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A four-component synthesis of novel spiro[pyrazoloquinoline-oxindoles] under solvent-free conditions

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ABSTRACT

A domino reaction for the rapid and diverse synthesis of spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]dihydroquinolin-4,3-indolin-2-ones] is reported. The synthesis represents a thermodynamically-favored four-component reaction between phenylhydrazine, isatins, naphthylamines, and 3-ketoesters giving the novel products in excellent yields under solvent-free conditions. Similar applications of anilines in place of naphthylamines have not led to formation of the expected 4-substituted pyrazolo[3,4-*b*]quinoline derivatives. The difference was ascribed to lower aromatic character of naphthylamines, with respect to anilines, which enables them to act easier as enamines in reaction with the postulated intermediates formed from condensation of isatins and the *in situ* generated pyrazolones. Surprisingly, 6-aminouracils in despite of their known enamine properties did not participate in reaction with isatins and pyrazolones, the merit of naphthylamines for this synthesis seems to be met by the favorable balance of their *N*- and *C*-nucleophilicity.

1. Introduction

Multicomponent reactions are elaborate combinations of compatible chemical transformations into convergent and concise syntheses of complex molecules from simple starting materials.[1] Nature, after several millions years of evolution, exploits many such reactions, enabling the living systems to efficiently assemble diverse functional molecules. Attempts of chemists to mimic nature's synthetic strategy without employing the enzymes have been so far limited to combining the operationally consistent individual transformations.[2] Recent developments in this discipline suggest that MCRs are not just a sequential occurrence of kinetically diverse events but may involve complex equilibriums, which bias toward formation of single products or key intermediates.[3] Both the kinetic and thermodynamic-based MCRs are cost-effective strategies that bring three or more simple and flexible molecules together to rapidly introduce structural complexity and diversity via minimal operations.[4] Typically, purification of the products resulting from MCRs is simple, since the incorporation of all the employed reactants into molecular structure of the product usually offers very different physical properties relative to the starting materials.[5] The implementation of MCRs without using toxic catalysts or solvents is another existing strategy of laboratories researching the green feature of MCRs.[6]

In this view and in line with our interest in synthesis of spirooxindole heterocycles,[7] we report an expedient synthesis of some novel spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]dihydroquinolin-4,3-indolin-2-ones] under solvent-free conditions. The heterocyclic spirooxindole ring systems are widely spread structural frameworks present in numerous pharmaceuticals and natural products.[8,9] Similarly, heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this nucleus is the main substructure in numerous biologically active compounds[10,11] and prominent drugs, such as celecoxib, pyrazofurine, celebrex, allopurinol, zaleplon, and many others.[12]

1*H*-Pyrazolo[3,4-*b*]quinolines constitute an important class of pyrazolo-annelated compounds, owing to their actions as possible antiviral agents inducing the formation of interferon,[13] antiviral properties,[14] and potential antimalarials.[15] They are also known for antibacterial, antitumor, hypotensive, and vasodilation activities.[16] Several derivatives of this ring system fluorescence in the blue region and due to their large electron charge transfer are considered as promising materials for application in optoelectronic devices and light emitting diodes.[17–19]

Upon these salient aspects, incorporation of the two pharmacophoric, pyrazolo[3,4-*b*]quinoline and oxindole, motifs into a single molecule via efficient and environmentally benign synthetic methods would be beneficial.

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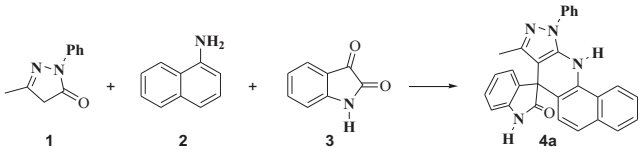
Friedländer condensation of 2-acylanilines with 1*H*-pyrazolin-5-ones is the first and the most widely used route for synthesis of pyrazolo[3,4-*b*]quinoline backbone.[20] An alternative variant of this reaction was later developed wherein aldehydes and anilines were used as separate partners instead of 2-acylanilines to make the synthesis more flexible with respect to its prototype version.[21] This three-component method in spite of extending the scope of pyrazolo[3,4-*b*]quinoline synthesis suffers from low yields and requires prolonged heating; this may be ascribed to the relatively high activation energy associated with reaction of anilines as carbon-nucleophiles.[22] In such conditions, the [2+1]-condensation of 1*H*-pyrazolin-5-ones and aldehydes usually predominates over the main synthesis to afford the relevant bis-pyrazolylmethane byproducts. Quiroga, Nageswar, and Shi have established improved three-component syntheses of pyrazolo[3,4-*b*]quinolines by employing 5-aminopyrazoles in place of anilines.[23] The significant enamine character of 5-aminopyrazoles makes these compounds useful precursors for the annelation of quinoline rings via reaction with aldehydes and 1,3-dicarbonyl compounds. In this context and based on recent recognition of naphthylamines as eligible enamines,[24,7a] we envisaged that spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]dihydroquinolin-4,3-indolin-2-ones] could be synthesized via a domino reaction between 1*H*-pyrazolin-5-ones, isatins, and naphthylamines.

