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Graphical Abstract

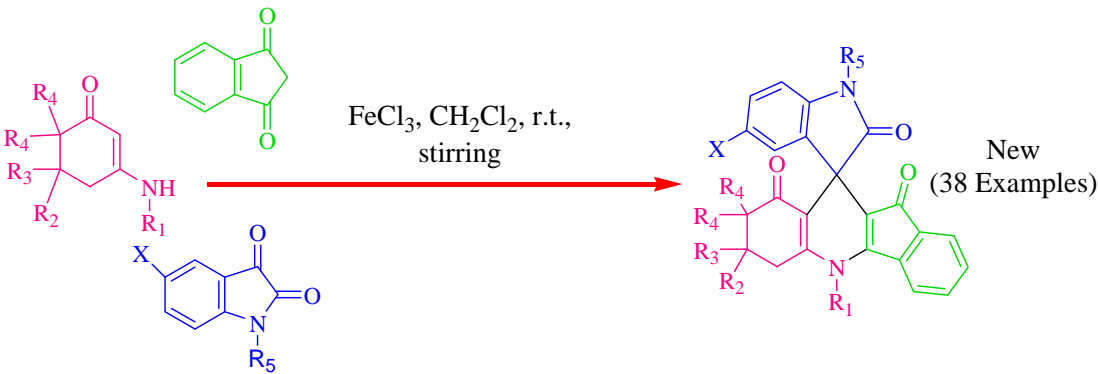
FeCl₃-catalyzed combinatorial synthesis of functionalized spiro[indolo-3,10'-indeno [1,2-b]quinolin]-trione derivatives

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Keywords: *environmentally friendly, multicomponent reactions, isatins, spirocyclic compounds, Lewis acid catalysis, ferric trichloride.*

Abstract: An efficient, inexpensive, environmentally friendly and high yield one-pot route to new spiro[indolo-3,10'-indeno [1,2-b]quinolin]-trione derivatives has been developed, involving three-component reaction of enaminones, N-substituted isatins and indane-1,3-dione catalysed by FeCl₃. The approach to this spiro-heterocycle is noteworthy because it results in the formation of three new σ (two C-C and one C-N) bonds in a single operation, leading to the construction of novel spiro skeleton. This method works on a large scale in excellent yields.

INTRODUCTION

Multicomponent reactions (MCRs) are important tools for medicinal and organic chemists because they offer significant advantages over the stepwise convergent construction of complex molecules¹. The structurally diverse enaminones have been of longstanding interest for the construction of biologically-relevant core structures via multicomponent reactions (MCRs).² Examples of such heterocyclic spiro-fragments are shown in **Figure 1**,³ including those derived

from isatin⁴, quinoline⁵, indenone⁶, and indole⁷, building blocks. Furthermore, C-3 spiroindoline compounds⁸ represents an important structural unit found in many natural alkaloids⁹ such as spirotryprostatins A and, B, which function as inhibitors of microtubule assembly, and pteropodine and isopteropodine alkaloids, which interact with muscarinic serotonin receptors. In this chemistry, our attention has been drawn to iron (III) chloride as a green and efficient Lewis acid catalyst for C-C bond and carbon–heteroatom formation^{10,11} including MCRs under mild reaction conditions¹². Several FeCl₃-based isatin-based multicomponent methods have been reported for the synthesis of spiro[indolo-3,10'-indeno [1,2-b]quinolin]-triones heterocycles⁴ and related molecules¹³.

