

Trisodium citrate dihydrate catalyzed one-pot four component synthesis of spiroprano-indenoquininoxaline derivatives and their molecular docking analysis on the anti-cancer efficacies

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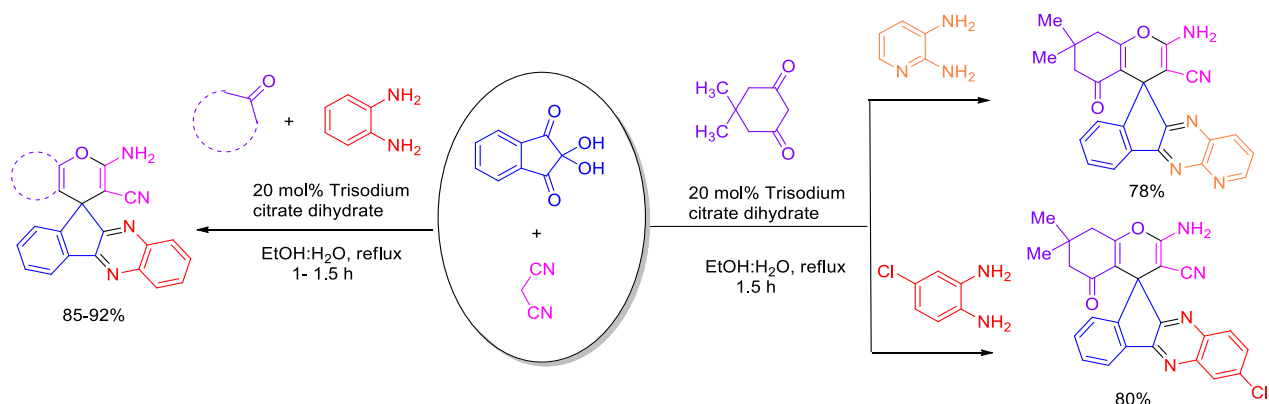
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Abstract

A efficient, simple and facile protocol has been developed for the synthesis of a series of spiroprano-indenoquininoxaline derivatives *via* one-pot four component reactions of ninhydrin, *o*-phenylenediamines, malononitrile and various C-H activated acids using a catalytic amount of trisodium citrate dihydrate as catalyst in an aqueous ethanol under refluxed conditions. The docking analysis revealed promising anti-cancer activities of these synthesized compounds.



Keywords: Spiro-indenoquininoxaline, organocatalysis, four component reactions, trisodium citrate dihydrate, Molecular docking

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Introduction

Quinoxaline and its derivatives are the building blocks of many marketed drug molecules such as varenicline (**A**),¹ brimonidine (**B**),² quinacillin (**C**),³ chlorosulfaquinoxaline (**D**),⁴ R-(+)-XK469 (**E**)⁵ (Figure 1). Quinoxaline bearing skeletons are also familiar in naturally occurring compounds such as echinomycin (**F**), triostin A (**G**) *etc* (Figure 2).^{6,7} On the other hand, spiro-skeletons are also widely distributed among several natural products especially in terpenoids, lactones and alkaloids.⁸ Various spiro-pyrans showed a vast range of biological efficacies which include anti-cancer,⁹ anti-virus,¹⁰ anti-allergic,¹¹ anti-microbial,¹² and many more activities.¹³ Likewise, indene skeleton has also been found to exhibit significant biological activities in many occasions.¹⁴ Specifically, spiro-indenoquinoxaline moiety (**I-1**) has been used as a precursor of many structurally diverse heterocyclic scaffolds having a broad range of pharmacological efficacies which include anti-cancer, anti-mycobacterial, anti-bacterial, anti-Alzheimer, anti-microbial, anti-oxidant, anti-fungal *etc* activities (Figure 3).¹⁵⁻²² Moreover, in 2016, Moosavi-Zareet *al.*²² found that specifically 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (**5a**) possesses significant antioxidant as well as antifungal activities. But, to the best of our knowledge, surprisingly we found only six protocols are accessible in the literature for the synthesis of this particular compounds and its derivatives (Table 1, entries 1-6).²²⁻²⁷ Though these reported methods definitely possess some merits but at the same time few are suffered from some common demerits such as longer reaction time, use of toxic organic solvents, the use of costly catalysts and harsh reaction conditions. This motivated us to synthesize these important scaffolds under much greener conditions involving a metal free organocatalyst by following multicomponent reaction strategy as it is more advantageous than the stepwise pathways.²⁸⁻³⁸

In prolongation of our strong interest with various organocatalysts,³⁹⁻⁵⁰ especially with trisodium citrate dihydrate as catalyst,⁵¹ this time also we wanted to check the catalytic activity of trisodium citrate dihydrate for the one-pot four component syntheses of various spiropyrano-indenoquinoxaline derivatives. It is our pleasure to mention that a catalytic amount of this organocatalyst was capable to catalyze a series of one-pot four component reactions which afforded a wide range of structurally diverse spiropyrano-indenoquinoxaline derivatives. We selected trisodium citrate dihydrate as catalyst due to its low-cost, commercial availability and non-toxicity. It has been used as a main component in Oral Rehydration Solution (ORS) recommended by the World Health Organization. It has also been used in many eatable substances like soft drinks, sweets, jams and many bakery products *etc.*⁵²⁻⁵³ In this article we wish to report a facile protocol for the efficient and environmentally benign synthesis of a series of spiropyrano-indenoquinoxaline derivatives (**5a-5j**) *via* one-pot four-component reactions of ninhydrin (**1**), *o*-phenylenediamine (**2**), malononitrile (**3**) and a variety of C-H activated acids (**4a-4j**) using a catalytic amount (20 mol%) of trisodium citrate dihydrate as catalyst in aqueous ethanol under refluxed conditions (Scheme 1). Under the same optimized reaction conditions, synthesis of 2-amino-7'-chloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (**5aa**) and 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,6'-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine]-3-carbonitrile (**5bb**) was also achieved in excellent yields from the reactions of ninhydrin (**1**), malononitrile (**3**) and dimedone (**4a**) and 4-chloro-1,2-phenylenediamine (**2a**) or pyridine-2,3-diamine (**2b**) (Scheme 2).

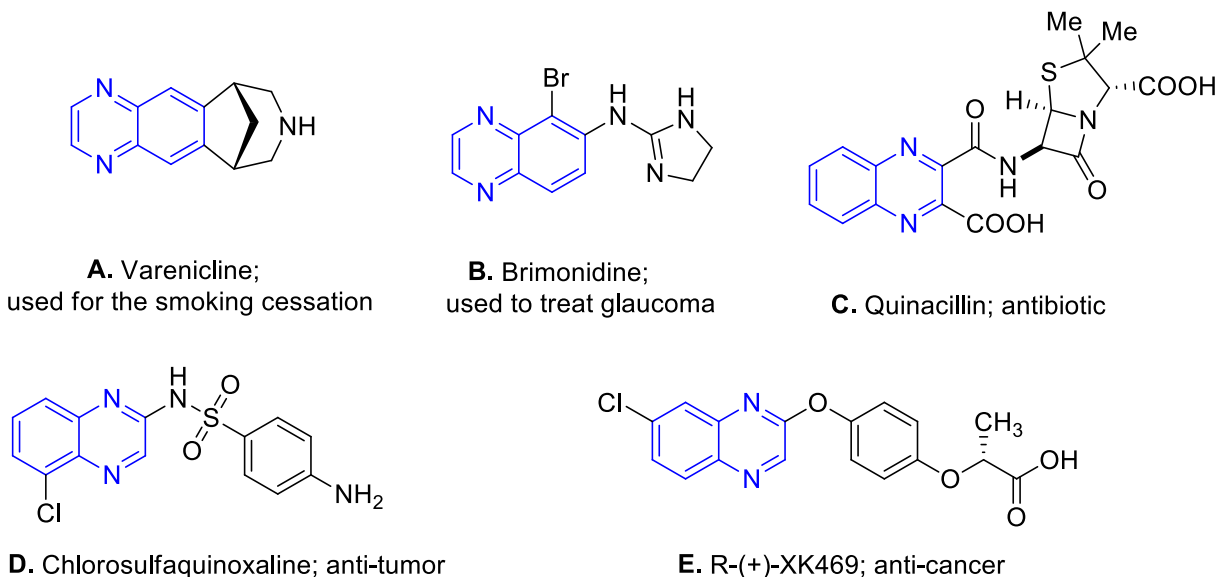


Figure 1: Quinoxaline containing commercially available drug molecules.

