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ARTICLE

Highly efficient regioselective synthesis of pyrroles *via* a tandem enamine formation-Michael addition-cyclization sequence under catalyst- and solvent-free conditions

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A convenient catalyst-free, three-component procedure was developed for the synthesis of tetrasubstituted pyrroles under solvent-free conditions and in green solvents glycerol, PEG-200 and water. A sequential enamine-formation, Michael addition and intramolecular cyclization of primary amines, 1,3-dicarbonyl compounds and isatin-derived Michael acceptors afforded 3-(1*H*-pyrrol-3-yl)indolin-2-ones in excellent yields. In this simple one-pot transformation the requirement of column chromatography purification of the products was completely avoided. Besides, the method is highly environmentally benign and atom-economical, and the only side product of this reaction was two molecules of water. A comparative study for the four developed conditions showed that the solvent-free condition was superior regardless of the nature of the starting materials, and the green solvents were effective for alkyl and benzylamines affording higher yields compared to arylamines. The preliminary *in vitro* cytotoxic studies of a representative compound against Ehrlich's ascites carcinoma (EAC) tumor cells showed significant activity with a CTC_{50} value of 15.64 μM.

Introduction

The majority of natural and synthetic drugs, agrochemicals and other biologically significant molecules are heterocyclic compounds, predominantly nitrogen heterocycles, as evident that the majority of top ten best-selling brand name drugs, headed by the antipsychotic aripiprazole (Abilify®) and the antiulcer esomeprazole (Nexium®) contain at least one heterocyclic ring, and most of them are nitrogen heterocycles.[1] In particular, pyrrole is one of the simplest nitrogen heterocycles and a very significant structural motif found in numerous biologically significant compounds including the marine natural compounds lamellarins **1** and lukianols **2**.[2] Moreover, pyrrole is the key structural fragment of porphyrins, corrins and chlorins found in, respectively, heme, vitamin B_{12} and chlorophyll. Besides, a large number of pyrrole derivatives serve as potential drugs for many diseases represented by the multi-targeted receptor tyrosine kinase inhibitors sunitinib **3a** and toceranib **3b** and the non-steroidal anti-inflammatory drug zomepirac **4** (Fig. 1).[3] Other notable pyrrole-derived drugs include the top-selling cholesterol-lowering agent atorvastatin, the anticancer drug tallimustine, the anthelmintic agent pyrvinium and the anti-inflammatory drug tolmetin among many others. Additionally, pyrrole-derived compounds are also known to exhibit remarkable biological activities including antitumoral,[4,5] anti-HIV,[6] antibacterial,[7] antifungal,[8] antimalarial,[9] antioxidant[10] and several others. In addition to biological significance pyrroles have found broad application in organic synthesis as building blocks and in materials science. Similarly oxindoles have drawn much

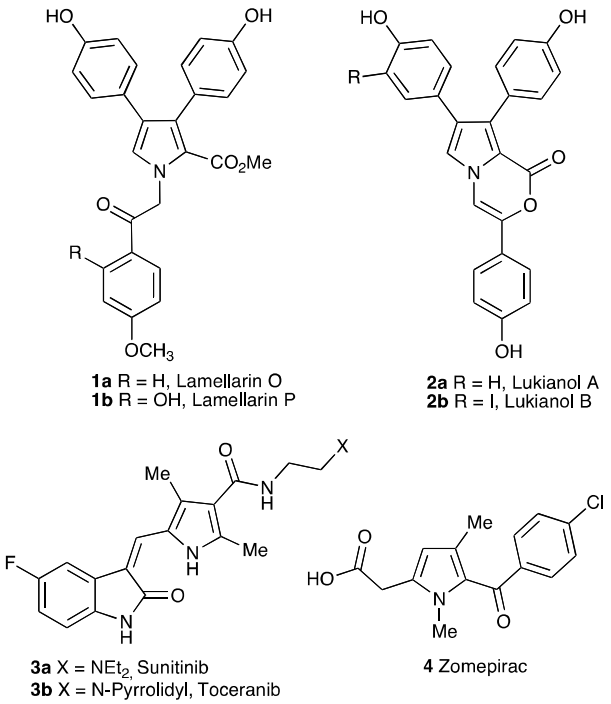

Fig. 1. Representative pyrrole natural products and bioactive compounds.

