cooled, and the solid was filtered off and washed with ethanol to afford the desired product.

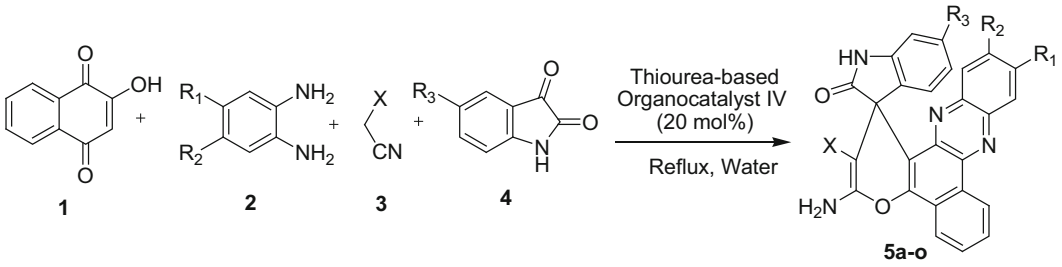
1-((1R,2S)-2,3-Dihydro-2-hydroxy-1H-inden-1-yl)-3-(2-(piperidin-1-yl)ethyl)thiourea **(I)**

White solid (0.104 g, 33 %): mp 185–187 °C. IR (KBr) cm^{-1}: 3456, 3210, 3050, 2923, 1592, 1230, 755. $[\alpha]_D^{r.t} = -75.0$ (c = 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.80–0.80 (m, 6H, CH_2), 2.41–2.32 (m, 5H, CH_2), 2.65 (brs, 1H, NH), 2.96–2.91 (m, 1H, CH), 3.17–3.12 (m, 1H, CH), 3.44–3.40 (s, 2H, CH_2), 4.30–4.10 (m, 1H, CH_2), 4.70–4.50 (m, 1H, CH_2), 5.90–5.60 (m, 1H, CH_2), 7.27–7.02 (m, 3H, Ar-H), 7.32 (d, J = 8.0 Hz, 1H, Ar-H), 8.04 (brs, 1H, NH), 8.99 (brs, 1H, OH) ppm. ^{13}C (100 MHz, $CDCl_3$) δ: 23.9, 25.0, 39.4, 41.5, 54.8, 62.8, 73.1, 125.2, 126.9, 128.2, 140.5, 182.8 ppm. Anal. Calcd for $C_{17}H_{25}N_3OS$ (319.46): C, 63.91; H, 7.89; N, 13.15; Found: C, 63.84; H, 7.86; N, 13.02.

*1-((S)-1-Hydroxy-3-phenylpropan-2-yl)-3-(2-(piperidin-1-yl)ethyl) thiourea (***II***)*

White needle-like solid (0.112 g, 32 %): mp 191–194 °C. IR (KBr) cm^{-1}: 3518, 3239, 2927, 1559, 1455, 1366, 1236, 1118, 1075, 978, 768. $[\alpha]_D^{r.t} = -3.0$ (c = 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.41–1.40 (m, 2H, CH_2), 1.55–1.49 (m, 4H, CH_2), 2.39–2.36 (m, 6H, CH_2), 2.88–2.77 (m, 2H, CH_2), 3.45–3.35 (m, 4H, CH_2), 4.41 (brs, 1H, NH), 4.82 (brs, 1H, NH), 7.20–7.15 (m, 1H, CH), 7.32–7.24 (m, 5H, Ar-H), 7.59 (brs, 1H, OH) ppm. ^{13}C (100 MHz, DMSO-d_6) δ: 23.8, 25.0, 30.2, 33.9, 42.2, 54.5, 60.6, 124.2, 124.7, 126.7, 127.8, 143.2, 182.4 ppm. Anal. Calcd for