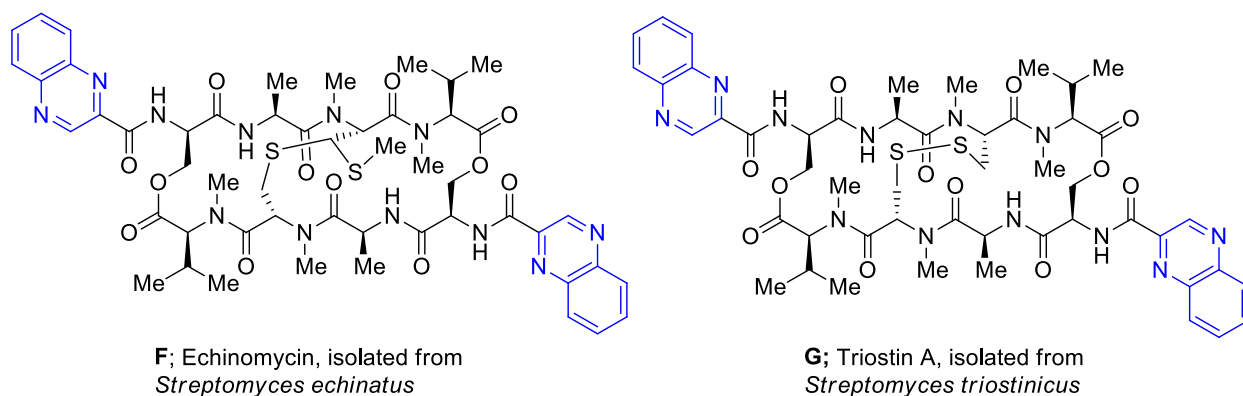


Figure 2: Naturally occurring quinoxaline bearing compounds

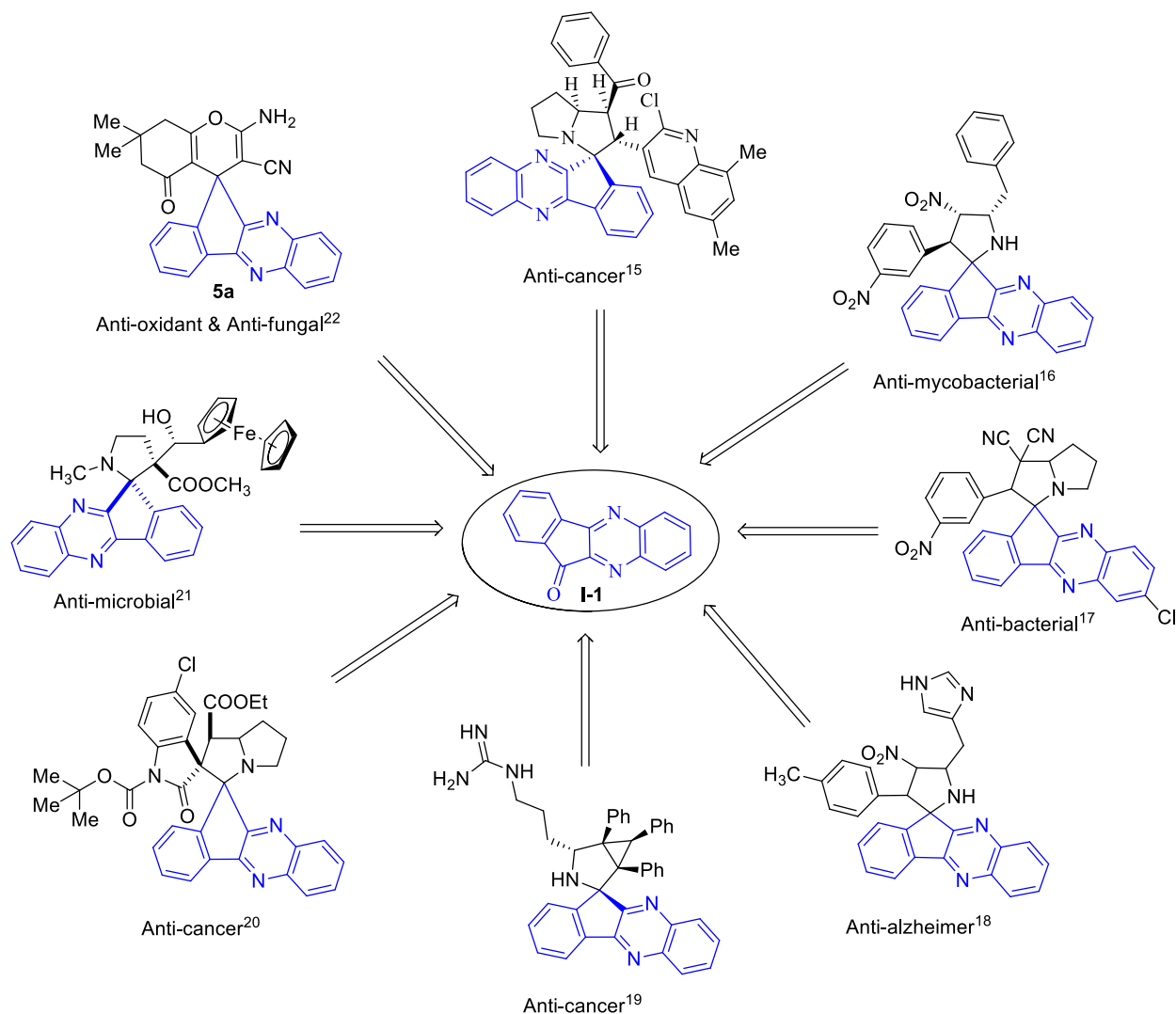
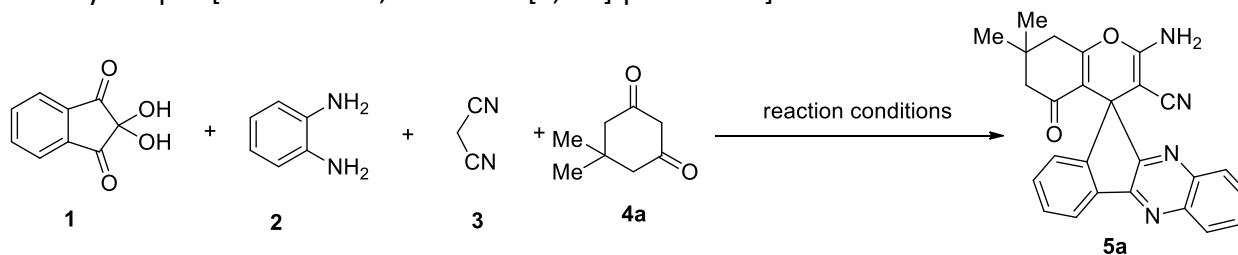