2. Results and discussion

We commenced our experiments by examining the model reaction of 1*H*-phenyl-3-methylpyrazolin-5-one, isatin, and naphthalene-1-amine in various temperatures, solvents, and presence of varying catalysts. The results are summarized in Table 1.

Table 1
Optimizations for the model three-component reaction[a]



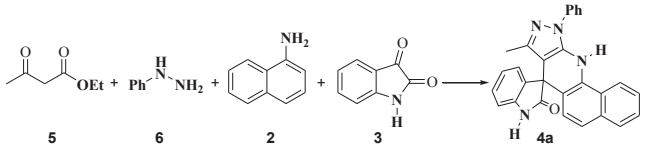
Entry	Solvent	Catalyst[c]	Temperature (°C)	Time (min)	Yield[b] (%)
1	EtOH	*p*-TSA·H_2O	80	100	65
2	H_2O/EtOH (1:1)	*p*-TSA·H_2O	80	100	68
3	CH_3CN	*p*-TSA·H_2O	80	100	44
4	C_6H_{12}	*p*-TSA·H_2O	80	100	Trace
5	—	*p*-TSA·H_2O	80	100	81
6	—	*p*-TSA·H_2O	50	170	76
7	—	*p*-TSA·H_2O	100	75	79
8	—	—	80	100	—
9	—	CAN	80	100	20
10	—	$LiClO_4$	80	100	74
11	—	Zn(L-proline)$_2$	80	100	23

[a] Equal amounts (1 mmol) of the reactants were used.
[b] Isolated yields of **4a**.
[c] Catalysts (20 mol %).

As this Table shows, the trial reaction gives the best yield under solvent-free conditions and proceeds smoothly at 80 °C (oil bath) with catalytic *p*-toluenesulfonic acid-monohydrate (*p*-TSA·H_2O) to afford the desired product, spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-1-phenyl-2′-one **4a**, in 100 min (entry 5). Note that no product is formed within a reasonable time in the absence of any catalyst. With other selected catalysts and solvents (Table 1) the reaction gave rather lower yields within comparable reaction times.

After this preliminary success, our study was followed for further advancements by using simpler trial starting materials. In this regard, we planned to carry out the synthesis via *in situ* preparation of 1*H*-phenylpyrazolin-5-one from condensation of 3-ketoesters and phenylhydrazine. This proposal was successfully testified for the synthesis of **4a** using the new model reaction involving ethyl acetoacetate, phenylhydrazine, isatin, and naphthalene-1-amine (Table 2). The viability of this four-component route seems to be relied on the consistence of 1*H*-phenylpyrazolin-5-one formation with the optimal conditions already set up for the three-component synthesis.

Table 2
Optimizations for the model four-component reaction[a]



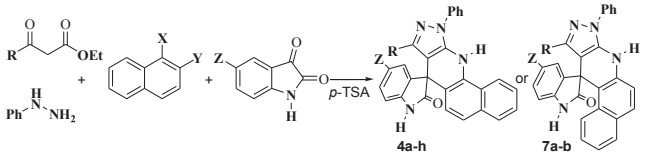
Entry	Solvent	Catalyst	Time (min)	Yield[b] (%)
1	EtOH	*p*-TSA·H_2O (20 mol %)	120	61
2	H_2O/EtOH (1:1)	*p*-TSA·H_2O (20 mol %)	120	65
3	—	*p*-TSA·H_2O (20 mol %)	120	79
4	—	—	120	Trace
5	—	$LiClO_4$ (20 mol %)	120	69
6	—	*p*-TSA·H_2O (10 mol %)	150	54
7	—	*p*-TSA·H_2O (30 mol %)	120	79

[a] Equal amounts (1 mmol) of the reactants were used at 80 °C.
[b] Isolated yields of **4a**.

Monitoring the model reaction by thin layer chromatography (TLC) on silica gel revealed the formation of 1*H*-phenyl-3-methylpyrazolin-5-one **1** as the initial event, preceding the production of **4a**. A correlation between the consumption of 1*H*-phenyl-3-methylpyrazolin-5-one **1** and the formation of **4a** is evident when the reaction is followed by TLC. This observation led us to explore the limitation and scope of applicable substrates for this synthetic route by testifying diverse reactants under the optimal conditions.

As shown in Table 3, this protocol is efficient for a variety of substrates, affording the corresponding spiro-products **4a**–**h** and **7a**,**b**, mostly in high yields. The reaction tolerates various substituents reside on the aromatic ring of indolin-2-one entity as well

Table 3
Synthesis of spiro[1*H*-pyrazolo[3,4-*b*]benzodihydroquinolin-4,3-indolin-2-ones] **4a**–**h** and **7a**,**b** under the optimized conditions

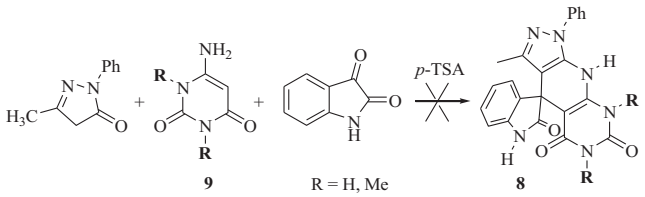


Product	R	X	Y	Z	Time (min)	Yields[a] (%)
4a	Me	NH_2	H	H	120	79
4b	Me	NH_2	H	Cl	120	84
4c	*n*-Pr	NH_2	H	H	140	75
4d	*n*-Pr	NH_2	H	CH_3O	150	53
4e	*n*-Pr	NH_2	H	Cl	120	81
4f	*n*-Pr	NH_2	H	NO_2	100	92
4g	Ph	NH_2	H	H	270	65
4h	Ph	NH_2	H	Cl	210	76
7a	*n*-Pr	H	NH_2	H	140	81
7b	Ph	H	NH_2	H	210	78

[a] Isolated yields.