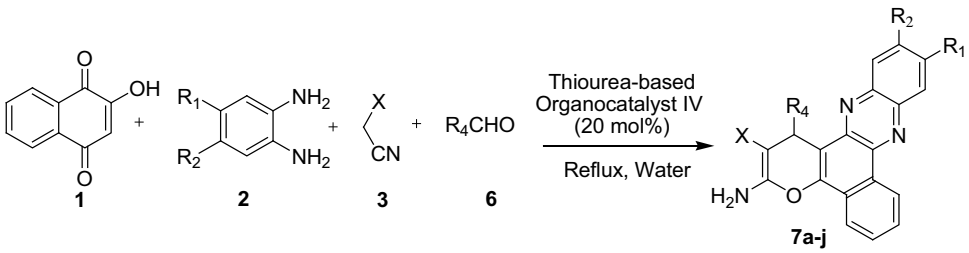
Table 3 Synthesis of pyrano benzophenazine-fused spirooxindoles **5a–o**



Entry	R_1	R_2	X	R_3	Product	Time (h)	% Yield[a]	M.P. (°C)
1	H	H	CN	Cl	**5a**	3	92	342–344 [34]
2	CH_3	H	CN	H	**5b**	3	81	345–346
3	CH_3	H	CN	I	**5c**	5	75	324–325
4	CH_3	H	CN	Cl	**5d**	4	81	337–339
5	H	H	CN	NO_2	**5e**	7	76	314–316
6	H	H	CN	I	**5f**	6	79	365–367
7	H	H	COOEt	I	**5g**	5	78	318–320
8	H	H	COOEt	H	**5h**	4	79	267–269 [34]
9	H	H	COOMe	H	**5i**	4	79	263–267 [35]
10	CH_3	CH_3	CN	Cl	**5j**	2	90	291–292 [34]
11	H	H	COOEt	Br	**5k**	3	84	306–308 [34]
12	H	H	COOMe	Br	**5l**	5	82	298–300 [35]
13	H	H	CN	H	**5m**	4	81	322–323 [35]
14	H	H	CN	F	**5n**	3	80	302–304 [35]
15	H	H	CN	Br	**5o**	4	79	338–340 [35]

