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# A strategic approach to the synthesis of novel class of dispiroheterocyclic derivatives through 1,3 dipolar cycloaddition of azomethine ylide with (*E*)-3-arylidene-2,3-dihydro-8-nitro-4-quinolone

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ABSTRACT

A series of novel dispiroheterocyclic system containing 4-quinolone nucleus are prepared by 1,3 dipolar cycloaddition of azomethine ylides with a newly prepared (*E*)-3-arylidene-2,3-dihydro-8-nitro-4-quinolone as dipolarophile. The ylide was generated in situ from isatin and sarcosine/1,3-thiazolane-4-carboxylic acid. The regio and stereochemistry of the synthesized product was established by $^{1}H$, $^{13}C$, 2D NMR techniques and single crystal X-ray analysis. The molecular mechanism of this cycloaddition has been investigated by means of the density functional theory (DFT) method. The experimental results of regioselectivity product of 1,3 dipolar cycloaddition have shown good agreement with the computed Frontier molecular orbital calculation (FMO) and fukui function analysis.



Recent years have witnessed an increased interest[1] on the use of 1,3 dipolar cycloaddition reaction of azomethine ylide with a dipolarophile to construct five membered heterocycles[2] and spiro compounds[3] in a regio and stereo controlled fashion.[4] The spiro pyrrolidinyl oxindole nucleus is found in the molecular framework of many natural products such as horsifiline,[5] elacomine,[6] spirotryptostatine A and B[7] and coreleucine.[8] The derivatives of spiropyrrolidinyl oxindole find important biological applications such as inhibition of microtubule assembly,[9] modulation of the function of muscarinic serotonin receptor,[10] potent non-peptide inhibitor of the p53–MDM2 interaction,[11] inhibitors of human NK-1 receptor,[12] poliovirus and rhinovirus 3C-proteinase inhibitor.[13] Similarly pyrrolothiazoles are endowed with a wide range of biological activities, namely hepatoprotective,[14] antibiotic,[15] antidiabetic[16] and anticonvulsant actions.[17] Further we have found that 2,3 dihydro-4-quinolone ring system is present in a large number of alkaloids[18] and as important intermediates in organic synthesis[19] and exhibits a range of pharmacological properties by serving as analgesic,[20] antibacterial,[21] antimalarial,[22] antitumour,[23] CRTH2 antagonist receptor[24] and 5HT6 serotonin receptor.[25] In particular, nitro substituted 2,3 dihydro-4-quinolone derivatives have also been found to act as poly(ADP-ribosyl) transferase (PARP) inhibitor[26] and induce necrotic death of leukaemic cells HL-60[27] besides acting as important biosensors.[28] It is pertinent to note that several quinolone heterocycles show improved biological activities when they are attached with other heterocycles.[29] Hence it would be an attractive idea to prepare quinolone attached spiro pyrrolidinyl oxindole system in order to utilize such derivatives for the above mentioned properties. Based on these expectations, we have devised a strategy to prepare a rare class of dispiroheterocycles containing spiropyrrolidine oxindole/spirothiapyrrolizidine oxindole and 2,3-dihydro-8-nitro-4-quinolone ring fragments. In this connection, we have chosen the dipolarophile (*E*)-3-arylidene-2,3-dihydro-8-nitro-4-quinolone to undergo 1,3 dipolar cycloaddition reaction with azomethine ylide.

To begin with, the dipolarophile (*E*)-3-arylidene-2,3-dihydro-8-nitro-4-quinolones **3a–g** were prepared by the pyrrolidine base catalysed condensation of 2,3-dihydro-8-nitro-4-quinolone[30] **1** with substituted aromatic aldehydes **2a–g** which is shown in

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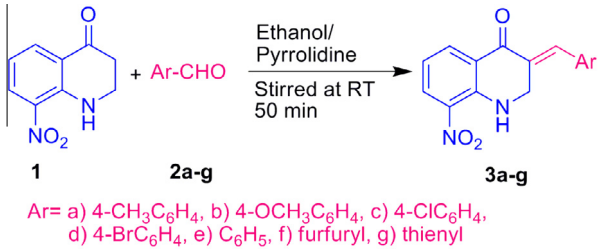



**Scheme 1.** Synthesis of (*E*)-3-arylidene-2,3-dihydro-8-nitro-4-quinolones **3a–g**.

**Table 2**
Optimization of the reaction condition for synthesis of compound **6a**

| Entry | Solvent | Temperature | Time (h) | Yield [a] (%) |
|---|---|---|---|---|
| 1 | Toluene | Reflux | 8 | 65 |
| 2 | 1,4-Dioxane | Reflux | 10 | 62 |
| 3 | Acetonitrile | Reflux | 10 | 53 |
| 4 | Ethanol | Reflux | 2.5 | 80 |
| 5 | Methanol | Reflux | 30 min | 97 |
| 6 | Tetrahydrofuran | Reflux | 10 | — |

[a] Isolated yield after recrystallization.