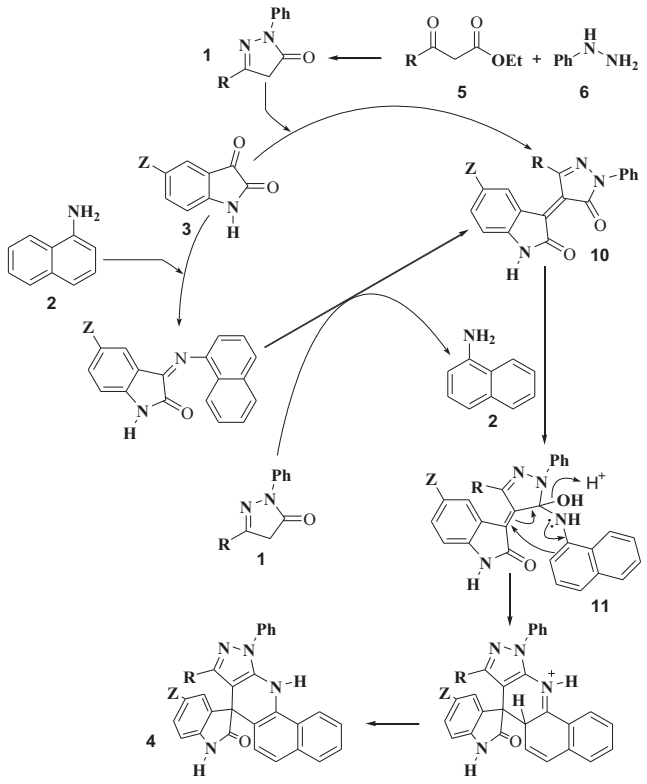
as the steric demands imposed by the residues of naphthalen-2-amine and 3-ketoesters. It is also noticeable that the presence of an electron-withdrawing nitro group at the 5-position of isatin increases the rate and yield of the reaction; in contrast, the rate and yield of the reaction are decreased when there is an electron-donating methoxy group at the same position.

Attempts to use anilines instead of naphthylamines, in the expectation to synthesize spiro[1*H*-pyrazolo[3,4-*b*]quinolin-4,3-indolines] under identical reaction conditions, was met with failure. These applications led to complex reaction mixtures in which the anilines remained largely unreacted, presumably due to their higher aromatic character and so to their weak enamine-like behavior. Surprisingly, our efforts to extend the scope of this reaction for synthesis of spiro[pyrazolo[3,4-*b*]pyrimido[4,5-*f*]quinoline-4,3-indoline]-5,7,2′-triones **8** under similar conditions by employing 6-aminouracils **9**, which are known for their enamine behavior, remained entirely unsuccessful (Scheme 1). In all of these attempts the 6-aminouracils were recovered unreacted.

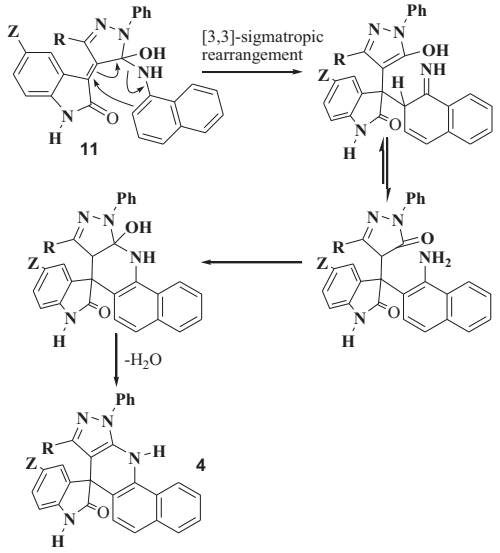


Scheme 1. The reaction of 6-amino-1,3-dimethyluracil with isatin and 3-methyl-1*H*-phenylpyrazolin-5-one in the presence of *p*-TSA.

While, we have not performed special experiments to determine the mechanism of this four-component synthesis, a reasonable sequence of events leading to formation of the products was suggested in Scheme 2. It is likely that the synthesis proceeds through a cascade of reactions initiating with parallel formation of 1*H*-phenylpyrazolin-5-ones and isatin imines. Knoevenagel condensation of these two intermediates, while liberating the naphthylamine, results in formation of the key diazafulvalene intermediate **10**. This reactive intermediate subsequently undergoes twice nucleophilic additions by the naphthylamine, at both the C- and N-termini of its enamine functionality, followed by elimination of water to give the product (Scheme 2). There is an alternative pathway for the reaction in which the intermediate **11**, formed from *N*-nucleophilic addition of naphthylamine onto the hydrazidic carbonyl group of the intermediate **10**, undergoes a [3,3]-sigmatropic rearrangement followed by intramolecular imination and then tautomerization to give the product (Scheme 3). The diazafulvalene intermediate **10** consists of a zwitterionic mesomeric form in which the oxindole ring gains aromatic stabilization energy in expense of charging the pyrazole ring with an



Scheme 2. A proposed mechanism for the synthesis of products.