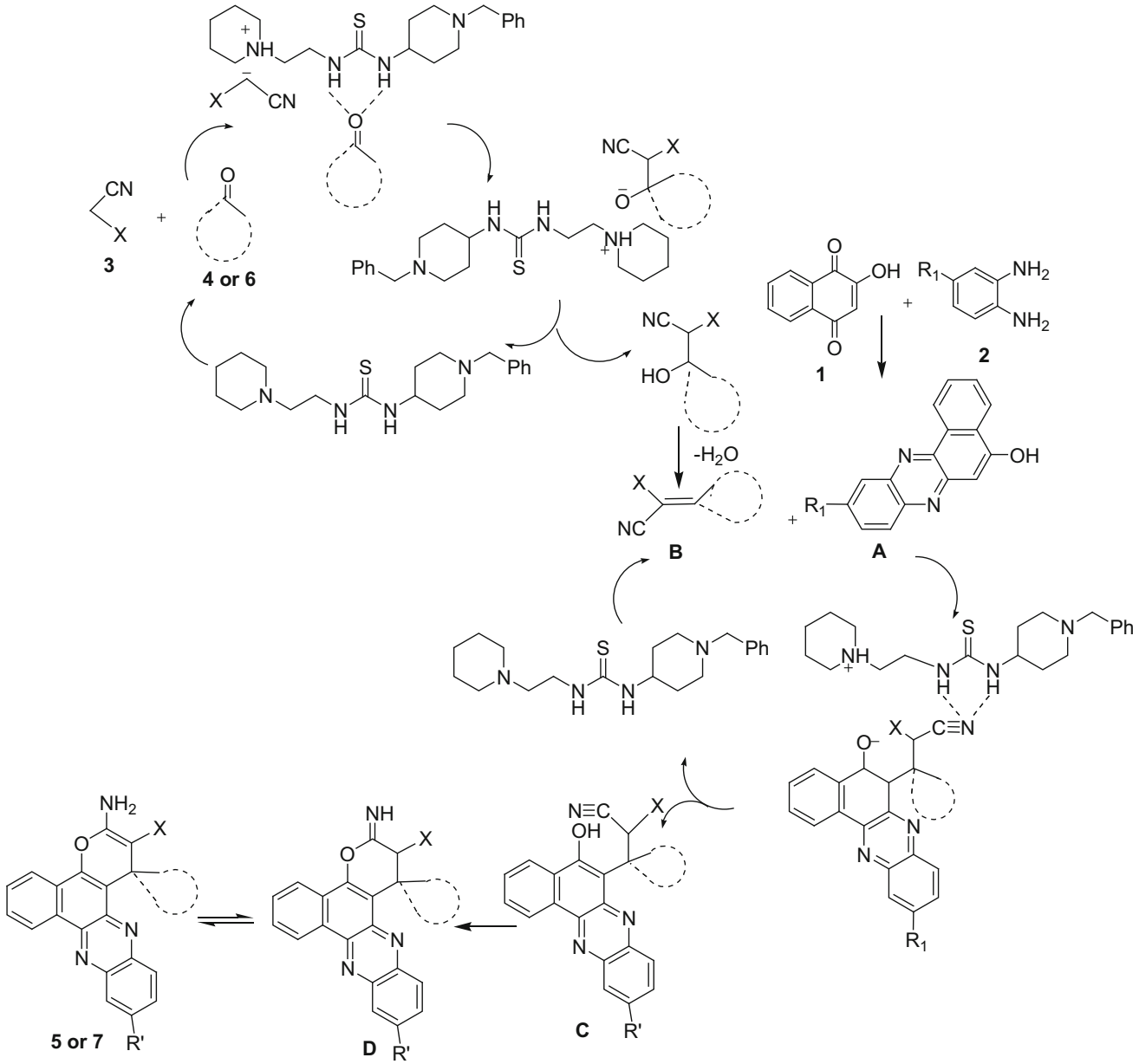
[a] Isolated yield

Table 4 Synthesis of pyrano-fused benzophenazines **7a–j**



Entry	R_1	R_2	X	R_4	Product	Time (h)	% Yield[a]	M.P. (°C)
1	H	H	CN	C_6H_5	**7a**	3	92	301–303 [33]
2	H	H	CN	4-$CH(Me)_2C_6H_4$	**7b**	3	81	352–353
3	CH_3	H	CN	4-$OCH_3C_6H_4$	**7c**	5	75	361–362
4	H	H	CN	2-ClC_6H_4	**7d**	4	81	301–303
5	CH_3	H	CN	4-$CH(Me)_2C_6H_4$	**7e**	7	76	321–323
6	H	H	CN	4-$CH_3C_6H_4$	**7f**	6	79	292–294 [33]
7	H	H	CN	3-$NO_2C_6H_4$	**7g**	5	78	282–283 [33]
8	H	H	CN	4-$NO_2C_6H_4$	**7h**	4	79	277–280 [33]
9	H	H	CN	4-ClC_6H_4	**7i**	4	79	289–291 [33]
10	H	H	CN	4-FC_6H_4	**7j**	2	90	277–279 [33]

[a] Isolated yield



Scheme 2 Proposed reaction mechanism

$C_{17}H_{27}N_3OS$ (321.48): C, 63.51; H, 8.47; N, 13.07; Found: C, 63.59; H, 8.50; N, 13.20.

*1-((S)-2,3-Dihydro-1H-inden-1-yl)-3-(2-(piperidin-1-yl)ethyl) thiourea (***III***)*

White crystalline solid (0.215 g, 70 %): mp 215–217 °C. IR (KBr) cm^{-1}: 3244, 3078, 2924, 1601, 1512, 1454, 1238, 964, 752. $[\alpha]_D^{r.t} = -31.0$ ($c = 0.5$, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28–1.20 (m, 6H, CH_2), 1.96–1.89 (m, 1H, CH), 2.40–2.10 (m, 4H, CH_2), 2.45–2.43 (m, 2H, CH_2), 2.75–2.74 (m, 1H, CH), 3.03–2.85 (m, 3H, CH_2), 3.47–3.32 (m, 2H, CH_2), 6.73 (brs, 1H, NH), 7.22–7.19 (m, 3H, Ar-H), 7.36 (d, $J = 8.0$ Hz, 1H, Ar-H), 9.82 (brs, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.8, 25.1, 30.2, 33.9, 42.3, 54.6, 60.8, 124.3, 124.8, 126.7, 127.9, 143.3, 180.4 ppm. Anal. Calcd for $C_{17}H_{25}N_3S$ (303.47): C, 67.28; H, 8.30; N, 13.85; Found: C, 67.34; H, 8.33; N, 13.97.