**Table 1**
Synthesis of (*E*)-3-arylidene-8-nitro-2,3-dihydro-4-quinolone **3a–g**

| Entry | Ar | Product | Yield[a] (%) | Mp (°C) |
|---|---|---|---|---|
| 1 | 4-$CH_3C_6H_4$ | **3a** | 95 | 166–168 |
| 2 | 4-$OCH_3C_6H_4$ | **3b** | 92 | 180–182 |
| 3 | 4-$ClC_6H_4$ | **3c** | 90 | 182–184 |
| 4 | 4- $BrC_6H_4$ | **3d** | 91 | 180–182 |
| 5 | $C_6H_5$ | **3e** | 93 | 154–156 |
| 6 | Furfuryl | **3f** | 88 | 184–186 |
| 7 | Thienyl | **3g** | 89 | 178–180 |

[a] Isolated yield after recrystallization.

**Table 3**
Synthesis of dispiropyrrolidine oxindole derivatives **6a–g**

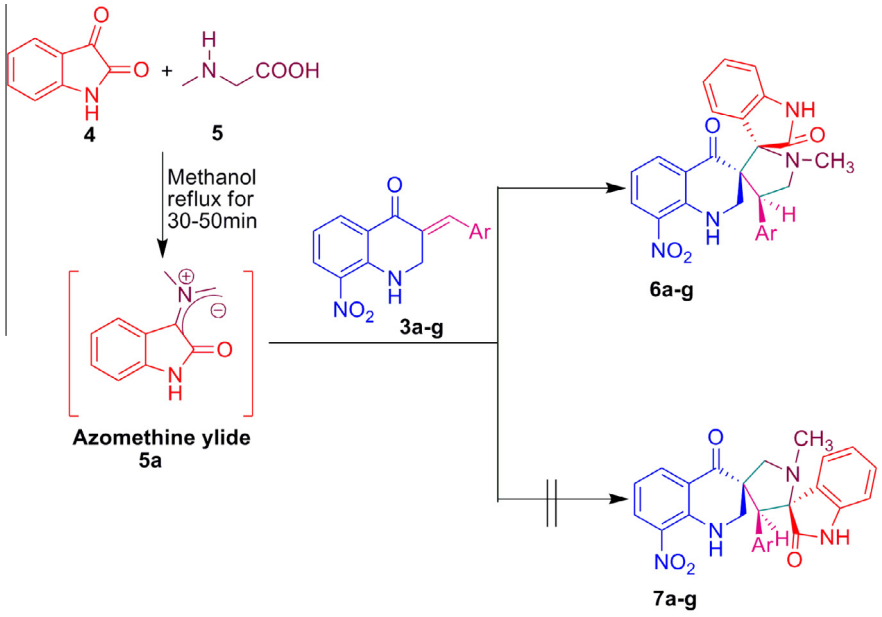
| Entry | Ar | Product | Time (min) | Yield[a] (%) | Mp (°C) |
|---|---|---|---|---|---|
| 1 | 4-$CH_3C_6H_4$ | **6a** | 30 | 97 | 202–204 |
| 2 | 4-$OCH_3C_6H_4$ | **6b** | 30 | 94 | 210–212 |
| 3 | 4-$C1C_6H_4$ | **6c** | 50 | 92 | 212–214 |
| 4 | 4-$BrC_6H_4$ | **6d** | 50 | 94 | 216–218 |
| 5 | $C_6H_5$ | **6e** | 50 | 95 | 208–210 |
| 6 | Furfuryl | **6f** | 40 | 91 | 206–208 |
| 7 | Thienyl | **6g** | 50 | 87 | 200–202 |

[a] Isolated yield after recrystallization.

Scheme 1 and Table 1.[31] Subsequent 1,3 dipolar cycloaddition of azomethine ylide **5a**, which was generated from the decarboxlative condensation of isatin **4** and sarcosine **5**, with **3a–g**, afforded novel dispiropyrrolidine oxindole derivatives **6a–g** (Scheme 2).

The choice of an appropriate reaction medium plays a pivotal role in the successful synthesis of 1,3 dipolar cycloaddition reaction. We have carried one-pot three component reaction of isatin **4** (1 mmol), sarcosine **5** (1.5 mmol) and (*E*)-3-(4-methylbenzylidene)-2,3-dihydro-8-nitro-4-quinolone **3a** (1 mmol) as a model substrate to optimize the reaction conditions. The reaction was conducted in diverse solvents such as toluene, 1,4-dioxane, acetonitrile, ethanol, methanol and tetrahydrofuran (Table 2). As seen from Table 2, the best results were obtained by refluxing the reaction mixture in methanol for 30 min to furnish dispiropyrrolidine oxindole derivative **6a** in good yield (97%) with high regioselectivity (Table 2, entry 5). After standardizing the optimum reaction conditions, we found that replacing the substituent in the aryl group ($OCH_3$, Cl, Br, H, furfuryl and thienyl) has not affected the yield of the product (Scheme 2, Table 3).[32]