Figure 3: Glimpse of the bioactive spiro-indenoquinoxaline derivatives

Table 1: Previously reported protocols for the synthesis of 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile



S.No	Catalyst	Solvent	Temp.	Time	Yield(%) ^{Ref}
1	Poly(Py-co-Ani)@GO-Fe ₃ O ₄	EtOH	Reflux	1 h	97 ²²
2	10 mol% Na ₂ CO ₃	EtOH	70 °C	12 h	93 ²³
3	20 mol% CH ₃ COONH ₄	EtOH	Reflux	12 h	91 ²⁴
4	Bleaching earth	EtOH	80 °C	3 h	90 ²⁵
5	15 mol% InCl ₃	CH ₃ CN	Reflux	11 h	91 ²⁶
6	APVPB	H ₂ O	Reflux	5 min	92 ²⁷
7	Trisodium citrate dihydrate	EtOH:H₂O	Reflux	1.5 h	92% ^[this work]

GO = Graphene oxide, APVPB = acetic acid functionalized poly (4-vinylpyridinium) salt

Results and Discussion

During optimization of the reaction conditions, a series of trial reactions were performed between ninhydrin (**1**; 0.25 mmol), *o*-phenylenediamine (**2**; 0.25 mmol), malononitrile (**3**; 0.25 mmol) and dimedone (**4a**; 0.25 mmol) under different reaction conditions. Firstly, we carried out the reaction at room temperature in the absence of both catalyst and solvent which failed to afford the desired product even after 4 hours (Table 2, entry 1). In the absence of any catalyst, the same reaction afforded trace of desired products after 4 hours in ethanol as solvent (Table 2, entry 2). After observing poor yields under catalyst-free conditions, we were interested to screen the catalytic activities of some commercially available low cost environmentally benign metal-free catalysts. In prolongation of our strong interest, for this transformation also we employed 20 mol% trisodium citrate dihydrate as catalyst in aqueous medium which afforded 26% of the desired products *i.e.*, 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (**5a**) after 4 hours (Table 2, entry 3). The same amount of catalyst in ethanol at room temperature, afforded 41% yield of the desired compound **5a** after 4 hours (Table 2, entry 4). Improvement in yield (77%) was observed when we carried out the same reaction with 20 mol% trisodium citrate dihydrate as catalyst in ethanol under refluxed conditions for 4 hours (Table 2, entry 5). Almost comparable yield (75%) was observed after 4 hours by replacing ethanol with methanol as solvent under the same reaction conditions (Table 2, entry 6). Surprisingly, with the same amount of catalyst, excellent yield (92%) of the desired product was obtained in aqueous-ethanol (1:1 v/v) as solvent under refluxed conditions within just 1.5 hours (Table 2, entry 7). From these preliminary screening it was established that aqueous-ethanol may be the best suitable solvent to carry out this reaction. Under the similar reaction conditions, we screened the efficiency of a number of other metal-free organocatalysts such as 20 mol% glycine (80%, 1.5 h) (Table 2, entry 8), 20 mol% sulfamic acid (45%, 1.5 h) (Table 2, entry 9), 20 mol% DBU (31%, 1.5 h) (Table 2, entry 10), 20 mol% DABCO (39%, 1.5 h) (Table 2, entry 11), 20 mol% sodium formate (67%, 1.5 h) (Table 2, entry 12), 20 mol% ammonium formate (54%, 1.5 h) (Table 2, entry 13), 20 mol% sodium acetate (64%, 1.5 h) (Table 2, entry 14), 20 mol% triammonium citrate (77%, 1.5 h) (Table 2, entry 15) but all of these afforded lesser yields of the desired compounds *i.e.*, compound **5a** than the 20 mol% trisodium citrate dihydrate provided as catalyst.

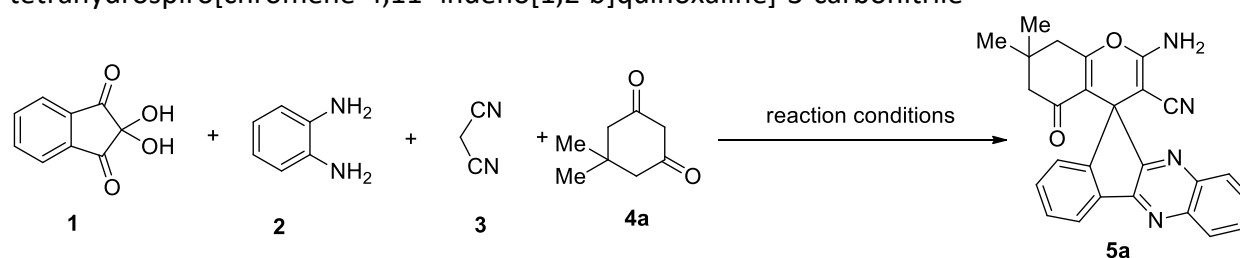
To standardize the amount of required catalyst, we then carried out the same reactions separately with 15 mol% and 25 mol% trisodium citrate dihydrate in aqueous-ethanol (1:1 v/v) at 100 °C (bath temperature). Interestingly, with decreasing the amount of the catalyst *i.e.*, with 15 mol% trisodium citrate dihydrate lesser amount of the expected product was isolated in aqueous-ethanol (1:1 v/v) at 100 °C (Table 2, entry 16) whereas comparable yield of **5a** was observed even after increasing the catalyst amount 5 mol% *i.e.*, with 25 mol% trisodium citrate dihydrate as catalyst in aqueous-ethanol (1:1 v/v) at 100 °C (Table 2, entry 17). To check the effect of temperature, we then carried out the same reactions separately at 110 °C (bath temperature) (Table 2, entry 18) as well as 90 °C (Table 2, entry 19) for the same 1.5 hours using 20 mol% trisodium citrate dihydrate as catalyst in aqueous-ethanol (1:1 v/v) as solvent and found that lowering the temperature below 100 °C affect the product formation. Therefore, it was come out that the use of 20 mol% trisodium citrate dihydrate as catalyst in aqueous-ethanol (1:1 v/v) as solvent under refluxed conditions at 100 °C is the best suitable conditions for the efficient synthesis of 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (**5a**) *via* one-pot four-component reactions between ninhydrin (**1**), *o*-phenylenediamine (**2**), malononitrile (**3**) and dimedone (**4a**) (Table 2, entry

7). In comparison with the earlier reported methods (Table 1), it is clear that the present developed protocol is much more economical, sustainable and environment friendly.

To check the generality as well as effectiveness of our developed protocol, instead of dimedone, we were interested to use a series of other C-H activated acids i.e., 1,3-cyclohexanedione (**4b**), *N,N*-dimethylbarbituric acid (**4c**), Meldrum's acid (**4d**), 4-hydroxycoumaric (**4e**), indane-1,3-dione (**4f**), 4-hydroxy-6-methyl pyrone (**4g**), 2-thiobarbituric acid (**4h**), 2-hydroxy-1,4-naphthoquinone (**4i**) and β -naphthol (**4j**). It is our pleasure to mention that under the similar optimized reaction conditions all the reactions go through smoothly and afforded the desired products (**5b-5j**) in good to excellent yields (85-90%). Under the same optimized reaction conditions we were able to synthesize 2-amino-8'-chloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (**5aa**) and 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,6'-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine]-3-carbonitrile (**5bb**) in good yields (78-80%) from the one-pot four component reactions between ninhydrin (**1**; 0.25 mmol), malononitrile (**3**; 0.25 mmol), dimedone (**4a**; 0.25 mmol) and 4-chlorobenzene-1,2-diamine (**2a**) or pyridine-2,3-diamine (**2b**; 0.25 mmol) respectively (Scheme 2).