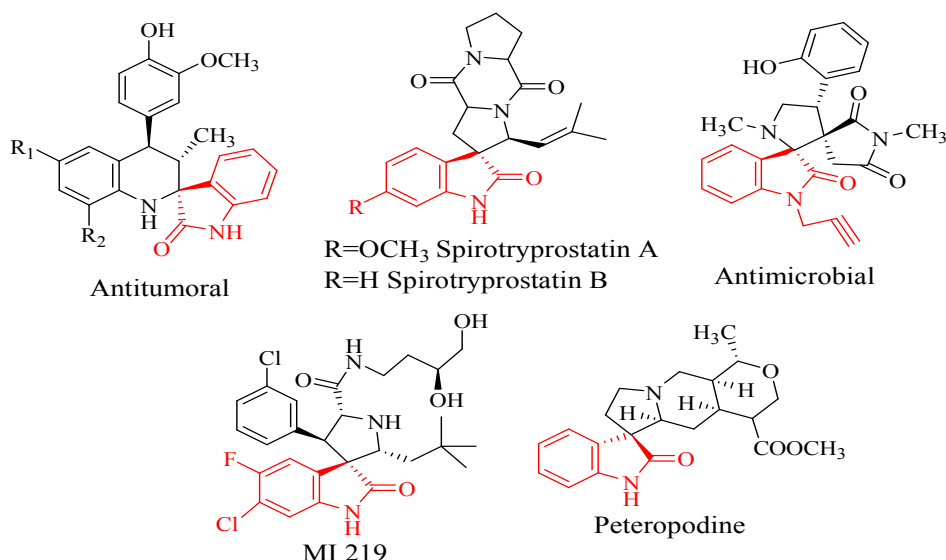
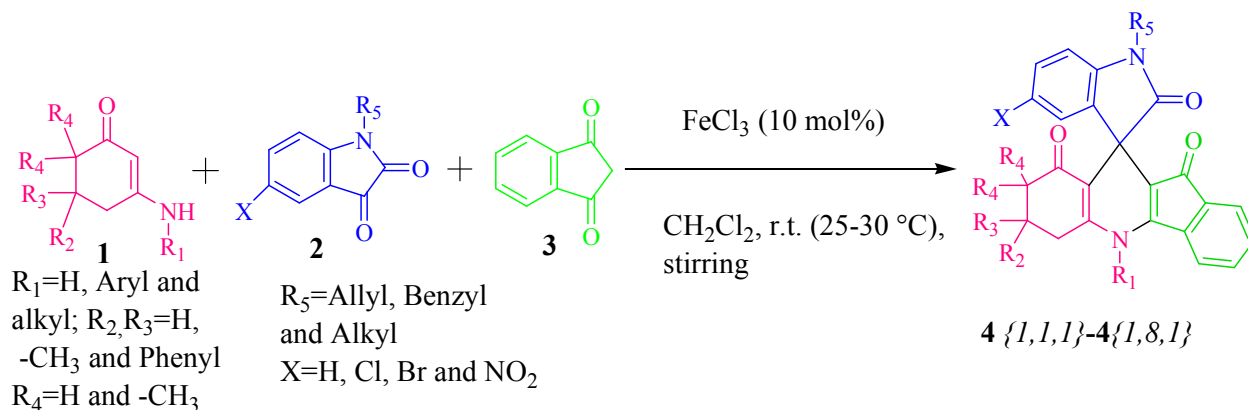


Figure 1. Examples of biologically important fused spiro-compounds.

We describe here the extension of FeCl₃-catalyzed three-component coupling methodology to commercially available cyclic 1,3-dicarbonyl compounds, amines and isatins for the synthesis of highly functionalized spiro-derivatives (**Scheme 1**). This process provides good to excellent yields of the desired compounds under mild conditions.

Scheme 1: MCR synthesis of spiro[indolo-3,10'-indeno [1,2-b]quinolin]-triones heterocycles.