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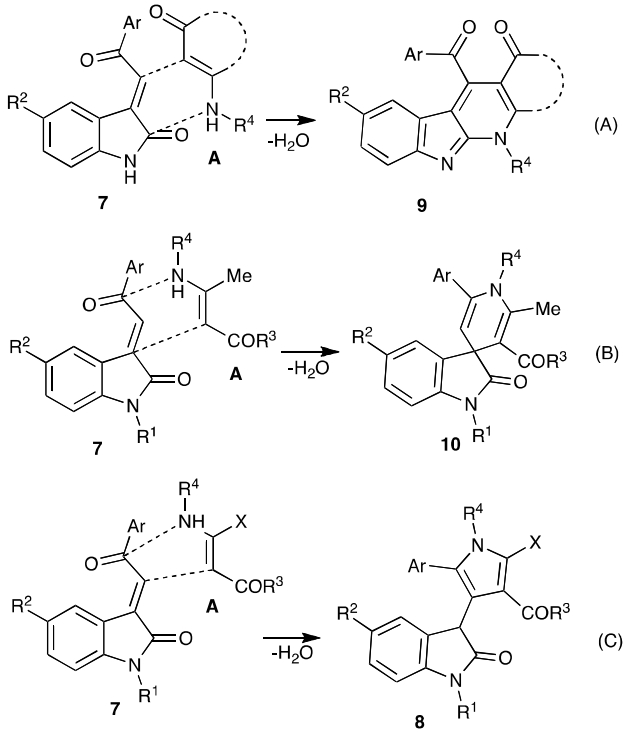
interest owing to their versatile pharmacological activities.[11] Consequently, we envisioned to synthesize tetrasubstituted pyrroles bearing an oxindole moiety, anticipating added biological activities, and to perform preliminary cytotoxicity studies.

The fundamental assets of an ideal synthesis, defined by Wender and co-workers, include ready and cheap availability of starting materials, high conversion and yield, simple, safe, often one-pot, environmentally friendly operation, step and atom economy.[12] In contemporary organic synthesis, the construction of complex molecules starting from simple and readily available materials, by creating molecular diversity and complexity by means of the generation of several bonds and rings in a single operation, is an essential and challenging task. One-pot, multi-bond forming processes, including multicomponent[13] and domino reactions,[14] are the best choice to attain atom and step economy and thus to develop ideal synthetic procedures for complex molecules. In the past two decades synthetic chemists have shown significant interest in the development of environmentally friendly organic processes involving green chemistry that comprises the use of green solvents, catalysts and techniques including microwave and ultrasonic synthesis etc.[15,16] The development of solvent-free protocols remains the most promising approach for environmentally friendly organic synthesis avoiding the use of toxic solvents and minimizing waste generation despite the difficulties often associated with their large-scale efficacy owing to the physical properties of the starting materials and nature of the reactions.[17] On the other hand, the use of readily available green solvents including water, glycerol, polyethylene glycol and lactic acid would overcome the drawbacks of the solvent-free reactions.[18] From the green chemistry point of view, the ideal reaction would be one involving the exclusion of catalysts[19] and column chromatography for purification.

Results and Discussion

With all these points in mind, we envisioned to develop an efficient green protocol for the synthesis of 3-(1*H*-pyrrol-3-yl)indolin-2-ones **8** comparing solvent-free conditions with the use of the green solvents glycerol, PEG-200 and water, starting from readily available primary amines **5**, 1,3-dicarbonyl compounds **6** and isatin-derived Michael acceptors **7** in the absence of any catalyst. β-Enaminone intermediates generated from various precursors are known to undergo regioselective Michael additions with compounds **7** followed by regioselective intramolecular cyclization to afford diverse products depending on the nature of the starting materials (Scheme 1). For instance, the enaminones derived from arylamines and cyclic 1,3-diketones afforded indolo[2,3-*b*]quinolines **9** in the presence of base under microwave irradiation (Scheme 1A).[20] On the other hand Alizadeh and Mokhtari reported the synthesis of spiro-indoline-3,4'-pyridines **10** starting from enamines derived from amines and acyclic 1,3-dicarbonyl compounds and *in situ* generated **7** (Scheme 1B).[21] Nevertheless, we reinvestigated the structural elucidation of their products and confirmed that they are pyrroles **8** and not the reported spiro-indoline-3,4'-pyridines **10** (*vide infra*). The third type of reactivity of enamines, generated *in situ* from arylamines and acetylenedicarboxylates, and compounds **7** involves the formation of 3-(1*H*-pyrrol-3-yl)indolin-2-ones **8** under acidic conditions (Scheme 1C).[22]

In spite of this diverse reactivity of enaminones we started our optimization studies by using butylamine **5a** (0.65 mmol), ethyl acetoacetate **6a** (0.5 mmol) and compound **7a** (0.5 mmol) under various reaction conditions (Table 1). At the outset, we carried out the reaction in ethanol at 25 °C in the absence of any catalyst. To our delight, 64% of pyrrole **8a** was obtained in two hours (entry 1) and at elongated reaction time (7 h) the yield was improved to 80% (entry 2). The reaction rate was increased at elevated temperature (70 °C) without significantly improving the yield (entry 3). Addition of CAN catalyst (10 mol%) reduced the reaction time to 3 h at 25 °C with almost identical yield.[23] In order to make the protocol greener, subsequently, we optimized the reaction conditions in readily available green solvents glycerol, PEG-200, lactic acid and water. At 25 °C, in glycerol, the reaction was completed only after 14 hours allowing 81% of the product (entry 5). It is likely that the poor solubility of compound **7a** and high viscosity of the solvent are responsible for the diminished reaction rate. Change of solvent quantity neither decreased the reaction time nor improved the yield (entries 6 and 7). Intriguingly, the reaction rate was increased many-fold at elevated temperatures; indeed, the reaction was completed just in one hour affording 86% of the product at 70 °C (entries 8 and 9).