Scheme 3. An alternative proposal for the mechanism of the synthesis.

antiaromatic electronic configuration.[25] This perturbation of electronic energy across the molecule would make the carbonyl group of pyrazolone ring system more reactive toward additions (Fig. 1). Addition to this group interrupts the cyclic π-system in the pyrazolone ring and thereby offers the diazafulvalene **10-II** to relief from the local antiaromaticity. Usually, the addition of amines to carbonyl groups is kinetically more favored than addition of carbon nucleophiles under similar conditions. This seems to be the case for naphthylamines, which prefer to add at nitrogen atom onto the carbonyl group of the pyrazolone ring. The resulting adduct then undergoes cyclization through an intramolecular conjugate addition associated with elimination of water.

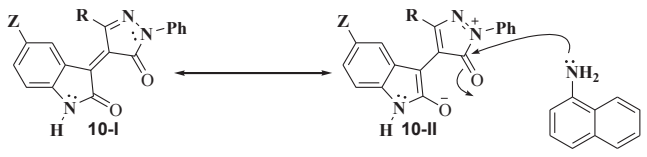


Fig. 1. Stabilization of indole and partial destabilization of pyrazolone ring created via resonance across the diazafulvalene.

The presence of the electron-donating methoxy group at the 5-position of oxindole ring enhances the extent of amidic resonance of this ring system and thus interrupts the resonance between the two heterocyclic rings in diazafulvalene **10**. In contrast, participation of the oxindole nitrogen in the amidic resonance is weakened by its cross-conjugation with the nitro substituent present at the 5-position of this ring whereby the resonance between the two heterocyclic rings makes a greater contribution to the electronic configuration of the molecule and hence facilitates the synthesis (Fig. 2).

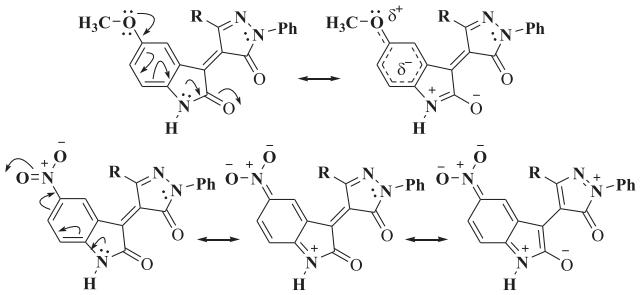


Fig. 2. Enhanced cross-resonances and their effects on reactivity of diazafulvalenes.

The structures of all the products **4a**–**h** and **7a**,**b** are consistent with their elemental analyses, IR, ^{1}H- and ^{13}C NMR as well as mass spectral data. For example, the IR spectrum of **4a** showed distinct absorptions at 3345, 3261, and 1689 cm^{-1} corresponding to vibrations of its –NH and C=O groups. A relatively wide range of chemical shifts, i.e., δ 6.00–8.26, were observed for the aromatic protons of these products, suggesting that they experience diverse anisotropic effects of the rings. ^{1}H NMR spectra of the products displayed characteristic upfield shifts for 4′-H proton at about δ 6.50 due to anisotropic shielding effect of 1*H*-pyrazolo[3,4-*b*]benzoquinoline backbone orienting roughly perpendicular to the plane of oxindole ring (Fig. 3).

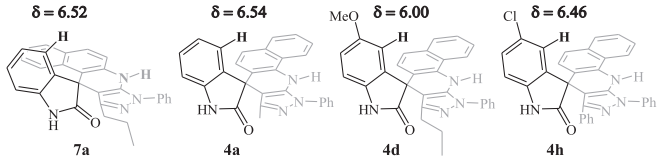


Fig. 3. Anisotropic shielding effects of the crossed rings on the incident protons.

The mass spectra of all the products exhibited the molecular ion peaks at appropriate *m*/*z* values. Loss of two hydrogen atoms and extrusion of CO from the molecular ions are the prevalent fragmentation patterns of these spectra.

3. Conclusion

In summary, an efficient route for synthesis of novel spiro[1*H*-pyrazolo[3,4-*b*]benzoquinolin-4,3-indolin-2-ones] via a four-component reaction between isatins, 3-ketoesters, naphthylamines, and phenylhydrazine was reported here. The high convergence of this synthetic method was attributed to intermediacy of the diazafulvalenes derived from condensation of isatins and the *in situ* generated pyrazolones. Neither anilines nor the enaminic 6-aminouracils gave the corresponding products when used in place of naphthylamines. A favorable balance of *N*- and *C*-nucleophilic reactivity is considered for naphthylamines and suggested to be the determinant of selectivity and efficiency of the syntheses presented here. This route offers additional advantages, such as mild and solvent-free conditions, reasonable reaction times, fairly high yields, and simple isolation procedures.