*1-(1-Benzylpiperidin-4-yl)-3-(2-(piperidin-1-yl)ethyl) thiourea (***IV***)*

White powdery solid (0.304 g, 84 %): mp 240–242 °C. IR (KBr) cm^{-1}: 3273, 3151, 3054, 2929, 1574, 1495, 1240, 961, 860, 747. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.48–1.47 (m, 2H, CH_2), 1.59–1.51 (m, 6H, CH_2), 2.05–2.02 (m, 2H,

CH_2), 2.15–2.09 (m, 2H, CH_2), 2.48–2.42 (m, 7H, CH_2, CH), 2.88–2.85 (m, 2H, CH_2), 3.45–3.38 (m, 2H, CH_2), 3.51 (s, 2H, CH_2), 4.02 (brs, 1H, NH), 6.72 (brs, 1H, NH), 7.33–7.22 (m, 5H, Ar-H) ppm. ^{13}C (100 MHz, $CDCl_3$) δ: 24.1, 25.8, 30.9, 32.2, 41.8, 52.4, 54.5, 62.9, 127.9, 128.4, 129.3, 138.3, 181.1 ppm. Anal. Calcd for $C_{20}H_{32}N_4S$ (360.56): C, 66.62; H, 8.95; N, 15.54; Found: C, 66.71; H, 8.98; N, 15.68.

General procedure for the synthesis of compounds (5a–o & 7a–j)

First 2-hydroxy-1,4-naphthoquinone (1 mmol) and benzene-1,2-diamine (1 mmol) were refluxed in water (3 mL) for 5 minutes in the presence of 20 mol% thiourea-based organocatalyst IV. Afterwards, isatin or an aldehyde (1 mmol) followed by malononitrile (1 mmol) was added and the reaction was continued until the reaction was complete as determined by TLC. Then, the reaction mixture was allowed to cool to room temperature, and the resulting precipitate was filtered, washed first with water and then with ethanol (5 mL), dried, and recrystallized from an ethanol, ethyl acetate (2:1) mixture to afford the pure product.

*3-Amino-11-methyl-2'-oxospiro[benzo[c]pyrano[3,2-a]phenazine-1,3-indoline]-2-carbonitrile (***5b***)*

Yellow solid. mp 345–346 °C. IR (KBr) cm^{-1}: 3364, 3218, 3182, 1697, 1713, 1658, 1605, 1473, 1373, 1165, 1064, 952, 813, 756. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.56 (s, 3H, CH_3), 6.75 (t, J = 8.0 Hz, 1H, Ar-H), 6.98 (d, J = 8.0 Hz, 1H, Ar-H), 7.05 (t, J = 8.0 Hz, 1H, Ar-H), 7.18 (t, J = 8.0 Hz, 1H, Ar-H), 7.50 (d, J = 8.0 Hz, 3H, Ar-H, NH_2), 7.61 (d, J = 8.0 Hz, 1H, Ar-H), 7.99 (d, J = 8.0 Hz, 1H, Ar-H), 8.03 (t, J = 8.0 Hz, 2H, Ar-H), 8.51 (d, J = 8.0 Hz, 1H, Ar-H), 9.24 (d, J = 8.0 Hz, 1H, Ar-H), 10.78 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 49.3, 56.4, 109.2, 110.4, 117.8, 121.6, 122.4, 123.4, 124.7, 125.4, 126.3, 127.3, 127.5, 128.6, 129.7, 130.3, 130.6, 133.3, 135.7, 138.7, 139.8, 140.9, 141.2, 142.8, 147.0, 159.4, 179.1 ppm. Anal. Calcd. For $C_{28}H_{17}N_5O_2$ (455.47): C, 73.84; H, 3.76; N, 15.38; Found: C, 73.93; H, 3.79; N, 15.42.