Scheme 1. Reactivity of (*E*)-3-(2-oxo-2-arylethylidene)indolin-2-one **7** with β-enaminones

A similar trend was observed in PEG-200, however, it took two hours to allow the maximum yield of 84% at 70 °C (entries 11-15). With an aim to achieve maximum yield at ambient temperature, we employed a few common Lewis acids as catalysts. Although the use of $InCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$ and CAN at ambient temperature increased the rate of the reaction notably, the yield was not improved remarkably (entries 16-19). $InCl_3$ was the most effective to afford 78% yield in 5 h. Replacement of glycerol or PEG-200 with another green solvent, namely lactic acid, was inefficient at 25 °C, furnishing only 21% yield even after 15 h; nonetheless, the yield was increased to 72% at 70 °C, although a longer reaction time was needed (entries 20 and 21). After identifying suitable reaction conditions in glycerol and PEG-200, our attention turned towards the use of the ideal green solvent i.e. water. It is apparent from entries 22-24 that water was the best solvent to this point, as the maximum yield of 92% was obtained at 70 °C in one hour. Here again the addition of a Lewis acid played no significant role at 25 °C (entry 25). Finally, as the greenest

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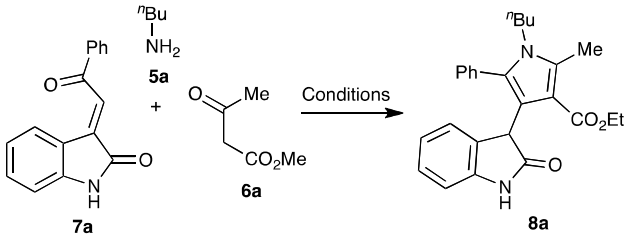
Table 1. Reaction Optimization[a]



S. No.	Solvent	Catalyst	Temp. (°C)	Reaction time (h)	Yield of **8a** (%)[b]
1	EtOH	-	25	2	64
2	EtOH	-	25	7	80
3	EtOH	-	70	1	82
4	EtOH	CAN	25	3	79
5	Glycerol	-	25	14	81
6[c]	Glycerol	-	25	14	69
7[d]	Glycerol	-	25	14	71
8	Glycerol	-	50	3	82
9	**Glycerol**	**-**	**70**	**1**	**86**
10	Glycerol	CAN	25	10	82
11	PEG-200	-	25	17	85
12[c]	PEG-200	-	25	17	77
13[d]	PEG-200	-	25	17	83
14	PEG-200	-	50	5	79
15	**PEG-200**	**-**	**70**	**2**	**84**
16	PEG-200	$InCl_3$	25	5	78
17	PEG-200	$Sc(OTf)_3$	25	8	74
18	PEG-200	$Yb(OTf)_3$	25	8	71
19	PEG-200	CAN	25	13	85
20	Lactic acid	-	25	15	21
21	Lactic acid	-	70	9	72
22	H_2O	-	25	13	77
23	H_2O	-	50	2	90
24	**H_2O**	**-**	**70**	**1**	**92**
25	H_2O	CAN	25	10	82
26	Neat	-	50	6	89 (78)[e]
27	**Neat**	**-**	**70**	**2**	**91**
28	Neat	-	100	1	88

[a] Reaction conditions: unless otherwise noted, all reactions were carried out with **5a** (0.65 mmol, 1.3 equiv), **6a** (0.5 mmol, 1 equiv) and **7a** (0.5 mmol, 1 equiv) in 3 mL solvent. [b] Isolated yield. [c] 1.5 mL of solvent was used. [d] 5 mL of solvent was used. [e] Yield in parenthesis was obtained from the reaction at 25 °C with occasional grinding for 15 h.

possible option, we carried out the reaction under catalyst- and solvent-free conditions. To our surprise, the reaction progressed efficiently to afford 89% of the product in a span of six hours at 50 °C (entry 26). As shown in entries 27 and 28, a further increase of temperature reduced the reaction time and improved the yield (70 °C, 2 h, 91% and 100 °C, 1 h, 88%). The reaction was also carried out at room temperature under neat conditions with occasional grinding to afford 78% product after 15 h (entry 26). It should be highlighted that the purification of the products was achieved through simple crystallization in ethanol, without use of column chromatography, in all the four developed conditions. It is also worth mentioning that the reaction was completely regioselective and the competitive regioisomeric products indolo[2,3-*b*]quinolines **9** or the spiro-indoline-3,4'-pyridines **10** were not obtained in any case.

