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Straightforward Strategy for the Stereoselective Synthesis of Spiro-Fused (C-5)Isoxazolino- or (C-3)Pyrazolino-(C-3)quinolin-2-ones from Baylis–Hillman Adducts by 1,3-Dipolar Cycloaddition and Reductive Cyclization[‡]

Virender Singh,[a] Vijay Singh,[a] and Sanjay Batra*[a]

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A straightforward and general approach for the stereoselective synthesis of spiro-fused (C-5)isoxazolino- or (C-3)pyrazolino-(C-3)quinolin-2-ones from the adducts offorded from the Baylis–Hillman reaction of 2-nitrobenzaldehyde and ethyl acrylate by sequential 1,3-dipolar cycloaddition and reductive cyclization is presented. It was found that the reductive cyclization of the isoxazoline derivatives proceeded efficiently in the presence of In/HCl, whereas similar reductions of pyrazolines gave better yields when carried out in the presence of an Fe/AcOH mixture. However, similar attempts employing the Baylis–Hillman adduct of 2-nitrobenzaldehyde and methyl vinyl ketone did not yield the desired compounds.

Introduction

Applications of substituted quinolines are profound and wide-ranging from pharmaceuticals and agrochemicals to electronics. In order to meet the requirements of differently substituted quinolines for various purposes, chemists have been relentlessly developing new synthetic strategies for their syntheses. These protocols may involve the discovery of a new catalyst or condition for known reactions or the use of novel substrates to engineer the synthesis of substituted quinolines in an innovative fashion or by robust well-optimized procedures. Recently, we have assimilated all the efforts reported during the last couple of years in the literature towards the synthesis of substituted quinolines and quinoline-annulated ring systems.[1] Of several methodologies currently in use, the Baylis–Hillman-reaction-assisted route for the synthesis of diverse substituted quinoline or quinoline-annulated ring systems has received considerable attention.[1,2] A critical analysis of different strategies developed for the synthesis of substituted quinolines through Baylis–Hillman chemistry revealed that the majority of them involve the reductive cyclization of adducts of 2-nitrobenzaldehyde and acrylate or (cyclo)alkeneone as the key step.[2] In this context, we have disclosed general approaches for the synthesis of 4-vinylquinolines, 2-amino-3-benzylquinolines, and 3-benzyl-2-quinolones from derivatives of Baylis–Hillman adducts.[3,4] In our continued interest to develop facile and general routes to pharmacologically important heterocyclic systems, which can be constructed from the derivatives obtained from the Baylis–Hillman reaction, we envisaged the synthesis of spiro-fused (C-5)isoxazolino- and (C-3)pyrazolino-(C-3)quinolin-2-ones. In principle, products afforded from the 1,3-dipolar cycloaddition of a dipole to the methylene group of the adducts of the Baylis–Hillman reaction of 2-nitrobenzaldehyde with acrylate, upon reductive cyclization between the aromatic amino group and the alkoxycarbonyl group, should lead to the desired spiro-fused system.

Spirocyclic systems are of considerable importance owing to their ubiquitous presence in several natural products and pharmacologically active compounds.[5,6] The recent literature reflects a renewed interest in the syntheses of different spirocyclic molecules employing diverse approaches.[7] Due to the propensity to deliver the α-anion equivalent of an electron-deficient alkene, the Baylis–Hillman adducts or their derivatives have already been demonstrated to be suitable starting materials for the synthesis of spiro-fused systems.[8] In most of these endeavors the cycloaddition reaction is the key step, which may be either conducted on the Baylis–Hillman derivative or the exocyclic methylene group of a heterocyclic system afforded from the Baylis–Hillman adduct to produce the spiro system. A literature search revealed that Yong et al. have reported the synthesis of 3′-spirocyclic oxoindoles by a strategy that is analogous to the one envisaged by us.[9] However, to the best of our knowledge, only a few methods known to date describe the synthesis of a spiro-fused quinoline core.[10] Therefore, we were

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[a] Medicinal and Process Chemistry Division, Central Drug Research Institute,
P. O. Box 173, Lucknow 226001, India
Fax: +91-522-2623405, -2623938
E-mail: batra_san@yahoo.co.uk

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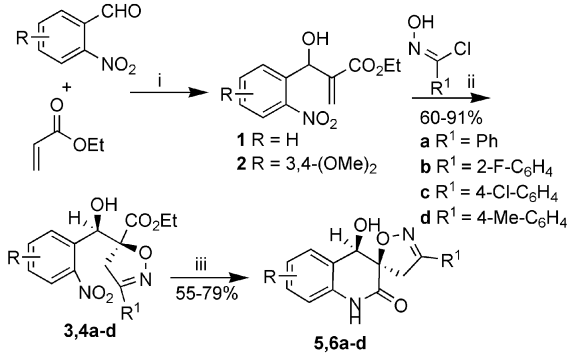
inspired to explore the feasibility of our strategy. During the present study, the 1,3-dipolar cycloadditions of nitrile oxides or nitrile imines to the Baylis–Hillman adducts of 2-nitrobenzaldehyde or substituted 2-nitrobenzaldehyde were stereoselective, furnishing only the *syn* isomer. Furthermore, the reductive cyclization of the isoxazoline derivatives to yield the spiro system was accomplished efficiently in the presence of an In/HCl mixture. On the other hand, similar reactions of pyrazoline derivatives proceeded better in the presence of an Fe/AcOH mixture but took a longer time to complete. The details of these results are presented in this paper.

Results and Discussion

Synthesis of Spiro-Fused 4′-Hydroxy-(C-5)isoxazolino-(C-3)quinolin-2-ones

Our synthesis commenced with the Baylis–Hillman reaction of 2-nitrobenzaldehyde and ethyl acrylate to deliver adduct **1**. The 1,3-dipolar cycloaddition of several nitrile oxides, which were generated in situ from the corresponding hydroximoyl chlorides, led to the corresponding substituted 2-isoxazolines **3a**–**d** (Scheme 1). It has been reported that such 1,3-dipolar additions of nitrile oxides to allylic alcohols are diastereoselective in favor of the *syn* isomer,[11] but we observed that the addition yielded exclusively the *syn* isomer of **3**, as evident from the NMR analysis. The NOE between the CH_2 signal at δ = 3.7 ppm and the benzylic proton signal at δ = 6.07 ppm in the NOESY spectrum of **3c** indicated the stereochemical assignment of these products. On the basis of literature precedence, we presumed that a transition state, as shown in Figure 1, may exist owing to the hydrogen bonding between the nitrile oxide and the hydroxy group of the Baylis–Hillman adduct. This transition state favors the formation of the *syn* isomer. In order to investigate the generality of this phenomenon, adduct **2**, afforded from the Baylis–Hillman reaction between 4,5-dimethoxy-2-nitrobenzaldehyde and ethyl acrylate, was also subjected to 1,3-dipolar cycloadditions with nitrile oxide. This resulted in the formation of **4a**–**d** having *syn* stereochemistry, as evident from the spectral assignments. With the desired isoxazoline derivatives **3a**–**d**,**4a**–**d** in hand, we next investigated the reductive cyclization of these compounds. It is noteworthy that reductive cyclizations involving aromatic nitro groups in Baylis–Hillman derivatives have been executed previously with a variety of reducing agents such as In/HCl, Fe/AcOH, and $SnCl_2{\cdot}2H_2O$.[2] Additionally, in view of our earlier observation that a substituted 2-isoxazoline carrying a nitro-substituted phenyl group did not undergo ring cleavage under catalytic hydrogenation,[12] the option of performing reductive cyclizations through catalytic hydrogenation was also available to us. In an attempt to discover efficient conditions that could be applied to all substrates, the aforementioned reagents were screened in reductive cyclizations on model substrate **3a**. As evident from the results summarized in Table 1, the reaction performed in the presence of In/HCl at 70 °C under aqueous condition was clean and provided the best yield of the desired spiro-fused 4′-hydroxy-(C-5)isoxazolino-(C-3)quinolin-2-one in a short period of time. If the same reaction was conducted at room temperature, the reaction was completed within 10 min and yielded a mixture of products, from which 45% of **5a** was recovered (Table 1, Entry 1). Surprisingly, if HCl was added to the reaction mixture at 0 °C, and then heated at reflux, the reaction did not go to completion, even if the mixture was refluxed for more than 12 h (Table 1, Entry 3). An Fe/AcOH mixture was unsuit-



Compd.	R	R^1
3a,5a	H	Ph
3b,5b	H	2-F-C_6H_4
3c,5c	H	4-Cl-C_6H_4
3d,5d	H	4-Me-C_6H_4
4a,6a	3,4-$(OMe)_2$	Ph
4b,6b	3,4-$(OMe)_2$	2-F-C_6H_4
4c,6c	3,4-$(OMe)_2$	4-Cl-C_6H_4
4d,6d	3,4-$(OMe)_2$	4-Me-C_6H_4

Scheme 1. Reagents and conditions: (i) DABCO, neat, room temp., 10–24 h; (ii) Et_3N, anhydrous diethyl ether, –78 °C to room temp., 3 h; (iii) In/HCl, 70 °C, THF/H_2O (3:2), 5–7 min.

Table 1. Result of the optimization study of reductive cyclization under different conditions with model substrate **3a**.

Entry	Reagent and conditions	Yield [%] of **5a**
1	In (4.0 equiv.) + HCl (6.0 equiv.), THF/H_2O, room temp., 10 min	45 + unidentified side products
2	In (4.0 equiv.) + HCl (6.0 equiv.), THF/H_2O, 70 °C, 7 min	64
3	In (4.0 equiv.) + HCl (6.0 equiv.), THF/H_2O, HCl added at 0 °C, then reflux for 1.5 h	33 + starting material + side products
4	Fe (6.0 equiv.) + AcOH, 120 °C, N_2, 1.5 h	nil (reaction was completed, but TLC analysis showed several spots)
5	$SnCl_2{\cdot}2H_2O$ (6.0 equiv., anhydrous MeOH, 80 °C, 3.0 h)	31 + other unidentified products
6	Pd/C (10%), MeOH, 40 psi, 3.0 h	27 + other unidentified products
7	Zn (1.5 equiv.) + HCO_2NH_4, anhydrous MeOH, room temp., 12.0 h	mixture of products

able for this reaction, since only a polymeric material was obtained. The $SnCl_2 \cdot 2H_2O$ and Pd/C reagents successfully produced the desired product **5a**, albeit in lower yields than the In/HCl-mediated reaction. Gratifyingly, the relative stereochemistry of the product was unaltered during the reductive cyclization to provide the product with *syn* geometry only. As a result, compounds **3b–d**,**4a–d** were also treated with In/HCl at reflux to furnish the corresponding spiro-fused 4′-hydroxy-(C-5)isoxazolino-(C-3)quinolin-2-ones **5b–d**,**6a–d** in good yields.

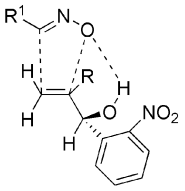
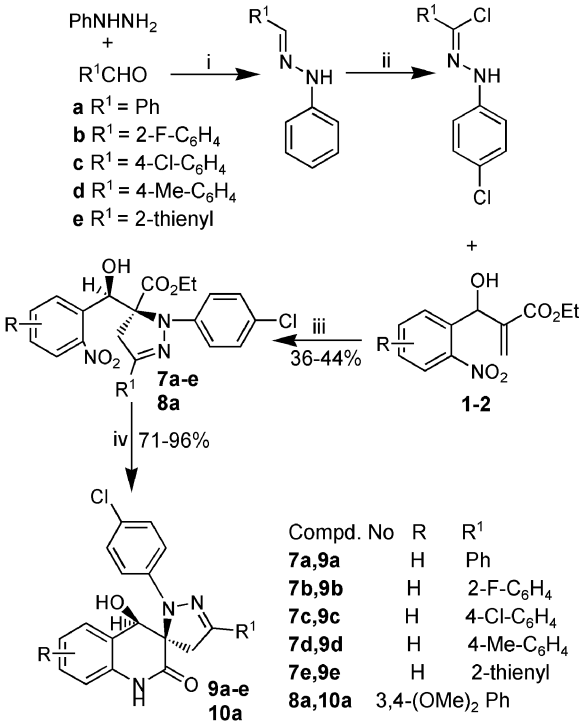


Figure 1. Hydrogen-bonded transition state favoring the formation of the *syn* isomer.

Synthesis of Spiro-Fused (C-3)Pyrazolino-4′-hydroxy-(C-3)quinolin-2-ones

In order to diversify the scope of the strategy, we envisaged the synthesis of (C-3)pyrazolino-4′-hydroxy-(C-3)-quinolin-2-ones by carrying out similar 1,3-dipolar cycloadditions employing nitrile imines on **1**–**2**, followed by reductive cyclization. Accordingly, the hydrazonyl chlorides required for the in situ generation of nitrile imines were prepared by the reaction of *N*-chlorosuccinimide with hydrazones, which were afforded by the treatment of phenylhydrazine with several benzaldehydes. Since the hydrazonyl chlorides were highly corrosive (skin irritant), they were utilized without purification or spectral analysis. Unlike the dipolar cycloadditions with nitrile oxides, which were complete in 3–4 h, the cycloadditions with nitrile imines took almost 5 d to go to completion (Scheme 2). With the objective to expedite the reaction, several solvents were screened with **1d** as a model substrate with one of the nitrile imines (R^1 = 4-Me-C_6H_4). The results of this study are summarized in Table 2.

Although the best isolated yields were obtained in anhydrous benzene, we observed that the reaction proceeded sluggishly, and the yields were low irrespective of solvent. This may be attributed to the choice of base used for the generation of the nitrile imine.[13] Nevertheless, similar to the cycloadditions with the nitrile oxides, this reaction also resulted in a single product. However, the mass spectrum of this product distinctly displayed an $[M + 34]^+$ peak (vide infra). A review of the literature revealed that during the preparation of a hydrazonyl bromide with *N*-bromosuccinimide, Reinov et al.[14] reported that regioselective bromination took place at the 4-position of the phenyl ring derived from phenylhydrazine. Indeed, the formation of a side product reported by these workers during the synthesis of a pyrazoline with an *N*-hydrazonyl bromide as the source of nitrile imine was attributed to this reaction. However, we



Scheme 2. Reagents and conditions: (i) C_6H_6, room temp. to reflux, 2–15 min; (ii) NCS, DMF, room temp., 30 min to 1 h; (iii) Et_3N, anhydrous C_6H_6, reflux, 5 d; (iv) Fe/AcOH, reflux, 3 h.

Table 2. Results of solvent screening for expediting the formation of pyrazoline with model substrate **1d**.