*3-Amino-5'-iodo-11-methyl-2'-oxospiro[benzo[c]pyrano[3,2-a]phenazine-1,3-indoline]-2-carbonitrile (***5c***)*

Yellow solid. mp 324–325 °C. IR (KBr) cm^{-1}: 3305, 3209, 3136, 2985, 1720, 1659, 1605, 1474, 1369, 1161, 1065, 952, 813, 763. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.60 (s, 3H, CH_3), 6.98 (d, J = 8.0 Hz, 1H, Ar-H), 7.44–7.43 (m, 1H, Ar-H), 7.59–7.54 (m, 1H, Ar-H), 7.60 (s, 2H, NH_2), 7.65 (d, J = 8.0 Hz, 1H, Ar-H), 7.82 (d, J = 8.0 Hz, 1H, Ar-H), 8.05 (d, J = 8.0 Hz, 1H, Ar-H), 8.12–8.08 (m, 2H, Ar-H), 8.55 (d, J = 8.0 Hz, 1H, Ar-H), 9.30 (d, J = 8.0 Hz, 1H, Ar-H), 11.01 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.5, 49.2, 56.5, 84.5, 109.6, 111.7, 122.5, 124.7, 125.5, 127.4, 129.7, 130.3, 130.6, 131.8, 133.4, 136.9, 138.3, 139.3, 139.5, 139.7, 140.2, 140.9, 142.7, 147.3, 159.5, 178.6 ppm. Anal. Calcd for $C_{28}H_{16}IN_5O_2$ (581.36): C, 57.85; H, 2.77; N, 12.05; Found: C, 57.93; H, 2.80; N, 12.18.

*3-Amino-5'-chloro-11-methyl-2'-oxospiro[benzo[c]pyrano[3,2-a]phenazine-1,3-indoline]-2-carbonitrile (***5d***)*

Yellow solid. mp 337–339 °C. IR (KBr) cm^{-1}: 3435, 3307, 3178, 2984, 1756, 1648, 1603, 1478, 1365, 1163, 1069, 956, 817, 756. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.54 (s, 3H, CH_3), 7.06 (t, J = 8.0 Hz, 1H, Ar-H), 7.16–7.15 (m, 1H, Ar-H), 7.26–7.22 (m, 1H, Ar-H), 7.62–7.59 (m, 3H, H-Ar, NH_2), 7.79–7.75 (m, 1H, Ar-H), 8.01 (t, J = 8.0 Hz, 1H, Ar-H), 8.06 (t, J = 8.0 Hz, 2H, Ar-H), 8.51 (d, J = 8.0 Hz, 1H, Ar-H), 9.26 (d, J = 8.0 Hz, 1H, Ar-H), 10.96 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 49.5, 56.6, 109.5, 110.5, 117.7, 122.5, 123.7, 124.7, 125.4, 125.5, 127.4, 128.2, 129.7, 130.3, 133.4, 137.7, 138.7, 139.3, 139.5, 139.7, 140.1, 140.9, 141.3, 141.8, 147.3, 159.6, 178.9 ppm. Anal. Calcd for $C_{28}H_{16}ClN_5O_2$ (489.91): C, 68.64; H, 3.29; N, 14.30; Found: C, 68.73; H, 3.33; N, 14.44.