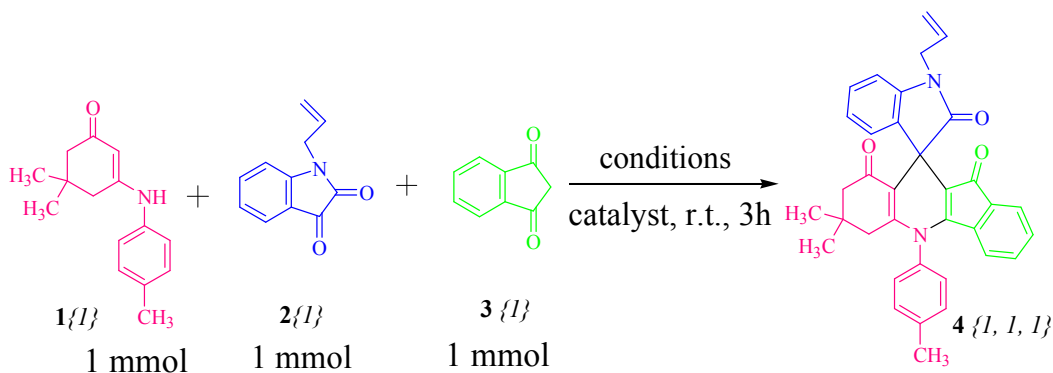


RESULTS AND DISCUSSION

Reaction conditions

Enaminone **1**{*I*}, N-substituted isatin **2**{*I*} and indane 1,3-dione **3**{*I*} served as model substrates to explore the three-component reaction conditions in the presence of various Lewis acidic catalysts in organic solvent (**Figure 2**, **Table 1**). FeCl_3 (10 mol %) was found to be the best catalyst, giving **4**{*I,I,I*} in 92% yield (**Table 1**, entry 5). While diminishing (entry 6) or increasing (entry 7) the amount of catalyst made no significant difference, the presence of catalyst was required (entry 1). Other Lewis acids (entries 2, 3, 4) and mild protic acids (entries 8, 9) gave the same product in moderate yield, but HCl provided only trace amounts, perhaps due to decomposition of the product in the presence of strong acid. Among the organic solvents tested (CH_3CN , EtOH, MeOH, Toluene, THF, DMF and DMSO; entries 11-17), CH_2Cl_2 gave the best yields by substantial amounts.

Table 1. Optimization of reaction conditions for the synthesis of compound **4**{*I,I,I*}^a



entry	catalyst (mol %) / solvent	Yield ^b 4{I, I, I} (%)
1	None (-), DCM	5
2	AlCl ₃ (10), DCM	45
3	SnCl ₂ (10), DCM	32
4	ZnCl ₂ (10), DCM	35
5	FeCl₃(10), DCM	92
6	FeCl ₃ (5), DCM	80
7	FeCl ₃ (20), DCM	87
8	AcOH (5), DCM	55
9	H ₃ BO ₃ (5), DCM	38
10	HCl (5), DCM	trace
11	FeCl ₃ (5), ACN	75
12	FeCl ₃ (5), EtOH	65
13	FeCl ₃ (5), MeOH	52
14	FeCl ₃ (5), Toluene	66
15	FeCl ₃ (5), THF	55
16	FeCl ₃ (5), DMF	30
17	FeCl ₃ (5), DMSO	25

^aReaction conditions: enaminone (**1{I}**, 1 mmol), isatin (**2{I}**, 1 mmol), indane-1,3-dione (**3{I}**, 1 mmol), different catalysts, different solvents. ^bYields of isolated products.

Substrate scope

With favorable reaction conditions established (10 mol% FeCl₃, CH₂Cl₂ solvent, room temperature), the substrate scope of this FeCl₃-catalyzed MCRs process was explored with 27 enaminones (**1{I}**-**1{27}**), 8 N-substituted isatins (**2{I}**-**2{8}**) and indane -1,3-dione (**3{I}**) (Figure 2 and Table 2).

