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Multicomponent Dipolar Cycloaddition Strategy: Combinatorial Synthesis of Novel Spiro Tethered Pyrazolo[3,4-*b*]quinoline Hybrid Heterocycles

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ABSTRACT:

The stereoselective syntheses of a library of novel spiro tethered pyrazolo[3,4-*b*]quinoline–pyrrolidine/pyrrolothiazole/indolizine–oxindole/acenaphthene hybrid heterocycles have been achieved through the 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from α-amino acids and 1,2-diketones to dipolarophiles derived from pyrazolo[3,4-*b*]quinoline derivatives.

Keywords: *1,3-Dipolar cycloaddition, Azomethine ylide, α-Amino acid, Isatin, Pyrazolo[3,4-b]quinoline, Spiro-oxindole, Spiro-pyrrolidine*

INTRODUCTION

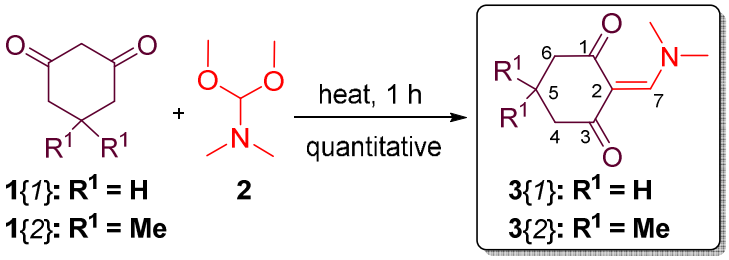
Pyrazolo[3,4-*b*]quinoline ring systems are privileged class of nitrogen containing heterocycles endowed with profound biological activities. For instance pyrazolo[3,4-*b*]quinoline derivatives have been investigated for their antimicrobial,[1] antimycobacterial[2] and antiviral[3] activities. Among the several methods available for the synthesis of pyrazolo[3,4-*b*]quinolines, the three-component reactions of 1,3-diketones, 5-aminopyrazoles and aromatic aldehydes or isatins have received much attention.[4] Moreover, in spite of their significances pyrazolo[3,4-*b*]quinoline derivatives have been less explored as precursors for further transformations. To the best of our knowledge these compounds have been used in the Vilsmeier-Haack formylation reaction and for the synthesis of bispyrazolo[3,4-*b*:4,3-*f*]quinolines[5] and pyrazolo[3,4-*b*]quinoline ribofuranosides.[6] Further, the analogous derivatives have been used to synthesize quinoxaline-fused benzo[*h*]isoxazolo[5,4-*b*]quinolines[7] and benzo[*a*]pyrazolo[4′,3′:5,6]pyrido-[2,3-*c*]phenazine.[8] In this context, we envisaged to investigate the feasibility of pyrazolo[3,4-*b*]-quinoline derivatives as dipolarophiles in the 1,3-dipolar cycloadditions of azomethine ylides with a view to construct spiro tethered pyrazolo[3,4-*b*]quinoline–pyrrolidine/pyrrolothiazole/ indolizine–oxindole/acenaphthene hybrids.

The syntheses of spiro compounds have received much attention in view of their wide range of applications.[9] For example spiro compounds have been shown to inhibit cholesteryl ester transfer protein, aspartyl proteases BACE1, acetylcholinesterase, bacterial type-II topoisomerase and kinesin spindle protein.[10] These compounds have also been investigated for their anticancer and antimicrobial activities apart from being identified as histamine-3 receptor and TRPM8 antagonists.[11] Among the various protocols reported for the synthesis of spiro compounds, the 1,3-dipolar cycloadditions involving dipolarophiles with exoyclic olefins have

occupied an eminent position.[12] This strategy allows the stereoselective construction of complex spiro heterocyclic hybrids in a single transformation with ease.[12] In particular the cycloaddition of azomethine ylides generated *in situ* from the decarboxylative condensation of α-amino acids and isatins, acenaphthenequinone or ninhydrin with dipolarophiles with exocyclic olefins have received substantial amount of attention as they lead to the synthesis of spiro oxindole/acenaphthene/indanone and pyrrolidine/pyrrolizine/pyrrolothiazole/indolizine hybrid heterocycles. It is noteworthy that spiro oxindole-pyrrolidine or pyrrolizine hybrids form the core of several bioactive natural products such as horsfiline[13] and elacomine,[14] whereas rhynchophylline[15] comprises spiro oxindole-indolizine unit and spirotryprostatins comprise spiro oxindole-pyrrolopyrazine motif.[16]

RESULTS AND DISCUSSION

Initially, the precursors 2-((dimethylamino)methylene)cyclohexane-1,3-dione **3**{*1*} and 2-((dimethylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione **3**{*2*} were synthesized from the reaction of 1,3-cyclohexanedione **1**{*1*} or dimedone **1**{*2*} with DMF-DMA **2**, respectively following literature procedure (Scheme 1).[17]



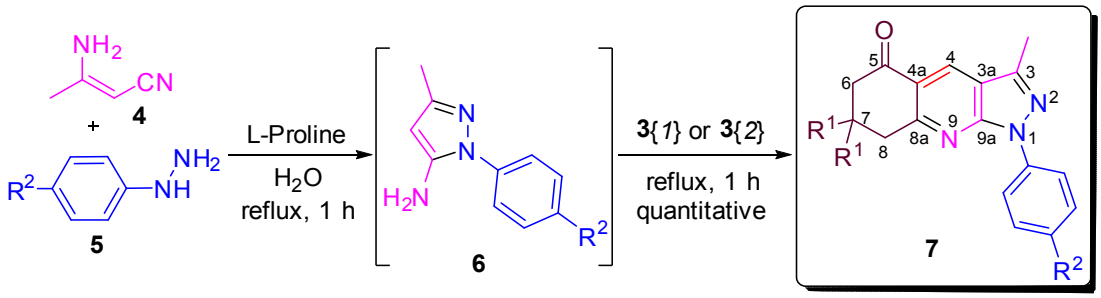
Seheme 1. Synthesis of precursors **3**

Subsequently, the pyrazolo[3,4-*b*]quinolin-5-ones **7** were synthesized *via* a one-pot three-component sequential procedure in water (Scheme 2). First of all, 3-aminocrotononitrile **4** and

the appropriate arylhydrazines **5**{*1–6*} were refluxed in water for 1 h in the presence of L-proline (40 mol%) to obtain 3-methyl-1-aryl-1*H*-5-pyrazolamines **6**{*1–6*}. Then without isolating **6**, the previously synthesized **3**{*1*} or **3**{*2*} was added and the reflux continued for another 1 h, which resulted in quantitative yields of **7**{*1–6*} or **7**{*2–5*}, respectively. The formation of **7** presumably occurred *via* a similar pathway as depicted by Perumal *et al*.[8] It is to be noted that Zheng *et al*. reported the synthesis of **7**{*2,1*} in 15% yield from a two-step reaction.[4b] Later, Dzvinchuk *et al*.[4c] synthesized **7**{*1,1*} in 87% yield from the reaction of 1,3-cyclohexanedione **1**, 3-methyl-1-phenyl-1*H*-5-pyrazolamine **6** and 4-(dimethylamino)-benzaldehyde in boiling acetic acid for 2 h. In this reaction *N*,*N*-dimenthylaniline was obtained as a by-product. Moreover, the protocol employed by us for the synthesis of **7** is more advantageous than the literature reports in terms of several green chemical aspects. The structure of all the pyrazolo[3,4-*b*]quinolin-5-ones **7** was elucidated using NMR spectroscopy. In addition, in two cases, **7**{*1,1*} and **7**{*2,5*}, the structure was also confirmed from their single crystal X-ray studies (Figure 1).[18]