All the synthesized products were extracted pure just by simple filtration and subsequent washing with aqueous-ethanol; there is no need of column chromatography. It is noteworthy to mention that we were also able to synthesize 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (**5a**; 1.963 g, 82%) in gram scale from the reactions of 5 mmol ninhydrin (**1**; 0.89 g), 5 mmol *o*-phenylenediamine (**2**; 0.54 g), 5 mmol malononitrile (**3**; 0.33 g) and 5 mmol dimedone (**4a**; 0.7 g) using 20 mol% trisodium citrate dihydrate (0.294 g) in aqueous-ethanol (20 ml) under refluxed conditions at 100 °C. During filtration, the catalyst containing filtrate was collected and reused further for the similar batch of reaction without adding any catalyst which afforded the targeted compound **5a** in 76% yield (1.784 g). All the synthesized compounds were characterized by the detail spectroscopic analyses of FTIR, ¹H & ¹³C NMR, and HRMS spectroscopy. Plausible mechanism and role of the catalyst is shown in Figure 4. It is assumed that under the influence of the catalytic amount of trisodium citrate dihydrate, the reaction between ninhydrin (**1**) and *o*-phenylenediamine (**2**) formed 11*H*-indeno[1,2-*b*]quinoxalin-11-one (**I-1**) *in situ*, which further reacted with malononitrile (**3**) to form the corresponding Knoevenagel intermediate (**I-2**). Further attack by the dimedone molecule (**4a**) on the Knoevenagel intermediate (**I-2**) generated the adduct **I-3** which eventually underwent cyclization to afford the desired product **5a**.

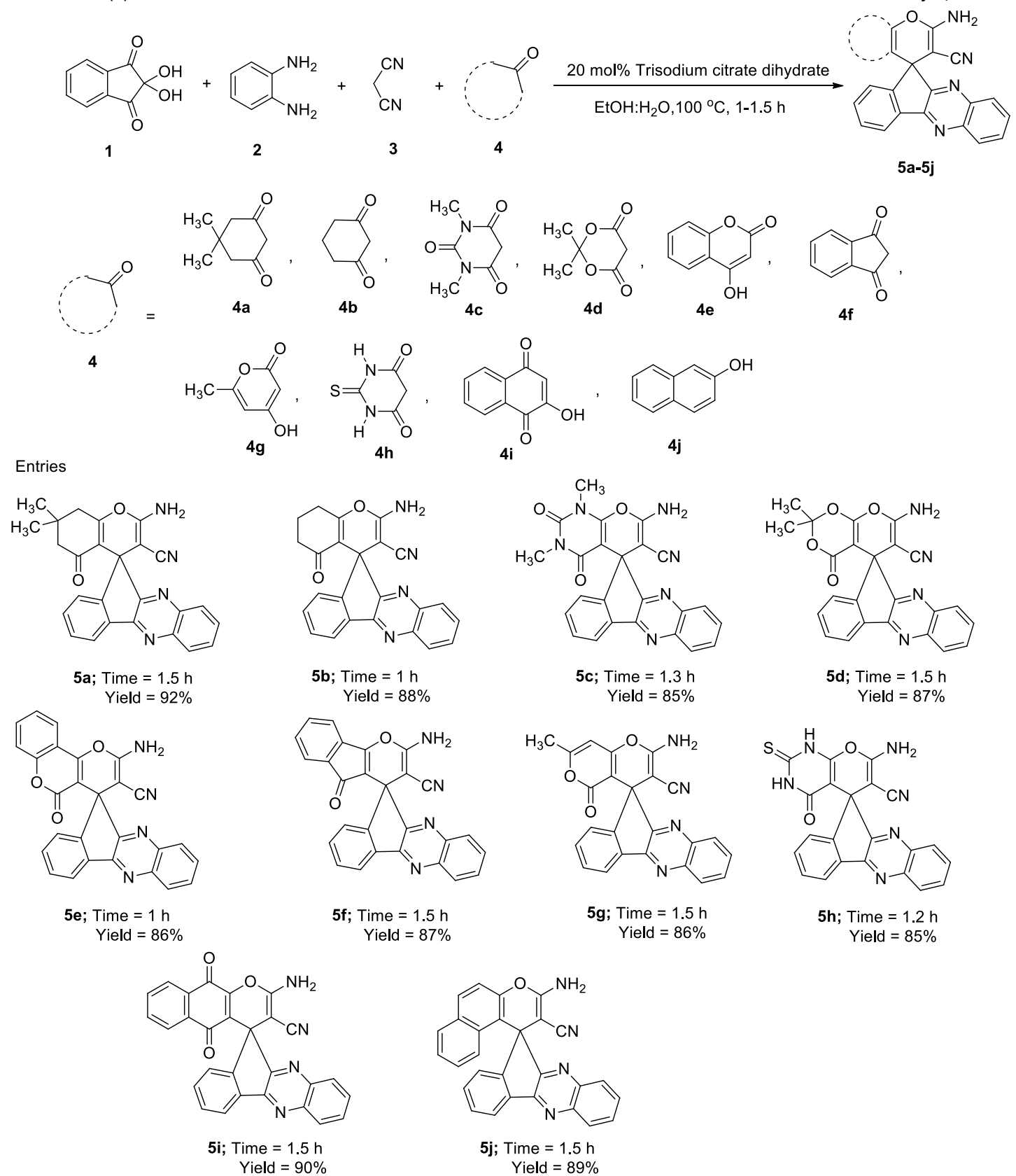
Table 2: Optimization of the reaction conditions for the synthesis of 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile



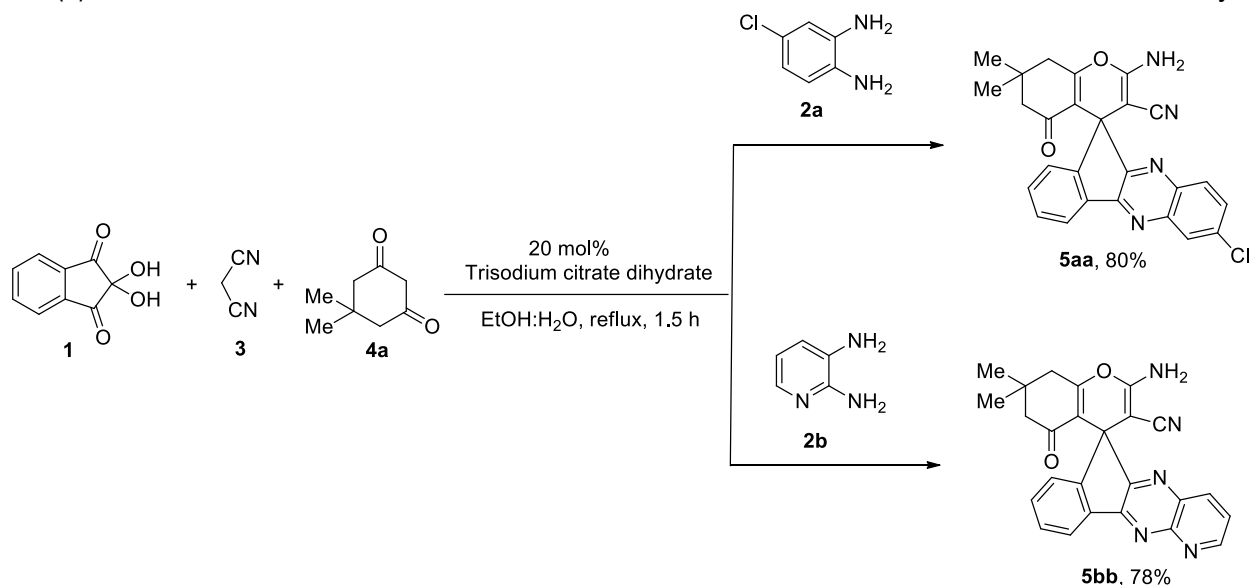
Entry	Catalyst (mol%)	Solvent	Temp. (°C) ^c	Time (h)	Yield (%) ^{a,b}
1	Catalyst-free	Neat	RT (28)	4	0
2	Catalyst-free	EtOH	RT (28)	4	trace
3	Tri-Sodium Citrate dihydrate (20)	H ₂ O	RT (30)	4	26
4	Tri-Sodium Citrate dihydrate (20)	EtOH	RT (30)	4	41