Entry	Solvent and conditions	Yield [%] of **7d**
1	anhydrous C_6H_6, Et_3N, reflux for 5 d	36, reaction complete
2	anhydrous 1,4-dioxane, Et_3N, reflux for 5 d	27, reaction complete
3	anhydrous CH_2Cl_2, reflux for 5 d	25, reaction incomplete
4	anhydrous diethyl ether, reflux for 6 d	32, reaction complete
5	anhydrous toluene, reflux for 5 d	31, reaction complete

isolated only a single product, which was established as **7d**. A careful NMR analysis ascertained that one of the phenyl rings was substituted at the 4-position. In order to examine whether this was a general trend for this series of compounds, **1** and **2** were treated with several nitrile imines to yield **7a–c**,**e**,**8a** in moderate yields only. The mass spectra of all products displayed an $[M + 34]^+$ peak. A possible explanation for the larger than expected mass was that the generation of the hydrazonyl chloride by *N*-chlorosuccinimide involved the regiospecific chlorination of the phenyl ring derived from phenylhydrazine. These compounds (**7a–e**,**8a**) were then subjected to reductive cyclization. Contrary to the reductive cyclization of substituted 2-isoxazoline derivatives, we observed that the reductive cyclization of **7d** with In/HCl was not clean. Chromatographic purification of the crude product furnished the desired compound in 55% yield only. In view of this result, we employed an Fe/AcOH mixture to carry out the reductive cyclization of **7d**. To our delight, heating at reflux provided a

clean reaction and furnished the required spiro-fused (C-3)-pyrazolino-4′-hydroxy-(C-3)quinolin-2-one derivative **9d** in 73% yield. This reagent worked well for other substrates (**7a**–**c**,**e**,**8a**) to furnish the corresponding spiro-fused systems **9a**–**c**,**e**,**10a** in 71–96% yields. In order to provide additional evidence for an 4-chloro-*N*-phenyl group by X-ray crystallography, we attempted to prepare crystals of these analogs. However, we failed to achieve the desired objective due to the poor solubility of these analogs in different organic solvents.

Synthesis of Spiro-Fused (C-3)Pyrazolino-(C-3)pyrolidin-2-ones

We recently reported the synthesis of the spiro-fused (C-5)-isoxazolino-(C-3)pyridine-2-ones from 3-methylene-2-pyridone, the structure and relative stereochemistry of which were unambiguously established on the basis of X-ray crystallographic analysis.[8a] In principle, the nitrile imine, generated through the above-described protocol, upon reaction with 3-methylene-2-pyridone, should furnish the spiro-fused pyrazoline–2-pyridone unit. A crystallographic analysis of such a system would provide evidence for the regiospecific chlorination of the phenyl ring derived from phenylhydrazine during the formation of the hydrazonyl chloride with *N*-chlorosuccinimide. Consequently, 3-methylene-2-pyridones (**11**–**14**,**15**) were generated as reported and treated with several nitrile imines, resulting in the formation of **16a**–**d**,**17a**–**d**,**18a**–**d**,**19a**–**d**,**20a**–**c** (Scheme 3). Like the 1,3-dipolar cycloaddition reactions of nitrile imines with Baylis–Hillman adducts, these reactions were also slow and produced only moderate yields. Nevertheless, the strategy was general in nature. The attempted crystallization of several analogs resulted in crystals for **17d** and **19c**, which were finally subjected to X-ray crystallographic analysis.[14–16] The results of this analysis provided unambiguous evidence that the phenyl ring originating from phenylhydrazine was regiospecifically chlorinated at the 4-position (Figures 2 and 3). Additionally, the X-ray structure also made it evident that the 2-pyridone and pyrazoline rings were perpendicular to each other in the spiro-fused (C-3)pyrazolino-(C-3)pyrolidin-2-ones, demonstrating that the addition of the nitrile imine to the 3-methylene-2-pyridone was diastereoselective.

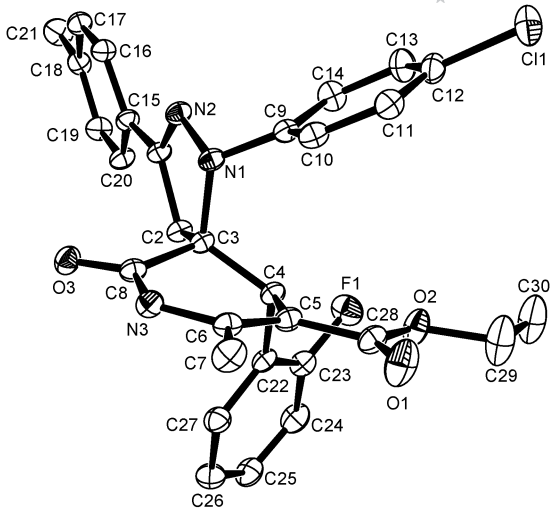


Figure 2. ORTEP structure of **17d**. The ellipsoids are drawn at a probability level of 20%.

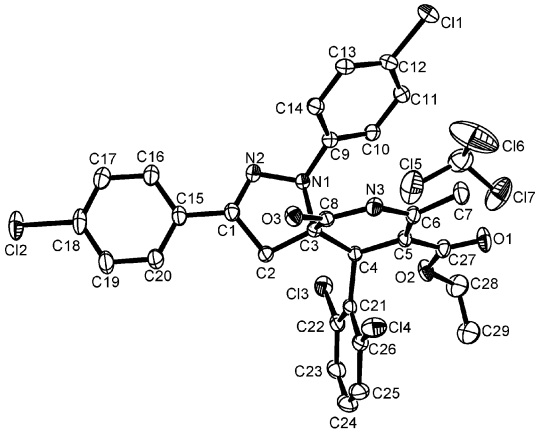
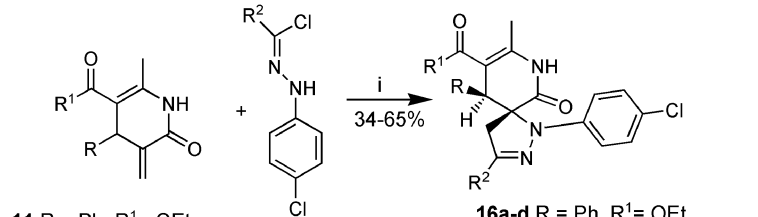


Figure 3. ORTEP structure of **19c** with a molecule of chloroform. The ellipsoids are drawn at a probability level of 20%.

Synthesis of Spiro-Fused (C-5)Isoxazolino-4′-hydro-(C-3)-quinolin-2-ones

With a focus to further enhance the scope of this strategy, we decided to perform similar syntheses employing **27**–**29** as substrates, which, in turn, could be readily synthesized from the $NaBH_4$-mediated S_N2'-S_N2' displacement reac-



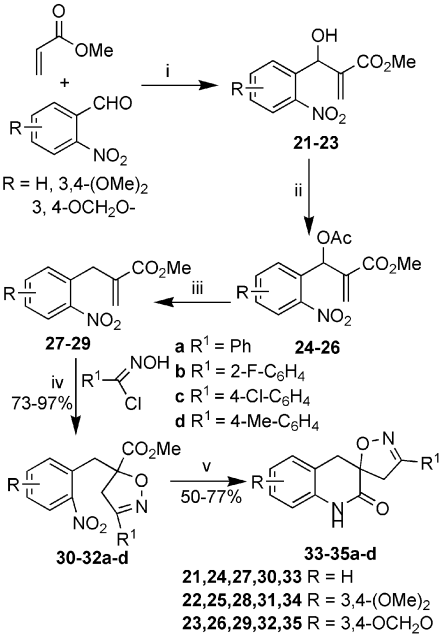
11 R = Ph, R^1= OEt
12 R = 2-F-C_6H_4, R^1= OEt
13 R = 4-Cl-C_6H_4, R^1= OEt
14 R = 2,6-Cl_2-C_6H_3, R^1= OEt
15 R = 4-Me-C_6H_4, R^1= Me

a R^2 = Ph
b R^2 = 2-F-C_6H_4
c R^2 = 4-Cl-C_6H_4
d R^2 = 4-Me-C_6H_4

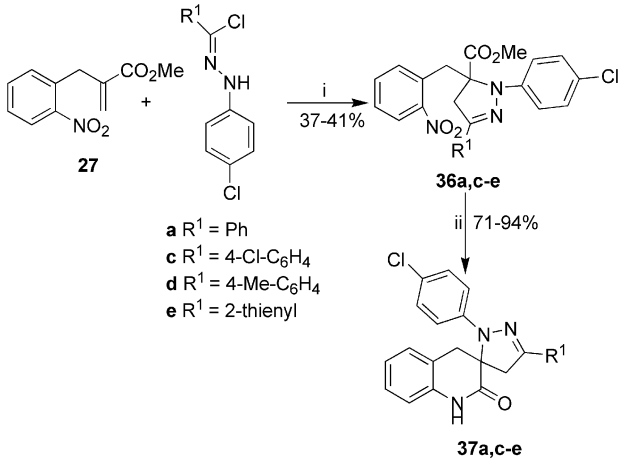
16a-d R = Ph, R^1= OEt
17a-d 2-F-C_6H_4, R^1= OEt
18a-d 4-Cl-C_6H_4, R^1= OEt
19a-d 2,6-Cl_2-C_6H_3, R^1= OEt
20a-c R = 4-Me-C_6H_4, R^1= Me

Scheme 3. Reagents and conditions: (i) Anhydrous C_6H_6, reflux, 5 d.

tion of Baylis–Hillman acetates **24**–**26** in the presence of DABCO in an aqueous medium.[2] Accordingly, **27**–**29** were prepared, and their 1,3-dipolar cycloaddition to different nitrile oxides was conducted to obtain the corresponding substituted 2-isoxazolines **30a**–**d**,**31a**–**d**,**32a**–**d** in good yields (Scheme 4). The reductive cyclization of **30a**–**d**,**31a**–**d**,**32a**–**d** in the presence of In/HCl resulted in the synthesis of spiro-fused (C-5)isoxazolino-4′-hydro-(C-3)quinolin-2-ones **33a**–**d**,**34a**–**d**,**35a**–**d** in 50–77% yields and in short reaction times. The spectral analysis confirmed the assigned structure for these compounds.



Scheme 4. Reagents and conditions: (i) DABCO, neat, room temp., 10–36 h; (ii) AcCl, pyridine, anhydrous CH_2Cl_2, 0 °C to room temp., 2–3 h; (iii) DABCO, THF/H_2O, room temp., 15 min, then $NaBH_4$, room temp., 5 min; (iv) Et_3N, anhydrous diethyl ether, –78 °C to room temp., 3–4 h; (v) In/HCl, 70 °C, 5–7 min.



Scheme 5. Reagents and conditions: (a) Et_3N, C_6H_6, reflux, 5 d; (b) Fe/AcOH, reflux, 3 h.

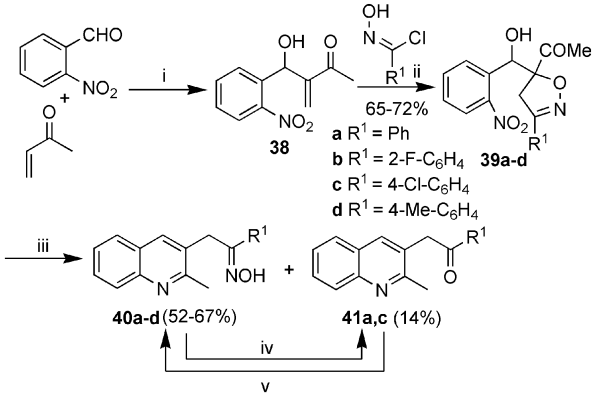
Synthesis of Spiro-Fused (C-3)Pyrazolino-4′-hydro-(C-3)-quinolin-2-ones

Having achieved the synthesis of isoxazolino-fused spirotetrahydroquinolines, we turned our attention to similar reactions of **27** with nitrile imines. The 1,3-dipolar cycloaddition of different nitrile imines to **27** resulted in the formation of pyrazolines **36a**,**c**–**e** (Scheme 5). As expected, the phenyl group originating from the hydrazine contained a chloro group at the 4-position for these analogs, too. Treatment of these pyrazolines with Fe/AcOH at reflux furnished the expected spiro-fused systems **37a**,**c**–**e** in 71–94% yields.

Attempted Synthesis of Spiro-Fused (C-5)Isoxazolino-4′-hydroxy-2-methyl-(C-3)quinolines

The reductive cyclization between an amino group and a keto moiety is more facile than that between an amino and an ester group.[3] Therefore, we envisaged that the 1,3-dipolar cycloaddition of a dipole to the Baylis–Hillman adduct of 2-nitrobenzaldehyde and methyl vinyl ketone, followed by a reductive cyclization, should lead to spiro-fused 2-methylquinolines. Consequently, Baylis–Hillman adduct **38** was prepared by a reaction between 2-nitrobenzaldehyde and methyl vinyl ketone. The 1,3-dipolar cycloaddition of different nitrile oxides to **38** led to the formation of **39a**–**d**. Unlike the cycloaddition reaction of the acrylate-based Baylis–Hillman derivatives, the reaction was stereoselective for the *syn* isomer, but a minor amount of the *anti* isomer was also formed, as evident from the NMR analysis. However, attempts to separate the two isomers by silica gel column chromatography did not give the desired results. Nevertheless, **39a**–**d** were subjected to reductive cyclization in the presence of In/HCl. Interestingly, substrate **39a** yielded two products, while all other substrates (**39b**–**d**) furnished a single product. Careful analysis of the spectroscopic data of the common product afforded by all the substrates led to the assignment of its structure as **40a**–**d**. The presence of a singlet signal for the aromatic proton indicated that the hydroxy group present at the 4-position of the quinoline nucleus was lost during the reductive cyclization. However, the second product isolated for **39a** was established as **41a**. We presumed that after the reductive cyclization, the isoxazoline ring of the generated spiro-fused (C-5)isoxazolino-4′-hydroxy-2-methyl-(C-3)quinoline underwent ring cleavage to produce an unstable intermediate, which dehydrated to produce oxime **40**. In the presence of HCl, the oxime may have been transformed into **41a**. In order to ascertain whether or not **41a** was derived from **40a**, **40a** was treated with 35% aqueous HCl at reflux temperature. The reaction was completed in 1 h to give the product, which was identical to **41a** in all respects. In the light of this observation, we desired to examine whether such transformations are limited to **40a** or if other substrates undergo similar transformations. Consequently, **40c** was heated with 35% aqueous HCl in aqueous THF and, to our satisfaction, the corresponding product **41c** was formed in 1 h. Furthermore, we envisaged that the treatment of **41** with hydroxylamine

hydrochloride should result in the formation of **40**. Thus, the reaction of **41a**,**c** with hydroxylamine hydrochloride in methanol at reflux furnished the expected products **40a**,**c**, respectively (Scheme 6). This transformation provided additional evidence that products **40a**–**d** were oximes. In contrast, the 1,3-dipolar cycloadditions of nitrile imines with **38** were unsuccessful, leading to a mixture of unidentified products.



Scheme 6. Reagents and conditions: (i) DABCO, neat, 0 °C, 10 min; (ii) Et_3N, anhydrous diethyl ether, –78 °C to room temp., 3 h; (iii) In/HCl, 70 °C, 5–7 min; (iv) 35% aqueous HCl, THF/H_2O, reflux, 1 h; (v) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, reflux, 1 h.