With optimized conditions in hand (glycerol, PEG-200, water or solvent-free, 70 °C), we explored the scope and limitations of the three-component protocol, and the results are summarized in Table 2. The reaction showed a broad scope and it allowed to employ a wide variety of primary amines **5** including alkyl amines, amino alcohols, naphthylamine, arylamines (*o*-, *m*- and *p*-substituted) bearing electron-donating and withdrawing substituents and benzylamine (entries 1-8). Gratifyingly, irrespective of the nature of the amines, our solvent-free conditions afforded the products in excellent yields (up to 93%). However, the aliphatic and benzylamines reacted in higher rates than that of the aromatic ones in all the three green solvents (entries 4, 7 and 8). The lower yields and longer reaction times could be attributed to the reactivity of the arylamines in the enamine formation step compared to the aliphatic amines as evidenced by the fact that the electron-rich arylamine afforded relatively higher yields than that of electron-deficient analog (entries 7 and 8). It is also apparent that the rate of the reaction was slow for amino alcohols both in PEG-200 and water (entries 2 and 3).

The reaction also tolerated the bromo- and methoxy-substituents on the oxindole moiety, and the reaction times and yields were similar to those observed for unsubstituted system (entries 9-12). Similar to β-ketoesters, β-diketones were also effective to afford the products under solvent-free conditions (entries 13-15). Here again, lower yields and higher reaction times were observed in green solvents for arylamines (entry 13). In the case of 1-phenylbutane-1,3-dione, only 73% yield was obtained even after 15 hours under solvent-free conditions, and the other three reaction conditions did not show any improvement (entry 16). Additionally, the *N*-benzyl substituted pyrrole derivative **8q** was also prepared under optimized conditions in good yield (entry 17). Finally, the role of the nature of the aryl substituents on substrate **7** was investigated. We introduced four different aryl units including electron-rich and deficient aryls, heteroaryl and naphthyl, and no significant difference in reactivity was observed under neat conditions (entries 18-25). Substrates bearing methyl- and chloro-substituents reacted smoothly with alkyl and arylamines, and β-ketoesters to afford 3-(1*H*-pyrrol-3-yl)indolin-2-ones **8** in high yields under all four optimized conditions (entries 18-21). In the case of 2-thienyl- and 2-naphthyl-substituted analogues, good yields were obtained under solvent-free conditions, however, the green solvent conditions were not equally effective (entry 22). A systematic comparison led to a conclusion that the use of solvent-free conditions is superior to the other methods affording high yields with alkyl, benzyl and arylamines. On the other hand, green solvent conditions are effective for alkyl and benzylamines.

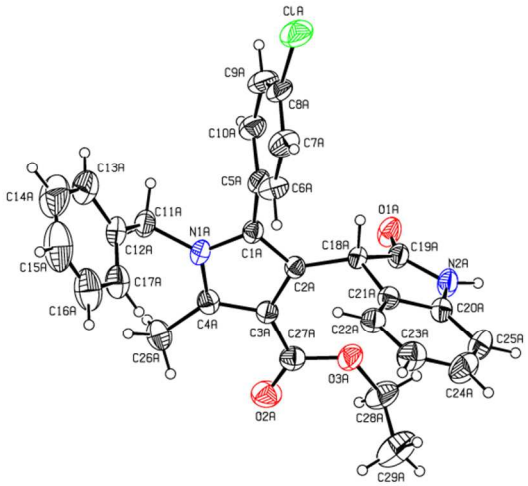


Fig. 2. ORTEP diagram of compound **8t**.

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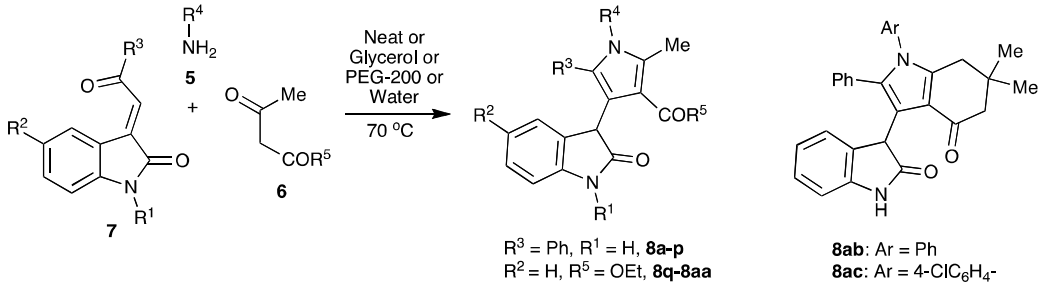
Table 2. Synthesis of 3-(1*H*-pyrrol-3-yl)indolin-2-ones **8**[a]