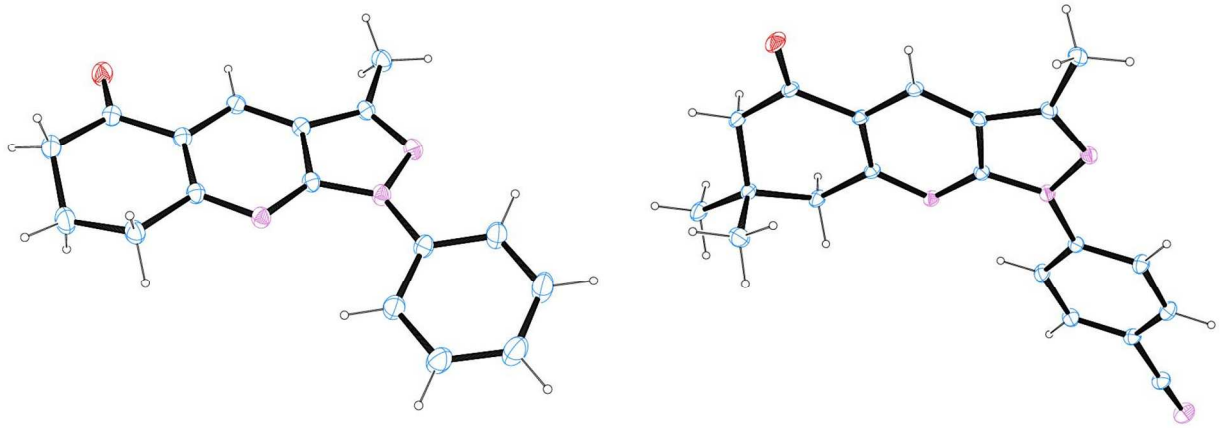
In the next step we chose 3-methyl-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]-quinolin-5-one **7**{*1,1*} and 3,7,7-trimethyl-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]-quinolin-5-one **7**{*2,1*} to investigate the base-promoted Knoevenagel condensation with aromatic aldehydes **8**{*1–7*} in order to induct an exocyclic alkene at position C-6 of the pyrazolo[3,4-*b*]quinolin-5-ones **7**. In the case of **7**{*1,1*}, the reaction occurred at ambient temperature in the presence of KOH in ethanol affording novel (*E*)-3-methyl-6-(arylidene)-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-ones **9** in quantitative yields (Scheme 3). However, under these and several other conditions the reaction of **7**{*2,1*} with aromatic aldehydes **8**{*1–7*} failed to occur, presumably due to the steric hindrance exerted by the methyl

groups at C-7. Further, in both the cases of **7**{*1,1*} and **7**{*2,1*}, the reaction failed to occur with aliphatic aldehydes.



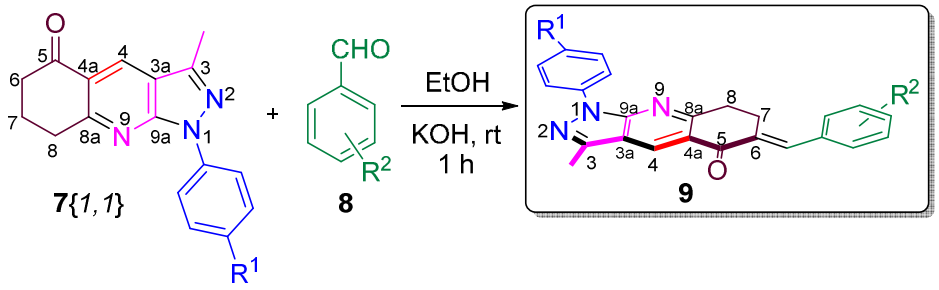
Entry	Comp	R^1	R^2	Yield (%)	Mp (°C)
1	**7**{*1,1*}	H	H	98 (87)[4b]	123–124
2	**7**{*1,2*}	H	Cl	97	149–150
3	**7**{*1,3*}	H	Br	98	153–154
4	**7**{*1,4*}	H	F	96	165–166
5	**7**{*1,5*}	H	CN	98	175–176
6	**7**{*1,6*}	H	Me	97	128–129
7	**7**{*2,1*}	Me	H	98 (15)[4c]	165–166
8	**7**{*2,2*}	Me	Cl	98	148–149
9	**7**{*2,3*}	Me	Br	97	140–141
10	**7**{*2,4*}	Me	F	96	164–165
11	**7**{*2,5*}	Me	CN	96	208–209

Scheme 2. Synthesis of pyrazolo[3,4-*b*]quinolin-5-ones **7**



7{*1,1*} **7**{*2,5*}

Figure 1. ORTEP diagrams of **7**{*1,1*} and **7**{*2,5*}



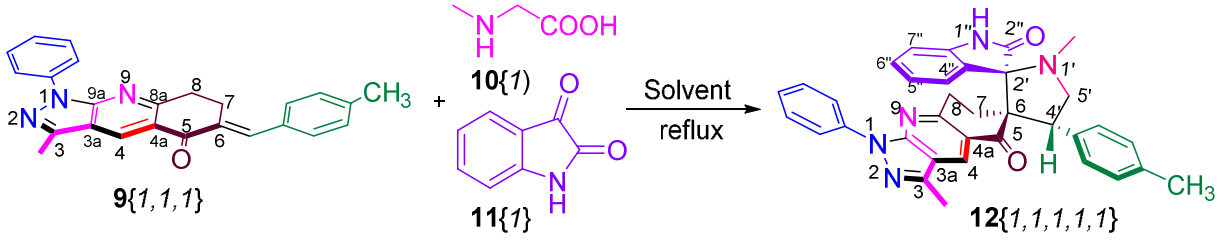
Entry	Comp	R^1	R^2	Yield (%)	mp (^oC)
1	**9**{*1,1,1*}	H	4-Me	98	182–183
2	**9**{*1,1,2*}	H	4-MeO	97	158–159
3	**9**{*1,1,3*}	H	4-Cl	98	179–180
4	**9**{*1,1,4*}	H	4-F	96	159–160
5	**9**{*1,1,5*}	H	2-Cl	98	180–181
6	**9**{*1,1,6*}	H	3-Br	96	207–208
7	**9**{*1,1,7*}	H	2,4-Cl_2	96	192–193
8	**9**{*1,2,3*}	Cl	4-Cl	98	183–184
9	**9**{*1,4,3*}	F	4-Cl	97	178–179
10	**9**{*1,5,3*}	CN	4-Cl	98	199–200
11	**9**{*1,6,3*}	Me	4-Cl	98	198–199