Conclusions

We have disclosed a straightforward and general approach for the diastereoselective synthesis of spiro-fused (C-5)-isoxazolino- or (C-3)pyrazolino-(C-3)quinolin-2-ones[17] from the Baylis–Hillman adducts of 2-nitobenzaldehyde by sequential 1,3-dipolar cycloaddition and reductive cyclization. This synthetic achievement involves simple steps and the use of readily available starting materials. Furthermore, in our hands, the *N*-chlorosuccinimide-mediated synthesis of hydrazonyl chlorides invariably led to the regioselective chlorination of the phenyl ring derived from phenyl hydrazine. The synthesis of spiro-fused (C-3)pyrazolino-(C-3)pyridin-2-ones accomplished during this study was stereo- and regioselective and illustrated that regioselective chlorination of the phenyl ring of the hydrazine unit occurred. The detailed work encompassed herein illustrates the scope and limitations of the strategy.

Experimental Section

General: Melting points are uncorrected and were determined in capillary tubes with a precision melting point apparatus containing silicon oil. IR spectra were recorded with a Perkin–Elmer Spectrum RX I FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with either a Bruker DPX-200 FT or a Bruker Avance DRX-300 spectrometer with TMS as an internal standard (chemical shifts in δ). The ^{13}C NMR spectra of 2-fluorophenyl derivatives display additional signals due to the C-F couplings. As **37c** was only partially soluble in [D_6]DMSO, its ^{13}C NMR spectrum could not be recorded. The ES and FAB mass spectra were recorded with a MICROMASS Quadro-II LCMS or a JEOL SX/102/DA 6000 system. The HR mass spectra were recorded in the EI mode with a JEOL system or as DART-HR (in the ES+ mode) with a JEOL-AccuTOF JMS-T100LC mass spectrometer with a DART (Direct Analysis in Real Time) source. Elemental analyses were performed with a Carlo Erba 108 or an Elementar Vario EL III microanalyzer.

General Procedure for the Synthesis of 3a–d, 4a–d, 30a–d, 32a–d, and 39a–d, as Exemplified for 3a: To a stirred solution of **1a** (1.0 g, 3.98 mmol) and *N*-hydroxybenzenecarboximidoyl chloride (0.926 g, 5.98 mmol) in anhydrous diethyl ether (15 mL) was added dropwise a solution of Et_3N (0.83 mL, 5.98 mmol) in anhydrous diethyl ether (5 mL) at –78 °C. The reaction was allowed to continue at room temperature for 3 h. The reaction mixture was then quenched with water (30 mL), and the ethereal layer was separated. The aqueous layer was again extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to yield a crude oily residue. The crude product was then purified by column chromatography on silica gel (60–120 mesh) with hexane/ethyl acetate (90:10, v/v) as the eluent to afford 1.24 g (85%) of **3a** as a white solid.

Ethyl 5-[Hydroxy(2-nitrophenyl)methyl]-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (3a): M.p. 139–142 °C. R_f = 0.32 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1734 (CO_2Et), 3438 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 3.38 (d, J = 5.7 Hz, 1 H, CHO*H*), 3.68 (d, J = 0.8 Hz, 2 H, CH_2), 4.21 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.07 (d, J = 5.7 Hz, 1 H, C*H*OH), 7.35–7.45 (m, 3 H, ArH), 7.48–7.51 (m, 1 H, ArH), 7.58–7.63 (m, 2 H, ArH), 7.67 (d, J = 7.6 Hz, 1 H, ArH), 7.89–7.93 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 40.5, 62.8, 69.3, 91.5, 124.6, 127.0, 127.7, 128.4, 128.9, 129.4, 129.5, 130.2, 130.7, 132.7, 133.3, 149.3, 157.0, 170.8 ppm. MS (ES^+): *m*/*z* (%) = 371.0 (80) $[M + H]^+$. $C_{19}H_{18}N_2O_6$ (exact mass: 370.1165): calcd. C 61.62, H 4.90, N 7.56; found C 61.46, H 5.07, N 7.51.

Ethyl 5-[(3,4-Dimethoxy-2-nitrophenyl)(hydroxy)methyl]-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (4a): Yield 73% (0.727 g from 0.725 g) as a white solid, m.p. 100–101 °C. R_f = 0.25 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1738 (CO_2Et), 3519 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 3.28 (d, J = 5.2 Hz, 1 H, CHO*H*), 3.51 (d, J = 17.5 Hz, 1 H, C*H*H), 3.64 (d, J = 17.5 Hz, 1 H, C*H*H), 3.92 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.27 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.24 (d, J = 5.2 Hz, 1 H, C*H*OH), 7.36–7.40 (m, 3 H, ArH), 7.44 (s, 1 H, ArH), 7.51–7.56 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 41.0, 56.4, 56.8, 62.8, 69.2, 91.5, 107.5, 111.5, 126.9, 127.0, 127.7, 128.4, 128.8, 128.9, 130.7, 141.6, 148.7, 153.3, 156.8, 171.3 ppm. MS (ES^+): *m*/*z* (%) = 430.8 (45) $[M + H]^+$. $C_{21}H_{22}N_2O_8$ (exact mass: 430.1376): calcd. C 58.60, H 5.15, N 6.51; found C 58.37, H 5.27, N 6.47.

Methyl 5-(2-Nitrobenzyl)-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (30a): Yield 91% (0.85 g from 0.62 g) as a white solid, m.p. 98–99 °C. R_f = 0.37 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1754 (CO_2Me) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.28 (d, J = 17.4 Hz, 1 H, C*H*H), 3.68 (d, J = 14.5 Hz, 1 H, C*H*H), 3.74 (d, J = 14.5 Hz, 1 H, CH*H*), 3.76 (s, 3 H, CO_2CH_3), 3.84 (d, J = 17.4 Hz, 1 H, CH*H*), 7.36–7.42 (m, 4 H, ArH), 7.50–7.63 (m, 4 H, ArH), 7.88 (d, J = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.2, 42.9, 53.3, 88.6, 124.8, 126.9, 127.7, 128.6, 128.8, 128.9, 129.4, 130.2, 130.6, 132.9, 133.8, 150.6, 156.9, 171.6 ppm. MS (ES^+): *m*/*z* (%) = 341.0 (100) $[M + H]^+$. $C_{18}H_{16}N_2O_5$ (exact mass: 340.1059): calcd. C 63.52, H 4.74, N 8.23; found C 63.38, H 4.56, N 8.02.

Methyl 5-(3,4-Dimethoxy-2-nitrobenzyl)-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (31a): Yield 91% (1.36 g from 1.0 g) as a white solid, m.p. 129–131 °C. R_f = 0.37 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1738 (CO_2Me) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.24 (d, J = 17.4 Hz, 1 H, C*H*H), 3.65 (d, J = 14.6 Hz, 1 H, C*H*H), 3.79 (s, 3 H, CO_2CH_3), 3.81 (d, J = 14.6 Hz, 1 H, CH*H*), 3.87 (d, J = 17.4 Hz, 1 H, CH*H*), 3.91 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 7.06 (s, 1 H, ArH), 7.33–7.44 (m, 3 H, ArH), 7.52 (s, 1 H, ArH), 7.56–7.59 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1, 42.2, 53.3, 56.4, 56.7, 89.0, 108.0, 115.1, 124.4, 126.9, 127.0, 128.8, 128.9, 130.5, 130.6, 142.6, 148.2, 152.8, 157.3, 171.7 ppm. MS (ES^+): m/z (%) = 401.1 (100) $[M + H]^+$. $C_{20}H_{20}N_2O_7$ (exact mass: 400.1271): calcd. C 60.00, H 5.03, N 7.00; found C 59.79, H 5.21, N 7.10.

Methyl 5-[(6-Nitrobenzo[*d*][1,3]dioxol-5-yl)methyl]-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (32a): Yield 96% (0.73 g from 0.50 g) as a light yellow solid, m.p. 133–135 °C. R_f = 0.30 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1734 (CO_2Me) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.25 (d, J = 17.4 Hz, 1 H, C*H*H), 3.63 (d, J = 14.6 Hz, 1 H, C*H*H), 3.70 (d, J = 14.6 Hz, 1 H, CH*H*), 3.78 (s, 3 H, CO_2CH_3), 3.85 (d, J = 17.4 Hz, 1 H,CH*H*), 6.08 (d, J = 3.2 Hz, 2 H, OCH_2O), 7.02 (s, 1 H, ArH), 7.37–7.51 (m, 4 H, ArH), 7.59 (t, J = 5.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.4, 42.5, 53.3, 88.8, 103.1, 105.6, 112.5, 126.3, 126.9, 127.7, 128.7, 129.0, 130.2, 130.7, 144.4, 147.5, 151.6, 157.2, 171.6 ppm. MS (ES^+): m/z (%) = 401.9 (60) $[M + H]^+$. $C_{19}H_{16}N_2O_7$ (exact mass: 400.1271): calcd. C 59.38, H 4.20, N 7.29; found C 59.27, H 4.01, N 7.39.

1-{5-[Hydroxy(2-nitrophenyl)methyl]-3-phenyl-4,5-dihydroisoxazol-5-yl}ethanone (39a): Yield 68% (1.10 g from 1.05 g) as a white solid, m.p. 113–115 °C. R_f = 0.35 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1719 ($COCH_3$), 3424 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, $COCH_3$), 3.30 (d, J = 5.6 Hz, 1 H, OH), 3.41 (d, J = 17.6 Hz, 1 H, C*H*H), 3.58 (d, J = 17.6 Hz, 1 H, CH*H*), 6.02 (d, J = 5.2 Hz, 1 H, C*H*OH), 7.35–7.41 (m, 2 H, ArH), 7.46–7.51 (m, 2 H, ArH), 7.56–7.59 (m, 2 H, ArH), 7.65–7.70 (m, 1 H, ArH), 7.93–7.96 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 40.5, 69.3, 96.2, 124.6, 126.9, 127.0, 128.3, 128.8, 128.9, 129.4, 129.7, 130.9, 133.1, 133.6, 148.7, 157.5, 211.4 ppm. MS (ES^+): m/z (%) = 341.0 (70) $[M + H]^+$. $C_{18}H_{16}N_2O_5$ (exact mass: 340.1059): calcd. C 63.52, H 4.74, N 8.23; found C 63.37, H 4.92, N 8.15.

General Procedure for the Synthesis of 7a–e, 8a, 36a,c–e, 16a–d, 19a–d, and 20a–c, as Exemplified for 7d: To a stirred solution of **1d** (0.20 g, 0.80 mmol) and *N*-(4-chlorophenyl)-4-methylbenzenecarbohydrazonoyl chloride (0.67 g, 2.40 mmol) in anhydrous benzene (15 mL) was added Et_3N (0.33 mL, 2.40 mmol) at room temperature whilst stirring. The reaction mixture was then refluxed at 80 °C for 5 d. After completion of the reaction, as evident by TLC analysis, the reaction was quenched with water (50 mL), and the resulting mixture was partitioned in a separating funnel. The aqueous layer was separated and further extracted with EtOAc (3 × 40 mL). The organic layers were pooled, washed with brine (50 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo to afford an oily residue, which was purified by silica gel (60–120 mesh) column chromatography. Elution with hexane/EtOAc (95:5, v/v) furnished 0.14 g (36%) of **7d** as a yellow solid.

Ethyl 1-(4-Chlorophenyl)-5-[hydroxy(2-nitrophenyl)methyl]-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (7d): M.p. 159–161 °C. R_f = 0.70 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1736 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.37 (s, 3 H, $ArCH_3$), 3.23 (s, 1 H, CHO*H*), 3.51 (d, J = 17.4 Hz, 1 H, C*H*H), 3.88 (d, J = 17.4 Hz, 1 H, CH*H*), 3.98 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.43 (s, 1 H, C*H*OH), 7.17 (d, J = 7.4 Hz, 2 H, ArH), 7.25–7.26 (m, 4 H, ArH), 7.35–7.45 (m, 2 H, ArH), 7.51 (d, J = 7.4 Hz, 2 H, ArH), 7.86–788 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 21.6, 41.9, 62.5, 67.4, 119.0, 124.6, 126.1, 127.0, 128.9, 129.2, 129.4, 130.0, 133.0, 139.7, 143.0, 148.6, 149.4, 171.1 ppm. MS (ES^+): m/z (%) = 494.2 (100) $[M + H]^+$, 496.2 (33) $[M + 3]^+$. $C_{26}H_{24}ClN_3O_5$ (exact mass: 493.1404): calcd. C 63.22, H 4.90, N 8.51; found C 62.96, H 4.74, N 8.36.

Ethyl 1-(4-Chlorophenyl)-5-[(4,5-dimethoxy-2-nitrophenyl)(hydroxy)-methyl]-3-phenyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (8a): Yield 51% (0.44 g from 0.50 g) as a pale yellow solid, m.p. 107–108 °C. R_f = 0.80 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1724 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 3.37 (s, J = 4.08 Hz, 1 H, CHO*H*), 3.52 (d, J = 17.5 Hz, 1 H, C*H*H), 3.74 (d, J = 17.5 Hz, 1 H, CH*H*), 3.88 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.57 (s, 1 H, C*H*OH), 7.24–7.28 (m, 3 H, ArH), 7.32–7.36 (m, 3 H, ArH), 7.44–7.48 (m, 3 H, ArH), 7.52–7.55 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 42.8, 56.3, 56.4, 62.7, 68.2, 107.6, 111.9, 117.1, 118.0, 125.9, 126.0, 128.7, 128.8, 129.0, 129.3, 131.4, 141.3, 142.9, 147.2, 148.5, 153.0, 171.8 ppm. MS (ES^+): m/z (%) = 540.0 (100) $[M + H]^+$. $C_{27}H_{26}ClN_3O_7$ (exact mass: 539.1459): calcd. C 60.06, H 4.85, N 7.78; found C 59.84, H 4.72, N 7.89.

Methyl 1-(4-Chlorophenyl)-5-(2-nitrobenzyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (36a): Yield 36% (0.37 g from 0.50 g) as a pale yellow solid, m.p. 143–145 °C. R_f = 0.75 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1735 (CO_2Me) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.37 (d, J = 17.6 Hz, 1 H, CH*H*), 3.58 (d, J = 17.6 Hz, 1 H, C*H*H), 3.66 (d, J = 14.7 Hz, 1 H, CH*H*), 3.74 (s, 3 H, CO_2Me), 4.00 (d, J = 14.7 Hz, 1 H, C*H*H), 7.07–7.10 (m, 1 H, ArH), 7.16 (d, J = 7.7 Hz, 1 H, ArH), 7.25–7.28 (m, 6 H, ArH), 7.30–7.31 (m, 1 H, ArH), 7.34–7.37 (m, 1 H, ArH), 7.39–7.42 (m, 2 H, ArH), 7.72–7.76 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.8, 44.3, 53.6, 72.3, 114.2, 115.2, 124.7, 125.4, 127.0, 128.5, 128.9, 129.4, 129.6, 129.9, 132.7, 133.6, 135.0, 141.6, 145.7, 151.1, 172.8 ppm. MS (ES^+): m/z (%) = 450.1 (50) $[M + H]^+$. $C_{24}H_{20}ClN_3O_4$ (exact mass: 449.1142): calcd. C 64.07, H 4.48, N 9.34; found C 63.90, H 4.56, N 9.21.