The formation of the cycloadduct **6a** was characterized unequivocally by spectroscopic and crystallographic studies. The IR spectrum of compound **6a** showed two intense absorption bands at 1713 and 1692 $cm^{-1}$ characteristic of 4-quinolone and oxindole ring carbonyl functionalities, respectively. The $^1H$ NMR spectrum (Fig. 1) of product **6a** showed a sharp singlet at $\delta$ 1.97 and two triplets at $\delta$ 3.30 ($J$ = 8.0 Hz) and 3.85 ($J$ = 10.0 Hz) which




**Scheme 2.** Synthesis of dispiropyrrolidine oxindole derivatives **6a–g**.

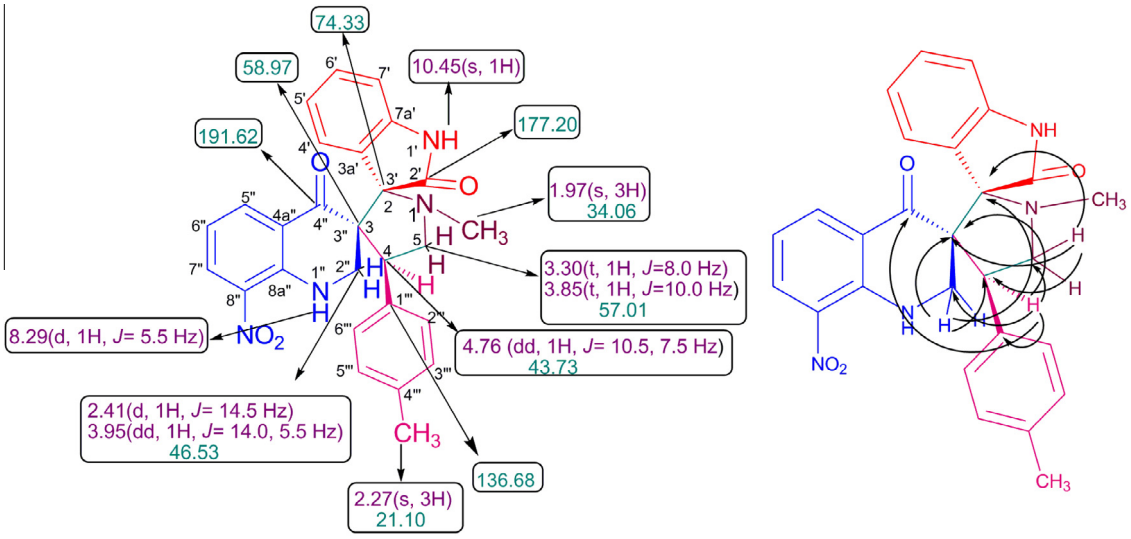
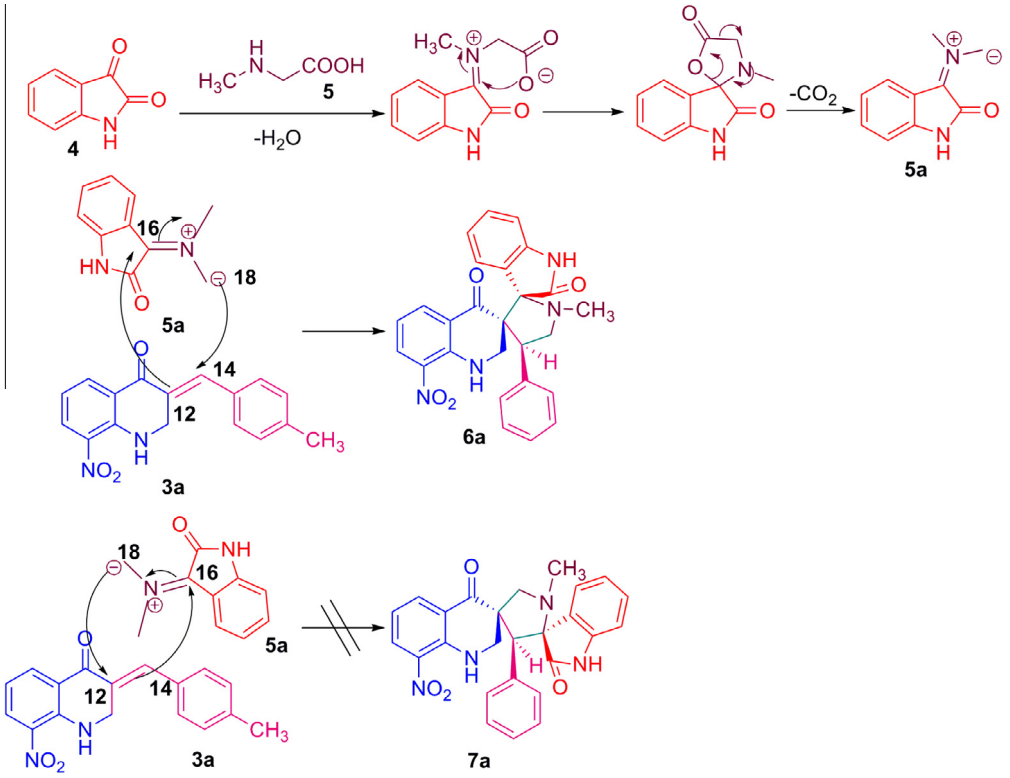