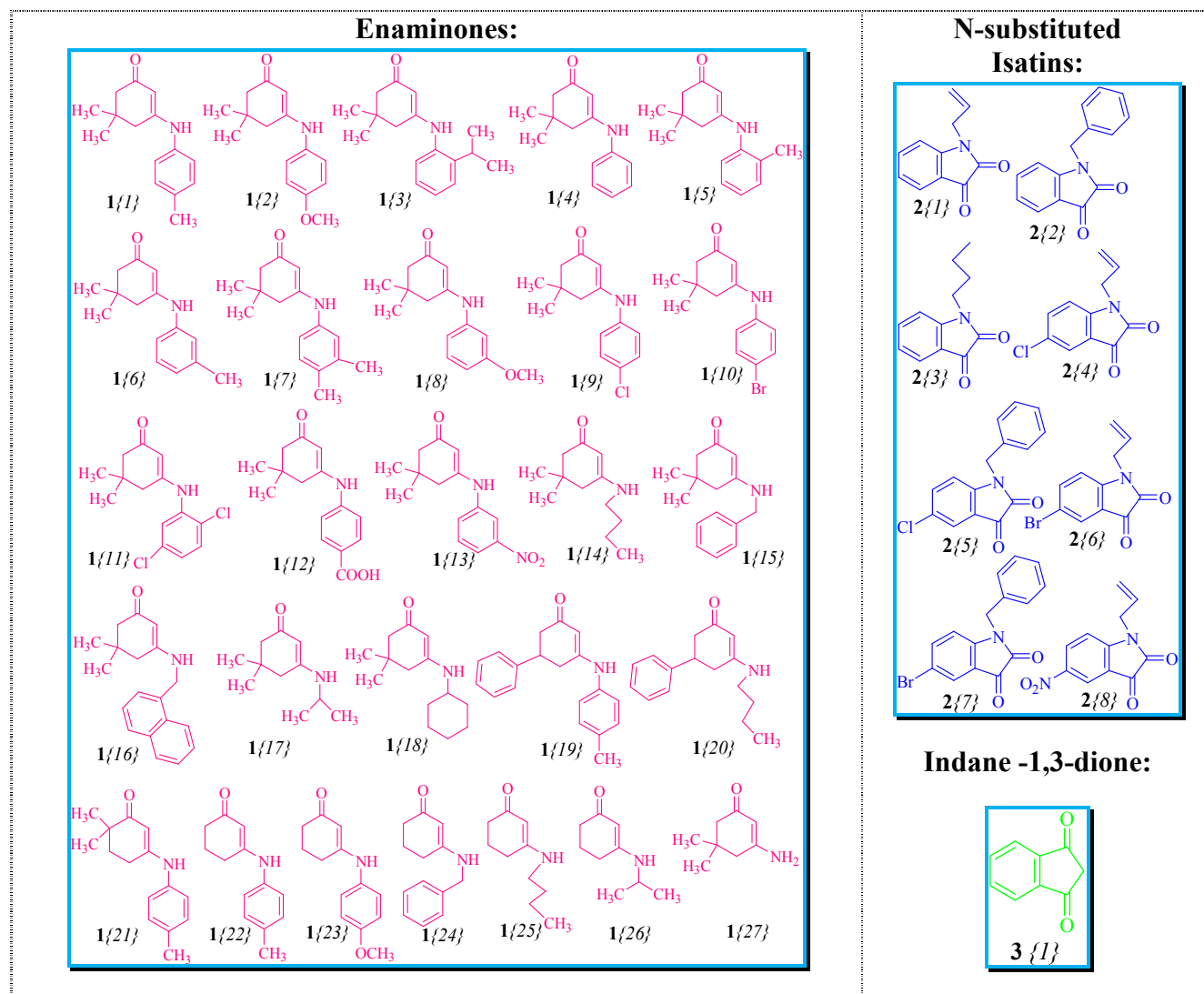
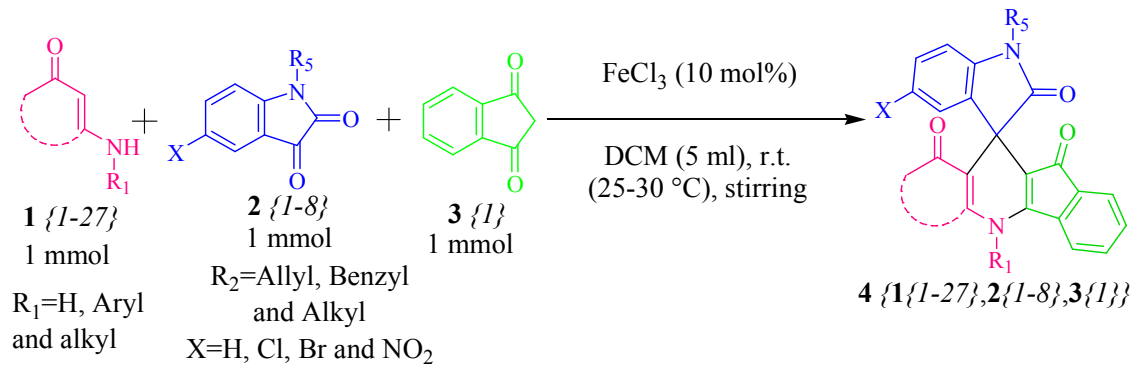