Ethyl 1-(4-Chlorophenyl)-8-methyl-6-oxo-3,10-diphenyl-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (16a): Yield 47% (0.09 g from 0.10 g) as a white solid, m.p. 183–185 °C. R_f = 0.40 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1639 (CONH), 1702 (CO_2Et) 3448 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.93 (s, 3 H, CH_3), 3.05 (d, J = 16.9 Hz, 1 H, C*H*H), 3.56 (d, J = 16.9 Hz, 1 H, CH*H*), 4.03 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.62 (s, 1 H, CH), 7.00 (s, 1 H, ArH), 7.19 (t, J = 8.8 Hz, 4 H, ArH), 7.27–7.33 (m, 7 H, ArH), 7.43 (s, 1 H, NH), 7.58 (s, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 18.8, 40.9, 48.6, 60.3, 75.4, 109.0, 126.3, 127.4, 127.8, 128.5, 128.6, 129.0, 129.5, 129.6, 131.1, 131.7, 133.7, 134.3, 139.7, 141.5, 143.5, 152.3, 166.0, 168.0 ppm. MS (ES^+): m/z (%) = 500.1 (100) $[M + H]^+$, 523.2 (35) $[M + Na]^+$. $C_{29}H_{26}ClN_3O_3$ (exact mass: 499.1663): calcd. C 69.66, H 5.24, N 8.40; found C 69.45, H 5.18, N 8.49.

Ethyl 1-(4-Chlorophenyl)-3-(2-fluorophenyl)-8-methyl-6-oxo-10-phenyl-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (16b): Yield 47% (0.12 g from 0.13 g) as a white solid, m.p. 210–212 °C. R_f = 0.25 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1667 (CONH), 1704 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.98 (s, 3 H, CH_3), 3.29 (d, J = 16.3 Hz, 1 H, C*H*H), 3.64 (d, J = 16.3 Hz, 1 H, CH*H*), 4.03 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.58 (s, 1 H, CH), 7.12 (t, J = 7.5 Hz, 3 H, ArH),

7.18–7.27 (m, 9 H, ArH), 7.40 (s, 1 H, NH), 7.74 (t, J = 7.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 18.8, 43.5, 48.0, 60.5, 74.4, 108.8, 116.2, 124.3, 125.2, 127.7, 128.5, 128.9, 130.9, 139.2, 142.9, 143.1, 147.4, 166.2, 168.8 ppm. MS (ES^+): m/z (%) = 518.0 (100) $[M + H]^+$. $C_{29}H_{25}ClFN_3O_3$ (exact mass: 517.1568): calcd. C 67.24, H 4.86, N 8.11; found C 67.35, H 4.76, N 8.02.

Ethyl 1,3-Bis(4-chlorophenyl)-8-methyl-6-oxo-10-phenyl-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (16c): Yield 34% (0.14 g from 0.21 g) as a white solid, m.p. 228–230 °C. R_f = 0.41 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1643 (CONH), 1699 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.95 (s, 3 H, CH_3), 3.03 (d, J = 16.9 Hz, 1 H, C*H*H), 3.51 (d, J = 16.9 Hz, 1 H, CH*H*), 4.04 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.55 (s, 1 H, CH), 7.06–7.12 (m, 3 H, ArH), 7.17–7.31 (m, 9 H, NH merged with ArH), 7.49 (d, J = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 19.1, 41.6, 48.8, 60.8, 75.0, 109.1, 126.3, 127.1, 127.7, 128.1, 128.7, 129.2, 129.4, 130.6, 131.8, 135.5, 139.8, 143.3, 143.6, 150.4, 166.3, 168.7 ppm. MS (ES^+): m/z (%) = 534.1 (100) $[M + H]^+$. $C_{29}H_{25}Cl_2N_3O_3$ (exact mass: 533.1273): calcd. C 65.17, H 4.71, N 7.86; found C 65.32, H 4.84, N 7.68.

Ethyl 1-(4-Chlorophenyl)-8-methyl-6-oxo-10-phenyl-3-(4-methylphenyl)-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (16d): Yield 42% (0.26 g from 0.34 g) as a white solid, m.p. 231–233 °C. R_f = 0.48 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1641 (CONH), 1701 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.95 (s, 3 H, CH_3), 2.35 (s, 3 H, $ArCH_3$), 3.03 (d, J = 16.9 Hz, 1 H, C*H*H), 3.56 (d, J = 16.9 Hz, 1 H, CH*H*), 4.04 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.53 (s, 1 H, CH), 7.13 (d, J = 7.9 Hz, 5 H, ArH), 7.23 (m, 7 H, NH merged with ArH), 7.47 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 18.9, 21.5, 41.5, 48.4, 60.5, 74.5, 108.9, 126.1, 126.2, 127.7, 128.4, 128.5, 129.0, 129.3, 131.3, 139.5, 139.6, 143.1, 151.5, 161.1, 168.7 ppm. MS (ES^+): m/z (%) = 514.1 (100) $[M + H]^+$. HRMS (EI): calcd. for $C_{30}H_{28}ClN_3O_3$ 513.1819; found 513.1804.

Ethyl 1-(4-Chlorophenyl)-10-(2-fluorophenyl)-8-methyl-6-oxo-3-phenyl-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (17a): Yield 48% (0.12 g from 0.14 g) as a white solid, m.p. 180–182 °C. R_f = 0.36 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1639 (CONH), 1705 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.94 (s, 3 H, CH_3), 3.04 (d, J = 16.7 Hz, 1 H, C*H*H), 3.60 (d, J = 16.7 Hz, 1 H, CH*H*), 4.05 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.16 (s, 1 H, CH), 7.03–7.11 (m, 4 H, ArH), 7.19–7.44 (m, 7 H, ArH), 7.59–7.62 (m, 3 H, ArH and NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.8, 40.5, 60.3, 75.2, 116.0, 124.9, 126.3, 126.7, 127.4, 128.3, 128.6, 128.8, 129.5, 131.0, 131.6, 133.7, 134.4, 141.4, 144.7, 152.6, 165.8, 167.4 ppm. MS (ES^+): m/z (%) = 518.1 (100) $[M + H]^+$. $C_{29}H_{25}ClFN_3O_3$ (exact mass: 517.1568): calcd. C 67.24, H 4.86, N 8.11; found C 66.96, H 4.74, N 8.20.

Ethyl 1-(4-Chlorophenyl)-3,10-bis(2-fluorophenyl)-8-methyl-6-oxo-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (17b): Yield 51% (0.27 g from 0.30 g) as a white solid, m.p. 231–233 °C. R_f = 0.37 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1643 (CONH), 1708 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.96 (s, 3 H, CH_3), 3.14 (d, J = 16.7 Hz, 1 H, C*H*H), 3.72 (d, J = 16.7 Hz, 1 H, CH*H*), 4.06 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.99 (s, 1 H, CH), 7.04–7.14 (m, 6 H, ArH), 7.20–7.30 (m, 6 H, ArH and NH), 7.80 (t, J = 7.7 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 18.7, 40.6, 60.4, 74.8, 115.7, 116.4, 124.8, 126.6, 126.5, 127.7, 128.6, 128.4, 129.7, 129.8, 130.0, 132.4, 133.5, 135.5, 143.7, 144.4, 150.5, 165.6, 167.5 ppm. MS (ES^+): m/z (%) = 536.1 (100) $[M + H]^+$. $C_{29}H_{24}ClF_2N_3O_3$ (exact mass: 535.1474): calcd. C 64.99, H 4.51, N 7.84; found C 65.15, H 4.38, N 7.61.

Ethyl 1,3-Bis(4-chlorophenyl)-10-(2-fluorophenyl)-8-methyl-6-oxo-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (17c): Yield 53% (0.22 g from 0.41 g) as a white solid, m.p. 218–220 °C. R_f = 0.37 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1644 (CONH), 1703 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.94 (s, 3 H, CH_3), 2.95 (d, J = 16.7 Hz, 1 H, C*H*H), 3.58 (d, J = 16.7 Hz, 1 H, CH*H*), 4.06 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.99 (s, 1 H, CH), 7.01–7.08 (m, 4 H, ArH), 7.21–7.32 (m, 7 H, ArH and NH), 7.52 (d, J = 7.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.8, 40.9, 60.5, 74.6, 115.8, 116.1, 124.9, 126.3, 126.7, 127.4, 128.4, 128.8, 129.6, 129.7, 130.3, 132.1, 135.2, 143.3, 144.3, 150.7, 165.7, 167.8 ppm. MS (ES^+): m/z (%) = 552.2 (100) $[M + H]^+$. DART-HRMS: calcd. for $C_{29}H_{25}Cl_2FN_3O_3$ $[M + H]^+$ 552.12570; found 552.12186.

Ethyl 1-(4-Chlorophenyl)-10-(2-fluorophenyl)-8-methyl-6-oxo-3-(4-methylphenyl)-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (17d): Yield 66% (0.12 g from 0.10 g) as a white solid, m.p. 222–224 °C. R_f = 0.38 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1639 (CONH), 1705 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.94 (s, 3 H, CH_3), 2.35 (s, 3 H, $ArCH_3$), 2.96 (d, J = 16.7 Hz, 1 H, C*H*H), 3.61 (d, 1 H, J = 16.7 Hz, CH*H*), 4.04 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.98 (s, 1 H, CH), 7.03–7.07 (m, 4 H, ArH), 7.14 (d, J = 8.1 Hz, 2 H, ArH), 7.22–7.27 (m, 5 H, ArH and NH), 7.49 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.8, 21.5, 41.2, 60.5, 74.3, 115.7, 124.9, 126.2, 126.6, 126.8, 128.3, 129.0, 129.5, 129.6, 131.9, 139.6, 143.8, 144.4, 152.1, 165.8, 168.0 ppm. MS (ES^+): m/z (%) = 532.1 (100) $[M + H]^+$. DART-HRMS: calcd. for $C_{30}H_{27}ClFN_3O_3$ $[M + H]^+$ 532.18032; found 532.17799.

Ethyl 1,10-Bis(4-chlorophenyl)-8-methyl-6-oxo-3-phenyl-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (18a): Yield 47% (0.17 g from 0.20 g) as a white solid, m.p. 148–150 °C. R_f = 0.40 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1643 (CONH), 1699 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.92 (s, 3 H, CH_3), 3.01 (d, J = 16.8 Hz,1 H, C*H*H), 3.56 (d, J = 16.8 Hz, 1 H, CH*H*), 4.05 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.60 (s, 1 H, CH), 7.11 (t, J = 8.5 Hz, 3 H, ArH), 7.20–7.29 (m, 5 H, ArH), 7.31–7.35 (m, 3 H, ArH), 7.44 (s, 1 H, NH), 7.44–7.61 (m, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3, 18.8, 48.0, 60.4, 75.2, 108.6, 126.0, 126.3, 127.5, 128.5, 128.7, 129.3, 129.6, 129.8, 131.0, 131.5, 133.6, 133.8, 138.2, 141.4, 143.4, 151.1, 152.3, 165.8, 167.8 ppm. MS (ES^+): m/z (%) = 534.1 (100) $[M + H]^+$. $C_{29}H_{25}Cl_2N_3O_3$ (exact mass: 533.1273): calcd. C 65.17, H 4.71, N 7.86; found C 65.39, H 4.63, N 7.70.

Ethyl 1,10-Bis(4-chlorophenyl)-3-(2-fluorophenyl)-8-methyl-6-oxo-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (18b): Yield 57% (0.14 g from 0.13 g) as a white solid, m.p. 198–200 °C. R_f = 0.38 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1645 (CONH), 1697 (CO_2Et) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.97 (s, 3 H, CH_3), 3.24 (d, J = 15.6 Hz, 1 H, C*H*H), 3.64 (d, J = 15.6 Hz, 1 H, CH*H*), 4.03 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.57 (s, 1 H, CH), 7.03–7.10 (m, 6 H, ArH), 7.16–7.29 (m, 6 H, ArH and NH), 7.71–7.79 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 18.8, 43.6, 47.3, 60.6, 74.2, 108.3, 124.5, 125.0, 128.6, 128.8, 129.1, 129.8, 130.9, 133.6, 133.6, 137.7, 142.9, 143.1, 166.0, 168.5 ppm. MS (ES^+): m/z (%) = 552.3 (100) $[M + H]^+$. $C_{29}H_{24}Cl_2FN_3O_3$ (exact mass: 551.1179): calcd. C 63.05, H 4.38, N 7.61; found C 63.26, H 4.46, N 7.83.

Ethyl 1,3,10-Tris(4-chlorophenyl)-8-methyl-6-oxo-1,2,7-triazaspiro-[4.5]deca-2,8-diene-9-carboxylate (18c): Yield 52% (0.30 g from 0.33 g) as a white solid, m.p. 138–140 °C. R_f = 0.40 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1643 (CONH), 1699 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.93 (s, 3 H, CH_3), 3.00 (d, J = 16.8 Hz, 1 H, C*H*H), 3.54 (d, J = 16.8 Hz, 1 H, CH*H*), 4.04 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.51 (s, 1 H, CH), 7.03 (d, J = 8.4 Hz, 2 H, ArH), 7.14–7.32 (m, 8 H, ArH), 7.45 (d, J = 8.4 Hz, 2 H, ArH), 7.65 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 18.9, 41.4, 48.0, 60.7, 74.5, 108.5, 126.0, 127.3, 128.5, 128.9, 129.3, 129.7, 130.1, 131.7, 133.7, 135.3, 138.0, 143.1, 143.2, 150.0, 165.8, 168.0 ppm. MS (ES^+): m/z (%) = 568.0 (100) $[M + H]^+$. $C_{29}H_{24}Cl_3N_3O_3$ (exact mass: 567.0883): calcd. C 61.23, H 4.25, N 7.39; found C 61.46, H 4.10, N 7.47.

Ethyl 1,10-Bis(4-chlorophenyl)-8-methyl-6-oxo-3-(4-methylphenyl)-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (18d): Yield 49% (0.18 g from 0.20 g) as a white solid, m.p. 223–225 °C. R_f = 0.41 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1677 (CONH), 1706 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.95 (s, 3 H, CH_3), 2.36 (s, 3 H, $ArCH_3$), 2.99 (d, J = 16.9 Hz, 1 H, C*H*H), 3.57 (d, J = 16.9 Hz, 1 H, CH*H*), 4.05 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.51 (s, 1 H, CH), 7.05 (d, J = 8.2 Hz, 2 H, ArH), 7.14–7.26 (m, 9 H, NH merged with ArH), 7.47 (d, J = 7.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3, 18.9, 21.5, 41.6, 47.8, 60.6, 74.3, 108.5, 126.0, 126.2, 128.4, 128.9, 129.2, 129.4, 129.8, 131.4, 133.6, 138.2, 139.7, 143.3, 143.5, 151.4, 165.9, 168.4 ppm. MS (FAB^+) m/z (%) = 548.1 (100) $[M + H]^+$. $C_{30}H_{27}Cl_2N_3O_3$ (exact mass: 547.1429): calcd. C 65.70, H 4.96, N 7.66; found C 65.89, H 5.14, N 7.87.