4. Experimental

4.1. General

All of the solvents and reagents were purchased from Fluka or Merck chemical companies. Melting points were measured on an Electrothermal apparatus and are uncorrected. IR spectra were obtained in KBr discs on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with Bruker DRX-400 AVANCE spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR spectra were expressed in parts per million downfield from tetramethylsilane. Mass spectra were recorded on an Agilent Technology 5973 Network MSD mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Foss Heraus CHN–O-rapid analyzer.

4.2. Typical procedure for preparation of spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-1-phenyl-2′-one (4a)

A mixture of isatin (0.147 g, 1 mmol), phenylhydrazine (0.11 g, 1 mmol), ethyl acetoacetate (0.130 g, 1 mmol), and naphthalen-1-amine (0.144 g, 1 mmol) was added to a vial containing a magnetic stirring bar. The reaction mixture was sealed and stirred at 80 °C until disappearance of the starting materials (monitored by TLC on silica gel using a 1:1 mixture of ethyl acetate/*n*-hexane). After completion of the reaction, the solid residue was washed with water (10 mL) and ethanol (95%, 10 mL) to obtain the pure product **4a** (0.34 g, 79% yield).

*4.2.1. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-1-phenyl-2′-one (**4a**).* White powder, Yield, 0.34 g (79%). Mp 255–258 °C, IR (KBr), ν_{max}: 3445 (NH), 3261 (NH), 3230, 3062, 2920, 1689 (C=O), 1610, 1550, 748 cm^{-1}. ^{1}H NMR (400.22 MHz, DMSO) δ: 11.35 (1H, s, NH), 9.39 (1H, s, NH), 8.24 (1H, d, *J* 8.0 Hz), 7.95 (1H, d, *J* 8.0 Hz), 7.66–7.55 (7H, m), 7.42 (1H, t, *J* 7.2 Hz, Ph 4-H), 7.22–7.13 (3H, m), 6.73 (1H, t, *J* 7.5 Hz, 5′-H), 6.54 (1H, d, *J* 7.5 Hz, 4′-H), 1.44 (3H, s, CH_3). ^{13}C NMR (100.63 MHz, DMSO) δ: 11.9, 53.1, 96.7, 117.8, 119.6, 120.8, 121.8, 122.9, 123.0, 123.2, 123.3, 126.5, 126.7, 127.1, 128.1, 128.5, 129.0, 130.0, 131.8, 133.7, 137.4, 138.9, 139.0, 140.3, 145.8, 181.5. MS (EI) *m*/*z* (%)=428 (M^+, 12), 426 (M^+–2H, 100), 400 (M^+–HCO, 45), 384 (16), 368 (12), 313 (8), 274 (21), 257 (43), 174 (82), 112 (76). Anal. Calcd for $C_{28}H_{20}N_4O$: C, 78.49; H, 4.70; N, 13.08%. Found: C, 78.36; H, 4.63; N, 13.29%.

*4.2.2. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5′-chloro-1-phenyl-2′-one (**4b**).* White powder, Yield, 0.39 g (84%). Mp 264–267 °C, IR (KBr), ν_{max}: 3379 (NH), 3181 (NH), 3060, 1688 (C=O), 1614, 1573, 1483, 778 cm^{-1}. ^{1}H NMR (400.22 MHz, DMSO) δ: 11.28 (1H, s, NH), 11.12 (1H, s, NH), 8.14 (1H, d, *J* 7.6 Hz), 7.96 (1H, d, *J* 7.2 Hz), 7.70–7.54 (5H, m), 7.38 (3H, m), 7.26 (1H, d, *J* 8.4 Hz), 7.15–7.09 (2H, m), 6.81 (1H, d, *J* 8.8 Hz), 6.48 (1H, d, *J* 2.0 Hz, 4′-H), 1.86 (3H, s, CH_3). ^{13}C NMR (100.63 MHz, DMSO) δ: 12.0, 56.0, 102.8, 118.3, 118.6, 119.8, 120.0, 122.1, 122.7, 122.8, 123.8, 124.8, 125.9, 126.4, 126.8, 128.1, 128.9, 129.3, 133.7, 137.4, 138.4, 138.5, 148.7, 149.1, 162.2, 180.7. MS (EI) *m*/*z* (%)=462 (M^+–2H, ^{37}Cl, 4), 460 (M^+–2H, ^{35}Cl, 9), 436 (M^+–CO, ^{37}Cl, 6), 434 (M^+–CO, ^{35}Cl, 6), 339 (7), 337 (11), 310 (37), 308 (85), 273 (77), 264

(36), 229 (21), 174 (87), 77 (100). Anal. Calcd for $C_{28}H_{19}ClN_4O$: C, 72.65; H, 4.14; N, 12.10%. Found: C, 72.73; H, 4.11; N, 12.06%.