5	Tri-Sodium Citrate dihydrate (20)	EtOH	100	4	77
6	Tri-Sodium Citrate dihydrate (20)	MeOH	100	4	75
7	Tri-Sodium Citrate dihydrate (20)	H₂O:EtOH	100	1.5	92
8	Glycine (20)	H ₂ O:EtOH	100	1.5	80
9	Sulfamic acid (20)	H ₂ O:EtOH	100	1.5	45
10	DBU (20)	H ₂ O:EtOH	100	1.5	31
11	DABCO (20)	H ₂ O:EtOH	100	1.5	39
12	HCOONa (20)	H ₂ O:EtOH	100	1.5	67
13	HCOONH ₄ (20)	H ₂ O:EtOH	100	1.5	54
14	CH ₃ COONa (20)	H ₂ O:EtOH	100	1.5	64
15	Tri-ammonium citrate (20)	H ₂ O:EtOH	100	1.5	77
16	Tri-Sodium Citrate dihydrate (15)	H ₂ O:EtOH	100	1.5	70
17	Tri-Sodium Citrate dihydrate (25)	H ₂ O:EtOH	100	1.5	92
18	Tri-Sodium Citrate dihydrate (20)	H ₂ O:EtOH	110	1.5	92
19	Tri-Sodium Citrate dihydrate (20)	H ₂ O:EtOH	90	1.5	88

^aReaction conditions: ninhydrin (**1**; 0.25 mmol), *o*-phenylenediamine (**2**; 0.25 mmol), malononitrile (**3**; 0.25 mmol) and dimedone (**3**; 0.25 mmol) in the absence or presence of catalyst in different solvents at room temperature or refluxed conditions. ^bIsolated yields. ^cBath temperature



Scheme 1: Synthesis of a series of 2'-aminospiro[indeno[1,2-*b*]quinoxaline-11,4'-pyran]-3'-carbonitrile derivatives



Scheme 2: Tri-Sodium Citrate dihydrate catalyzed synthesis of 2-amino-8'-chloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (**5aa**) and 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,6'-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine]-3-carbonitrile (**5bb**)

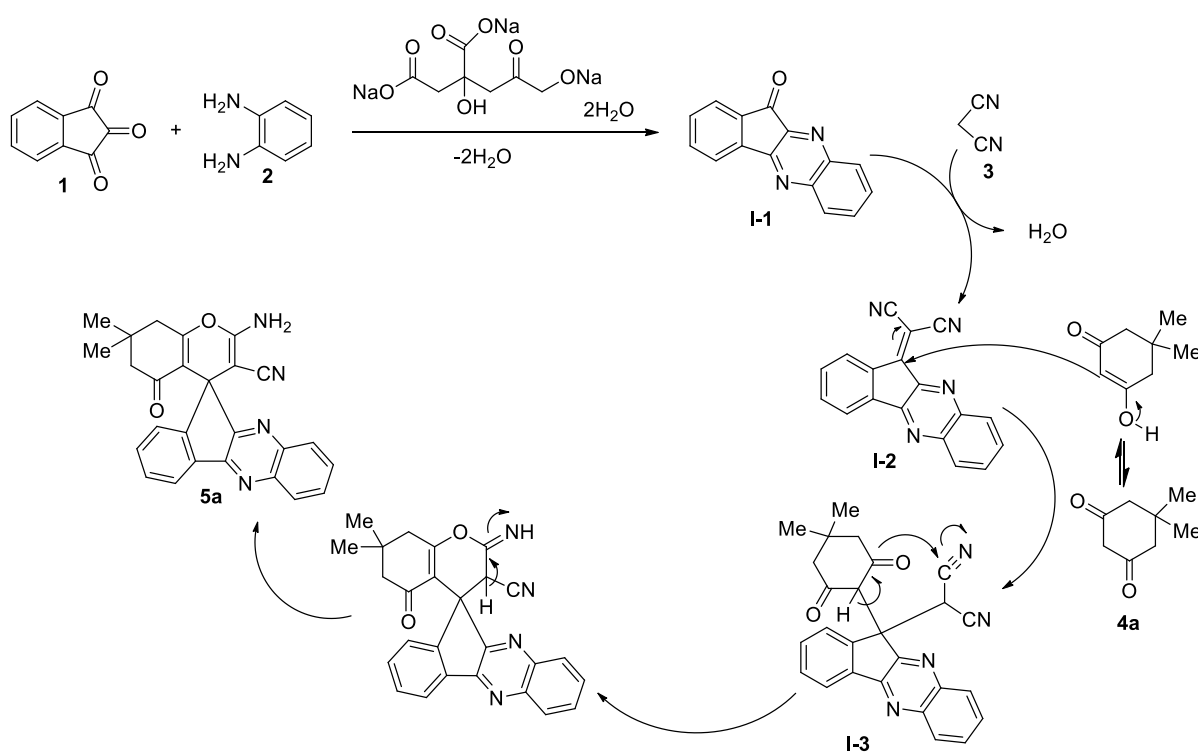


Figure 4: Plausible mechanism for the synthesis of 2'-aminospiro[indeno[1,2-*b*]quinoxaline-11,4'-pyran]-3'-carbonitrile (**5a**) using trisodium citrate dihydrate as catalyst

Molecular docking studies: Anti-cancer activities

The Auto-dock software package was utilized for molecular simulation, and the results were visualized using the Discovery Studio Visualizer. Additionally, the preparation of the protein was conducted using the same software. The protein structures were obtained from the RCSB-PDB database and prepared for docking by removing water molecules and adding polar hydrogen bonds using the AutoDock software. The compounds were docked into different proteins associated with breast cancer (PDB ID: 5JRS), hepatic cancer (PDB ID: 1PMV), and lung cancer (PDB ID: 3I5Z). During the docking process, the ligands (derivatives) were computationally positioned and oriented within the binding site of the target protein. Various scoring functions and algorithms were employed to evaluate the binding affinity and estimate the binding free energy between the ligands and the protein. The results of the docking simulations revealed that the highest binding energy was observed in breast cancer with a value of -9.2 kcal/mol. For hepatic cancer, the binding energy was -10.3 kcal/mol, and for lung cancer, it was -8.8 kcal/mol. The ligands **5i** exhibited the highest binding energies for breast cancer while **5e** showed the highest binding affinity for both hepatic cancer and lung cancer. The ligand **5i** showed hydrogen bond interaction with Arg525 and Arg562 in breast cancer and also unfavorable donor-donor with Arg562. The ligand **5e** showed three hydrogen bond interactions (Lys191, Arg230 and Thr103) with amino acids in hepatic cancer, and showed two hydrogen bond interactions (Ser151, Lys149) with lung cancer protein. Ligands also showed various other interactions. The corresponding docking scores are mentioned in Table 3. To calculate the physicochemical (ADMET) properties, the Swiss ADEME online tool was used; data is represented in Table 4.