Figure 2. Enaminone and isatin reagents tested in FeCl_3 -catalyzed multicomponent condensation.

Various 5,5 disubstituted enaminones **1** were found to give corresponding products **4{1,1,1}**-**4{18,1,1}**, in yields ranging from 60% to 93% (**Table 2**, entries 1 to 11). Unsubstituted enaminones also gave good yields (**Table 2**, entries 18-20, 24, 25, 27 and 31). Phenyl substitution at the 5 position (**1{19}** and **1{20}**), as well as 6,6-disubstitution (**1{21}**) provided lower yields (**Table 2**, entries 12, 16, 17, 34), the latter most probably due to steric factors. The electronic nature of N-aryl enaminone substituents had little effect, with electron-donating

(methyl, isopropyl, methoxy) or electron-withdrawing (chloro, bromo, nitro, carboxylic acid) aromatic groups (R_1) giving similar results (**Table 2**, entries 1-6).

Table 2: Synthesized spiro compounds.



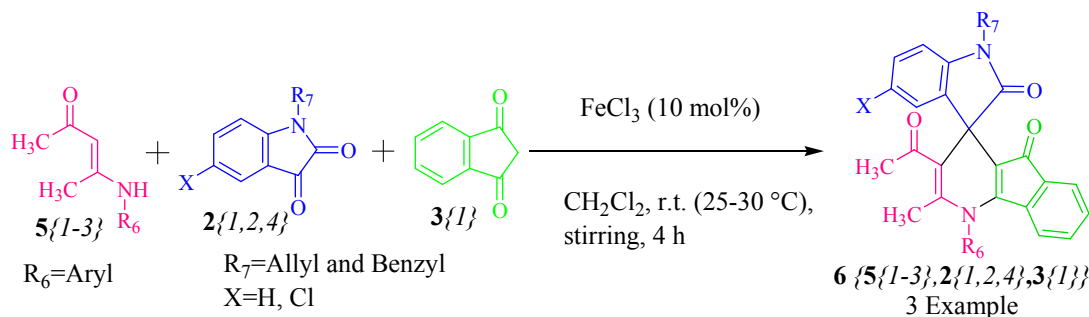
entry	product (4) / time (h)	yield (%) / mp (°C)
1	4 {1,1,1}, 3	92, 286-288
2	4 {2,1,1}, 3	93, 280-282
3	4 {3,1,1}, 4	86, 240-242
4	4 {9,1,1}, 3.5	90, 304-305
5	4 {12,1,1}, 4	88, 132-134
6	4 {13,1,1}, 4	87, 310-312
7	4 {14,1,1}, 5	74, 158-160
8	4 {15,1,1}, 3.5	83, 248-250
9	4 {16,1,1}, 3	85, 280-281
10	4 {17,1,1}, 5	75, 238-240
11	4 {18,1,1}, 3.5	84, 254-255
12	4 {20,1,1}, 6	60, 254-256
13	4 {23,1,1}, 3.5	92, 340-342
14	4 {6,2,1}, 3.5	85, 278-279
15	4 {10,2,1}, 3	86, 292-293
16	4 {19,2,1}, 5	72, 200-202
17	4 {20,2,1}, 6	65, 210-212
18	4 {23,2,1}, 3	87, 328-330
19	4 {24,2,1}, 4	70, 296-298
20	4 {25,2,1}, 5	75, 277-278
21	4 {2,3,1}, 3.5	88, 266-268
22	4 {15,3,1}, 3	80, 268-270
23	4 {10,4,1}, 3	91, 258-260
24	4 {22,4,1}, 3.5	86, >350
25	4 {25,4,1}, 6	72, 216-218
26	4 {7,5,1}, 2.5	94, 328-330