Ethyl 1-(4-Chlorophenyl)-10-(2,6-dichlorophenyl)-8-methyl-6-oxo-3-phenyl-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (19a): Yield 34% (0.14 g from 0.25 g) as a white solid, m.p. 250–251 °C. R_f = 0.49 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1635 (CONH), 1700 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.95 (s, 3 H, CH_3), 2.80 (d, J = 16.4 Hz, 1 H, C*H*H), 3.71 (d, J = 16.4 Hz, 1 H, CH*H*), 4.00 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.77 (s, 1 H, CH), 7.04 (d, J = 9.5 Hz, 1 H, ArH), 7.16 (d, J = 8.0 Hz, 1 H, ArH), 7.23–7.26 (m, 5 H, ArH), 7.32–7.43 (m, 3 H, ArH), 7.43 (d, J = 8.0 Hz, 1 H, ArH), 7.58–7.60 (m, 2 H, NH and ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.2, 40.3, 45.4, 60.2, 74.7, 102.7, 125.8, 126.4, 127.4, 128.6, 129.0, 129.5, 129.8, 131.3, 133.6, 136.6, 146.0, 153.1, 166.1 ppm. MS (ES^+) m/z (%) = 568.0 (100) $[M + H]^+$. $C_{29}H_{24}Cl_3N_3O_3$ (exact mass: 567.0883): calcd. C 61.23, H 4.25, N 7.39; found C 60.98, H 4.37, N 7.51.

Ethyl 1-(4-Chlorophenyl)-10-(2,6-dichlorophenyl)-3-(2-fluorophenyl)-8-methyl-6-oxo-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (19b): Yield 45% (0.19 g from 0.25 g) as a white solid, m.p. 223–225 °C. R_f = 0.49 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1646 (CONH), 1703 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.01 (s, 3 H, CH_3), 2.85, 2.88 (dd, ^1J = 17.4, ^2J = 1.8 Hz, 1 H, C*H*H), 3.86, 3.90 (dd, ^1J = 17.4, ^2J = 1.8 Hz, 1 H, CH*H*), 4.01 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.73 (d, J = 1.1 Hz, 1 H, CH), 6.98–7.04 (m, 1 H, ArH), 7.09–7.16 (m, 3 H, ArH), 7.33–7.37 (m, 7 H, ArH and NH), 7.81–7.86 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.2, 43.3, 46.2, 60.3, 73.4, 102.8, 116.5, 119.9, 124.3, 125.7, 128.4, 128.7, 129.1, 129.8, 131.5, 135.2, 136.4, 138.3, 143.1, 145.7, 148.4, 165.9, 167.6 ppm. MS (ES^+): m/z (%) = 586.0 (100) $[M + H]^+$. $C_{29}H_{23}Cl_3FN_3O_3$ (exact mass: 585.0789): calcd. C 59.35, H 3.95, N 7.16; found C 59.13, H 4.11, N 7.19.

Ethyl 1,3-Bis(4-chlorophenyl)-10-(2,6-dichlorophenyl)-8-methyl-6-oxo-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (19c): Yield 38% (0.07 g from 0.10 g) as a white solid, m.p. 240–242 °C. R_f = 0.34 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1646 (CONH), 1702 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.99 (s, 3 H, CH_3), 2.70 (d, J = 16.6 Hz, 1 H, C*H*H), 3.75 (d, J = 16.6 Hz, 1 H, CH*H*), 4.01 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.75 (s, 1 H, CH), 7.00 (s, 1 H, ArH), 7.15 (t, J = 8.0 Hz, 1 H, ArH), 7.26–7.31 (m, 7 H, ArH and NH), 7.35–7.38 (m, 1 H, ArH), 7.51 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.2, 46.4, 60.4, 73.5, 102.7, 125.8, 127.5, 128.4, 128.8, 129.2, 129.8, 130.3, 131.7, 135.2, 136.4, 138.3, 143.2, 145.6, 150.9, 165.9, 167.1 ppm. MS (ES^+): m/z (%) = 601.9 (80) $[M + H]^+$. HRMS (EI): calcd. for $C_{29}H_{23}Cl_4N_3O_3$ 601.04935; found 601.05116.

Ethyl 1-(4-Chlorophenyl)-10-(2,6-dichlorophenyl)-8-methyl-3-(4-methylphenyl)-6-oxo-1,2,7-triazaspiro[4.5]deca-2,8-diene-9-carboxylate (19d): Yield 36% (0.06 g from 0.10 g) as a white solid, m.p. 228–230 °C. R_f = 0.50 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1635 (CONH), 1700 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.99 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.72 (d, J = 16.6 Hz, 1 H, C*H*H), 3.76 (d, J = 16.6 Hz, 1 H, CH*H*), 4.00 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.76 (d, J = 1.2 Hz, 1 H, CH), 6.99 (s, 1 H, ArH), 7.14 (t, J = 7.7 Hz, 3 H, ArH), 7.25–7.29 (m, 5 H, ArH and NH), 7.33–7.37 (m, 1 H, ArH), 7.48 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.2, 21.6, 41.5, 46.4, 60.3, 73.1, 102.7, 125.8, 126.3, 128.3, 128.7, 129.0, 129.3, 129.8, 131.4, 135.1, 136.6, 138.4, 139.5, 143.6, 145.8, 152.2, 166.0, 167.5 ppm. MS (ES^+): m/z (%) = 582.0 (100) $[M + H]^+$. $C_{30}H_{26}Cl_3N_3O_3$ (exact mass: 581.1040): calcd. C 61.81, H 4.50, N 7.21; found C 61.66, H 4.63, N 7.08.

9-Acetyl-1-(4-chlorophenyl)-8-methyl-10-(4-methylphenyl)-3-phenyl-1,2,7-triazaspiro[4.5]deca-2,8-dien-6-one (20a): Yield 58% (0.38 g from 0.35 g) as a white solid, m.p. 203–205 °C. R_f = 0.27 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1681 (CONH), 1701 ($COCH_3$) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, CH_3), 1.94 (s, 3 H, CH_3), 2.28 (s, 3 H, $ArCH_3$), 3.26 (d, J = 17.0 Hz, 1 H, C*H*H), 3.53 (d, J = 17.1 Hz, 1 H, CH*H*), 4.47 (s, 1 H, CH), 6.97 (d, J = 8.0 Hz, 2 H, ArH), 7.05 (d, J = 8.0 Hz, 2 H, ArH), 7.16 (d, J = 6.8 Hz, 2 H, ArH), 7.24 (d, J = 6.5 Hz, 2 H, ArH), 7.33 (d, J = 6.8 Hz, 3 H, ArH), 7.54–7.57 (m, 2 H, ArH), 7.92 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 21.1, 41.4, 48.3, 74.6, 117.3, 124.9, 126.2, 128.6, 129.4, 130.0, 130.6, 131.7, 134.9, 137.9, 141.6, 143.3, 150.7, 168.5, 197.9 ppm. MS (ES^+): m/z (%) = 484.2 (100) $[M + H]^+$ DART-HRMS: calcd. for $C_{29}H_{27}Cl_1N_3O_2$ $[M + H]^+$ 484.17918; found 484.17656.

9-Acetyl-1-(4-chlorophenyl)-3-(2-fluorophenyl)-8-methyl-10-(4-methylphenyl)-1,2,7-triazaspiro[4.5]deca-2,8-dien-6-one (20b): Yield 44% (0.13 g from 0.15 g) as a white solid, m.p. 197–199 °C. R_f = 0.19 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1661 (CONH), 1702 ($COCH_3$) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.94 (s, 3 H, CH_3), 1.98 (s, 3 H, $COCH_3$), 2.27 (s, 3 H, $ArCH_3$), 3.50 (d, J = 17.7 Hz, 1 H, C*H*H), 3.59 (d, J = 17.7 Hz, 1 H, CH*H*), 4.58 (s, 1 H, CH), 6.96–7.12 (m, 5 H, ArH), 7.16 (d, J = 6.8 Hz, 2 H, ArH), 7.24–7.33 (m, 5 H, ArH and NH), 7.67–7.73 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 21.1, 30.2, 43.5, 47.5, 74.4, 116.1, 116.4, 117.4, 123.6, 124.3, 128.7, 128.8, 129.8, 130.7, 130.8, 134.4, 137.9, 141.1, 142.7, 146.5, 168.8, 198.4 ppm. MS (ES+): m/z (%) = 502.1 (100) $[M + H]^+$, 504.1 (33) $[M + 3]^+$. $C_{29}H_{25}ClFN_3O_2$ (exact mass: 501.1619): calcd. C 69.39, H 5.02, N 8.37; found C 69.52, H 4.86, N 8.49.

9-Acetyl-1,3-bis(4-chlorophenyl)-8-methyl-10-(4-methylphenyl)-1,2,7-triazaspiro[4.5]deca-2,8-dien-6-one (20c): Yield 56% (0.17 g from 0.15 g) as a white solid, m.p. 203–205 °C. R_f = 0.25 (80:20,

hexane/EtOAc). IR (KBr): ṽ = 1671 (CONH), 1699 ($COCH_3$) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3), 2.29 (s, 3 H, $ArCH_3$), 3.21 (d, J = 16.9 Hz, 1 H, C*H*H), 3.45 (d, J = 16.9 Hz, 1 H, CH*H*), 4.48 (s, 1 H, CH), 6.96 (d, J = 7.9 Hz, 2 H, ArH), 7.06 (d, J = 7.9 Hz, 2 H, ArH), 7.14 (d, J = 8.5 Hz, 2 H, ArH), 7.24–7.31 (m, 5 H, ArH and NH), 7.47 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 21.1, 30.2, 41.4, 48.3, 74.8, 117.4, 124.8, 127.3, 128.6, 128.9, 130.0, 130.7, 134.9, 135.2, 138.0, 141.3, 143.0, 149.4, 168.3, 197.9 ppm. MS (ES+): *m*/*z* (%) = 517.1 (100) $[M + H]^+$. $C_{29}H_{25}Cl_2N_3O_2$ (exact mass: 517.1324): calcd. C 67.19, H 4.86, N 8.11; found C 67.38, H 4.70, N 8.18.

General Procedure for the Synthesis of 5a–d, 6a–d, 33a–d, 35a–d, 40a–d, and 41, as Exemplified for 5a: A two-neck flask charged with a suspension of **3a** (0.5 g, 1.35 mmol) in THF (5 mL) was heated at 70 °C. When the compound was properly dissolved, water (3.0 mL) and indium powder (0.621 g, 5.40 mmol) were added whilst stirring. Concentrated HCl (0.88 mL, 8.10 mmol) was added dropwise, and the reaction was continued for 5 min. The reaction was quenched with 10% aqueous $NaHCO_3$ whilst stirring, and EtOAc (50 mL) was added. The mixture was passed thorough a bed of Celite with EtOAc, and the resulting mixture was partitioned in a separating funnel. The aqueous layer was separated and further extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed with brine (50 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo to afford a residue, which upon column chromatography on deactivated silica gel (60–120 mesh) (25 mL of water was added to 100 g of silica gel and thoroughly mixed) with $CHCl_3$/MeOH (99.5:0.5, v/v) as the eluent, furnished 0.26 g (66%) of **9a** as a white solid.

4′-Hydroxy-3-phenyl-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (5a): M.p. 258–260 °C. R_f = 0.39 (94:6, $CHCl_3$/MeOH). IR (KBr): ṽ = 1672 (CONH), 3405 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.62 (d, J = 17.4 Hz, 1 H, C*H*H), 3.82 (d, J = 17.4 Hz, 1 H, CH*H*), 4.70 (d, J = 4.5 Hz, 1 H, CHO*H*), 6.12 (d, J = 4.5 Hz, 1 H, C*H*OH), 6.95 (d, J = 7.8 Hz, 1 H, ArH), 7.04 (t, J = 7.3 Hz, 1 H, ArH), 7.28 (t, J = 7.4 Hz, 1 H, ArH), 7.36 (d, J = 7.4 Hz, 1 H, ArH), 7.46–7.48 (m, 3 H, ArH), 7.70–7.72 (m, 2 H, ArH), 10.53 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 37.9, 69.3, 87.0, 115.3, 122.4, 124.9, 126.7, 128.6, 128.7, 128.8, 128.9, 130.3, 136.4, 156.3, 166.7 ppm. MS (ES+): *m*/*z* (%) = 295.0 (100) $[M + H]^+$. $C_{17}H_{14}N_2O_3$ (exact mass: 294.1004): calcd. C 69.38, H 4.79, N 9.52; found C 69.26, H 4.88, N 9.39.

3-(2-Fluorophenyl)-4′-hydroxy-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (5b): Yield 64% (0.06 g from 0.12 g) as a white solid, m.p. 183–185 °C. R_f = 0.40 (94:6, $CHCl_3$/MeOH). IR (KBr): ṽ = 1672 (CONH), 3399 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 3.65 (d, J = 16.8 Hz, 1 H, C*H*H), 3.84 (d, J = 16.8 Hz, 1 H, C*H*H), 4.71 (s, 1 H, CHO*H*), 6.15 (br. s, 1 H, C*H*OH), 6.94 (d, J = 7.8 Hz, 1 H, ArH), 7.01–7.06 (m, 1 H, ArH), 7.26–7.43 (m, 4 H, ArH), 7.51–7.58 (m, 1 H, ArH), 7.77–7.80 (m, 1 H, ArH), 10.55 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 69.3, 86.8, 115.4, 116.5, 116.8, 122.5, 124.9, 125.0, 128.8, 129.1, 129.4, 132.5, 136.4, 138.1, 152.9, 158.0, 161.3, 166.6 ppm. MS (ES+): *m*/*z* (%) = 313.0 (100) $[M + H]^+$. $C_{17}H_{13}FN_2O_3$ (exact mass: 312.0910): calcd. C 65.38, H 4.20, N 8.97; found C 65.50, H 4.33, N 9.10.

3-(4-Chlorophenyl)-4′-hydroxy-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (5c): Yield 79% (0.24 g from 0.37 g) as a white solid, m.p. >250 °C. R_f = 0.38 (94:6, $CHCl_3$/MeOH). IR (KBr): ṽ = 1672 (CONH), 3399 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 3.60 (d, J = 17.5 Hz, 1 H, C*H*H), 3.80 (d, J = 17.5 Hz, 1 H, C*H*H), 4.71 (d, J = 4.8 Hz, 1 H, CHO*H*), 6.14 (d, J = 4.8 Hz, 1 H, C*H*OH), 6.94 (d, J = 7.8 Hz, 1 H, ArH), 7.04 (t, J = 7.4 Hz, 1 H, ArH), 7.28 (t, J = 7.7 Hz, 1 H, ArH), 7.36 (d, J = 7.4 Hz, 1 H, ArH), 7.52 (d, J = 8.5 Hz, 2 H, ArH), 7.71–7.75 (m, 1 H, ArH), 10.55 (s, 1 H. NH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 37.8, 69.3, 87.4, 115.4, 122.6, 125.0, 127.7, 128.6, 128.7, 129.0, 129.1,135.0, 136.4, 155.7, 166.7 ppm. MS (ES+): *m*/*z* (%) = 329.4 (100) $[M + H]^+$. $C_{17}H_{13}ClN_2O_3$ (exact mass: 328.0615): calcd. C 62.11, H 3.99, N 8.52; found C 61.94, H 4.15, N 8.72.