Table 3: Docking Score of the interactions of our synthesized compounds with known anti-cancer protein targets

Sr. No	Compounds	Breast Cancer PDB ID: 5JRS		Hepatic Cancer PDB ID: 1PMV		Lung Cancer PDB ID: 3I5Z	
		(Docking Score) (kcal/mol)	H-Bonding Interactions	(Docking Score) (kcal/mol)	H-Bonding Interactions	(Docking Score) (kcal/mol)	H-Bonding Interactions
1.	5a	-7.9	Arg525	-9.5	Asp189, Arg230	-7.7	Lys149, Ser151
2.	5b	-7.7	Arg525	-9.5	Thr102, Lys191, Arg230, Asp189	-7.8	Asp109, Ser151, Lys149
3.	5c	-7.9	Asn603, Phe559, Ser557	-8.3	Ser193	-8.6	Ser151, Tyr111, Lys149
4.	5d	-7.8	Asn603, Phe559	-9.6	Arg107, Asp189	-8.0	Lys149, Ser151
5.	5e	-8.4	Arg562, Phe559	-10.3	Lys191, Arg230, Thr103	-8.8	Ser151, Lys149
6.	5f	-8.6	Phe559, Arg562	-10.0	Lys191, Asp189, Thr226, Arg230, Thr103	-8.5	Tyr111, Ser151
7.	5g	-7.9	-	-10.1	Lys191, Arg230, Asp189, Thr103	-7.9	Lys149, Ser151
8.	5h	-8.0	Asp521, Asn603, Arg562	-9.9	Gln75, Lys191, Asp189, Arg230, Thr103	-7.8	Asn152, Ser151, Lys149
9.	5i	-9.2	Arg525, Arg562	-9.6	Arg230	-8.7	Lys149, Ala33
10.	5j	-8.2	Arg562, Phe559	-9.6	Lys191, Asp189, Thr226	-8.4	Tyr111, Ser151

11.	5aa	-8.5	Arg525	-9.7	Thr103, Thr107, Asp189	-8.3	Ser151, Tyr28, Glu31
12.	5bb	-8.4	-	-9.4	Thr103, Arg107, Thr226	-7.4	Lys149, Ser151

Table 4: ADME profile of the synthesized compounds

Derivatives	MW	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA	iLOGP	Lipinski violations	Bioavailability Score
5a	420.46	0	5	1	101.89	3.13	0	0.56
5b	392.41	0	5	1	101.89	2.78	0	0.56
5c	436.42	0	6	1	128.82	2.8	0	0.55
5d	424.41	0	7	1	120.35	3.01	0	0.56
5e	442.43	0	6	1	115.03	3.08	0	0.55
5f	426.43	0	5	1	101.89	2.94	0	0.56
5g	406.39	0	6	1	115.03	2.83	0	0.55
5h	424.43	0	5	3	165.56	2.13	0	0.55
5i	454.44	0	6	1	118.96	2.7	0	0.56
5j	424.45	0	4	1	84.82	3.24	0	0.55
5aa	454.91	0	5	1	101.89	3.29	0	0.56
5bb	421.45	0	6	1	114.78	2.76	0	0.56

Conclusions

In summary, the utilization of trisodium citrate dihydrate as a catalyst in the one-pot four-component synthesis of 2'-aminospiro[indeno[1,2-*b*]quinoxaline-11,4'-pyran]-3'-carbonitrile derivatives presents a promising and efficient method for obtaining these valuable compounds. The use of trisodium citrate dihydrate as a catalyst offers several benefits, including its ready availability, cost-effectiveness, and environmentally friendly characteristics. Furthermore, the molecular docking analysis performed on the synthesized derivatives has provided valuable insights into their potential as anti-cancer agents. By docking the compounds into the active sites of cancer-related proteins, their binding modes and affinities have been elucidated, offering a deeper understanding of their mechanisms of action. The docking simulations have demonstrated favorable binding energies for the derivatives in target proteins associated with breast cancer, hepatic cancer, and lung cancer. These findings suggest that the synthesized compounds have the potential to effectively target and inhibit cancer-related processes specific to these types of cancer. Overall, the successful combination of the efficient synthesis of 2'-aminospiro[indeno[1,2-*b*]quinoxaline-11,4'-pyran]-3'-carbonitrile derivatives using trisodium citrate dihydrate catalysis and the molecular docking analysis on their anti-cancer efficacies highlights the prospect of these compounds as valuable candidates for further development as anti-cancer agents.

Experimental Section

General. Melting points were recorded on a Digital Melting Point Apparatus (Model No. MT-934) and are uncorrected. TLC was performed on silica gel 60 F254 (Merck) plates. ^1H and ^{13}C NMR spectra were obtained at 500 MHz Jeol (JNM ECX-500) NMR machines with $\text{DMSO-d}_6/\text{CDCl}_3$ as the solvent. Mass spectra (TOF-MS ES^+) were measured on a Bruker Impact HD QTOF Micro mass spectrometer.

Molecular docking. A three-dimensional (3D) conformer of spiropyrano-indenoquinoxaline series was prepared from ChemDraw. The 3D structure of cancer proteins (Breast, Hepatic and Lung) were obtained from the protein data bank (PDB ID: 5JRS, 1PMV, 3I5Z) respectively at (<https://www.rcsb.org>) in a PDB format. The 2D structures of all the compounds of spiropyrano-indenoquinoxaline series were drawn in ChemBiodraw 15.0 and were saved as ".cdx" files followed by energy minimization using the Molecular mechanics 2 fields in the ChemDraw 3D module of ChemBioOffice v16 (Perkin-Elmer) and was saved as ".pdb" file and then converted into "pdbqt" file with the help of autodock tool. Initially, the docking protocol was validated by removing the co-crystals from the protein and again docked back into the active site of the proteins. The 2D interaction was generated using the Discovery Studio visualizer (DassaultSystemesBiovia). The root mean square deviation of the protein in co-crystal complex formation and the best-docked conformation was zero. Ligand showed a negligible deviation. This indicated the ability of the docking protocol to reproduce the binding mode of the co-crystal inhibitor.⁵⁴

General procedure for the synthesis 2'-aminospiro[indeno[1,2-*b*]quinoxaline-11,4'-pyran]-3'-carbonitriles (5a-5j). A magnetic stir bar, ninhydrin (**1**; 0.25 mmol), *o*-phenylenediamine (**2**; 0.25 mmol), malononitrile (**3**; 0.25 mmol), dimedone (**4**; 0.25 mmol), 4 ml aqueous ethanol and 20 mol% tri-sodium citrate dihydrate were taken sequentially in a dry and clean round bottom flask. The whole reaction mixture was then refluxed for 1.5 hours at 100 °C. The progress of the reaction was monitored by TLC. All the reactions were completed within 1.5 hours. After completion of the reaction, the mixture was allowed to cool down slowly at room temperature and the desired product was isolated pure just by simple filtration and subsequent washing with aqueous ethanol ($\text{EtOH}:\text{H}_2\text{O} = 1:1$). The structure of the synthesized compound was determined by the detailed spectral analysis including FTIR, ^1H NMR, ^{13}C NMR and HRMS studies. Characterization data of the known compounds (**5a**, **5b** and **5e**) are in well agreement with the literature values.