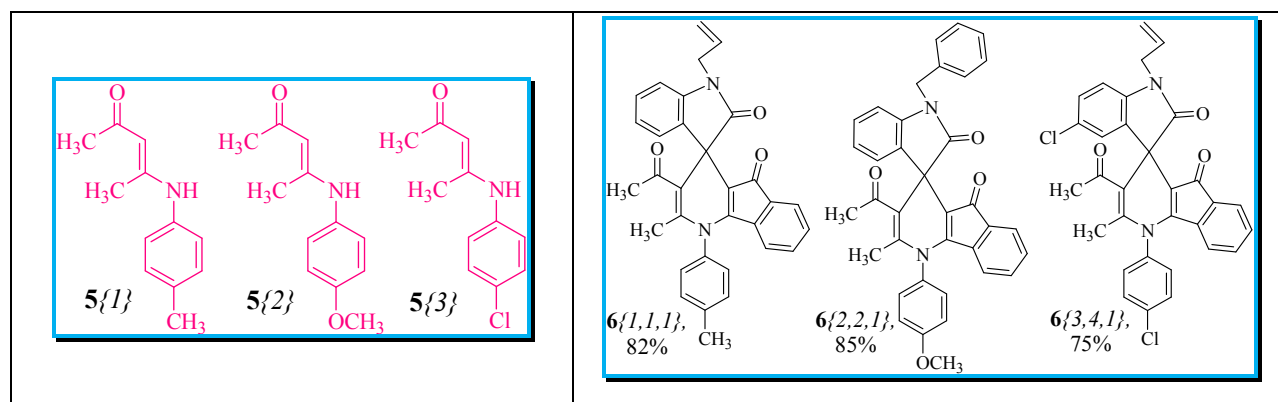
27	$4\{26,5,1\}, 4$	83, 336-338
28	$4\{27,5,1\}, 3.5$	82, >350
29	$4\{4,6,1\}, 3$	92, 308-310
30	$4\{5,6,1\}, 3.5$	88, 320-322
31	$4\{22,6,1\}, 3$	88, >350
32	$4\{8,7,1\}, 3$	90, >350
33	$4\{11,7,1\}, 5$	84, 340-342
34	$4\{21,7,1\}, 3$	75, 318-320
35	$4\{1,8,1\}, 2$	92, 284-286

N-alkyl enaminones also gave good yields (**Table 2**, entries 7-10) with this method. To further broaden the scope of this reaction, we investigated the electronic properties of the substituents (X= chloro, bromo and nitro) at the isatin C5 position and the N-substituent (R_5 = allyl, benzyl and n-butyl). Each variation was well tolerated, giving structurally diverse spiro-products in excellent yields (82–94%). Note that N-protected isatins bearing electron-withdrawing substituents (X) at the C5 position afforded reproducibly higher yields than other analogues, suggesting an electronic effect (**Table 2**, entries 23 –38).