S. No.	Product **8**	Neat condition		Glycerol		PEG-200		Water	
		Reaction time (h)	Yield (%)[b]	Reaction time (h)	Yield (%)[b]	Reaction time (h)	Yield (%)[b]	Reaction time (h)	Yield (%)[b]
1	R^2 = H, R^5 = OEt, R^4 = ^{n}Bu, **8a**	2	91 (84)[c]	1	86	2	84	1	92
2	R^2 = H, R^5 = OEt, R^4 = -$(CH_2)_2$OH, **8b**	5	88	1	85	4	82	8	75
3	R^2 = H, R^5 = OEt, R^4 = -$(CH_2)_3$OH, **8c**	5	83	1	83	4	80	-	-
4	R^2 = H, R^5 = OEt, R^4 = Ph, **8d**	5	93	10	51	10	54	10	59
5	R^2 = H, R^5 = OEt, R^4 = Bn, **8e**	2	89	1	81	1	83	1	85
6	R^2 = H, R^5 = OEt, R^4 = 1-naph, **8f**	3	89	-	-	-	-	-	-
7	R^2 = H, R^5 = OEt, R^4 = 4-MeC_6H_4, **8g**	2	78	10	67	10	71	10	65
8	R^2 = H, R^5 = OEt, R^4 = 4-ClC_6H_4, **8h**	3	73	10	57	10	56	10	58
9	R^2 = Br, R^5 = OEt, R^4 = ^{n}Bu, **8i**	3	87	1	80	1	84	1	79
10	R^2 = Br, R^5 = OEt, R^4 = Bn, **8j**	3	91	1	87	1	89	1	83
11	R^2 = OMe, R^5 = OEt, R^4 = ^{n}Bu, **8k**	2	77	-	-	-	-	-	-
12	R^2 = OMe, R^5 = OEt, R^4 = Ph, **8l**	2	81	-	-	-	-	-	-
13	R^2 = H, R^5 = Me, R^4 = Ph, **8m**	3	84	8	66	8	78	8	69
14	R^2 = H, R^5 = Me, R^4 = 4-ClC_6H_4, **8n**	3	74	-	-	-	-	-	-
15	R^2 = Br, R^5 = Me, R^4 = 1-naph, **8o**	4	79	-	-	-	-	-	-
16	R^2 = H, R^5 = Ph, R^4 = Ph, **8p**	15	73	15	50	15	54	15	55
17	R^3 = Ph, R^1 = Bn, R^4 = Ph, **8q**	2	86	10	58	10	45	10	55
18	R^3 = 4-MeC_6H_4, R^1 = H, R^4 = ^{n}Bu, **8r**	4	89	1	83	1	79	1	80
19	R^3 = 4-MeC_6H_4, R^1 = H, R^4 = 3-MeC_6H_4, **8s**	3	75	-	-	-	-	-	-
20	R^3 = 4-ClC_6H_4, R^1 = H, R^4 = Bn, **8t**	2	83	1	78	1	75	2	74
21	R^3 = 4-ClC_6H_4, R^1 = H, R^4 = Ph, **8u**	4	79	-	-	-	-	-	-
22	R^3 = 2-thienyl, R^1 = H, R^4 = Ph, **8v**	2	80	10	65	10	63	10	59
23	R^3 = 2-thienyl, R^1 = H, R^4 = 2-MeC_6H_4, **8w**	1	78	-	-	-	-	-	-
24	R^3 = 2-naph, R^1 = H, R^4 = Ph, **8x**	4	63	-	-	-	-	-	-
25	R^3 = 2-naph, R^1 = H, R^4 = -$(CH_2)_3$OH, **8y**	3	74	-	-	-	-	-	-
26[d]	R^3 = Me, R^1 = H, R^4 = ^{n}Bu, **8z**	2	78	-	-	-	-	-	-
27[e]	R^3 = Me, R^1 = H, R^4 = Ph, **8aa**	5	81	-	-	-	-	-	-
28[f]	**8ab**	18	8[h]	-	-	18	22	-	-
29[g]	**8ac**	18	10[h]	-	-	18	26	-	-

[a] Reaction conditions: unless otherwise noted, all reactions were carried out with **5** (0.65 mmol, 1.3 equiv for alkylamines; 0.5 mmol, 1 equiv for arylamines), **6** (0.5 mmol, 1 equiv) and **7** (0.5 mmol, 1 equiv) under solvent-free conditions or in 3 mL of solvent at 70 °C. [b] Isolated yield. [c] Yield in parenthesis refers to the reaction between isolated enaminone **A** and compound **7a**. [d] Two rotamers with 1:0.7 ratio was obtained. [e] Two rotamers with 1:0.68 ratio was obtained. [f] Two rotamers with 1:0.23 ratio was obtained. [g] Two rotamers with 1:0.37 ratio was obtained. [h] Unreacted starting material **7** was recovered.