2-Amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (5a). Orange solid; yield 92%; mp 295-297 °C, (lit. 282 °C)²²; FTIR (cm^{-1}): 3429, 3310, 3172, 2960, 2197, 1671, 1471, 1354, 1208, 765, 705; ^1H NMR (500 MHz, DMSO-d_6): δ_{H} /ppm: 8.12 (dd, 1H, J 8.25 Hz, aromatic H), 8.06 (d, 1H, J 7.5 Hz, aromatic H), 8.00 (t, 1H, J 7 Hz, aromatic H) 7.81-7.78 (m, 1H, aromatic H), 7.75-7.71 (m, 1H, aromatic H), 7.59-7.56 (m, 1H, aromatic H), 7.53-7.48 (m, 2H, aromatic H), 7.26 (s, 2H, $-\text{NH}_2$), 2.65 (q, 2H, J 17.5 Hz, $-\text{CH}_2-$), 1.99 (q, 2H, J 16 Hz, $-\text{CH}_2-$), 1.00 (s, 3H, $-\text{CH}_3$), 0.98 (s, 3H, $-\text{CH}_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_{C} /ppm: 195.49, 166.05, 165.38, 159.44, 154.67, 152.42, 142.18, 141.52, 132.85 (2C), 130.18 (2C), 129.58, 129.36 (2C), 124.99, 122.5 (2C), 118.01, 112.45, 59.21, 50.69, 47.67, 32.49, 28.14, 27.56; MS (ESI-TOF) m/z : 419.1146.

2-Amino-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (5b). Orange solid; yield 88% mp 287-290 °C, (lit. 282 °C)²²; FTIR (cm^{-1}): 3353, 3288, 3123, 2960, 2233, 1667, 1462, 1346, 1205, 764, 708; ^1H NMR (500 MHz, DMSO-d_6): δ_{H} /ppm: 8.12 (d, 1H, J 8 Hz, aromatic H), 8.04 (t, 2H, J 8 Hz, aromatic H), 7.79 (t, 1H, J 8 Hz, aromatic H), 7.73 (t, 1H, J 7.5 Hz, aromatic H), 7.56 (t, 1H, J 7.5 Hz, aromatic H), 7.51 (t, 2H, J 7.5 Hz, aromatic H), 7.25 (s, 2H, $-\text{NH}_2$), 2.75 (q, 2H, J 11.75 Hz, $-\text{CH}_2-$), 2.08 (q, 2H, J 10.75 Hz, -

CH₂-), 1.90 (t, 2H, *J* 6.5 Hz, -CH₂-); ¹³C NMR (125 MHz, DMSO-d₆): δ_C/ppm: 195.60, 167.21, 166.15, 159.30, 154.70, 152.59, 142.15, 141.45, 136.63, 132.82, 130.14, 129.53, 129.42, 129.34, 129.31, 125.16, 121.94, 118.04, 113.54, 59.29, 47.74, 37.12, 27.51, 20.29; MS (ESI-TOF) *m/z*: 391.0892.

7'-Amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,5'-pyrano[2,3-*d*]pyrimidine]-6'-carbonitrile (5c). Orange solid; yield 85% mp 317-318 °C; FTIR (cm⁻¹): 3548, 3161, 3023, 2879, 2226, 1556, 1465, 1343, 1202, 765, 703; ¹H NMR (500 MHz, DMSO-d₆): δ_H/ppm: 8.41 (d, 1H, *J* 9 Hz, aromatic H), 8.14 (q, 3H, *J* 8 Hz, aromatic H), 8.07 (d, 1H, *J* 7 Hz, aromatic H), 7.92-7.81 (m, 4H, aromatic 2H & -NH₂), 7.71-7.67 (m, 1H, aromatic H), 2.60 (s, 3H, -CH₃), 2.33 (s, 3H, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ_C/ppm: 153.53 (2C), 143.42, 136.04, 135.41, 135.13, 132.82, 132.55, 131.31, 130.45, 130.31, 129.71, 127.09 (2C), 126.79 (2C), 123.20 (2C), 119.28, 113.20, 111.53, 87.87, 57.68 (2C); MS (ESI-TOF) *m/z*: 437.2362.

7'-Amino-2',2'-dimethyl-4'-oxo-4'-H-spiro[indeno[1,2-*b*]quinoxaline-11,5'-pyrano[2,3-*d*][1,3]dioxine]-6'-carbonitrile (5d). Orange solid; yield 87% mp 312-315 °C; FTIR (cm⁻¹): 3377, 3208, 2958, 2880, 2226, 1557, 1462, 1343, 1200, 764, 698; ¹H NMR (500 MHz, DMSO-d₆): δ_H/ppm: 8.17-8.12 (m, 3H, aromatic H), 8.07 (d, 1H, *J* 7.5 Hz, aromatic H), 7.91-7.81 (m, 5H, aromatic 3H & -NH₂), 7.69 (t, 1H, *J* 7.5 Hz, aromatic H), 2.43 (s, 6H, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ_C/ppm: 155.52, 143.30, 141.92, 138.63, 136.04, 135.41, 132.82, 132.55, 131.31 (2C), 130.51 (2C), 129.69 (2C), 126.79 (2C), 123.22 (2C), 111.53, 103.91, 90.21, 89.95, 29.71 (2C); MS (ESI-TOF) *m/z*: 424.3493.

2'-Amino-5'-oxo-5'-H-spiro[indeno[1,2-*b*]quinoxaline-11,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile (5e). Orange solid; yield 86% mp 312 °C, (lit. 299 °C)²²; FTIR (cm⁻¹): 3418, 3023, 2963, 2226, 1622, 1415, 1346, 1248, 764, 700; ¹H NMR (500 MHz, DMSO-d₆): δ_H/ppm: 8.41 (d, 1H, *J* 6 Hz, aromatic H), 8.18-8.07 (m, 4H, aromatic 2H & -NH₂), 8.03 (dd, 1H, *J* 8, 7 Hz, aromatic H), 7.88-7.82 (m, 3H, aromatic H) 7.77 (t, 3H, *J* 9, 7 Hz, aromatic H), 7.60-7.57 (m, 1H, aromatic H), 7.43 (d, 1H, *J* 8 Hz, aromatic H). ¹³C NMR (125 MHz, CDCl₃): δ_C/ppm: 167.21, 153.73, 151.34, 151.03, 136.20 (2C), 136.06 (2C), 132.84 (2C), 132.57 (2C), 132.47 (2C), 131.31 (2C), 130.54 (2C), 129.93 (2C), 129.69 (2C), 123.22, 121.40, 120.88, 54.16, 50.03. MS (ESI-TOF) *m/z*: 441.0979.

2-Amino-5-oxo-5H-spiro[indeno[1,2-*b*]pyran-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (5f). Orange solid; yield 87% mp 315-320 °C; FTIR (cm⁻¹): 3413, 3156, 2967, 2226, 1617, 1463, 1347, 1248, 764, 700; ¹H NMR (500 MHz, DMSO): δ_H/ppm: 8.55 (d, 1H, *J* 7.5 Hz, aromatic H), 8.22 (d, 1H, aromatic 1H), 8.14-8.09 (m, 3H, aromatic 1H & -NH₂), 7.83 (t, 1H, *J* 8 Hz, aromatic H), 7.76 (q, 3H, *J* 8, 7.5 Hz, aromatic H), 7.63 (t, 1H, *J* 8 Hz, aromatic H), 7.25 (d, 4H, *J* 3.5 Hz, aromatic H). ¹³C NMR (125 MHz, CDCl₃): δ_C/ppm: 187.62, 153.57, 149.69, 143.25, 141.90, 140.95, 138.90, 136.06, 135.40, 132.84 (2C), 132.57 (2C), 131.31 (2C), 130.51 (2C), 129.69 (2C), 126.79 (2C), 123.22 (2C), 113.21, 111.55, 88.80, 78.57. MS (ESI-TOF) *m/z*: 427.2750.