Enaminones derived from acyclic 1,3-diketones ($5\{1-3\}$) also proved to be effective in this ferric-catalyzed process, reacting cleanly with isatins ($3\{1,2,4\}$) and indane -1,3-dione ($3\{1\}$) compounds under the same reaction conditions. The corresponding spiro[indolo-3,4'-indeno[1,2-b]pyridin]-2,5'dione derivatives were isolated in good yields (75-85%, **Scheme 3**, $6\{1,1,1\}$ - $6\{3,4,1\}$). All compounds were characterized by ^1H , ^{13}C NMR and IR spectroscopy analysis.

Scheme 3: Synthesis of spiro[indolo-3,4'-indeno[1,2-b]pyridin]-2,5'diones derivatives.





To the best of our knowledge, this is the first report of the synthesis of spiro-heterocycle using FeCl_3 as a lewis acid catalyst via multicomponent protocols and is perfectly amenable to automation for combinatorial synthesis. Here, lewis acidic nature of FeCl_3 helps to co-ordinate with oxygen and nitrogen atoms, thereby increasing the electrophilic character of carbonyl carbon and finally, facilitating the dehydration process^{6,14} (A detailed mechanistic pathway is proposed in Supporting Information.) The structures of the above spiro-compounds were confirmed unambiguously from single crystal Xray diffraction of the compound **4{16,1,1}** and all the compounds were well characterized by ^1H , ^{13}C NMR and IR spectroscopy. The ORTEP plot of compound **4{16,1,1}** (**Figure 3**) is shown in Supporting Information 1.

CONCLUSION

In summary, we have successfully developed a novel, straightforward, cheap, and environmentally friendly one-pot three-component reaction to synthesize highly functionalized spiro[indolo-3,10'-indeno [1,2-b]quinolin]-2,9',11'-triones derivatives in DCM at room temperature (25-30 °C) in presence of the Lewis acid catalyst FeCl_3 (10 mol %). The procedure has the following advantages: (1) it is highly efficient, has good atom economy and uses an

ecologically benign multicomponent reaction strategy, (2) a wide variety of functional groups are tolerated, (3) the FeCl₃ catalyst is easily available and environmentally friendly, and (4) it should be readily scalable.

Experimental Section

Representative procedure for FeCl₃-catalyzed three component synthesis of functionalized spiro derivatives:

A 25 mL flask was charged with a mixture of enamenones (**1**, 1 mmol), N-protected isatin (**2**, 1 mmol), indane-1,3-dione (**3**, 1 mmol), and catalytic amount of anhydrous FeCl₃ (16 mg, 0.1 mmol) in dichloromethane (5 mL). The mixture was magnetically stirred at room temperature (25-30°C) for the appropriate time mentioned in **Table 2**. The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was poured into water. Then it was extracted with DCM (20 ml) for three times and followed by brine solution. Next, it was dried over Na₂SO₄, and evaporated under reduced pressure to remove the excess solvent. Finally the crude residue was directly purified by silica gel column chromatography using 30% ethyl acetate in petroleum ether (60-80 °C) as eluant to afford the desired product as red solid. All the obtained products were characterized by ¹H NMR, ¹³C NMR, and IR spectral data. The spectra data for two representative compounds are given bellow.

1-Allyl-7',7'-dimethyl-5'-p-tolyl-1,3,6',7',8'-pentahydro-5H-spiro[indolo-3,10'-indeno [1,2-b]quinolin]-2,9',11'triones: (**Table 2**, **4{I,I,I}**): Yield 92 % (484 mg); red solid; Mp: 286-288 °C (EtOH); R_f [50 % EtOAc / petroleum ether (60-80°C)]: 0.60; IR (ν_{max}, KBr, cm⁻¹): 3044, 2955, 2343, 1719, 1690, 1654, 1631, 1487, 1396, 1356, 1281, 1172, 1086, 897, 739, 501; ¹H NMR (300 MHz, CDCl₃) δ_H: 7.30-7.04 (m, 6H, ArH), 6.94 (t, *J*=7.4 Hz, 2H, ArH), 6.82-6.72 (m,