*3-Amino-5'-nitro-2'-oxospiro[benzo[c]pyrano[3,2-a]phenazine-1,3-indoline]-2-carbonitrile (***5e***)*

Yellow solid. mp 314–316 °C. IR (KBr) cm^{-1}: 3452, 3275, 3167, 2989, 1724, 1631, 1601, 1589, 1489, 1388, 1168, 1080, 956, 829, 759. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.30 (d, J = 8.0 Hz, 1H, Ar-H), 7.69 (s, 2H, NH_2), 7.75 (d, J = 8.0 Hz, 1H, Ar-H), 7.91–7.87 (m, 2H, Ar-H), 7.97 (s, 1H, Ar-H), 8.03 (t, J = 8.0 Hz, 1H, Ar-H), 8.05 (t, J = 8.0 Hz, 1H, Ar-H), 8.22 (d, J = 8.0 Hz, 1H, Ar-H), 8.29 (d, J = 8.0 Hz, 1H, Ar-H), 8.59 (d, J = 8.0 Hz, 1H, Ar-H), 9.33 (d, J = 8.0 Hz, 1H, Ar-H), 11.59 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 49.3, 55.7, 108.8, 109.4, 116.8, 117.5, 119.6, 122.7, 124.8, 125.5, 125.9, 127.6, 129.1, 129.9, 130.4, 130.5, 130.8, 131.0, 136.6, 139.6, 140.1, 140.9, 142.4, 148.2, 149.4, 159.7, 179.6 ppm. Anal. Calcd for $C_{27}H_{14}N_6O_4$ (486.44): C, 66.67; H, 2.90; N, 17.28; Found: C, 66.74; H, 2.93; N, 17.40.

*3-Amino-5'-iodo-2'-oxospiro[benzo[c]pyrano[3,2-a]phenazine-1,3-indoline]-2-carbonitrile (***5f***)*

Yellow solid. mp 365–367 °C. IR (KBr) cm^{-1}: 3450, 3275, 3163, 2985, 1724, 1635, 1489, 1388, 1315, 1168, 1080, 829, 756. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.90 (d, J = 8.0 Hz, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.53–7.48 (m, 3H, Ar-H), 7.74 (d, J = 8.0 Hz, 1H, Ar-H), 7.87 (s, 2H, NH_2), 8.02–

7.98 (m, 2H, Ar-H), 8.26 (d, J = 8.0 Hz, 1H, Ar-H), 8.52 (d, J = 8.0 Hz, 1H, Ar-H), 9.30 (d, J = 8.0 Hz, 1H, Ar-H), 10.94 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 49.2, 56.6, 84.5, 109.5, 111.7, 117.7, 122.6, 124.9, 125.6, 127.8, 129.1, 129.8, 130.3, 130.5, 130.8, 130.9, 131.8, 136.9, 138.2, 139.5, 140.1, 140.2, 141.0, 142.7, 147.8, 159.5, 178.6 ppm. Anal. Calcd for $C_{27}H_{14}IN_5O_2$ (567.34): C, 57.16; H, 2.49; N, 12.34; Found: C, 57.25; H, 2.52; N, 12.46.

*3-Amino-5'-iodo-2'-oxospiro[benzo[c]pyrano[3,2-a]phenazine-1,3-indoline]-2-carboxylate (**5g**)*

Yellow solid. mp 318–320 °C. IR (KBr) cm^{-1}: 3460, 3367, 2978, 1697, 1647, 1604, 1470, 1373, 1172, 1091, 952, 879, 756. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.97 (t, J = 8.0 Hz, 3H, CH_3), 3.89 (t, J = 8.0 Hz, 2H, CH_2), 6.80 (d, J = 8.0 Hz, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 7.42 (t, J = 8.0 Hz, 1H, Ar-H), 7.88 (d, J = 8.0 Hz, 1H, Ar-H), 7.94–7.92 (m, 2H, Ar-H), 8.01 (t, J = 8.0 Hz, 1H, Ar-H), 8.06 (t, J = 8.0 Hz, 1H, Ar-H), 8.23 (s, 2H, NH_2), 8.28 (d, J = 8.0 Hz, 1H, Ar-H), 8.62 (d, J = 8.0 Hz, 1H, Ar-H), 9.26 (d, J = 8.0 Hz, 1H, Ar-H), 10.79 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.3, 49.2, 59.1, 75.5, 82.9, 110.6, 111.8, 122.9, 124.7, 125.7, 127.8, 128.9, 129.7, 130.2, 130.4, 130.6, 130.7, 130.9, 135.9, 139.2, 139.6, 139.7, 140.8, 140.9, 145.2, 146.7, 159.7, 167.6, 180.2 ppm. Anal. Calcd for $C_{29}H_{19}IN_4O_4$ (614.39): C, 56.69; H, 3.12; N, 9.12; Found: C, 56.76; H, 3.15; N, 9.24.