2'-Amino-7'-methyl-5'-oxo-5'-H-spiro[indeno[1,2-*b*]quinoxaline-11,4'-pyrano[4,3-*b*]pyran]-3'-carbonitrile (5g). Orange solid; yield 86% mp 316-317 °C; FTIR (cm⁻¹): 3483, 3017, 2957, 2226, 1614, 1557, 1344, 1200, 764, 703; ¹H NMR (500 MHz, DMSO-d₆): δ_H/ppm: 8.14 (q, 3H, *J* 8.5, 7.5 Hz, aromatic H), 8.07 (d, 1H, *J* 7 Hz, aromatic H), 7.92-7.81 (m, 6H, aromatic 4H & -NH₂), 7.69 (t, 1H, *J* 7.5 Hz, aromatic H), 2.60 (s, 3H, -CH₃). ¹³C NMR (125 MHz, CDCl₃): δ_C/ppm: 195.54, 171.42, 155.60, 153.79, 141.98, 138.76, 136.18, 135.36, 132.80 (2C), 132.55 (2C), 131.31, 130.49, 129.69, 126.79, 123.20 (2C), 120.52, 113.13, 106.32, 83.58, 78.60, 29.71. MS (ESI-TOF) *m/z*: 430.2016.

7'-Amino-4'-oxo-2'-thioxo-1',2',3',4'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,5'-pyrano[2,3-*d*]pyrimidine]-6'-carbonitrile (5h). Orange solid; yield 85% mp >300 °C; FTIR (cm⁻¹): 3415, 3230, 3016, 2955, 2226, 1618, 1557, 1345, 1248, 764, 702; ¹H NMR (500 MHz, DMSO-d₆): δ_H/ppm: 8.41 (d, 1H, *J* 7.5 Hz, aromatic H), 8.14, (br s, 2H, NH), 8.75 (d, 2H, *J* 6.5 Hz, aromatic 4H), 7.90-7.81 (m, 6H, 4 x aromatic H & -NH₂), 7.70-7.67 (m, 1H, aromatic H); ¹³C NMR (125 MHz, CDCl₃): δ_C/ppm: 212.31, 203.16, 158.63, 154.59, 142.14, 138.176,

135.03, 131.77, 131.48, 130.26 (2C), 129.44, 129.13, 128.64 (2C), 125.73 (2C), 122.26, 122.14, 115.33, 112.06, 93.21; MS (ESI-TOF) m/z : 425.2723.

2-Amino-5,10-dioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (5i). Orange solid; yield 90% mp 318-319 °C; FTIR (cm^{-1}): 3413, 3014, 2949, 2226, 1617, 1558, 1345, 1199, 764, 705; ^1H NMR (500 MHz, DMSO-d_6): δ_{H} /ppm: 8.41 (d, 1H, J 8 Hz, aromatic H), 8.16-8.12 (m, 3H, aromatic 1H & $-\text{NH}_2$), 8.08 (dd, 2H, J 7.5 Hz, aromatic H), 7.95-7.90 (m, 2H, aromatic H), 7.86 (t, 4H, J 8 Hz, aromatic H), 7.79 (t, 1H, J 7.5 Hz, aromatic H), 7.69 (t, 1H, J 7.5 Hz, aromatic H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_{C} /ppm: 195.79 (2C), 158.10, 147.24, 146.77, 141.92, 141.49, 141.16, 138.13, 137.53, 137.30, 134.99, 133.72, 133.54, 133.07, 131.63, 131.26, 130.35, 129.63, 129.55, 129.24, 127.89, 126.44, 125.73, 123.55, 103.98, 103.76, 89.07; MS (ESI-TOF) m/z : 455.5160.

3-Aminospiro[benzo[*f*]chromene-1,11'-indeno[1,2-*b*]quinoxaline]-2-carbonitrile (5j). Orange solid; yield 89% mp 303-305 °C; FTIR (cm^{-1}): 3413, 3020, 2880, 2226, 1614, 1556, 1342, 1200, 825, 764; ^1H NMR (500 MHz, DMSO-d_6): δ_{H} /ppm: 8.17-8.12 (m, 4H, aromatic 2H & $-\text{NH}_2$), 8.07 (d, 2H, J 7.5 Hz, aromatic H), 7.90-7.83 (m, 8H, aromatic H), 7.69 (t, 2H, J 7.5 Hz, aromatic H); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} /ppm: 143.31, 141.92, 141.57 (2C), 138.73 (2C), 136.79 (2C), 136.13 (2C), 132.82 (2C), 132.54 (2C), 131.63 (2C), 131.31 (2C), 130.49 (2C), 129.69 (2C), 126.79, 123.20, 117.486, 114.31, 113.20, 89.66; MS (ESI-TOF) m/z : 425.2837.

2-Amino-7'-chloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11'-indeno[1,2-*b*]quinoxaline]-3-carbonitrile (5aa). Brown solid; yield 85% mp 289 °C; FTIR (cm^{-1}): 3321, 3081, 2952, 2178, 1659, 1593, 1466, 1310, 1211, 750, 711; ^1H NMR (500 MHz, DMSO-d_6): δ_{H} /ppm: 8.19-8.02 (m, 3H, aromatic H), 7.83-7.75 (m, 1H, aromatic H), 7.59 (s, 1H, aromatic H), 7.51 (s, 2H, aromatic H), 7.30 (s, 2H, $-\text{NH}_2$), 2.65 (q, 2H, $-\text{CH}_2$), 2.00 (q, 2H, $-\text{CH}_2$), 0.99 (t, 6H, J 5.5, 4.5 Hz, $-\text{CH}_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_{C} /ppm: 195.54, 166.60, 165.50, 159.46, 155.62, 152.65, 142.67, 134.51, 133.36, 131.11, 130.03 (2C), 129.51 (2C), 128.13 (2C), 125.08 (2C), 122.32 (2C), 117.94, 112.29, 58.89, 50.61, 47.73, 32.50, 28.13, 27.55; MS (ESI-TOF) m/z : 454.0525.

2-Amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,6'-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine]-3-carbonitrile (5bb). Brown solid; yield 80% mp 277-280 °C; FTIR (cm^{-1}): 3389, 3290, 3175, 2959, 2193, 1651, 1591, 1317, 1214, 861, 783; ^1H NMR (500 MHz, DMSO-d_6): δ_{H} /ppm: 9.04 (br s, 1H, aromatic H), 8.47 (d, 1H, J 7 Hz, aromatic H), 8.12 (d, 1H, J 7.5 Hz, aromatic H), 7.77 (t, 1H, J 4, 3.5 Hz, aromatic H), 7.62 (d, 1H, J 7 Hz, aromatic H), 7.55 (q, 2H, J 7, 7.5 Hz, aromatic H), 7.33 (s, 2H, $-\text{NH}_2$), 2.66 (q, 2H, $-\text{CH}_2$), 2.00 (q, 2H, $-\text{CH}_2$), 0.99 (s, 6H, $-\text{CH}_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_{C} /ppm: 195.58, 167.03, 165.58, 159.51, 157.64, 153.50, 153.03, 151.49, 138.42, 136.25, 133.68, 129.63, 125.12, 122.71, 122.29, 119.85, 117.92, 112.24, 111.63, 58.76, 50.58, 47.59, 32.50, 28.15, 27.54; MS (ESI-TOF) m/z : 444.1320.

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Supplementary Material

Scanned spectra including FTIR, ^1H -NMR, ^{13}C -NMR and HRMS of all the synthesized compounds along with the 3D and 2D docking interactions of all the compounds are supplemented in supporting information.

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