**Figure 1.** Selected $^{1}H$ and $^{13}C$ NMR and HMBC chemical shifts of **6a**.

were accounted for pyrrolidine N–$CH_3$ and N–$CH_2$ protons, respectively. The pyrrolidinyl methine proton appeared as a doublet of doublet at $\delta$ 4.76 ($J$ = 10.5 Hz, 7.5 Hz) clearly demonstrating the regiochemistry of the cycloaddition reaction. Had the other regio isomer **7a** formed, the pyrrolidinyl methine proton would have appeared as a singlet in the $^{1}H$ NMR spectrum. The doublet, resonating at $\delta$ 8.29 ($J$ = 5.5 Hz) and a singlet at $\delta$ 10.45, were assignable to quinolone and oxindole N–H protons ($D_2O$ exchangeable proton), respectively. In $^{13}C$ NMR spectrum (Fig. 1) the peaks resonated at $\delta$ 34.06, 57.01, 58.97, 74.33, 177.20 and 191.62 ppm, and were assignable to N–$CH_3$, N–$CH_2$, spirocarbons, amide and 4-quinolone carbonyl, respectively. The presence of spiro carbons was also confirmed by the disappearance of peaks at $\delta$ 58.97 and 74.33 in DEPT-135 spectrum.

The long range HMBC correlation (Fig. 1) was noticed between pyrrolidinyl methylene H-5 ($\delta$ 3.30) and quinolonyl methylene H-2″ ($\delta$ 3.95) with C-4 ($\delta$ 43.73), C-3 ($\delta$ 58.97) and C-2 ($\delta$ 74.33) carbons. The pyrrolidinyl methine H-4 ($\delta$ 4.76) correlated with C-2″ ($\delta$ 46.53), C-3 ($\delta$ 58.97), C-5 ($\delta$ 57.01), C-4″ ($\delta$ 191.62) and C-1‴ ($\delta$ 136.68) supporting the structure **6a**. The presence of a molecular ion peak at $m/z$ = 468 (M+) in the mass spectrum further confirmed the formation of **6a**. Finally, the regio and stereochemical outcome of the cycloaddition was determined unambiguously by single crystal X-ray analysis[33] of cycloadduct **6b** (Fig. S1, Supplementary data).

The formation of regioisomers **6a** could be explained as follows: decarboxylative condensation of the isatin **4** with sarcosine **5** gives the azomethine ylide (dipole **5a**) which then undergoes 1,3 dipolar




**Scheme 3.** Formation of compound **6a**.

cycloaddition reaction with the dipolarophile **3a** in a regioselective manner as shown in Scheme 3. To understand the relative stereochemistry of cycloadduct **6a**, the conformation of ylide **5a** was studied by the quantum chemical density functional theory (DFT) method. The anti conformation has higher structural stability and showed strong hydrogen bond (2.073 Å) between one of the methylene hydrogen atoms and amide carbonyl oxygen leading to huge stabilization energy compared with syn conformation (Fig. S2, Supplementary data).

Frontier molecular orbital (FMO) calculations were carried out to understand the observed regio selectivity. The FMO calculation revealed that the HOMO of dipole and LUMO of dipolarophile interaction (normal electron demand condition) are more feasible than the HOMO of dipolarophile and LUMO of dipole (inverse electron demand condition) as it involves lower energy transition which is shown in Figure S3. [34] The DFT based local chemical reactivity fukui function parameters, for nucleophilic ($f_k^+$) and electrophilic attack ($f_k^-$), were calculated through the Mullikan atomic charges.[34,35] The calculated local chemical reactivity parameters of azomethine ylide **5a** and dipolarophile **3a** are given in Table 4. For the dipole **5a**, C18 (0.032 a.u.) has a larger $f_k^-$ value than C16 (0.022 a.u.). The C14 site of dipolarophile **3a** (the β position) exhibits larger local electrophilicity value than C12 site. Therefore, C14 of the dipolarophile **3a** is the preferred position for a nucleophilic attack by C18 of the azomethine ylide **5a**, which is good agreement with experimental observation.