4′-Hydroxy-3-(4-methylphenyl)-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (5d): Yield 69% (0.22 g from 0.40 g) as a white solid, m.p. >250 °C. R_f = 0.34 (94:6, $CHCl_3$/MeOH). IR (KBr): ṽ = 1668 (CONH), 3402 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 2.37 (s, 3 H, $ArCH_3$), 3.60 (d, J = 16.9 Hz, 1 H, C*H*H), 3.81 (d, J = 16.9 Hz, 1 H, C*H*H), 4.70 (s, 1 H, CHO*H*), 6.13 (s, 1 H, C*H*OH), 6.96 (d, J = 7.4 Hz, 2 H, ArH), 7.30–7.52 (m, 5 H, ArH), 7.62 (d, J = 7.4 Hz, 1 H, ArH), 10.53 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 21.0, 38.0, 69.4, 86.9, 115.3, 122.5, 125.0, 126.0, 126.7, 128.7, 129.0, 129.5, 136.5, 140.2, 156.2, 166.8 ppm. MS (ES+): *m*/*z* (%) = 309.0 (100) $[M + H]^+$. $C_{18}H_{16}N_2O_3$ (exact mass: 308.1161): calcd. C 70.12, H 5.23, N 9.09; found C 69.93, H 5.11, N 9.21.

4′-Hydroxy-6′,7′-dimethoxy-3-phenyl-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (6a): Yield 56% (0.18 g from 0.40 g) as a white solid, m.p. 240–242 °C. R_f = 0.36 (94:6, $CHCl_3$/MeOH). IR (KBr): ṽ = 1678 (CONH), 3469 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.61 (d, J = 17.5 Hz, 1 H, C*H*H), 3.73 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.79 (d, J = 17.5 Hz, 1 H, CH*H*), 4.61 (d, J = 4.8 Hz, 1 H, C*H*OH), 5.98 (d, J = 4.8 Hz, 1 H, CHO*H*), 6.59 (s, 1 H, ArH), 6.97 (s, 1 H, ArH), 7.46–7.48 (m, 3 H, ArH), 7.70–7.73 (m, 2 H, ArH), 10.28 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 37.9, 55.6, 56.0, 69.2, 87.2, 100.6, 113.0, 116.3, 126.7, 128.8, 129.9, 130.3, 144.2, 149.3, 156.2, 166.4 ppm. MS (ES+): *m*/*z* (%) = 354.9 (100) $[M + H]^+$ DART-HRMS: calcd. for $C_{19}H_{19}N_2O_5$ $[M + H]^+$ 355.1294; found 355.12797.

3-(2-Fluorophenyl)-4′-hydroxy-6′,7′-dimethoxy-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (6b): Yield 59% (0.20 g from 0.40 g) as a white solid, m.p. 236–238 °C. R_f = 0.38 (94:6, $CHCl_3$/MeOH). IR (KBr): ṽ = 1681 (CONH), 3373 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.65 (d, J = 17.2 Hz, 1 H, CH*H*), 3.74 (s, 6 H, 2 × OCH_3), 3.82 (d, J = 17.2 Hz, 1 H, C*H*H), 4.62 (d, J = 4.8 Hz, 1 H, CHO*H*), 6.02 (d, J = 4.8 Hz, 1 H, C*H*OH), 6.58 (s 1 H, ArH), 6.97 (s, 1 H, ArH), 7.27–7.38 (m, 2 H, ArH), 7.51–7.57 (m, 1 H, ArH), 7.77 (t, J = 7.5 Hz, 1 H, ArH), 10.32 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.3, 55.7, 56.1, 69.2, 87.0, 100.5, 113.1, 116.2, 116.8, 124.9, 129.4, 130.0, 132.3, 132.4, 144.3, 149.4, 152.7, 166.3 ppm. MS (ES+): *m*/*z* (%) = 373.0 (100) $[M + H]^+$. $C_{19}H_{17}FN_2O_5$ (exact mass: 372.1122): calcd. C 61.29, H 4.60, N 7.52; found C 60.95, H 4.73, N 7.58.

3-(4-Chlorophenyl)-4′-hydroxy-6′,7′-dimethoxy-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (6c): Yield 55% (0.46 g from 1.0 g) as a white solid, m.p. 243–245 °C. R_f = 0.37 (94:6, $CHCl_3$/MeOH). IR (KBr): ṽ = 1689 (CONH), 3276 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.59 (d, 1 H, J = 17.3 Hz, C*H*H), 3.73 (s, 6 H, 2 × OCH_3), 3.76 (d, J = 17.3 Hz, 1 H, CH*H*), 4.63 (d, J = 4.8 Hz, 1 H, C*H*OH), 6.00 (d, J = 4.8 Hz, 1 H, CHO*H*), 6.60 (s, 1 H, ArH), 6.98 (s, 1 H, ArH), 7.53 (d, J = 8.4 Hz, 2 H, ArH), 7.74 (d, J = 8.4 Hz, 2 H, ArH), 10.29 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 37.8, 55.7, 56.0, 69.2, 87.6, 100.6, 112.9, 116.3, 127.7, 128.5, 129.0, 129.9, 135.0, 144.3, 149.3, 155.6, 166.4 ppm. MS (ES+): *m*/*z* (%) = 388.9 (100) $[M + H]^+$.

$C_{19}H_{17}ClN_2O_5$ (exact mass: 388.0826): calcd. C 58.69, H 4.41, N 7.21; found C 58.83, H 4.29, N 7.03.

4′-Hydroxy-6′,7′-dimethoxy-3-(4-methylphenyl)-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (6d): Yield 58% (0.16 g from 0.34 g) as a white solid, m.p. 247–248 °C. R_f = 0.65 (94:6, $CHCl_3$/MeOH): IR (KBr): $\tilde{\nu}$ = 1676 (CONH), 3438 (OH) cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.34 (s, 3 H, $ArCH_3$), 3.58 (d, J = 17.4 Hz, 1 H, C*H*H), 3.72 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.78 (d, J = 17.4 Hz, 1 H, CH*H*), 4.58 (d, J = 4.8 Hz, 1 H, C*H*OH), 5.96 (d, J = 4.8 Hz, 1 H, CHO*H*), 6.58 (s, 1 H, ArH), 6.96 (s, 1 H, ArH), 7.26 (d, J = 8.0 Hz, 2 H, ArH), 7.59 (d, J = 8.0 Hz, 2 H, ArH), 10.24 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 21.1, 38.7, 55.7, 56.0, 69.3, 87.1, 100.5, 113.0, 116.4, 126.1, 126.8, 129.6, 130.0, 140.3, 144.3, 149.3, 156.3, 166.6 ppm. MS (ES+): m/z (%) = 368.9 (100) $[M + H]^+$. $C_{20}H_{20}N_2O_5$ (exact mass: 368.1372): calcd. C 65.21, H 5.47, N 7.60; found C 65.21, H 5.47, N 7.60.

3-Phenyl-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (33a): Yield 65% (0.11 g from 0.20 g) as a white solid, m.p. 240–242 °C. R_f = 0.71 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1687 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.21 (d, J = 16.8 Hz, 2 H, CH_2), 3.42 (d, J = 16.4 Hz, 1 H, C*H*H), 4.17 (d, J = 16.4 Hz, 1 H, CH*H*), 6.84 (d, J = 7.8 Hz, 1 H, ArH), 7.04 (t, J = 7.4 Hz, 1 H, ArH), 7.21 (t, J = 7.1 Hz, 2 H, ArH), 7.40–7.42 (m, 2 H, ArH), 7.67–7.70 (m, 3 H, ArH), 8.20 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 36.6, 41.1, 83.7, 115.1, 121.3, 122.4, 126.7, 127.4, 128.5, 128.9, 130.3, 137.1, 156.7, 166.2 ppm. MS (ES+): m/z (%) = 279.1 (100) $[M + H]^+$. DART-HRMS: calcd. for $C_{17}H_{15}N_2O_2$ $[M + H]^+$ 279.1134; found 279.1187.

3-(2-Fluorophenyl)-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (33b): Yield 50% (0.21 g from 0.50 g) as a white solid, m.p. 218–220 °C. R_f = 0.70 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1692 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.22 (d, J = 16.4 Hz, 1 H, C*H*H), 3.33 (dd, ^1J = 17.5, ^2J = 2.1 Hz, 1 H, C*H*H), 3.43 (d, J = 16.4 Hz, 1 H, CH*H*), 4.20 (dd, ^1J = 17.5, ^2J = 2.1 Hz, 1 H, C*H*H), 7.03 (d, J = 7.5 Hz, 1 H, ArH), 7.07–7.12 (m, 2 H, ArH), 7.15–7.23 (m, 3 H, ArH), 7.37–7.44 (m, 1 H, ArH), 7.87–7.92 (m, 1 H, ArH), 8.17 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 37.4, 43.7, 43.8, 83.7, 83.8, 115.6, 116.1, 116.4, 116.9, 117.0, 120.5, 122.9, 124.2, 124.3, 127.7, 128.4, 128.9, 130.0, 131.7, 131.8, 136.7, 152.7, 152.8, 167.0 ppm. MS (ES+): m/z (%) = 297.0 (100) $[M + H]^+$. $C_{17}H_{13}FN_2O_2$ (exact mass: 296.0961): calcd. C 68.91, H 4.42, N 9.45; found C 69.19, H 4.25, N 9.31.

3-(4-Chlorophenyl)-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (33c): Yield 65% (0.16 g from 0.30 g) as a white solid, m.p. 200–202 °C. R_f = 0.72 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1676 (CONH), 3446 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.31 (s, 2 H, CH_2), 3.99 (d, J = 16.5 Hz, 1 H, C*H*H), 4.07 (d, J = 16.5 Hz, 1 H, CH*H*), 6.96 (d, J = 7.8 Hz, 2 H, ArH), 7.21–7.32 (m, 2 H, ArH), 7.50–7.55 (m, 2 H, ArH), 7.71–7.73 (m, 2 H, ArH), 10.62 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 36.5, 41.0, 84.1, 115.1, 121.2, 122.5, 127.4, 127.8, 128.4, 128.5, 128.9, 134.9, 137.1, 155.9, 166.1 ppm. MS (ES+): m/z (%) = 313.1 (100) $[M + H]^+$. $C_{17}H_{13}ClN_2O_2$ (exact mass: 312.0666): calcd. C 69.57, H 4.86, N 9.01; found C 69.28, H 4.98, N 9.12.

3-(4-Methylphenyl)-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (33d): Yield 65% (0.16 g from 0.30 g) as a white solid, m.p. 207–209 °C. R_f = 0.75 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1687 (CONH), 3460 f (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, $ArCH_3$), 3.30 (s, 2 H, CH_2), 3.33 (d, J = 17.0 Hz, 1 H, C*H*H), 4.00 (d, J = 17.0 Hz, 1 H, CH*H*), 6.93–7.18 (m, 1 H, ArH), 7.18–7.29 (m, 4 H, ArH), 7.55–7.60 (m, 3 H, ArH), 10.58 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 21.0, 36.6, 41.2, 83.5, 115.1, 121.3, 122.4, 127.4, 128.5, 129.4, 137.1, 140.1, 156.5, 166.3 ppm. MS (ES+): m/z (%) = 293.0 (100) $[M + H]^+$. $C_{18}H_{16}N_2O_2$ (exact mass: 292.1212): calcd. C 73.95, H 5.52, N 9.58; found C 74.12, H 5.72, N 9.45.

6′,7′-Dimethoxy-3-phenyl-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (34a): Yield 63% (0.083 g from 0.155 g) as a white solid, m.p. 225–227 °C. R_f = 0.62 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1683 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.22 (s, 2 H, CH_2), 3.34 (s, 1 H, C*H*H), 3.73 (s, 6 H, 2 × OCH_3), 3.99 (d, J = 17.2 Hz, 1 H, CH*H*), 6.61 (s, 1 H, ArH), 6.87 (s, 1 H, ArH), 7.48–7.50 (m, 3 H, ArH), 7.69–7.72 (m, 2 H, ArH), 10.35 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 36.3, 41.3, 55.7, 56.0, 83.9, 100.6, 112.6, 113.0, 126.7, 128.9, 130.3, 130.5, 144.3, 148.2, 156.6, 165.9 ppm. MS (ES+): m/z (%) = 339.0 (100) $[M + H]^+$. $C_{19}H_{18}N_2O_4$ (exact mass: 338.1267): calcd. C 67.44, H 5.36, N 8.28; found C 67.69, H 5.24, N 8.32.

3-(2-Fluorophenyl)-6′,7′-dimethoxy-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (34b): Yield 53% (0.18 g from 0.40 g) as a white solid, m.p. 230–232 °C. R_f = 0.59 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1684 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.76–2.94 (m, 3 H, 3 × C*H*H), 3.33 (s, 6 H, 2 × OCH_3), 3.66 (d, J = 16.8 Hz, 1 H, CH*H*), 6.21 (s, 1 H, ArH), 6.47 (s, 1 H, ArH), 6.89–7.00 (m, 2 H, ArH), 7.13–7.19 (m, 1 H, ArH), 7.36–7.40 (m, 1 H, ArH), 10.01 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 36.1, 42.8, 55.6, 56.0, 83.8, 100.6, 112.5, 113.0, 116.4, 116.7, 124.9, 129.2, 130.4, 132.3, 132.4, 144.3, 148.2, 153.1, 165.7 ppm. MS (ES+): m/z (%) = 357.0 (100) $[M + H]^+$. $C_{19}H_{17}FN_2O_4$ (exact mass: 356.1172): calcd. C 64.04, H 4.81, N 7.86; found C 63.87, H 4.96, N 7.61.

3-(4-Chlorophenyl)-6′,7′-dimethoxy-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (34c): Yield 60% (0.18 g from 0.35 g) as a white solid, m.p. 228–230 °C. R_f = 0.75 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1683 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.21 (d, J = 17.1 Hz, 1 H, C*H*H), 3.33 (d, J = 2.1 Hz, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.02 (d, J = 17.1 Hz, 1 H, CH*H*), 6.59 (s, 1 H, ArH), 6.85 (s, 1 H, ArH), 7.28–7.38 (m, 2 H, ArH), 7.51–7.58 (m, 1 H, ArH), 7.74–7.79 (m, 1 H, ArH), 10.38 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 36.2, 42.8, 55.6, 56.0, 83.8, 100.5, 112.5, 112.9, 116.5, 116.8, 125.0, 129.3, 130.4, 132.4, 144.3, 148.1, 153.14, 165.8 ppm. MS (ES+): m/z (%) = 373.1 (100) $[M + H]^+$. $C_{19}H_{17}ClN_2O_4$ (exact mass: 372.0877): calcd. C 61.21, H 4.60, N 7.51; found C 61.47, H 4.46, N 7.68.