Scheme 3. Synthesis of 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones **9**

The structure of these 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones **9** was elucidated with the help of FT-IR, ESI-mass and NMR spectroscopic techniques. In general, the NMR spectra of **9** was found to be similar to that of **7**{*1,1*} apart from the presence of arylidene -CH and aromatic ring protons and the absence of one -CH_2 signal in the aliphatic region. The mass spectrum of **9**{*1,1,1*} had a characteristic molecular ion peak at 380.18 $[M+H]^+$. The IR spectrum of **9**{*1,1,1*} showed strong absorption at 1686 cm^{-1} due to the carbonyl group. In the ^1H NMR of **9**{*1,1,1*}, the methyl protons at C-3 and phenyl ring appeared as singlets at 2.70 and 2.41 ppm, respectively. The singlet at 3.26 ppm accounting for 4 protons was assigned to the 7- and 8-CH_2 protons. The arylidene CH and 4-CH protons appeared as singlets at 7.95 and 8.85 ppm, respectively while the remaining protons of the aromatic rings appeared as multiplets in the range 7.25–8.31 ppm.

Having synthesized the 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones **9**, we then concentrated on the solvent optimization for the 1,3-dipolar cycloaddition of azomethine ylide generated *in situ* from the decarboxylative condensation of α-amino acids and non-enolizable 1,2-diketones to the above diplarophiles. For this we selected the reaction of **9**{*1,1,1*}, sarcosine **10**{*1*} and isatin **11**{*1*} that presumably affords 1',3-dimethyl-1-phenyl-4'-(*p*-tolyl)-7,8-dihydro-dispiro[indoline-3",2'-pyrrolidine-3',6-pyrazolo[3,4-*b*]quinoline]-2",5(1*H*)-dione **12**{*1,1,1,1,1*}, as a model reaction, under reflux in various solvents (Table 1). From the data in Table 1 we observed that either methanol or ethanol was the optimal solvent for this cycloaddition reaction, wherein quantitative yield of **12**{*1,1,1,1,1*} was obtained (>90%). After completion of the reaction as evident from the TLC, the reaction mixture was poured into ice cold water and the resultant precipitate was filtered and dried to obtain the product **12**{*1,1,1,1,1*}. It is noteworthy that the crude reaction product was clean enough to be purified just by crystallization, thereby obviating the need for column chromatography, which is the main source of waste.

Table 1. Solvent optimization for the cycloaddition



Entry	Solvent	Time (h)	Yield (%)[a]
1	MeOH	4	>90
2	EtOH	3	>90
3	*i*-PrOH	6	40[b]
4	1,4-Dioxane	6	55[b]
5	MeCN	8	40[b]

[a]Isolated yield; [b]Yield after column chromatography

The structure of the isolated product was elucidated with the help of FT-IR, ESI-mass and NMR spectroscopic studies. The mass spectrum of **12**{*1,1,1,1,1*} had a characteristic molecular ion peak at 554.22 $[M+H]^+$. The IR spectrum of **12**{*1,1,1,1,1*} showed strong absorptions at 1686 and 1670 cm^{-1} due to the C-5 and C2" carbonyl groups, respectively. The ^1H and ^{13}C NMR chemical shifts of **12**{*1,1,1,1,1*} are shown in Figure 2. The discussion on the complete assignment of ^1H and ^{13}C NMR chemical shifts of **12**{*1,1,1,1,1*} are given in the supporting information.

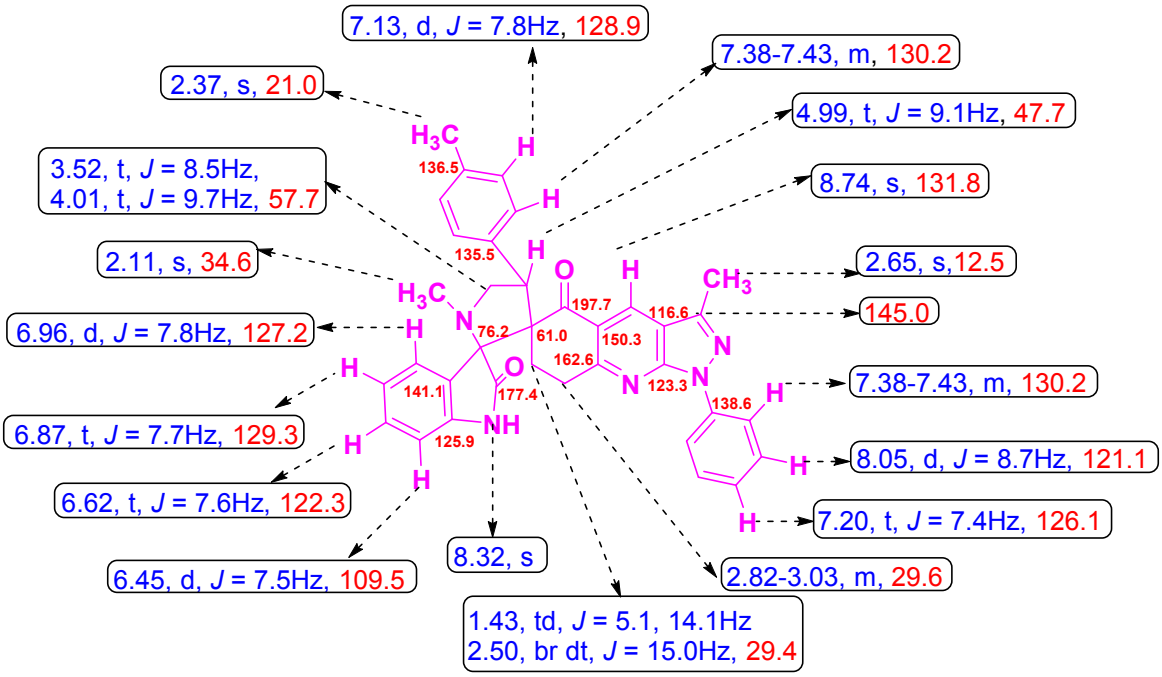
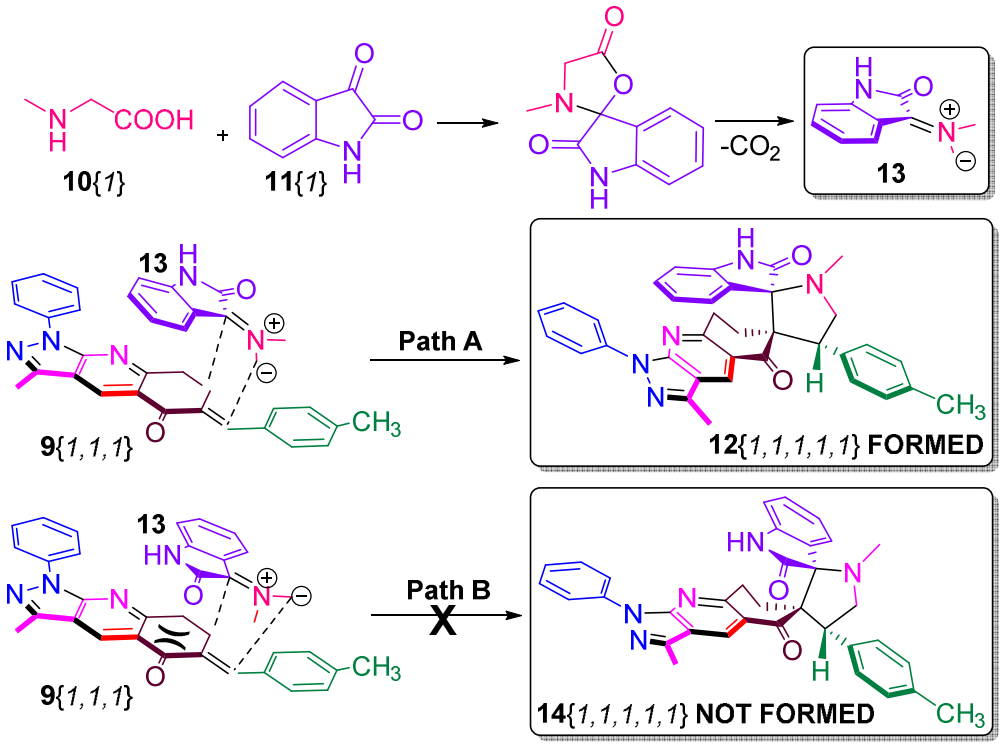