A detailed spectral analysis of the synthesized compounds proved that they are pyrroles **8** and not the spiro compounds **10**. Thus, the singlet at 4.11 ppm in proton NMR of compound **8a** can be attributed to the H-3 of the oxindole moiety. This δ value is too low to account for the olefinic hydrogen of the dihydropyridine of the spiro compound. Moreover the C-3 carbon at 45.1 ppm is confirmed as the C-3 methine carbon and not the quaternary spiro carbon from DEPT experiments. Finally, the structure was unequivocally assigned by single crystal X-ray analysis of compound **8t**[24] (Fig. 2). It is also crucial to mention that we have also synthesized a previously reported compound (**8e**) and carried out a systematic structural analysis and proved that the structure was wrongly assigned as the spiro compound **10** instead of pyrrole **8**.[21] Another

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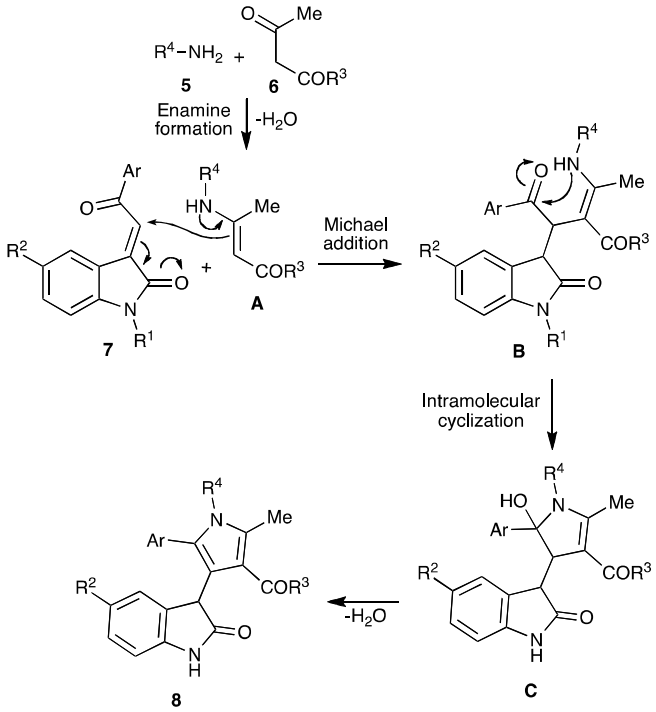
interesting structural feature of these compounds is their tendency to exist as conformer mixtures owing to restricted rotation around the pyrrole-oxindole bond. For most of our compounds (R^3 = Ph) the rotamer ratio is ca. 95:5. In the case of compounds **8z** and **8aa** (R^3 = Me) the rotamer ratios were 1:0.7 and 1:0.68 respectively, and for pyrroles derived from cyclic 1,3-diketones (**8ab** and **8ac**) 1: 0.23 and 1:0.37 rotameric ratios were observed. Computational studies agree well with these observations, since both possible conformations of the compounds arising from the methyl ketone have almost identical energies (ΔE 0.09 kJ.mol^{-1}), while for the compounds where R^3 = Ph there is a difference of 1.8 kJ/mol that explains why almost a single compound is observed.

The formation of pyrrole **8** can be visualized through an enamine formation-Michael addition-intramolecular cyclization domino sequence. The initial reaction between primary amines **5** and 1,3-dicarbonyl compounds **6** should afford the enaminone intermediate **A**. Successive regioselective Michael addition of enaminone **A** to compounds **7** followed by regioselective intramolecular cyclocondensation would furnish pyrroles **8** through the intermediacy of species **B** and **C** after a final dehydration (Scheme 2).[25] The regioselective Michael addition can be explained by steric hindrance, and the regioselective intramolecular cyclization is due to the competition between the amide carbonyl and ketone carbonyl of intermediate **B.** In order to confirm the proposed enaminone formation-initiated mechanism, we synthesized enaminone **A** starting from butylamine and ethyl acetoacetate and treated it with compound **7** under optimized solvent-free condition. As expected, the product **8a** was isolated in 84% yield, supporting the proposed reaction sequence. The reaction was completely regioselective and the other possible Michael addition-cyclization modes that would afford indolo[2,3-*b*]quinolines **9** and spiro-indoline-3,4'-pyridines **10** were not observed. It is relevant to mention here



Scheme 2. Mechanistic proposal involving enamine formation-Michael addition-intramolecular cyclization sequence.