*3-Amino-1-phenyl-1H-benzo[c]pyrano[3,2-a]phenazine-2-carbonitrile (**7a**)*

Yellow powder. mp 301–303 °C. IR (KBr) cm^{-1}: 3457, 3315, 3168, 2193, 1350, 1270. ^{1}HNMR (400 MHz, DMSO-d_6) δ: 5.37 (s, 1H, CH), 7.08 (t, J = 7.4 Hz, 1H, Ar-H), 7.21 (t, J = 7.6 Hz, 2H, Ar-H), 7.36–7.38 (m, 4H Ar-H, NH_2), 7.85–7.86 (m, 3H, Ar-H), 7.86 (t, J = 4.8 Hz, 1H, Ar-H), 8.00–8.12 (m, 1H, Ar-H), 8.13–8.15 (m, 1H, Ar-H), 8.36 (d, J = 8.0 Hz, 1H, Ar-H), 9.06 (d, J = 8.0 Hz, 1H, Ar-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 37.8, 58.5, 114.2, 120.7, 122.4, 125.1, 125.9, 126.9, 128.1, 129.0, 129.3, 129.4, 130.3, 130.5, 130.8, 131.0, 140.0, 140.3, 140.9, 141.8, 145.7, 146.5, 160.2, 160.3 ppm. Anal. Calcd. for $C_{26}H_{16}N_4O$: C, 77.99; H, 4.03; N, 13.99; Found: C, 76.28; H, 4.19; N, 13.57.

*3-Amino-1-(4-isopropylphenyl)-1H-benzo[c]pyrano[3,2-a]phenazine-2-carbonitrile (**7b**)*

Yellow solid. mp 352–353 °C. IR (KBr) cm^{-1}: 3348, 3155, 2958, 1662, 1635, 1597, 1496, 1384, 1288, 1153, 1049, 948, 833, 752. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (d, J = 8.0 Hz, 6H, $CH(CH_3)_2$), 2.77–2.74 (m, 1H, CH), 5.56 (s, 1H, CH), 7.08 (d, J = 8.0 Hz, 2H, Ar-H), 7.29 (s, 2H, NH_2), 7.36 (d, J = 8.0 Hz, 2H, Ar-H), 7.96–7.92 (m, 3H, Ar-H), 7.99 (t, J = 8.0 Hz, 1H, Ar-H), 8.25–8.21 (m, 1H, Ar-H), 8.31–8.29 (m, 1H, Ar-H), 8.49 (d, J = 8.0 Hz, 1H, Ar-H), 9.30 (d, J = 8.0 Hz, 1H, Ar-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.7, 23.7, 36.8, 58.0, 114.3, 120.3, 121.9, 122.1, 124.9, 125.5, 125.7, 126.3, 127.4, 128.8, 129.1, 130.3, 130.6, 130.9, 139.6, 139.9, 140.8, 141.6, 142.6, 145.3, 146.2, 146.6, 160.0, 170.3 ppm. Anal. Calcd for $C_{29}H_{22}N_4O$ (442.51): C, 78.71; H, 5.01; N, 12.66; Found: C, 78.80; H, 5.04; N, 12.79.

*3-Amino-11-methyl-1-(4-methoxy)-1H-benzo[c]pyrano[3,2-a]phenazine-2-carbonitrile (**7c**)*