Figure 2. ^1H and ^{13}C chemical shifts of **12**{*1,1,1,1,1*}

The formation of **12**{*1,1,1,1,1*} can be rationalized through the pathway depicted in Scheme 4. Initially, the condensation of sarcosine **10**{*1*} and isatin **11**{*1*} forms the azomethine ylide dipole **13** *via* spontaneous decarboxylation. Subsequently, the 1,3-dipole **13** undergoes cycloaddition with the exocyclic dipolarohile **9**{*1,1,1*}, which may be visualized in two different

pathways *viz*. path A and B. However, the exclusive formation of dispiro-oxindole-pyrrolidine-pyrazoloquinoline **12**{*1,1,1,1,1*} discloses that this cycloaddition occurs through Path A, wherein the carbonyls of the dipole and the dipolarophile are *trans* to each other. Path B, which leads to the formation of **14**{*1,1,1,1,1*}, is presumably less favored in view of the electrostatic repulsion between the *cis* carbonyls.



Scheme 4. Formation of **12**{*1,1,1,1,1*}

Furthermore, it is evident that the cycloaddition proceeded regioselectively involving the addition of electron rich carbon of the dipole **13** to the β-carbon of the α,β-unsaturated dipolarophile **9**{*1,1,1*} (Scheme 4). This is also evident form ^{1}H NMR spectrum of **12**{*1,1,1,1,1*}, wherein three triplets appeared in the range between 3.52–4.99 ppm due to 4′-CH and 5′-CH_2 protons. If the other regioisomer **12′**{*1,1,1,1,1*} was formed (Figure 3), a singlet and

two doublets would have been expected for these protons. Moreover, this regiochemistry is in accord with the polarization of the C=C bond with a more electron-deficient β-carbon in **9**{*1,1,1*}, which could preferentially react with the electron-rich site of the approaching 1,3-dipole **13**. In addition, the cycloaddition occurred diastereoselectively to afford a single diastereoisomer exclusively in quantitative yields, albeit more than one contiguous stereocentres are present in the cycloadduct **12**{*1,1,1,1,1*}.

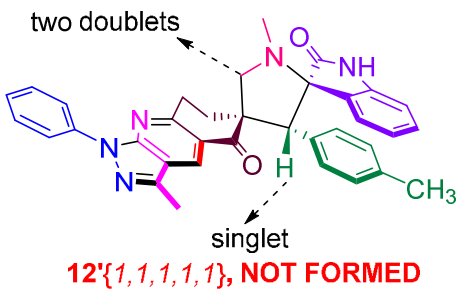


Figure 3. The regioisomer of **12**{*1,1,1,1,1*} not formed in the reaction

With the optimized reaction condition established and the structure arrived at for **12**{*1,1,1,1,1*}, we then explored the viability of this protocol for library generation. It is pertinent to note that forty-two novel spiro tethered pyrazolo[3,4-*b*]quinoline–pyrrolidine/pyrrolothiazole/indolizine–oxindole/acenaphthene hybrids **12** and **15–19** were synthesized employing eleven 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones **9**, three α-amino acids **10** and two 1,2-diketones **11** (Figure 4, Scheme 5 and Table 2). From the data in Table 2 it is apparent that the cycloaddition works well with all the substrates affording quantitative yields of the products. The structure of all the dispiro hybrid heterocycles **12** and **15–19** was elucidated unambiguously as done for **12**{*1,1,1,1,1*}. In the case of **12**{*1,1,7,1,1*} the structure was further confirmed from single crystal X-ray analysis (Figure 5).[18] The ORTEP diagram of **12**{*1,1,7,1,1*}

discloses that C-5 and C2″ carbonyls are *trans*, providing conclusive evidence to the proposed reaction pathway (Scheme 4). In addition, the C–N bond lengths of pyrazolo[3,4-*b*]quinoline ring varied from 1.312 (7) to 1.381 (8) Å. These distances were observed to be shorter than the relevant single bond length (1.443 Å) and longer than the double bond length (1.269 Å). The variation in bond length may be due to the electron delocalization around the ring. The pyrrolidine and the oxindole rings were oriented nearly perpendicular to each other at an angle of 87.01 (1)°. Further the pyrrolidine ring was making an angle of 75.22 (1)° with the dichlorophenyl plane.

CONCLUSIONS

We have developed an environmentally benign three-component sequential protocol for the synthesis of pyrazolo[3,4-*b*]quinolin-5-ones **7** in water. The base-promoted Knoevenagel reaction of **7** with aromatic aldehydes afforded novel 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones **9**. Subsequently, the 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the decarboxylative condensation of sarcosine, thiazolidine-4-carboxylic acid or piperidine-2-carboxylic acid and isatin or acenaphthenequinone to these exocyclic alkenenic dipolarophiles **9** led to the stereoselective formation of novel structurally intriguing spiro tethered pyrazolo[3,4-*b*]quinoline–pyrrolidine/pyrrolothiazole/indolizine–oxindole/acenaphthene hybrids **12** and **15–19**, in quantitative yields. As the products were obtained in pure form just by filtration, additional purification steps such as column chromatography, which is the main source of waste generation, was avoided. The quantitative yield of the product in combination with the high atom economy observed (>90%) makes this protocol efficient and green. Ultimately, we have demonstrated that pyrazolo[3,4-*b*]quinoline derivatives are potential precursors for further transformations into complex heterocycles *via* 1,3-dipolar cycloaddition.