The possible regiochemical approach of azomethine ylide **5a** and dipolarophile **3a** was further studied by the transition state (TS) analysis as shown in Figure S5. It reveals that the favourable secondary orbital interaction (SOI) takes place through the hydrogen bond between one of the methylene hydrogen atoms of quinolone dipolarophile **3a** with amide carbonyl of azomethine ylide **5a** (2.030 Å) and the methyl hydrogen atom of azomethine ylide **5a** with quinolone carbonyl of dipolarophile **3a** (2.147 Å).[36] Moreover, low activation energy (9.44, 12.83 kcal/mol) and reaction energy (−19.63, −17.88 kcal/mol) indicate the formation of compound **6a** was exothermic in nature and the calculated energy barrier, at B3LYP/6-31G* and MO5-2X/6-31G* levels, which are shown in Figure S6 (Supplementary data). All the computational calculations were performed using the GAUSSIAN 09W program.[37]

**Table 4**
Local properties of dipolarophile **3a** and azomethine ylide **5a**

| Reactant | Site | $f_k^+$ (a.u.) | $f_k^-$ (a.u.) |
|---|---|---|---|
| Dipolarophile **3a** | C12 | 0.076 | 0.003 |
| Dipolarophile **3a** | C14 | 0.329 | 0.004 |
| Azomethine ylide **5a** | C16 | 0.022 | 0.057 |
| Azomethine ylide **5a** | C18 | 0.032 | 0.081 |

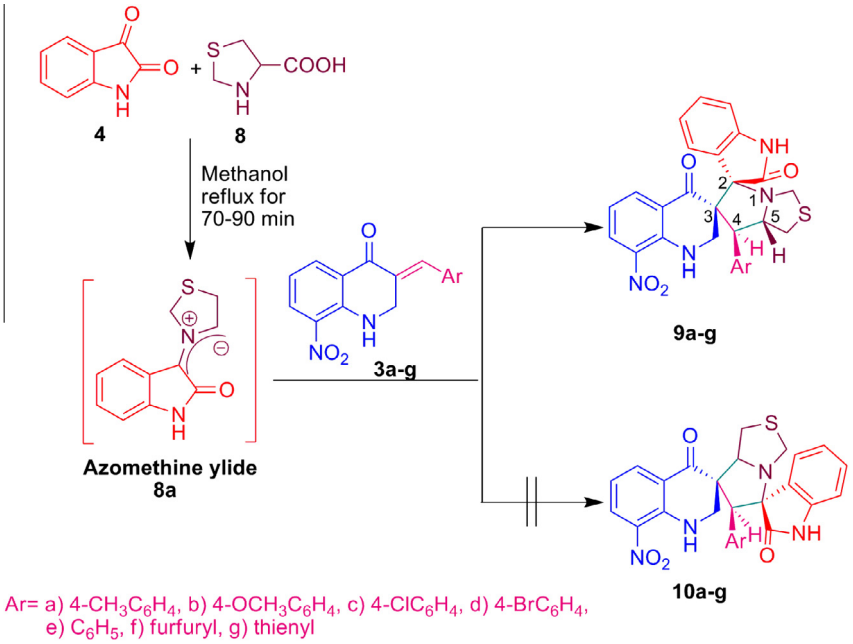
**Table 5**
Synthesis of dispirothiapyrrolozidine oxindole derivatives **9a–g**

| Entry | Ar | Product | Time (min) | Yield[a] (%) | Mp (°C) |
|---|---|---|---|---|---|
| 1 | 4-$CH_3C_6H_4$ | **9a** | 70 | 96 | 236–238 |
| 2 | 4-$OCH_3C_6H_4$ | **9b** | 80 | 94 | 216–218 |
| 3 | 4-$ClC_6H_4$ | **9c** | 90 | 93 | 228–230 |
| 4 | 4-$BrC_6H_4$ | **9d** | 90 | 91 | 234–236 |
| 5 | $C_6H_5$ | **9e** | 80 | 94 | 218–216 |
| 6 | Furfuryl | **9f** | 80 | 90 | 208–210 |
| 7 | Thienyl | **9g** | 90 | 89 | 214–216 |

[a] Isolated yield after recrystallization.

The scope and generality of the aforementioned cycloaddition methodology were further established by the reaction of derivatives of (*E*)-3-arylidene-2,3-dihydro-8-nitro-4-quinolone **3a–g** with azomethine ylide generated in situ from isatin **4** and thiaproline **8** to afford the corresponding dispirothiapyrrolizidines **9a–g** in good yield (Scheme 4, Table 5).

In conclusion, we have developed a simplified approach for the synthesis of novel dispiropyrrolidines/dispirothiapyrrolizidines oxindole by using the substrate of the type (*E*)-3-arylidene-8-nitro-2,3 dihydro-4-quinolone for the first time as dipolarophile. The method is carried out by one-pot, three-component 1,3-dipolar cycloaddition of azomethine ylides which affords high yield of products in short reaction time with high regio and stereoselectivity. The regiochemistry of the cycloaddition has been explained by using the density functional theory based on FMO calculation and Fukui function analysis. The presence of the 8-nitro group in




**Scheme 4.** Synthesis of dispirothiapyrrolozidine oxindole derivatives **9a–g**.

dihydroquinolone provides scope for preparing products in a wide range of applications such as sensors, drugs and other materials of biological importance.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.077.