*4.2.3. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-1-phenyl-3-propyl-2′-one (**4c**).* White powder, Yield, 0.34 g (75%). Mp 304–307 °C, IR (KBr), ν_{max}: 3433 (NH), 3215 (NH), 3057, 2967, 1702 (C=O), 1600, 1542, 1478, 802, 741 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 11.37 (1H, s, NH), 9.38 (1H, s, NH), 8.25 (1H, d, *J* 8.4 Hz), 7.95 (1H, d, *J* 8.0 Hz), 7.67–7.51 (7H, m), 7.42 (1H, t, *J* 7.2 Hz), 7.22–7.12 (3H, m), 6.72 (1H, t, *J* 7.4 Hz, 5′-H), 6.53 (1H, d, *J* 7.4 Hz, 4′-H), 1.83–1.71 (2H, m, α-H), 1.24–1.16 (1H, m, β-H_A), 1.07–0.97 (1H, m, β-H_B), 0.46 (3H, t, *J* 7.4 Hz, CH_3). ^{13}C NMR (100.63 MHz, DMSO) δ: 14.4, 21.5, 28.7, 53.2, 96.3, 117.7, 119.6, 120.9, 121.8, 122.8, 122.98, 123.01, 123.3, 126.6, 126.7, 127.1, 128.0, 128.5, 129.0, 129.9, 132.2, 133.7, 137.4, 138.9, 139.0, 140.1, 149.9, 181.8. MS (EI) *m*/*z* (%)=457 (M^++1, 11), 456 (M^+, 33), 454 (M^+−2H, 44), 428 (64), 427 (M^+−CO, 66), 413 (M^+−HNCO, 43), 384 (30), 257 (20), 228 (19), 202 (26), 77 (100). Anal. Calcd for $C_{30}H_{24}N_4O$: C, 78.92; H, 5.30; N, 12.27%. Found: C, 79.03; H, 5.37; N, 12.18%.

*4.2.4. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-5′-methoxy-1-phenyl-3-propyl-2′-one (**4d**).* White powder, Yield, 0.26 g (53%). Mp 294–296 °C, IR (KBr), ν_{max}: 3358 (NH), 3250 (NH), 2933, 1719 (C=O), 1570, 1512, 1380, 1231 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 11.35 (1H, s, NH), 9.14 (1H, s, NH), 8.24 (1H, d, *J* 8.4 Hz), 7.96 (1H, d, *J* 8.0 Hz), 7.67–7.55 (5H, m), 7.42 (1H, t, *J* 7.2 Hz), 7.19–7.15 (2H, m), 6.85 (1H, dd, *J* 8.8 and 2.4 Hz, 6′-H), 6.00 (1H, d, *J* 2.4 Hz, 4′-H), 3.50 (3H, s, OCH_3), 1.82–1.72 (2H, m, α-H), 1.24–1.14 (1H, m, β-H_A), 1.04–0.97 (1H, m, β-H_B), 0.45 (3H, t, *J* 7.2 Hz, CH_3). ^{13}C NMR (100.63 MHz, DMSO) δ: 14.4, 21.5, 28.7, 53.5, 55.7, 95.7, 113.0, 114.2, 118.8, 119.6, 121.9, 122.8, 122.9, 123.0, 126.6, 126.7, 126.9, 129.0, 129.8, 129.9, 131.8, 133.0, 133.7, 137.6, 139.1, 140.7, 149.8, 154.4, 181.8. MS (EI) *m*/*z* (%)=486 (M^+, 3), 458 (M^+−CO, 5), 457 (M^+−Et, 9), 443 (M^+−Pr, 6), 307 (2), 279 (3), 77 (100). Anal. Calcd for $C_{31}H_{26}N_4O_2$: C, 76.52; H, 5.39; N, 11.51%. Found: C, 76.59; H, 5.43; N, 11.43%.

*4.2.5. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-5′-chloro-1-phenyl-3-propyl-2′-one (**4e**).* White powder, Yield, 0.40 g (81%). Mp 298–301 °C, IR (KBr), ν_{max}: 3362 (NH), 3221 (NH), 3058, 2947, 1689 (C=O), 1582, 1532, 1467, 795 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 11.44 (1H, s, NH), 9.56 (1H, s, NH), 8.26 (1H, d, *J* 8.0 Hz), 7.97 (1H, d, *J* 8.0 Hz), 7.65–7.56 (7H, m), 7.43 (1H, t, *J* 7.2 Hz), 7.27–7.20 (3H, m), 6.44 (1H, d, *J* 1.6 Hz, 4′-H), 1.82–1.68 (2H, m, α-H), 1.23–1.14 (1H, m, β-H_A), 1.05–0.96 (1H, m, β-H_B), 0.44 (3H, t, *J* 7.2 Hz, CH_3). ^{13}C NMR (100.63 MHz, DMSO) δ: 14.3, 21.5, 28.7, 53.3, 96.0, 119.5, 119.7, 122.7, 122.8, 122.9, 123.2, 123.4, 124.9, 126.7, 126.9, 127.1, 127.2, 128.6, 129.1, 130.0, 131.5, 133.8, 137.7, 138.2, 138.8, 139.8, 149.8, 181.5. MS (EI) *m*/*z* (%)=490 (M^+−2H, ^{35}Cl, 6), 489 (4), 488 (M^+−2H, ^{35}Cl, 9), 464 (M^+−CO, ^{37}Cl, 4), 463 (6), 462 (M^+−CO, ^{35}Cl, 11), 461 (12), 418 (7), 265 (4), 69 (*n*-Pr−CN, 81). Anal. Calcd for $C_{30}H_{23}ClN_4O$: C, 73.39; H, 4.72; N, 11.41%. Found: C, 73.46; H, 4.75; N, 11.35%.