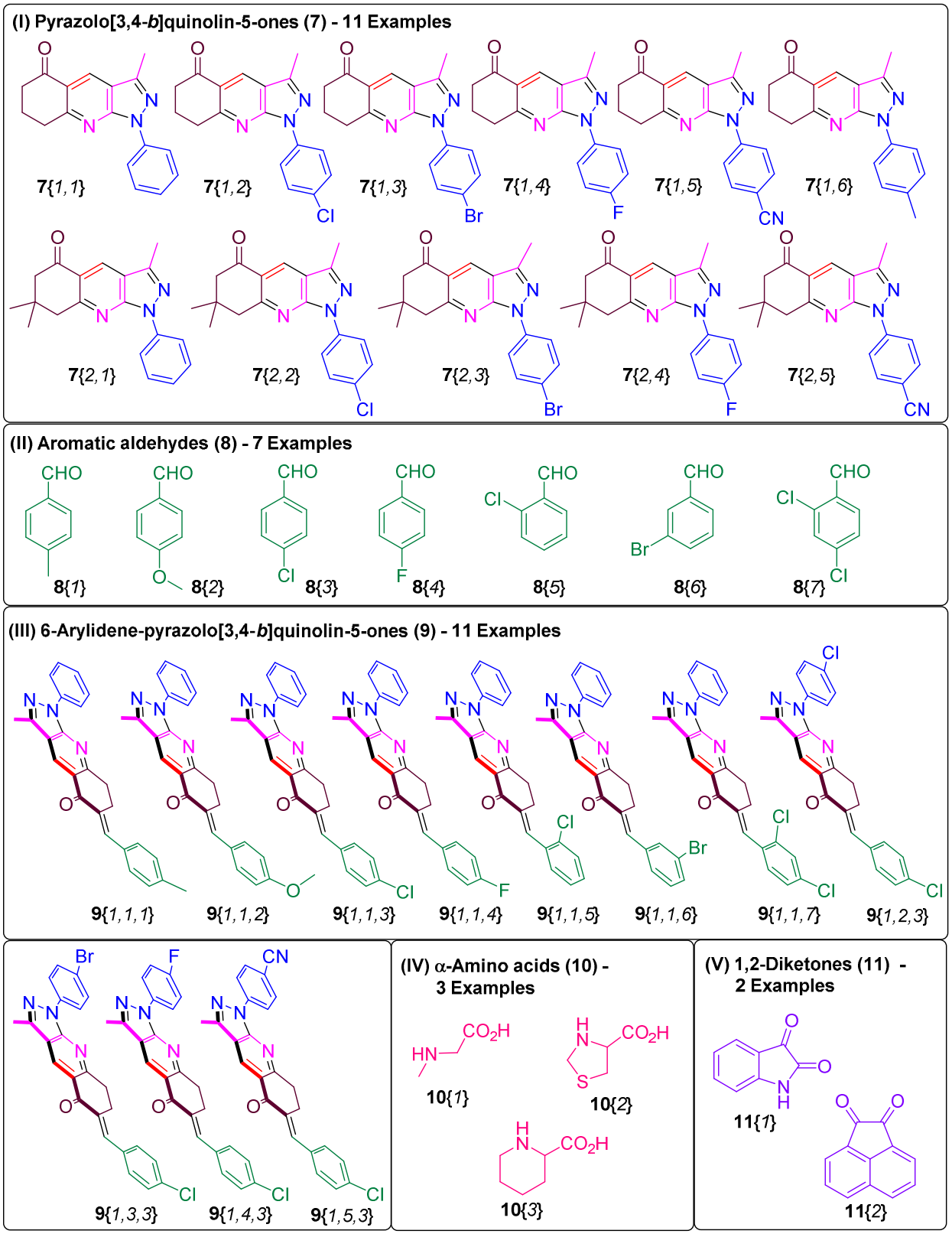
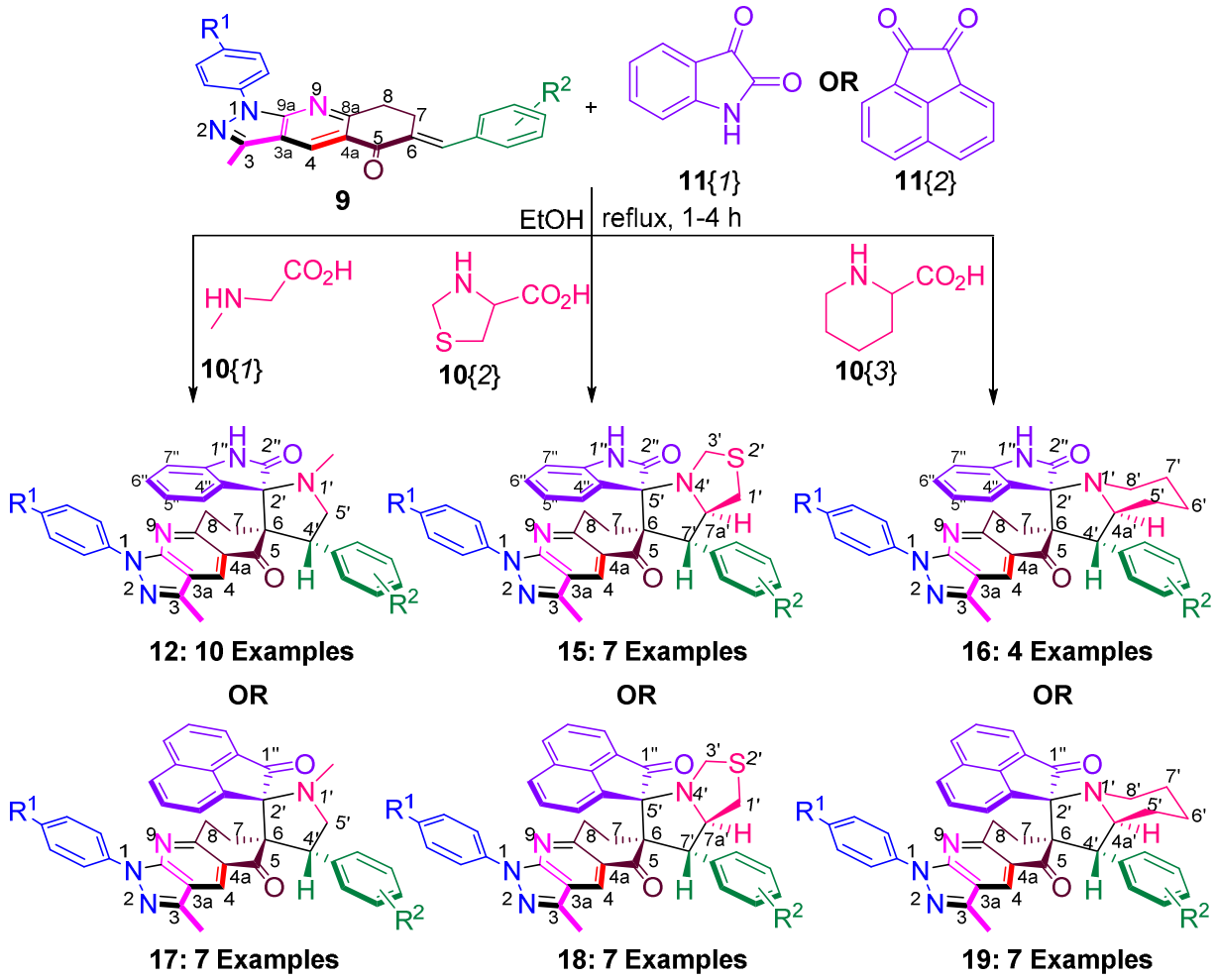