3H, ArH), 6.02-5.92 (m, 1H, allyl-CH), 5.58-5.52 (m, 1H, N-CH₂), 5.20 (d, *J*=10.5 Hz, 1H, N-CH₂), 5.12 (d, *J*=7.5 Hz, 1H, ArH), 4.46-4.41 (m, 2H, allyl-CH₂), 2.42 (s, 3H, Ar-CH₃), 2.18-2.10 (m, 2H, CH₂), 1.97 (d, *J*=17.4 Hz, 2H, CH₂), 0.84 (d, *J*=18.0 Hz, 6H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_C: 194.9, 190.1, 177.8, 154.5, 152.5, 143.3, 140.7, 136.8, 135.7, 134.6, 133.1, 132.1, 131.3, 130.7, 129.5, 129.0, 128.2, 122.4, 121.9, 121.3, 121.0, 117.2, 114.6, 110.3, 108.7, 50.0, 47.3, 43.1, 41.2, 32.2, 29.4, 26.5, 21.3; Anal. calcd. for C₃₅H₃₀N₂O₃; C: 79.82; H: 5.74; N: 5.32. Found: C: 79.98; H: 5.77; N: 5.24%.

1-Butyl-5'-(4-methoxy-phenyl)-7',7'-dimethyl-1,3,6',7',8'-pentahydro-5H-spiro[indolo-3,10'-indeno[1,2-b]quinolin]-2,9',11'-triones: (Table 2, 4{2,3,1}): Yield 88 % (492 mg); red solid; Mp: 266-268 °C (EtOH); R_f [50 % EtOAc / petroleum ether (60-80°C)]: 0.70; IR (ν_{max}, KBr, cm⁻¹): 2956, 2345, 1719, 1661, 1511, 1403, 1360, 1251, 1086, 986, 677; ¹H NMR (300 MHz, CDCl₃) δ_H: 7.44-7.35 (m, 2H, ArH), 7.28-7.20 (m, 2H, ArH), 7.12-7.06 (m, 4H, ArH), 6.95-6.90 (m, 3H, ArH), 5.33 (d, *J*=7.5 Hz, 1H, ArH), 3.97 (s, 3H, -OCH₃), 3.89-3.84 (m, 2H, N-CH₂), 2.30-2.08 (m, 4H, CH₂), 1.94-1.88 (m, 2H, CH₂), 1.60-1.53 (m, 2H, CH₂), 1.07-1.02 (m, 9H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_C: 194.8, 190.1, 177.8, 160.6, 154.7, 152.8, 143.8, 136.9, 134.9, 133.2, 131.4, 130.9, 130.8, 130.4, 129.5, 128.2, 122.5, 121.6, 121.3, 121.0, 115.2, 115.0, 114.8, 110.4, 107.8, 55.7, 50.1, 47.4, 41.3, 40.3, 32.2, 29.4, 28.9, 26.6, 20.4, 13.8; Anal. calcd. for C₃₆H₃₆N₂O₃; C: 77.12; H: 6.47; N: 5.00. Found: C: 77.25; H: 6.46; N: 5.07%.

ASSOCIATED CONTENT

Supporting Information.

Details experimental procedures for synthesis of spiro[indolo-3,10'-indeno [1,2-b]quinolin]-2,9',11'-triones derivatives, scale up reaction and spectral data, copies of ¹H and ¹³C NMR

spectra and IR analysis data of all the new synthesised compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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Author Contributions

All authors contributed equally.

Notes

The authors declare no competing financial interest.

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FeCl₃-catalyzed combinatorial synthesis of functionalized spiro[indolo-3,10'-indeno [1,2-b]quinolin]-trione derivatives

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