*4.2.6. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-5′-nitro-1-phenyl-3-propyl-2′-one (**4f**).* White powder, Yield, 0.46 g (92%). Mp 295–298 °C, IR (KBr), ν_{max}: 3372 (NH), 3223 (NH), 3025, 2942, 1705 (C=O), 1614, 1547, 1509, 1434, 1320 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 11.54 (1H, s, NH), 1040 (1H, s, NH), 8.28 (1H, d, *J* 8.4 Hz), 8.07 (1H, dd, *J* 8.8 and 2.4 Hz, 6′-H), 8.00 (1H, d, *J* 8.0 Hz), 7.69–7.60 (7H, m), 7.49–7.46 (1H, m), 7.40 (1H, d, *J* 9.2 Hz), 7.31 (1H, d, *J* 2.4 Hz, 4′-H), 7.29 (1H, d, *J* 8.4 Hz), 1.84–1.70 (2H, m, α-H), 1.24–1.15 (1H, m, β-H_A), 1.08–0.98 (1H, m, β-H_B), 0.45 (3H, t, *J* 7.4 Hz, CH_3). ^{13}C NMR (100.63 MHz, DMSO) δ: 14.3, 21.4, 28.6, 53.2, 96.8, 117.8, 119.7, 121.4, 122.8, 122.9, 123.6, 124.1, 124.2, 124.8, 126.9, 127.2, 127.8, 129.1, 130.1, 131.4, 134.0, 137.7, 138.4, 138.7, 141.0, 144.9, 149.7, 181.2. MS (EI) *m*/*z* (%)=501 (M^+, 2), 499 (M^+−2H, 16), 469 (M^+−2O, 21), 443 (11), 407 (7), 382 (7), 363 (5), 308 (7), 69 (*n*-Pr−CN, 62), 77 (78). Anal. Calcd for $C_{30}H_{23}N_5O_3$: C, 71.84; H, 4.62; N, 13.96%. Found: C, 71.79; H, 4.58; N, 14.07%.

*4.2.7. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-1,3-diphenyl-2′-one (**4g**).* White powder, Yield, 0.32 g (65%). Mp 307–310 °C, IR (KBr), ν_{max}: 3379 (NH), 3218 (NH), 3105, 2956, 1701 (C=O), 1606, 1546, 1490, 752 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 11.15 (1H, s, NH), 9.52 (1H, s, NH), 8.06 (1H, d, *J* 8.0 Hz), 7.88 (1H, d, *J* 7.6 Hz), 7.76 (2H, d, *J* 7.7 Hz, Ph 2-H), 7.65 (2H, t, *J* 7.7 Hz, Ph 3-H), 7.56–7.47 (4H, m), 7.23 (1H, d, *J* 8.4 Hz), 7.17 (1H, d, *J* 8.0 Hz), 7.16 (1H, t, *J* 8.4 Hz), 7.03–6.98 (1H, m), 6.88–6.78 (4H, m), 6.72 (1H, t, *J* 8.0 Hz, 6′-H), 6.55 (1H, d, *J* 8.0 Hz, 4′-H). ^{13}C NMR (100.63 MHz, DMSO) δ: 53.5, 96.2, 117.7, 119.8, 121.1, 121.9, 122.7, 122.8, 122.9, 123.8, 123.9, 126.4, 126.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 128.8, 130.1, 133.50, 133.53, 137.4, 138.4, 138.7, 140.9, 149.9, 181.8. MS (EI) *m*/*z* (%)=491 (M^++1, 8), 490 (M^+, 22), 488 (M^+−2H, 20), 462 (M^+−CO, 51), 461 (M^+−HCO, 100), 385 (7), 369 (7), 358 (7), 257 (23), 245 (16), 230 (13), 112 (37). Anal. Calcd for $C_{33}H_{22}N_4O$: C, 80.80; H, 4.52; N, 11.42%. Found: C, 80.87; H, 4.49; N, 11.36%.