Figure 4. Diversity of reagents



Scheme 5. Synthesis of dispiro hybrid heterocycles

Table 2. Yield and melting point of **12**, **15–19**

Entry	Comp	R^1	R^2	Yield (%)	mp (^oC)
1	**12**{*1,1,1,1,1*}	H	4-Me	98	249–250
2	**12**{*1,1,2,1,1*}	H	4-MeO	96	230–231
3	**12**{*1,1,3,1,1*}	H	4-Cl	98	238–239
4	**12**{*1,1,4,1,1*}	H	4-F	97	258–259
5	**12**{*1,1,5,1,1*}	H	2-Cl	95	209–210
6	**12**{*1,1,6,1,1*}	H	3-Br	96	258–259
7	**12**{*1,1,7,1,1*}	H	2,4-Cl_2	98	242–243
8	**12**{*1,2,3,1,1*}	Cl	4-Cl	94	250–251
9	**12**{*1,5,3,1,1*}	CN	4-Cl	92	250–251
10	**12**{*1,6,3,1,1*}	Me	4-Cl	93	228–229
11	**15**{*1,1,1,2,1*}	H	4-Me	96	242–243
12	**15**{*1,1,2,2,1*}	H	4-MeO	97	232–233
13	**15**{*1,1,3,2,1*}	H	4-Cl	98	210–211
14	**15**{*1,1,4,2,1*}	H	4-F	96	233–234
15	**15**{*1,1,5,2,1*}	H	2-Cl	94	215–216
16	**15**{*1,1,6,2,1*}	H	3-Br	96	185–186
17	**15**{*1,1,7,2,1*}	H	2,4-Cl_2	95	238–239
18	**16**{*1,1,3,3,1*}	H	4-Cl	97	243–244
19	**16**{*1,1,5,3,1*}	H	2-Cl	95	236–237
20	**16**{*1,1,6,3,1*}	H	3-Br	93	254–256
21	**16**{*1,1,7,3,1*}	H	2,4-Cl_2	96	258–259
22	**17**{*1,1,1,1,2*}	H	4-Me	97	208–209
23	**17**{*1,1,2,1,2*}	H	4-MeO	95	105–106
24	**17**{*1,1,3,1,2*}	H	4-Cl	96	210–211
25	**17**{*1,1,4,1,2*}	H	4-F	93	190–191
26	**17**{*1,1,5,1,2*}	H	2-Cl	94	130–131
27	**17**{*1,1,6,1,2*}	H	3-Br	96	192–193
28	**17**{*1,1,7,1,2*}	H	2,4-Cl_2	93	158–159
29	**18**{*1,1,1,2,2*}	H	4-Me	98	168–169
30	**18**{*1,1,2,2,2*}	H	4-MeO	98	137–138
31	**18**{*1,1,3,2,2*}	H	4-Cl	97	138–139
32	**18**{*1,1,4,2,2*}	H	4-F	94	148–149
33	**18**{*1,1,5,2,2*}	H	2-Cl	96	160–161
34	**18**{*1,1,6,2,2*}	H	3-Br	93	162–163
35	**18**{*1,1,7,2,2*}	H	2,4-Cl_2	92	203–204
36	**19**{*1,1,1,3,2*}	H	4-Me	98	230–231
37	**19**{*1,1,2,3,2*}	H	4-MeO	97	205–206
38	**19**{*1,1,3,3,2*}	H	4-Cl	98	220–221
39	**19**{*1,1,4,3,2*}	H	4-F	95	226–227
40	**19**{*1,1,5,3,2*}	H	2-Cl	94	215–216
41	**19**{*1,1,6,3,2*}	H	3-Br	96	210–211
42	**19**{*1,1,7,3,2*}	H	2,4-Cl_2	93	225–226

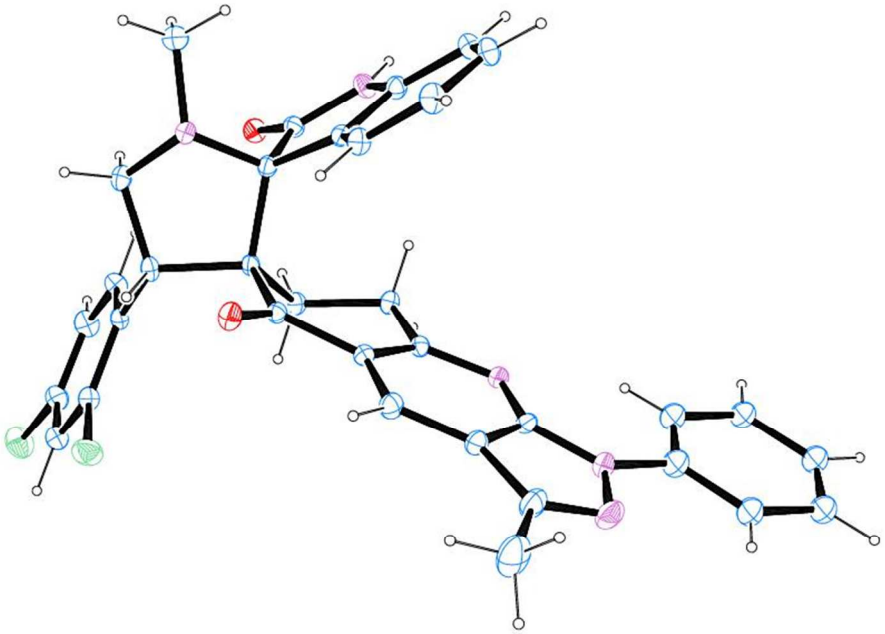


Figure 5. ORTEP diagram of **12**{*1,1,7,1,1*}

EXPERIMENTAL SECTION

General

The melting points were measured in open capillary tubes and are uncorrected. Electronspray ionization mass spectrometry (ESI-MS) analyses were recorded in LCQ Fleet, Thermo Fisher Instrument in negative or positive ion mode. The collision voltage and ionization voltage were +35 V and +5 kV, respectively, using nitrogen as atomization and desolvation gas. The desolvation temperature was set at 300^{o} C. The scan range of mass spectrum was 300-2000 *m/z*. The relative amount of each component was determined from the LC-MS chromatogram, using the area normalization method. Infrared spectra were recorded on a Thermo Scientific FT-IR instrument by ATR method. The ^{1}H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument (^{1}H: 300 MHz, ^{13}C: 75 MHz) using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout the spectral