that Shanthi and Perumal have reported a mechanistically different (Michael addition/Paal-Knorr condensation), $InCl_3$-catalyzed procedure for the synthesis of related compounds albeit with a limited substrate scope, since it is restricted only to ammonium acetate.[26]

A representative 3-(1*H*-pyrrol-3-yl)indolin-2-one derivative **8a** was evaluated for *in vitro* cytotoxicity against Ehrlich's ascites carcinoma (EAC) tumor cells using tryphan blue exclusion method. The compound induced 100% cell death at a concentration of 200 µg/mL with a CTC_{50} of 15.64 µM (Table 3). With this encouraging preliminary result, screening of other pyrroles **8** bearing a wide range of substitutions are under investigation to identify a potential lead compound for an antitumor drug discovery program. Studies to understand the mechanism of the cytotoxic action will also be undertaken.

Table 3. Cytotoxicity of compound **8a** against EAC tumor cells

Compound	Conc. (µg/mL)	% GI[a]	CTC_{50}[b] (µM)
8a	200	100	15.64
	100	95	
	50	78	
	20	52	
	10	40	

[a] % Growth inhibition (GI) = 100−[{(Celltotal-Celldead)×100}/ Celltotal]. [b] CTC_{50} = Cytotoxic concentration inhibiting 50 % of percentage growth.

Conclusions

We have developed an efficient, environmentally benign and atom-economical procedure for the synthesis of 3-(1*H*-pyrrol-3-yl)indolin-2-ones from readily available starting materials. This one-pot, three-component reaction between primary amines, 1,3-dicarbonyl compounds and isatin-derived Michael acceptors afforded the products in high yields *via* an enamine formation-Michael addition-intramolecular cyclization sequence. The reaction was carried out under perfect green conditions, since our protocol excludes the use of catalyst, solvent and column chromatography. Some green solvents such as glycerol, PEG-200 and water were also effective for a set of substrates to furnish the products in high yields. This simple protocol allowed the formation of two C-N and a C-C bonds in a single operation affording two molecules of water as the only side product. One of the synthesized compounds showed significant *in vitro* cytotoxicity against Ehrlich's ascites carcinoma (EAC) tumor cells.

Experimental

General

All reagents and solvents were purchased from commercial suppliers (Avra, Alfa Aesar, Sigma-Aldrich, CDH) and used without further purification. The reactions were monitored by thin-layer chromatography using Merck silica gel 60 F254 and visualized by UV detection or using *p*-anisaldehyde stain or molecular iodine. Melting points were recorded on a melting point apparatus in capillaries and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at room temperature on a Bruker Avance 300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts (δ) are expressed in ppm using TMS as internal standard and coupling constants (*J*) are given in Hz. Infrared (IR) spectra were obtained in an Agilent Cary630 FTIR spectrometer with a

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diamond ATR accessory for solid and liquid samples, requiring no sample preparation and the major frequencies were reported in cm^{-1}. Elemental analyses were determined at the CAI de Microanálisis Elemental, Universidad Complutense, by using a Leco 932 CHNS combustion microanalyzer.

General procedure for the synthesis of 3-(1*H*-pyrrol-3-yl)indolin-2-ones 8

Solvent-free conditions: All the reactions were carried out in a clean and dry open RB flask fitted with a glass rod. To a mixture of primary amine **5** (alkyl amines: 0.65 mmol, arylamines: 0.5 mmol) and 1,3-dicarbonyl compound **6** (0.5 mmol) was added compound **7** (0.5 mmol). The mixture was kept at 70 ^oC with occasional stirring with the glass rod for the time periods specified in Table 2. After completion of the reaction, as indicated by TLC, the crude product was precipitated by adding a minimum amount of 5:1 petroleum ether-DCM mixture. The solid was recrystallized in ethanol to afford the pure products **8**.

In green solvents: A mixture of primary amines **5** (alkyl amines: 0.65 mmol, arylamines: 0.5 mmol) and 1,3-dicarbonyl compound **6** (0.5 mmol) in glycerol or PEG-200 or H_2O (3 mL) was stirred at 25 ^oC. After 30 minutes, compound **7** (0.5 mmol) was added and stirring was continued at 70 ^oC for the time periods specified in Table 2. After completion of reaction, as indicated by TLC, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was recrystallized in ethanol to afford the pure products **8**. In the case of aromatic amines (entries 4, 7, 8, 13, 16, 17, 22, 28 and 29 Table 2), where the reactions were incomplete, double recrystallization or column chromatography was required to separate the products completely from the unreacted starting materials, while under solvent-free conditions all the products were purified by recrystallization in ethanol except entries 28 and 29.