## References and notes


1. (a) Rao, J. N. S.; Raghunathan, R. *Tetrahedron Lett.* **2012**, *53*, 854; (b) Rajesh, S. M.; Bala, B. D.; Perumal, S. *Tetrahedron Lett.* **2012**, *53*, 5367; (c) Taghizadeh, M. J.; Arvinnezhad, H.; Samadi, S.; Jadidi, K.; Javidan, A.; Notash, B. *Tetrahedron Lett.* **2012**, *53*, 5148; (d) Lanka, S.; Thennarasu, S.; Perumal, P. T. *Tetrahedron Lett.* **2012**, *53*, 7052.
2. (a) Tsuge, O.; Kanemasa, S. Advances in Heterocyclic Chemistry In In Katritzky, A. R., Ed.; Academic: San Diego, CA, 1989; Vol. 45, p 231; (b)*1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, NY, 1984. Vols. 1 and 2.
3. (a) Poornachandran, M.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *62*, 11274; (b) Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *63*, 8010; (c) Pellissier, H. *Tetrahedron Lett.* **2007**, *63*, 3235; (d) Kumar, R. R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *Tetrahedron Lett.* **2008**, *64*, 2962; (e) Kumar, R. S.; Rajesh, S. M.; Perumal, S.; Banerjee, D.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2010**, *45*, 411; (f) Lakshmi, N. V.; Arun, Y.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 3437.
4. (a) Harwood, L. M.; Vickers, R. J. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products In Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; p 169; (b) Gothelf, K. V. Cycloaddition Reactions in Organic Synthesis In Kobaya-shi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; p 211. Chapter 6; (c) Ganguly, A. K.; Seak, N.; Popov, V.; Wang, C. H.; Kuang, R.; Saksena, A. K.; Pramanik, B. N.; Chan, T. M.; McPhail, A. F. *Tetrahedron Lett.* **2002**, *43*, 898; (d) Shanmugam, P.; Viswambharan, B.; Madhavan, S. *Org. Lett.* **2007**, *9*, 4095; (e) Kumar, R. R.; Loganayaki, B.; Perumal, S. *Synth. Commun.* **2009**, *39*, 3197.
5. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.
6. James, M. N. G.; Williams, G. J. B. *Can. J. Chem.* **1972**, *50*, 2407.
7. (a) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832; (b) Hiton, S. T.; Ho, T. C.; Pjevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639; (c) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135.
8. Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Watanabe, R. I. *Phytochemistry* **1998**, *48*, 437.
9. Usui, T.; Kondoh, M.; Cui, C.-B.; Mayumi, T.; Osada, H. *Biochem. J.* **1998**, *333*, 543.
10. Kang, T. H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39.
11. Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432.
12. Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892.
13. Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277.
14. Hasegawa, M.; Nakayama, A.; Yokohama, S.; Hosokami, T.; Kurebayashi, Y.; Ikeda, T.; Shimoto, Y.; Ide, S.; Honda, Y.; Suzuki, N. *Chem. Pharm. Bull.* **1995**, *43*, 1125.
15. (a) Baldwin, J. E.; Freeman, R. T.; Lowe, C.; Schofield, C. J.; Lee, E. *Tetrahedron Lett.* **1989**, *45*, 4537; (b) Baldwin, J. E.; Lowe, C.; Schofield, C. J.; Lee, E. *Tetrahedron Lett.* **1986**, *27*, 3461.
16. (a) Aicher, T. D.; Knorr, D. C.; Smith, H. C. *Tetrahedron Lett.* **1998**, *39*, 8579; (b) Aicher, T. D.; Balkan, B.; Bell, P. A.; Brand, L. J.; Cheon, S. H.; Deems, R. O.; Fell, J. B.; Fillers, W. S.; Fraser, J. D.; Gao, J.; Knorr, D. C.; Kahle, G. G.; Leone, C. L.; Nadelsen, J.; Simpson, R.; Smith, H. C. *J. Med. Chem.* **1998**, *41*, 4556.