*4.2.8. Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-5′-chloro-1,3-diphenyl-2′-one (**4h**).* White powder, Yield, 0.40 g (76%). Mp 295–298 °C, IR (KBr), ν_{max}: 3393 (NH), 3221 (NH), 3049, 1709 (C=O), 1612, 1548, 1467 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 11.22 (1H, s, NH), 9.71 (1H, s, NH), 8.08 (1H, d, *J* 7.6 Hz), 7.90 (1H, d, *J* 7.6 Hz), 7.76 (2H, d, *J* 7.6 Hz, Ph 2-H), 7.65 (2H, t, *J* 7.6 Hz, Ph 3-H), 7.60–7.48 (4H, m), 7.30–7.21 (3H, m), 7.02–6.98 (1H, m), 6.85–6.80 (4H, m), 6.46 (1H, d, *J* 1.6 Hz, 4′-H). ^{13}C NMR (100.63 MHz, DMSO) δ: 53.6, 97.0, 119.5, 119.9, 122.6, 122.9, 123.0, 123.2, 124.0, 125.1, 126.5, 126.8, 126.9, 127.7, 127.8, 128.0, 128.1, 128.6, 128.9, 130.1, 132.7, 133.3, 133.7, 137.6, 137.9, 138.6, 140.6, 149.9, 181.6. MS (EI) *m*/*z* (%)=524 (M^+, ^{35}Cl, 5), 522 (M^+−2H, ^{35}Cl, 13), 498 (M^+−H_2CO, ^{37}Cl, 1), 496 (M^+−H_2CO, ^{35}Cl, 3), 308 (5), 236 (47), 194 (10), 103 (Ph−CN, 59), 77 (100). Anal. Calcd for $C_{33}H_{21}ClN_4O$: C, 75.50; H, 4.03; N, 10.67%. Found: C, 75.44; H, 4.09; N, 10.59%.

*4.2.9. Spiro[1H-pyrazolo[3,4-b]benzo[f]quinolin-4,3-indoline]-4,11-dihydro-1-phenyl-3-propyl-2′-one (**7a**).* Cream powder, Yield, 0.40 g (81%). Mp>310 °C, IR (KBr), ν_{max}: 3384 (NH), 3247 (NH), 3036, 2959, 1697 (C=O), 1599, 1546, 1482, 816, 753 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 1080 (1H, s, NH), 9.70 (1H, s, NH), 7.95 (1H, d, *J* 8.8 Hz), 7.90–7.87 (1H, m), 7.68 (2H, d, *J* 7.4 Hz, Ph 2-H), 7.60 (2H, t, *J* 7.4 Hz, Ph 3-H), 7.42 (1H, t, *J* 7.4 Hz, Ph 4-H), 7.38–7.32 (2H, m), 7.27–7.22 (3H, m), 7.12 (1H, t, *J* 7.6 Hz), 6.68 (1H, t, *J* 7.6 Hz, 5′-H), 6.52 (1H, d, *J* 7.6 Hz, 4′-H), 1.84–1.77 (1H, m, α-H_A), 1.74–1.67 (1H, m, α-H_B), 1.14–1.05 (1H, m, β-H_A), 0.90–0.81 (1H, m, β-H_B), 0.45 (3H, t, *J* 7.4 Hz, CH_3). ^{13}C NMR (100.63 MHz, DMSO) δ: 14.3, 21.4, 28.6, 52.6, 96.8, 111.9, 117.7, 121.7, 121.8, 123.1, 123.2, 123.7, 127.0, 127.4, 127.5, 128.4, 128.5, 129.2, 129.9, 130.0, 130.4, 130.6, 138.95, 139.04, 139.7, 149.8, 153.6, 181.5. MS (EI) *m*/*z* (%)=457 (M^++1, 11), 456 (M^+, 33), 428 (M^+−H_2CO, 74), 413 (M^+−Pr, 86), 385 (M^+−2H−C_3H_7CN, 15), 368 (10), 351 (9), 308 (17), 192 (20), 55 (100). Anal. Calcd for $C_{30}H_{24}N_4O$: C, 78.92; H, 5.30; N, 12.27%. Found: C, 78.96; H, 5.34; N, 12.25%.

*4.2.10. Spiro[1H-pyrazolo[3,4-b]benzo[f]quinolin-4,3-indoline]-4,11-dihydro-1,3-diphenyl-2′-one (**7b**).* Cream powder, Yield, 0.39 g (79%). Mp>310 °C, IR (KBr), ν_{max}: 3436 (NH), 3264 (NH), 1706 (C=O), 1605, 1553, 1489, 759 cm^{-1}. ^1H NMR (400.22 MHz, DMSO) δ: 10.59 (1H, s, NH), 9.64 (1H, s, NH), 7.85 (2H, t, *J* 7.0 Hz), 7.80 (2H, d, *J* 7.6 Hz), 7.66 (2H, t, *J* 7.6 Hz), 7.51–7.45 (2H, m), 7.32–7.22 (3H, m), 7.17–7.10 (3H, m), 7.01 (2H, t, *J* 7.6 Hz), 6.72–6.66 (3H, m), 6.55

(1H, d, *J* 8.0 Hz, 4′-H). ^{13}C NMR (100.63 MHz, DMSO) δ: 52.7, 96.8, 112.0, 117.7, 121.3, 121.6, 122.0, 123.6, 123.8, 127.1, 127.2, 127.6, 127.7, 127.8, 128.1, 128.5, 129.0, 129.7, 129.8, 130.1, 130.3, 130.4, 133.5, 138.5, 138.8, 139.6, 140.7, 150.0, 181.5. MS (EI) *m*/*z* (%)=491 (M^++1, 7), 490 (M^+, 21), 462 (58), 461 (M^+−HCO, 100), 385 (M^+−2H−PhCN, 13), 265 (8), 245 (25), 178 (12). Anal. Calcd for $C_{33}H_{22}N_4O$: C, 80.80; H, 4.52; N, 11.42%. Found: C, 80.93; H, 4.45; N, 11.34%.

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Supplementary data

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