Yellow solid. mp 361–362 °C. IR (KBr) cm^{-1}: 3356, 3204, 3162, 2978, 1654, 1607, 1508, 1384, 1242, 1157, 1033, 952, 825, 763. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.63 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 5.50 (s, 1H, CH), 6.79 (d, J = 8.0 Hz, 2H, Ar-H), 7.35–7.33 (m, 4H, Ar-H, NH_2), 7.81 (d, J = 8.0 Hz, 1H, Ar-H), 7.95 (t, J = 8.0 Hz, 1H, Ar-H), 8.01 (t, J = 8.0 Hz, 1H, Ar-H), 8.11 (t, J = 8.0 Hz, 2H, Ar-H), 8.46 (d, J = 8.0 Hz, 1H, Ar-H), 9.25 (d, J = 8.0 Hz, 1H, Ar-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.5, 32.9, 36.8, 58.1, 59.7, 114.2, 120.5, 121.8, 121.9, 124.7, 125.5, 126.2, 127.4, 128.6, 128.7, 128.9, 129.9, 130.1, 130.2, 139.6, 139.8, 140.1, 140.4, 142.7, 145.6, 146.5, 159.9, 170.3 ppm. Anal. Calcd for $C_{28}H_{20}N_4O_2$ (444.48): C, 75.66; H, 4.54; N, 12.60; Found: C, 75.75; H, 4.57; N, 12.73.

*3-Amino-1-(2-chlorophenyl)-1H-benzo[c]pyrano[3,2-a]phenazine-2-carbonitrile (**7d**)*

Yellow solid. mp 301–303 °C. IR (KBr) cm^{-1}: 3336, 3234, 3147, 2984, 1658, 1585, 1477, 1388, 1276, 1157, 1041, 952, 836, 752. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.02 (s, 1H, CH), 7.15–7.11 (m, 2H, Ar-H), 7.25–7.23 (m, 1H, Ar-H), 7.37 (s, 2H, NH_2), 7.44–7.42 (m, 1H, Ar-H), 7.95–7.92 (m, 2H, Ar-H), 8.07–7.96 (m, 3H, Ar-H), 8.32–8.29 (m, 1H, Ar-H), 8.50 (d, J = 8.0 Hz, 1H, Ar-H), 9.29 (d, J = 8.0 Hz, 1H, Ar-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 36.7, 56.8, 112.9, 119.6, 122.3, 124.9, 125.6, 127.5, 128.1, 128.6, 129.1, 129.2, 129.3, 130.2, 130.3, 130.6, 130.8, 132.3, 140.0, 140.1, 140.8, 141.6, 142.7, 146.7, 159.5, 170.4 ppm. Anal. Calcd for $C_{26}H_{15}ClN_4O$ (434.88): C, 71.81; H, 3.48; N, 12.88; Found: C, 71.90; H, 3.51; N, 13.01.

*3-Amino-11-methyl-1-(4-isopropylphenyl)-1H-benzo[c]pyrano[3,2-a]phenazine-2-carbonitrile (**7e**)*

Yellow Solid. mp 321–323 °C. IR (KBr) cm^{-1}: 3333, 3174, 2966, 1658, 1608, 1508, 1384, 1273, 1157, 1049, 948, 817, 759. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (d, J = 8.0 Hz, 6H, $CH(CH_3)_2$), 2.52 (s, 3H, CH_3), 2.63–2.62 (m, 1H, CH),

5.51 (s, 1H, CH), 7.09–7.06 (m, 2H, Ar-H), 7.25 (s, 2H, NH_2), 7.34 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.73 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.89 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.93 (d, $J = 8.0$ Hz, 1H, Ar-H), 8.04 (d, $J = 8.0$ Hz, 1H, Ar-H), 8.12 (d, $J = 8.0$ Hz, 1H, Ar-H), 8.45 (d, $J = 8.0$ Hz, 1H, Ar-H), 9.22 (d, $J = 8.0$ Hz, 1H, Ar-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.7, 21.5, 23.8, 32.9, 36.8, 58.1, 114.2, 120.4, 121.9, 124.7, 125.6, 126.3, 127.0, 127.4, 128.8, 129.9, 130.1, 133.2, 138.7, 139.6, 139.8, 140.4, 140.5, 141.1, 141.6, 142.7, 145.6, 146.5, 160.0, 171.4, ppm. Anal. Calcd for $C_{30}H_{24}N_4O$ (456.54): C, 78.92; H, 5.30; N, 12.27; Found: C, 79.01; H, 5.33; N, 12.40.

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