analysis. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Elemental analyses were performed on Perkin Elmer 2400 Series II CHNS analyzer. The single crystal X-ray data set for compounds **7**{*1,1*}, **7**{*2,5*} and **12**{*1,1,7,1,1*} was collected on Bruker AXS KAPPA APEX-2 diffractometer equipped with graphite monochromator. The structure was solved by direct methods and refined by full-matrix least-squares calculations using SHELXL–2014.[19] Silica gel-G plates (Merck) were used for TLC analysis with a mixture of *n*-hexane and ethyl acetate as eluent. All the chemicals were purchased from commercial sources and used without any further purification.

General procedure for the synthesis of 7

A mixture of 3-aminocrotononitrile **4** (1 mmol), arylhydrazine **5** (1 mmol) and L-proline (0.4 mmol) was taken in water (10 mL) and heated to reflux. After 1 h of continuous reflux, methylene-cyclohexane-1,3-dione **3** (1 mmol) was added and the reflux continued for another 1 h. Upon addition of **3** the mixture turns homogeneous. The completion of the reaction was evident from the formation of precipitate, which was filtered, washed with water and dried under vacuum to obtain pure **7**.

Compound 7{*1,2*}. Obtained as Pale yellow solid; Yield 97%; m.p. 149–150°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.25 (qui, J = 5.0 Hz, 2H), 2.65 (s, 3H), 2.77 (t, J = 6.5 Hz, 2H), 3.28 (t, J = 6.1 Hz, 2H), 7.47 (dd, J = 6.9, 2.1 Hz, 2H), 8.30 (d, J = 9.0 Hz, 2H), 8.74 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.4, 21.8, 33.6, 36.7, 116.7, 121.4, 123.0, 128.9, 130.3, 130.8, 137.7, 145.2, 150.9, 163.8, 197.2 ppm.

General procedure for the synthesis of 9

To an equimolar mixture of **7** (1 mmol) and aromatic aldehyde (**8**, 1 mmol) in ethanol (5 mL) was added 10 mL of ethanolic solution of KOH (5%). The mixture was stirred at ambient temperature for about 1 h. The completion of the reaction was noted when the product **9** precipitated out of the reaction mixture, which was filtered, washed with water and dried.

Compound 9{*1,1,1*}. Obtained as pale yellow solid; Yield 98%; m.p. 182–183°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.41 (s, 3H), 2.70 (s, 3H), 3.26 (s, 4H), 7.26 (d, *J* = 8.1 Hz, 3H), 7.32 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.53 (tt, *J* = 8.4, 1.2 Hz, 2H), 7.95 (s, 1H), 8.30 (dt, *J* = 7.5, 1.2 Hz, 2H), 8.85 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.5, 21.4, 26.2, 32.7, 116.9, 120.8, 123.7, 125.8, 129.0, 129.2, 130.1, 131.2, 132.6, 133.6, 137.6, 139.0, 139.1, 145.0, 150.9, 162.5, 187.0 ppm. Anal. Calcd. for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.07. Found: C, 79.22; H, 5.48; N, 11.19. ESI-MS m/z calcd $[M + H]^+$ 379.17, found 380.18. FT IR (cm^{-1}): 1686, 3022.

General procedure for the synthesis of dispiro hybrid heterocycles 12 and 15–19.

A mixture of **9** (1 mmol), sarcosine/thiazolidine-4-carboxylic acid/piperidine-2-carboxylic acid (**10**, 1.1 mmol) and isatin/acenaphthenequinone (**11**, 1.1 mmol) was taken in 10 mL of ethanol in a 50 mL round bottom flask and heated to reflux on a boiling water bath for 1–4 h. After completion of the reaction as evident from TLC, the reaction mixture was poured into ice cold water (50 mL). The precipitated solid was filtered, washed with water and dried to get the dispiro hybrid heterocycles **12** or **15–19**. The crude product was purified through crystallization from ethanol.

Compound 12{*1,1,1,1,1*}: Obtained as pale yellow solid; Yield 98%; m.p. 249–250°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.43 (td, *J* = 14.0, 5.1 Hz, 1H), 2.12 (s, 3H), 2.32 (s, 3H), 2.50 (d, *J* = 14.9 Hz, 1H), 2.65 (s, 3H), 2.81–3.00 (m, 2H), 3.52 (t, *J* = 8.5 Hz, 1H), 4.01 (t, *J* = 9.7 Hz, 1H), 4.92–5.05 (m, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 6.62 (t, *J* = 7.6 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 4H), 8.05 (d, *J* = 8.4 Hz, 2H), 8.32 (s, 1H), 8.74 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.5, 21.0, 29.4, 29.6, 34.6, 47.7, 57.7, 61.0, 76.2, 109.5, 116.6, 121.1, 122.3, 123.3, 126.0, 126.1, 127.2, 129.0, 129.2, 130.3, 131.8, 135.6, 136.5, 138.7, 141.1, 145.0, 150.3, 162.7, 177.4, 197.8 ppm. Anal. Calcd. for $C_{35}H_{31}N_5O_2$: C, 75.93; H, 5.64; N, 12.65. Found: C, 75.83; H, 5.52; N, 12.54. ESI-MS m/z calcd $[M + H]^+$ 553.67, found 554.22. FT IR (cm^{-1}): 3735, 2864, 1688, 1591.