6′,7′-Dimethoxy-3-(4-methylphenyl)-1′*H*,4*H*-spiro[isoxazole-5,3′-quinolin]-2′(4′*H*)-one (34d): Yield 67% (0.17 g from 0.30 g) as a white solid, m.p. 230–232 °C. R_f = 0.75 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1683 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, $ArCH_3$), 3.15 (d, J = 17.1 Hz, 1 H, C*H*H), 3.27 (d, J = 2.2 Hz, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.97 (d, J = 17.1 Hz, 1 H, CH*H*), 6.59 (s, 1 H, ArH), 6.85 (s, 1 H, ArH), 7.27 (d, J = 7.8 Hz, 2 H, ArH), 7.58 (d, J = 7.8 Hz, 2 H, ArH), 10.35 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$] DMSO): δ = 21.0, 36.3, 41.4, 55.7, 56.0, 83.7, 100.5, 112.6, 112.9, 126.2, 130.5, 140.2, 144.3, 148.2, 156.5, 166.0 ppm. MS (ES+): m/z (%) = 353.1 (100) $[M + H]^+$. $C_{20}H_{20}N_2O_4$ (exact mass: 352.1423): calcd. C 68.17, H 5.72, N 7.95; found C 67.96, H 5.76, N 7.88.

3′-Phenyl-5,8-dihydro-4′*H*,6*H*-spiro[1,3-dioxolo[4,5-*g*]quinoline-7,5′-isoxazol]-6-one (35a): Yield 56% (0.09 g from 0.20 g) as a white solid, m.p. 218–220 °C. R_f = 0.70 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1687 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.15 (d, J = 16.6 Hz, 1 H, C*H*H), 3.25 (d, J = 16.9 Hz, 1 H, C*H*H), 3.33

(d, J = 16.6 Hz, 1 H, CH*H*), 4.10 (d, J = 16.9 Hz, 1 H, CH*H*), 5.97 (d, J = 2.0 Hz, 2 H, OCH_2O), 6.49 (s, 1 H, ArH), 6.68 (s, 1 H, ArH), 7.30–7.45 (m, 3 H, ArH), 7.65–7.68 (m, 2 H, ArH), 9.45 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + TFA): δ = 37.1, 42.8, 83.6, 98.6, 98.7, 101.8, 109.0, 113.5, 113.6, 127.2, 127.9, 128.6, 128.7, 129.1, 131.3, 145.1, 147.9, 157.3 ppm. MS (ES+): m/z (%) = 323.0 (100) $[M + H]^+$ DART-HRMS: calcd. for $C_{18}H_{15}N_2O_4$ $[M + H]^+$ 323.1032; found 323.1020.

3′-(2-Fluorophenyl)-5,8-dihydro-4′*H*,5*H*-spiro[1,3-dioxolo[4,5-*g*]quinoline-7,5′-isoxazol]-6-one (35b): Yield 77% (0.19 g from 0.30 g) as a white solid, m.p. 238–240 °C. R_f = 0.60 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1687 (CONH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 3.47 (d, J = 6.9 Hz, 2 H, CH_2), 4.08–4.18 (m, 2 H, CH_2), 6.09 (d, J = 1.6 Hz, 2 H, OCH_2O), 6.67 (s, 1 H, ArH), 6.85 (s, 1 H, ArH), 7.40–7.51 (m, 2 H, ArH), 7.63–7.70 (m, 1 H, ArH), 7.86–7.91 (m, 1 H, ArH), 10.58 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 36.3, 42.6, 42.7, 83.4, 97.2, 101.0, 108.7, 113.5, 116.4, 116.7, 124.8, 124.9, 129.2, 131.0, 131.1, 132.3, 132.4, 142.6, 146.3, 153.0, 153.1, 165.7 ppm. MS (ES+): m/z (%) = 341.0 (100) $[M + H]^+$. $C_{18}H_{13}ClN_2O_4$ (exact mass: 340.0859): calcd. C 63.53, H 3.85, N 8.23; found C 63.81, H 3.70, N 8.03.

3′-(4-Chlorophenyl)-5,8-dihydro-4′*H*,5*H*-spiro[1,3-dioxolo[4,5-*g*]quinoline-7,5′-isoxazol]-6-one (35c): Yield 58% (0.22 g from 0.38 g) as a white solid, m.p. >254 °C. R_f = 0.73 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1680 (CONH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 3.21 (s, 2 H, CH_2), 3.35 (d, J = 17.1 Hz, 1 H, C*H*H), 3.98 (d, J = 17.1 Hz, 1 H, CH*H*), 5.98 (d, J = 1.3 Hz, 2 H, OCH_2O), 6.57 (s, 1 H, ArH), 6.85 (s, 1 H, ArH), 7.55 (d, J = 8.5 Hz, 2 H, ArH), 7.73 (d, J = 8.5 Hz, 2 H, ArH), 10.44 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 36.4, 41.0, 83.9, 97.2, 101.0, 108.7, 113.5, 127.8, 128.4, 128.9, 131.1, 134.9, 142.6, 146.4, 155.9, 165.8 ppm. MS (ES+): m/z (%) = 356.9 (100) $[M + H]^+$. $C_{18}H_{13}ClN_2O_4$ (exact mass: 356.0564): calcd. C 60.60, H 3.67, N 7.85; found C 60.35, H 3.79, N 7.98.

3′-(4-Methylphenyl)-5,8-dihydro-4′*H*,5*H*-spiro[1,3-dioxolo[4,5-*g*]quinoline-7,5′-isoxazol]-6-one (35d): Yield 61% (0.26 g from 0.40 g) as a white solid, m.p. >250 °C. R_f = 0.61 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1683 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, $ArCH_3$), 2.66 (s, 1 H, CH), 3.33 (s, 1 H, CH), 3.49 (d, J = 17.1 Hz, 1 H, C*H*H), 4.11 (d, J = 17.1 Hz, 1 H, CH*H*), 6.12 (d, J = 1.4 Hz, 2 H, OCH_2O), 6.70 (s, 1 H, ArH), 6.99 (s, 1 H, ArH), 7.43 (d, J = 8.0 Hz, 2 H, ArH), 7.73 (d, J = 8.0 Hz, 2 H, ArH), 10.58 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + TFA): δ = 21.0, 36.4, 41.3, 83.3, 97.2, 100.9, 108.7, 113.6, 126.1, 126.6, 129.4, 131.2, 140.1, 142.5, 146.3, 156.4, 165.9 ppm. MS (ES+): m/z (%) = 337.0 (100) $[M + H]^+$. DART-HRMS: calcd. for $C_{19}H_{17}N_2O_4$ $[M + H]^+$ 337.1188; found 337.1168.

2-(2-Methylquinolin-3-yl)-1-phenylethan-1-one Oxime (40a): Yield: 52% (0.48 g from 1.20 g) as a shiny white solid, m.p. 233–235 °C. R_f = 0.65 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1719 ($COCH_3$), 3424 (OH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 2.50 (s, 3 H, CH_3), 4.04 (s, 2 H, CH_2), 7.08–7.15 (m, 3 H, ArH), 7.18–7.23 (m, 1 H, ArH), 7.36–7.42 (m, 2 H, ArH), 7.44–7.48 (m, 2 H, ArH), 7.52 (d, J = 7.5 Hz, 1 H, ArH), 7.66 (d, J = 8.4 Hz, 1 H, ArH), 11.40 (s, 1 H, NOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 28.7, 125.7, 126.0, 126.7, 127.2, 127.8, 128.4, 128.6, 128.8, 129.3, 133.3, 135.8, 145.8, 153.9, 158.2 ppm. MS (ES+): m/z (%) = 277.2 (100) $[M + H]^+$. HRMS (EI): calcd. for $C_{18}H_{16}N_2O$ $[M]^+$ 276.1263; found 276.1267.

1-(2-Fluorophenyl)-2-(2-methylquinolin-3-yl)ethan-1-one Oxime (40b): Yield 65% (0.27 g from 0.50 g) as a white solid, m.p. 165–166 °C. R_f = 0.64 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1610 (C=N), 3321 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.73 (s, 3 H, CH_3), 4.35 (s, 2 H, CH_2), 6.97–7.08 (m, 2 H, ArH), 7.26 (d, J = 5.7 Hz, 2 H, ArH), 7.43 (d, J = 6.3 Hz, 2 H, ArH), 7.60–7.68 (m, 2 H, ArH), 7.88 (s, 1 H, ArH), 7.99 (d, J = 7.4 Hz, 1 H, ArH), 9.38 (s, 1 H, NOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 31.8, 116.1, 116.4, 124.0, 124.1, 124.4, 124.5, 126.0, 127.3, 128.1, 128.8, 129.1, 130.1, 131.0, 131.1, 135.8, 146.4, 154.2, 158.6 ppm. MS (ES+): m/z (%) = 295.2 (100) $[M + H]^+$. $C_{18}H_{15}FN_2O$ (exact mass: 294.1168): calcd. C 73.45, H 5.14, N 9.52; found C 73.64, H 5.02, N 9.47.

1-(4-Chlorophenyl)-2-(2-methylquinolin-3-yl)ethan-1-one Oxime (40c): Yield 65% (0.16 g from 0.30 g) as a white solid, m.p. 202–204 °C. R_f = 0.36 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1610 (C=N), 3389 (OH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 2.71 (s, 3 H, CH_3), 4.25 (s, 2 H, CH_2), 7.40 (d, J = 8.7 Hz, 2 H, ArH), 7.45 (d, J = 7.1 Hz, 1 H, ArH), 7.60–7.65 (m, 1 H, ArH), 7.69 (d, J = 8.7 Hz, 2 H, ArH), 7.77 (d, J = 7.8 Hz, 1 H, ArH), 7.87 (d, J = 8.3 Hz, 1 H, ArH), 11.70 (s, 1 H, NOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 28.5, 125.8, 126.7, 127.2, 127.8, 128.5, 128.7, 129.1, 133.3, 134.6, 145.8, 153.0, 158.3 ppm. MS (ES+): m/z (%) = 311.2 (100) $[M + H]^+$. $C_{18}H_{15}ClN_2O$ (exact mass: 310.0873): calcd. C 69.57, H 4.86, N 9.01; found C 69.34, H 5.03, N 9.12.

1-(4-Methylphenyl)-2-(2-methylquinolin-3-yl)ethan-1-one Oxime (40d): Yield 67% (0.33 g from 0.60 g) as a white solid, m.p. 188–189 °C. R_f = 0.34 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1607 (C=N), 3417 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, $ArCH_3$), 2.84 (s, 3 H, CH_3), 4.28 (s, 2 H, CH_2), 7.13 (d, J = 8.1 Hz, 1 H, ArH), 7.39–7.44 (m, 1 H, ArH), 7.52 (d, J = 8.1 Hz, 2 H, ArH), 7.61–7.64 (m, 2 H, ArH), 7.77 (s, 1 H, ArH), 8.03 (d, J = 8.2 Hz, 1 H, ArH), 9.24 (s, 1 H, NOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 23.2, 28.6, 125.8, 126.0, 126.7, 127.2, 127.9, 128.7, 129.1, 129.5, 133.0, 133.3, 138.3, 145.8, 153.8, 158.3 ppm. MS (ES+): m/z (%) = 291.2 (100) $[M + H]^+$. $C_{19}H_{18}N_2O$ (exact mass: 290.1419): calcd. C 78.59, H 6.25, N 9.65; found C 78.41, H 6.11, N 9.76.

2-(2-Methylquinolin-3-yl)-1-phenylethan-1-one (41a): Yield 14% (0.13 g from 1.20 g) as a white solid, m.p. 111–113 °C, R_f = 0.80 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1687 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H, CH_3), 4.49 (s, 2 H, CH_2), 7.25–7.28 (m, 1 H, ArH), 7.44–7.54 (m, 3 H, ArH), 7.60–7.73 (m, 3 H, ArH), 7.88 (s, 1 H, ArH), 8.01–8.08 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 43.1, 126.0, 127.2, 127.5, 128.4, 128.5, 128.9, 129.2, 133.7, 136.6, 137.2, 147.1, 158.6, 196.7 ppm. MS (ES+) m/z (%) = 262.2 (100) $[M + H]^+$. $C_{19}H_{16}O_2$ (exact mass: 261.1154): calcd. C 82.58, H 5.84; found C 82.58, H 5.84.

1-(4-Chlorophenyl)-2-(2-methylquinolin-3-yl)ethan-1-one (41c): Yield 95% (0.18g from 0.20 g) as a white solid, m.p. 148–149 °C, R_f = 0.81 (94:6, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 1679 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, CH_3), 4.46 (s, 2 H, CH_2), 7.48–7.51 (m, 3 H, ArH), 7.64–7.74 (m, 2 H, ArH), 7.87 (s, 1 H, ArH), 7.99–8.04 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 29.8. 43.0, 126.1, 127.2, 128.1, 128.4, 129.2, 129.3, 129.4, 129.8, 134.9, 137.3, 140.2, 147.1, 158.5, 195.5 ppm. MS (ES+): m/z (%) = 296.2 (100) $[M + H]^+$. $C_{18}H_{14}ClNO$ (exact mass: 295.0764): calcd. C 73.10; H, 4.77; N, 4.74; found C 73.03, H 4.44, N, 4.83.

General Procedure for the Synthesis of 41a,c from 40a,c, as Exemplified for 41a: To a stirred solution of **40a** (0.05 g, 0.18 mmol) in THF/H_2O (3.0 mL, 1:1) was added aqueous HCl (1.0 mL, 35% v/v), and the mixture was refluxed for 1 h. After completion of the reaction, the THF was evaporated, the reaction mixture was

poured into 10% $NaHCO_3$, and the resulting mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to afford a white solid residue. The crude product was recrystallized from EtOAc/hexanes to afford 0.042 g (89%) of **41a** as a white solid.

General Procedure for the Synthesis of 40a,c from 41a,c, as Exemplified for 40a: A reaction mixture containing **41a** (0.05 g, 0.19 mmol), $NH_2OH{\cdot}HCl$ (0.02 g, 0.28 mmol), and CH_3CO_2Na (0.02 g, 0.28 mmol) in MeOH (3.0 mL) was refluxed for 1 h. Excess MeOH was then evaporated from the reaction mixture, cold water (10 mL) was added, and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to furnish a white solid residue. The crude product was recrystallized from EtOAc/hexanes to afford 0.05 g (94%) of **40a** as a white solid.

General Procedure for the Synthesis of 9a–e, 10a, 37a,c–e, as Exemplified for 9d: To a stirred solution of **7d** (0.13 g, 0.35 mmol) in glacial acetic acid (10 mL) iron powder (0.12 g, 2.11 mmol) was added, and the reaction mixture was refluxed at 120 °C under nitrogen for 3 h. Upon completion of the reaction, the reaction mixture was poured into ice-cold water whilst stirring to yield a solid, which was filtered and washed with 10% $NaHCO_3$, followed by water. The product was recrystallized from EtOAc to furnish 0.10 g (73%) of **9d** as a white solid.