17. Trapani, G.; Franco, M.; Latrofa, A.; Genchi, G.; Brigiani, M.; Mazzoccoli, M.; Persichel-la, M.; Serra, M.; Biggio, G.; Liso, G. *Eur. J. Med. Chem.* **1994**, *29*, 197; (b) Trapani, G.; Franco, M.; Latrofa, A.; Carotti, A.; Cellamare, S.; Serra, M.; Ghiani, C. A.; Tuligi, G.; Biggio, G.; Liso, G. *J. Pharm. Pharmacol.* **1996**, *48*, 834.
18. (a) Huges, G. K.; Lahey, F. N.; Price, J. R.; Webb, L. J. *Nat. Protoc.* **1948**, *162*, 223; (b) Svoboda, G. H.; Poore, G. A.; Simpson, P. J.; Bodor, G. B. *J. Pharm. Sci.* **1966**, *55*, 758.
19. (a) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *2*, 1395; (b) Nieman, J. A.; Ennis, M. D. *J. Org. Chem.* **2001**, *66*, 2175; (c) Cheng, D.; Zhou, J.; Saiah, E.; Beaton, G. *Org. Lett.* **2002**, *4*, 4411; (d) Hara, O.; Sugimoto, K.; Hamada, Y. *Tetrahedron Lett.* **2004**, *60*, 9381; (e) Chandrasekhar, S.; Vijeender, K.; Sridhar, C. *Tetrahedron Lett.* **2007**, *48*, 4935; (f) Lee, H.; Suzuki, M.; Cui, J.; Kozmin, S. A. *J. Org. Chem.* **2010**, *75*, 1756.
20. Atwal, M. S.; Bauer, L.; Dixit, S. N.; Gearien, J. E.; Morris, R. W. *J. Med. Chem.* **1965**, *8*, 566.
21. Morrissey, I.; Smith, J. T. *J. Med. Microbiol.* **1995**, *43*, 4.
22. La Montagne, M. P.; Blumbergs, P.; Smith, D. C. *J. Med. Chem.* **1989**, *32*, 1728.
23. (a) Xia, Y.; Yang, Z. Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S. C.; Hamel, E.; Hackl, T.; Lee, K. H. *J. Med. Chem.* **1998**, *41*, 1155; (b) Zhang, S. X.; Kuo, S.-C.; Brossi, A.; Hamel, E.; Tropsha, A.; Lee, K.-H. *J. Med. Chem.* **2000**, *43*, 167.
24. Liu, J.; Wang, Y.; Sun, Y.; Marshall, D.; Miao, S.; Tonn, G.; Anders, P.; Tocker, J.; Tang, H. L.; Medina, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6840.
25. Park, C. M.; Choi, J.; Choi, J. H.; Kim, S. Y.; Park, W. K.; Seong, C. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 698.
26. Jones, P.; Kinzel, O.; Koch, U.; Ontoria, J. M.; Pescatore, G.; Scarpelli, R.; Torrisi, C. International Patent WO 027,730, 2009.
27. Jantova, S.; Letašiova, S.; Konarikova, K.; Milata, V.; Brezova, V. *Acta Chim. Slov.* **2010**, *3*, 51.
28. (a) Fletcher, M. P.; Diggle, S. P.; Cámara, M.; Williams, P. *Nat. Protoc.* **2007**, *2*, 1254; (b) Fletcher, M. P.; Diggle, S. P.; Crusz, S. A.; Chhabra, S. R.; Cámara, M.; Williams, P. *Environ. Microbiol.* **2007**, *9*, 2683; (c) Huse, H.; Whiteley, M. *Chem. Rev.* **2011**, *111*, 152.
29. (a) Carabateas, P. M.; Brundage, R. P.; Gellote, M. D.; Lorenz, R. R.; Opalka, C. J.; Thielking, W. H.; Williams, G. L.; Lesher, G. Y. *J. Heterocycl. Chem* **1857**, *1984*, 21; (b) Kiely, J. S.; Schroeder, M. C.; Sesnie, J. C. *J. Med. Chem.* **2004**, *1988*, 31; (c) Kohlbrenner, W. E.; Wideburg, N.; Weigl, D.; Saldivar, A.; Chu, D. T. *Antimicrob. Agents Chemother.* **1992**, *36*, 81; (d) Wentland, M. P.; Lesher, G. Y.; Reuman, M.; Gruett, M. D.; Singh, B.; Aldous, S. C. *J. Med. Chem.* **1993**, *36*, 2801; (e) Eissenstat, M. A.; Kuo, G.; Weaver, J. D.; Wentland, M. P. *Bioorg. Med. Chem. Lett* **1995**, *5*, 1021.
30. Dullweber, F.; Klein, T.; Wagner, T.; Weinbrenner, S.; Boer, R. International Patent WO 103,666, 2003.
31. *General procedure for synthesis of (E)-3-arylidene-2,3-dihydro-8-nitro-4-quinolone* ***3a–g****:* An equimolar mixture of 2,3-dihydro-8-nitro-4-quinolone **1** (1 mmol) and the appropriate aldehydes **2a–g** (1 mmol) were dissolved in 15 ml of ethanol, five drops of pyrrolidine base was added and stirred at room temperature for 50 min. The solid formed in the reaction mixture was separated by filtration, dried, and recrystallized from mixture of chloroform/ethanol (1:1) to obtain the pure product **3a–g** in good yields (89–95%). Spectral data for a representative compound **3a** is given below.