15{*1,1,1,2,1*}: Obtained as yellow solid; Yield 96%; m.p. 242–243°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.51 (td, *J* = 13.5, 5Hz, 1H), 2.32 (s, 3H), 2.60 (s, 3H), 2.77 (d, *J* = 12.3 Hz, 1H), 2.87–2.03 (m,3H), 3.15 (td, *J* = 15.8, 5 Hz, 1H), 3.45 (d, *J* = 6.1 Hz, 1H), 3.57 (d, *J* = 6.1 Hz, 1H), 4.64 (d, *J* = 10.0 Hz, 1H), 4.83 (ddd, *J* = 10.0, 7.7, 5.5 Hz, 1H), 6.46 (d, *J* = 7.7 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.18–7.25(m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.40–7.47 (m, 2H), 7.55 (s, 1H), 8.12 (d, *J* = 7.6 Hz, 2H), 8.45 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.3, 20.9, 27.8, 33.0, 46.8, 51.0, 66.7, 66.9, 69.1, 71.7, 109.8, 116.3, 120.6, 120.8, 121.8, 123.1, 125.0, 125.7, 127.4, 128.8, 128.9, 129.0, 129.3, 129.8, 134.1, 136.7, 141.1, 144.8, 162.2, 177.4, 196.1 ppm. Anal. Calcd. for $C_{36}H_{31}N_5O_2S$: C, 72.34; H, 5.23; N, 11.72. Found: C, 72.20; H, 5.10; N, 11.61. ESI-MS m/z calcd $[M + H]^+$ 597.74, found 554.22.

16{*1,1,3,3,1*}: Pale yellow solid; Yield 97%; m.p 243–244°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18–1.57 (m, 6H), 1.77 (s, 2H), 2.20 (s, 2H), 2.63 (s, 3H), 2.91–3.04 (m, 2H), 3.85 (t, *J* = 9.1 Hz, 1H), 4.49 (d, *J* = 9.8 Hz, 1H), 6.46 (d, *J* = 7.7 Hz, 1H), 6.62 (t, *J* = 7.5 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 7.17–7.25 (m, 2H), 7.29–7.56 (m, 5H), 7.98 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 2H), 8.63 (s, 1H) ppm. ^{1}C NMR (300 MHz, $CDCl_3$) δ_C: 12.1, 23.6, 25.1, 28.8, 29.5, 30.6, 44.9, 53.9, 59.3, 62.4, 75.3, 109.3, 116.1, 120.3, 121.4, 123.1, 125.4, 125.9, 126.6, 127.9, 128.5, 131.0, 132.0, 137.0, 138.6, 141.7, 144.5, 150.1, 162.2, 177.2, 196.8 ppm. Anal. Calcd. for $C_{37}H_{32}ClN_5O_2$: C, 72.36; H, 5.25; N, 11.40. Found: C, 72.27; H, 5.13; N, 11.30.

17{*1,1,1,1,2*}: Obtained as yellow solid; Yield 97%; m.p. 208–209°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.40 (td, *J* = 14.3, 4 Hz, 1H), 2.04 (s, 3H), 2.24 (td, *J* = 15.0, 5.0 Hz, 1H), 2.33 (s, 3H), 2.40 (s, 1H), 2.54 (s, 1H), 2.63 (s, 3H), 3.59 (t, *J* = 8.5 Hz, 1H), 4.10 (t, *J* = 9.8 Hz, 1H), 5.09 (t, *J* = 9.0 Hz, 1H), 7.18 (t, *J* = 8.7 Hz, 3H), 7.28–7.43 (m, 4H), 7.50 (dd, *J* = 16.7, 7.6 Hz, 3H), 7.60–7.68 (m, 1H), 7.81–8.05 (m, 4H), 8.67 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.5, 21.0, 29.2, 30.4, 34.5, 48.1, 58.3, 62.5, 79.2, 116.4, 120.6, 123.4, 124.1, 125.1, 125.7, 127.9, 128.2, 128.8, 129.0, 130.1, 130.2, 131.3, 131.7, 131.9, 135.7, 136.4, 136.5, 138.7, 142.0, 144.8, 150.3, 162.4, 198.1, 206.7 ppm. Anal. Calcd. for $C_{39}H_{32}N_4O_2$: C, 79.57; H, 5.48; N, 9.52. Found: C, 79.61; H, 5.36; N, 9.42. ESI-MS m/z calcd $[M + H]^+$ 588.71, found 589.24. FT IR (cm^{-1}): 2843, 2162, 1703, 1678, 1596.

18{*1,1,1,2,2*}: Obtained as pale orange solid; Yield 98%; m.p. 168–169°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.51–1.62 (m, 1H), 2.33 (s, 3H), 2.53 (s, 3H), 2.66–2.72 (m, 2H), 2.8 (dt, *J* = 15.0, 3.0 Hz, 1H), 2.96 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.10 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.44 (d, *J* = 6.8 Hz, 1H), 3.60 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 10.1 Hz, 1H), 4.89–4.98 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.38 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 3H), 7.45–7.51 (m, 2H), 7.58 (s,

1H), 7.60–7.69 (m, 2H), 7.79 (d, *J* = 4.9 Hz, 1H), 7.81 (d, *J* = 6.3 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 8.12 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.3, 21.0, 26.8, 29.8, 33.9, 48.3, 52.1, 67.8, 69.8, 76.4, 116.1, 120.6, 121.3, 123.5, 124.8, 125.3, 125.8, 127.7, 128.1, 128.9, 129.2, 129.9, 130.0, 130.4, 131.1, 131.7, 134.1, 134.9, 136.9, 138.7, 141.2, 144.5, 150.5, 161.6, 196.6, 205.0 ppm. Anal. Calcd. for $C_{40}H_{32}N_4O_2S$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.83; H, 5.03; N, 8.79. ESI-MS m/z calcd. $[M + H]^+$ 632.78, found 633.18. FT IR (cm^{-1}): 3040, 2035, 1701, 1590.

19{*1,1,1,3,2*}: Obtained as brown solid; Yield 98%; m.p. 230–231°C^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.20–1.52 (m, 6H), 1.74 (d, *J* = 12.7 Hz, 1H), 1.86 (d, *J* = 13.1 Hz, 1H), 2.02–2.19 (m, 2H), 2.33 (s, 3H), 2.38–2.51 (m, 2H), 2.60 (s, 3H), 3.99 (t, *J* = 9.1 Hz, 1H), 4.58 (d, *J* = 10.0 Hz, 1H), 7.09–7.23 (m, 3H), 7.28–7.43 (m, 5H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.57–7.64 (m, 1H), 7.86 (t, *J* = 7.5 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 2H), 8.54 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.4, 21.0, 24.0, 25.7, 28.8, 30.6, 31.2, 45.4, 55.0, 61.5, 63.0, 79.1, 116.3, 120.4, 120.6, 123.7, 123.9, 124.8, 125.7, 127.9, 128.2, 128.9, 129.0, 129.9, 131.0, 131.7, 131.8, 135.4, 136.3, 137.2, 138.8, 141.9, 144.7, 150.3, 162.3, 197.7, 206.6 ppm. Anal. Calcd. for $C_{42}H_{36}N_4O_2$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.11; H, 5.68; N, 8.82. ESI-MS m/z calcd $[M + H]^+$ 628.78, found 629.22.

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ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic characterization of all the compounds. ^{1}H and ^{13}C spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Multicomponent Dipolar Cycloaddition Strategy: Combinatorial Synthesis of Novel Spiro Tethered Pyrazolo[3,4-*b*]quinoline Hybrid Heterocycles

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