2-(4-Chlorophenyl)-4′-hydroxy-5-phenyl-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (9a): Yield 95% (0.24 g from 0.30 g) as a white solid, m.p. >250 °C. R_f = 0.25 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1670 (CONH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.18 (d, J = 17.4 Hz, 1 H, CH*H*), 3.63 (d, J = 17.4 Hz, 1 H, C*H*H), 5.59 (d, J = 4.9 Hz, 1 H, CHO*H*), 6.21 (d, J = 4.9 Hz, 1 H, C*H*OH), 6.99 (d, J = 7.6 Hz, 1 H, ArH), 7.09 (t, J = 7.3 Hz, 1 H, ArH), 7.16 (d, J = 9.0 Hz, 2 H, ArH), 7.25–7.31 (m, 2 H, ArH), 7.34–7.45 (m, 5 H, ArH), 7.67 (d, J = 7.6 Hz, 2 H, ArH), 10.63 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.8, 73.4, 115.1, 115.9, 122.0, 122.9, 125.6, 126.2, 126.6, 128.4, 128.5, 128.6, 131.8, 135.1, 141.5, 145.9, 168.5 ppm. MS (ES+): m/z (%) = 404.1 (100) $[M + H]^+$, 406.1 (33%) $[M + 3]^+$. $C_{23}H_{18}ClN_3O_2$ (exact mass: 403.1088): calcd. C 68.40, H 4.49, N 10.40; found C 68.67, H 4.26, N 10.49.

2-(4-Chlorophenyl)-5-(2-fluorophenyl)-4′-hydroxy-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (9b): Yield 96% (0.37 g from 0.45 g) as a white solid, m.p. >250 °C. R_f = 0.23 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1676 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.18 (d, J = 17.5 Hz, 1 H, CH*H*), 3.69 (d, J = 17.5 Hz, 1 H, C*H*H), 5.58 (d, J = 6.1 Hz, 1 H, CHO*H*), 6.23 (d, J = 6.1 Hz, 1 H, C*H*OH), 6.97 (d, J = 7.3 Hz, 1 H, ArH), 7.09 (d, J = 7.3 Hz, 1 H, ArH), 7.15–7.18 (m, 2 H, ArH), 7.22–7.28 (m, 5 H, ArH), 7.37–7.43 (m, 2 H, ArH), 7.83 (t, J = 7.3 Hz, 1 H, ArH), 10.63 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.9, 73.2, 115.1, 116.1, 116.3, 122.5, 122.9, 124.7, 126.1, 126.6, 128.3, 128.5, 128.6, 128.8, 130.5, 135.0, 141.2, 168.4 ppm. MS (ES+) m/z (%) = 422.0 (30) $[M + H]^+$. $C_{23}H_{17}ClFN_3O_2$ (exact mass: 421.0993): calcd. C 65.48, H 4.06, N 9.96; found C 65.63, H 4.19, N 10.6.

2,5-Bis(4-chlorophenyl)-4′-hydroxy-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (9c): Yield 77% (0.12 g from 0.18 g) as a white solid, m.p. >250 °C. R_f = 0.26 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1672 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 1 H, CHO*H*), 3.10 (d, J = 17.1 Hz, 1 H, CH*H*), 3.80 (d, J = 17.1 Hz, 1 H, C*H*H), 5.67 (s, 1 H, C*H*OH), 6.97 (d, J = 7.5 Hz, 1 H, ArH), 7.06–7.11 (m, 1 H, ArH), 7.20–7.31 (m, 6 H, ArH), 7.46–7.58 (m, 4 H, ArH), 10.19 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.9, 73.7, 115.1, 116.1, 122.3, 123.0, 126.2, 126.6, 127.3, 128.5, 128.7, 130.7, 133.1, 135.1, 141.3, 144.9, 168.4 ppm. MS (FAB+) m/z (%) = 437 (100) $[M + H]^+$. $C_{23}H_{17}Cl_2N_3O_2$ (exact mass: 437.0698): calcd. C 63.03, H 3.91, N 9.59; found C 63.27, H 4.11, N 9.41.

2-(4-Chlorophenyl)-4′-hydroxy-5-(4-methylphenyl)-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (9d): M.p. >250 °C. R_f = 0.27 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1673 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, $ArCH_3$), 3.11 (d, J = 17.1 Hz, 1 H, CH*H*), 3.80 (d, J = 17.1 Hz, 1 H, C*H*H), 5.49 (d, J = 5.7 Hz, 1 H, CHO*H*), 5.66 (s, 1 H, C*H*OH), 6.97 (d, J = 7.5 Hz, 1 H, ArH), 7.08–7.23 (m, 7 H, ArH), 7.50–7.56 (m, 4 H, ArH), 10.09 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 64.8, 73.2, 115.0, 115.8, 121.8, 122.9, 125.6, 126.2, 126.5, 128.4, 128.6, 129.0, 129.2, 135.1, 138.3, 141.6, 146.0, 168.5 ppm. MS (ES+): m/z (%) = 418.0 (100) $[M + H]^+$. $C_{24}H_{20}ClN_3O_2$ (exact mass: 417.1244): calcd. C 68.98, H 4.82, N 10.06; found C 69.13, H 4.72, N 10.18.

2-(4-Chlorophenyl)-4′-hydroxy-5-(thiophen-2-yl)-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (9e): Yield 80% (0.14 g from 0.18 g) as a white solid, m.p. >250 °C. R_f = 0.21 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1681 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.16 (d, J = 17.3 Hz, 1 H, CH*H*), 3.61 (d, J = 17.3 Hz, 1 H, C*H*H), 5.56 (d, J = 5.8 Hz, 1 H, CHO*H*), 6.24 (d, J = 5.8 Hz, 1 H, C*H*OH), 6.95 (d, J = 7.6 Hz, 1 H, ArH), 7.04–7.07 (m, 4 H, ArH), 7.18–7.25 (m, 4 H, ArH), 7.41 (d, J = 7.2 Hz, 1 H, ArH), 7.55 (d, J = 7.2 Hz, 1 H, ArH), 10.63 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 59.8, 64.8, 73.5, 115.1, 115.9, 122.1, 122.9, 126.1, 126.5, 127.5, 127.8, 128.5, 135.0, 141.2, 142.4, 168.2 ppm. MS (ES+): m/z (%) = 410.1 (100) $[M + H]^+$. $C_{21}H_{16}ClN_3O_2S$ (exact mass: 409.0652): calcd. C 61.53, H 3.93, N 10.25; found C 61.40, H 4.12, N 10.14.

2-(4-Chlorophenyl)-4′-hydroxy-6′,7′-dimethoxy-5-phenyl-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (10a): Yield 50% (0.44 g from 0.50 g) as a pale yellow solid, m.p. 107–108 °C. R_f = 0.80 (80:20, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1685 (CONH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.15 (d, J = 17.4 Hz, 1 H, CH*H*), 3.66 (d, J = 17.4 Hz, 1 H, C*H*H), 3.74 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 5.51 (d, J = 6.0 Hz, 1 H, CHO*H*), 6.15 (d, J = 6.0 Hz, 1 H, C*H*OH), 6.64 (s, 1 H, ArH), 6.99 (s, 1 H, ArH), 7.13 (d, J = 8.9 Hz, 2 H, ArH), 7.36 (d, J = 8.9 Hz, 2 H, ArH), 7.36–7.41 (m, 3 H, ArH), 7.66 (d, J = 6.6 Hz, 2 H, ArH), 10.37 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 55.9, 64.8, 73.6, 100.4, 110.6, 115.8, 117.3, 121.9, 125.5, 125.6, 128.3, 128.5, 128.7, 141.5, 144.7, 145.9, 148.9, 168.4 ppm. MS (ES+): m/z (%) = 464.1 (50) $[M + H]^+$. HRMS (EI): calcd. for $C_{25}H_{22}ClN_3O_4$ 463.1299; found 463.1313.

2-(4-Chlorophenyl)-5-phenyl-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (37a): Yield 94% (0.16 g from 0.20 g) as a white solid, m.p. >250 °C. R_f = 0.51 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1685 (CONH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.93 (d, J = 15.8 Hz, 1 H, CH*H*), 3.40 (s, 2 H, CH_2), 3.61 (d, J = 15.8 Hz, 1 H, C*H*H), 6.96 (d, J = 7.0 Hz, 2 H, ArH), 7.11 (d, J = 8.6 Hz, 2 H, ArH), 7.17–7.28 (m, 4 H, ArH), 7.36 (d, J = 6.3 Hz, 3 H, ArH), 7.67 (d, J = 6.3 Hz, 2 H, ArH), 10.62 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 44.8, 68.1, 115.2, 116.3, 120.7, 122.8, 125.8, 127.9, 128.6, 129.0, 129.5, 131.7, 137.2, 141.3, 146.0, 168.7 ppm. MS (ES+): m/z (%) = 388.1 (33) $[M + H]^+$. $C_{23}H_{18}ClN_3O$ (exact mass: 387.1138): calcd. C 71.22, H 4.68, N 10.83; found C 71.47, H 4.79, N 10.77.

2,5-Bis(4-chlorophenyl)-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (37c): Yield 71% (0.31 g from 0.50 g) as a white

solid, m.p. >250 °C. R_f = 0.53 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1688 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.95 (d, J = 16.0 Hz, 1 H, CH*H*), 3.41 (d, J = 2.2 Hz, 2 H, CH_2), 3.65 (d, J = 16.0 Hz, 1 H, CH*H*), 6.97–6.99 (m, 2 H, ArH), 7.13 (d, J = 9.0 Hz, 2 H, ArH), 7.19–7.26 (m, 2 H, ArH), 7.28 (d, J = 9.0 Hz, 2 H, ArH), 7.43 (d, J = 8.5 Hz, 2 H, ArH), 7.71 (d, J = 8.5 Hz, 2 H, ArH), 10.61 (s, 1 H, NH) ppm. MS (ES+): *m/z* (%) = 422.1 (100) $[M + H]^+$. $C_{23}H_{17}Cl_2N_3O$ (exact mass: 421.0749): calcd. C 65.41, H 4.06, N 9.95; found C 65.22, H 4.19, N 10.14.

2-(4-Chlorophenyl)-5-(4-methylphenyl)-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (37d): Yield 81% (0.18 g from 0.22 g) as a light brown solid, m.p. >250 °C. R_f = 0.54 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1690 (CONH) cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.32 (s, 3 H, $ArCH_3$), 2.93 (d, J = 15.6 Hz, 1 H, CH*H*), 3.39 (s, 2 H, CH_2), 3.65 (d, J = 15.6 Hz, 1 H, CH*H*), 6.98 (s, J = 6.9 Hz, 1 H, ArH), 7.12 (d, J = 8.6 Hz, 4 H, ArH), 7.19–7.29 (m, 6 H, ArH), 7.58 (d, J = 7.6 Hz, 2 H, ArH), 10.61 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 33.6, 45.5, 69.2, 116.1, 117.0, 121.6, 123.4, 123.6, 126.7, 128.8, 129.5, 129.8, 130.1, 130.4, 138.3, 139.5, 142.3, 147.1, 170.0 ppm. MS (ES+): *m/z* (%) = 402.1 (100) $[M + H]^+$. $C_{24}H_{20}ClN_3O$ (exact mass: 401.1295): calcd. C 71.73, H 5.02, N 10.46; found C 71.87, H 5.23, N 10.27.

2-(4-Chlorophenyl)-5-(thiophen-2-yl)-2,4-dihydro-1′*H*-spiro[pyrazole-3,3′-quinolin]-2′(4′*H*)-one (37e): Yield: 85% (0.17 g from 0.20 g) as a light blue solid, m.p. >250 °C. R_f = 0.50 (70:30, hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 1685 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.75 (d, J = 15.9 Hz, 1 H, CH*H*), 3.39 (s, 2 H, CH_2), 3.68 (d, J = 15.9 Hz, 1 H, C*H*H), 6.98–7.01 (m, 4 H, ArH), 7.10–7.24 (m, 5 H, ArH), 7.32–7.34 (m, 1 H, ArH), 7.43 (s, 1 H, ArH), 10.16 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 45.5, 68.2, 115.2, 116.2, 120.7, 122.8, 127.9, 128.1, 128.7, 129.5, 134.9, 137.1, 141.1, 142.6, 168.4 ppm. MS (ES+): *m/z* (%) = 394.1 (100) $[M + H]^+$. $C_{21}H_{16}ClN_3OS$ (exact mass: 393.0703): calcd. C 64.03, H 4.09, N 10.67; found C 64.21, H 3.86, N 10.75.

Supporting Information (see footnote on the first page of this article): Spectroscopic data for all the starting substrates and copies of NMR spectra for all the compounds.

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[15] Crystal data for **17d** (crystallized from $CHCl_3$/EtOAc): Empirical formula: $C_{30}H_{27}Cl_1F_1N_3O_3$, formula mass = 532.00 g/mol, T = 298(2) K, wavelength = 0.71073 Å, triclinic, space group = $P\bar{1}$, a = 9.367(2), b = 9.858(2), c = 14.818(4) Å, α = 90.982(4), β = 106.384(4), γ = 91.166(5)°, V = 1312.1(5) Å^3, Z = 2, D = 1.347 mg/m^3, μ(Mo-K_α) = 0.190 mm^{-1}, F(000) = 556, colorless block, size 0.2 × 0.2 × 0.2 mm, 8535 reflections collected, R(int) = 0.0327, unique reflections = 6183, final R indices [$I > 2\sigma(I)$] on F^2: $R1$ = 0.0897, $wR2$ = 0.2376, GoF = 1.014; R indices (all data): $R1$ = 0.1701, $wR2$ = 0.3080. Data were collected with a Bruker SMART CCD4 X-ray diffraction instrument with graphite-monochromated Mo-K_α radiation (λ = 0.710 Å) at room temp. The structure was solved by direct methods with the SIR92 programme and refined with full-matrix least squares on F^2 (SHELX97). The structure was expanded with the Fourier technique. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at geometrically idealized positions. All the software packages were integrated into the WINGX software package. CCDC-699461 (**17d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] Crystal data for **19c** (crystallized from $CHCl_3$): Empirical formula: $C_{30}H_{24}Cl_7N_3O_3$, formula mass = 532.00 g/mol, T = 298(2) K, wavelength = 0.71073 Å, triclinic, space group = $P\bar{1}$, a = 9.367(2), b = 9.858(2), c = 14.818(4) Å, α = 90.982(4), β = 106.384(4), γ = 91.166(5)°, V = 1312.1(5) Å^3, Z = 2, D = 1.347 mg/m^3, μ(Mo-K_α) = 0.190 mm^{-1}, F(000) = 556, colorless block, size 0.2 × 0.2 × 0.2 mm, 8535 reflections collected, R(int) = 0.0327, unique reflections = 6183, final R indices [$I > 2\sigma(I)$] on F^2: $R1$ = 0.0897, $wR2$ = 0.2376, GoF = 1.014; R indices (all data): $R1$ = 0.1603, $wR2$ = 0.2679. Data were collected with a Bruker SMART CCD4 X-ray diffraction instrument with graphite-monochromated Mo-K_α radiation (λ = 0.710 Å) at room temp. The structure was solved by direct methods with the SIR92 programme and refined with full-matrix least squares on F^2 (SHELX97). The structure was expanded with the Fourier technique. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at geometrically idealized positions. All the software packages were integrated into the WINGX software package. CCDC-699462 (**19c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] All the spirocyclic derivatives were evaluated as antimalarials in a chloroquine-sensitive *P. falciparum* strain (3D-7), but none of them displayed any significant activity.

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