*(E)-3-(4-Methylbenzylidene)-8-nitro-2,3-dihydroquinolin-4(1H)-one* ***3a****:* Isolated as red solid, yield (95%); mp = 166–168 °C; IR (KBr) $\nu_{max}$: 3363, 1656, 1623 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.36 (s, 3H), 4.78 (t, 2H, $J$ = 4.0 Hz), 6.79 (t, 1H, $J$ = 7.9 Hz, Ar-H), 7.31 (d, 2H, $J$ = 7.4 Hz, Ar-H), 7.38 (d, 2H, $J$ = 8.7 Hz, Ar-H), 7.65 (s, 1H), 8.17–8.33 (m, 2H, Ar-H), 8.67 (br s, 1H, N–H, $D_2O$ exchangeable proton). $^{13}C$ APT (100 MHz, DMSO-$d_6$): 21.63, 44.29, 115.32, 121.75, 129.27, 129.84, 130.92, 132.00, 132.99, 133.11, 136.29, 136.57, 140.27, 146.38, 181.77. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found C, 69.29; H, 4.86; N, 9.61.
32. *General procedure for the synthesis of dispiro pyrrolidine oxindole derivatives* ***6a–g****:* A mixture of isatin **4** (1 mmol), sarcosine **5** (1.5 mmol) and (*E*)-3-arylidene-2,3-dihydro-8-nitro-4-quinolone **3a–g** in methanol was refluxed for 30–50 min. The solid formed in the reaction mixture was cooled to room temperature, the solid separated by filtration, dried and recrystallized from mixture of methanol/dimethylforamide (3:1) to obtain the pure products **6a–g** in good yields (87–97%). Spectral data for a representative compound **6a** is given below.
*4-(4‴-Methylphenyl)-1-methylpyrrolidine-spiro[2.3′]oxindole-spiro[3.3″]-8″-nitro-1″H-quinolin-4(2″H)-one* ***6a****.* Isolated as red solid. yield (97%); mp = 202–204 °C; IR (KBr) $\nu_{max}$: 3402, 3297, 1713, 1692, 1618 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.97 (s, 3H), 2.27 (s, 3H), 2.41 (d, 1H, $J$ = 14.5 Hz), 3.30 (t, 1H, $J$ = 8.0 Hz), 3.85 (t, 1H, $J$ = 10.0 Hz), 3.95 (dd, 1H, $J$ = 14.0, 5.5 Hz), 4.76 (dd, 1H, $J$ = 10.5, 7.5 Hz), 6.46–6.54 (m, 4H, Ar-H), 6.84–6.88 (m, 1H, Ar-H), 7.15 (d, 2H, $J$ = 7.5 Hz, Ar-H), 7.30 (d, 2H, $J$ = 8.0 Hz, Ar-H), 7.85 (dd, 1H, $J$ = 7.5, 1.0 Hz, Ar-H), 7.96 (dd, 1H, $J$ = 8.0, 1.5 Hz, Ar-H), 8.29 (d, 1H, $J$ = 5.5 Hz, N–H, $D_2O$ exchangeable proton), 10.45 (s, 1H, N–H, $D_2O$ exchangeable proton). $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$ 21.10, 34.60, 43.73, 46.53, 57.01, 58.97, 74.33, 109.19, 115.11, 121.25, 122.83, 126.35, 126.51, 129.37, 129.48, 129.61, 131.85, 132.09, 134.80, 136.68, 143.19, 145.60, 177.20, 191.62. Mass (ESI) $m/z$; 468 $[M+H]^+$. Anal. Calcd for $C_{27}H_{24}N_4O_4$: C, 69.22; H, 5.16; N, 11.96. Found C, 69.12; H, 5.24; N, 12.02.
33. Crystallographic data for compound **6b** in this paper have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no: CCDC-858966. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 01223 336033 or email:deposit@ccdc.cam.ac.uk.
34. Babu, A. R. S.; Raghunathan, R.; Gayatri, G.; Sastry, G. N. *J. Heterocycl. Chem* **2006**, *43*, 1.
35. (a) Domingo, L. R.; Arno, M.; Contreras, R.; Perez, P. *J. Phys. Chem. A* **2002**, *106*, 952; (b) Domingo, L. R. *Tetrahedron Lett.* **2002**, *58*, 3765; (c) Domingo, L. R.; Aurell, M. J. *J. Org. Chem.* **2002**, *67*, 959; (d) Domingo, L. R.; Aurell, M. J.; Perez, P.; Contreras, R. *J. Org. Chem.* **2003**, *68*, 3884; (e) Domingo, L. R.; Andres, J. *J. Org. Chem.* **2003**, *68*, 8662.

36. Yuvaraj, P.; Reddy, B. S. R. *Tetrahedron Lett.* **2013**, *54*, 821.
37. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E., Jr.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzales, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN 09, Revision A.11. 2;* Gaussian Inc.: Pittsburgh, PA.