Ethyl 1-butyl-2-methyl-4-(2-oxoindolin-3-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate (8a). Off-white solid, mp. 177-179 ^oC; IR (Neat): 3142, 3084, 2959, 1689, 1619, 1528, 1469, 1262, 1195 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.70 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.2 Hz, 3H), 1.05-1.12 (m, 2H), 1.40-1.47 (m, 2H), 2.56 (s, 3H), 3.71 (q, *J* = 7.5 Hz, 2H), 3.82 (t, *J* = 7.2 Hz, 2H), 4.11 (s, 1H), 6.76-6.82 (m, 3H), 7.07-7.12 (m, 1H), 7.48-7.54 (m, 5H), 10.29 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.3, 13.2, 13.8, 19.1, 31.9, 43.4, 45.1, 57.8, 108.6, 108.9, 114.7, 120.8, 122.4, 126.9, 128.5, 128.7, 130.9, 131.0, 131.2, 134.8, 136.2, 142.7, 163.9, 178.4. Anal Calcd for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.73. Found: C, 74.67; H, 6.69; N, 6.82.

Ethyl 1-(2-hydroxyethyl)-2-methyl-4-(2-oxoindolin-3-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate (8b). Pale brown solid, mp. 202-204 ^oC; IR (Neat): 3469, 3241, 2952, 1709, 1663, 1618, 1467, 1273, 1192, 1124 cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ 0.80 (t, *J* = 6.9 Hz, 3H), 2.54 (s, 3H), 3.70 (q, *J* = 6.9 Hz, 2H), 3.89 (t, *J* = 6.3 Hz, 2H), 4.06 (s, 1H), 4.95 (t, *J* = 5.4 Hz, 2H), 6.76-6.82 (m, 3H), 7.06-7.12 (m, 1H), 7.40-7.55 (m, 5H), 10.27 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.5, 13.8, 45.1, 46.1, 57.8, 59.9, 108.6, 108.8, 114.7, 120.7, 122.5, 126.9, 128.5, 128.7, 130.8, 131.2, 131.3, 134.9, 137.0, 142.6, 163.9, 178.4. Anal Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 70.98; H, 5.90; N, 6.93.

Ethyl 2-methyl-4-(2-oxoindolin-3-yl)-1,5-diphenyl-1*H*-pyrrole-3-carboxylate (8d). Off-white solid, mp. 225-227 ^oC; IR (Neat): 3151, 2981, 1698, 1620, 1471, 1262, 1139, 1099 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.85 (t, *J* = 6.6 Hz, 3H), 2.29 (s, 3H), 3.80 (q, *J* = 6.6 Hz, 2H), 4.31 (s, 1H), 6.81-6.97 (m, 3H), 7.11-7.39 (m, 11H), 10.38 (s, 1H); ^{13}C NMR (DMSO-d_6,75 MHz)* δ 12.4, 13.8, 45.1,58.2, 108.7, 109.9, 115.2, 120.8, 122.6, 127.1, 127.7, 128.1, 128.3, 128.5, 129.1, 130.6, 131.2, 135.6, 137.1, 137.2, 142.7, 163.9, 178.3; Anal Calcd for $C_{28}H_{24}N_2O_3$: C, 77.04; H, 5.54; N, 6.42. Found: C, 76.76; H, 5.41; N, 6.30. *one sp^2 carbon merged with others.

Ethyl 1-benzyl-2-methyl-4-(2-oxoindolin-3-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate (8e).[21] Off-white solid, mp. 207-209 ^oC; IR (Neat): 3245, 2973, 1710, 1691, 1618, 1468, 1329, 1272, 1119 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.82 (t, *J* = 6.9 Hz, 3H), 2.37 (s, 3H), 3.74 (q, *J* = 6.9 Hz, 2H), 4.20 (s, 1H), 5.14 (t, *J* = 2.7 Hz, 2H), 6.79-6.91 (m, 5H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.23-7.41 (m, 8H), 10.34 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz)* δ 16.6, 19.0, 50.4, 52.4, 63.3, 113.9, 114.8, 120.2, 126.1, 127.7, 130.8, 132.3, 132.4, 133.8, 133.9, 135.6, 135.9, 136.6, 140.8, 142.0, 142.8, 147.9, 169.1, 183.6. Anal Calcd for $C_{29}H_{26}N_2O_3$: C, 77.31; H, 5.82; N, 6.22. Found: C, 76.97; H, 5.77; N, 6.31. *one sp^2 carbon merged with others.

Ethyl 4-(5-bromo-2-oxoindolin-3-yl)-1-butyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (8i). Off-white solid, mp. 184-187 ^oC; IR (Neat): 3102, 2960, 1688, 1617, 1528, 1471, 1324, 1235, 1168, 1093 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.70 (t, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 6.6 Hz, 3H), 1.05-1.13 (m, 2H), 1.41-1.46 (m, 2H), 2.54 (s, 3H), 3.75-3.82 (m, 4H), 4.16 (s, 1H), 6.75-6.90 (d, *J* = 8.1 Hz, 1H), 7.02 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.50-7.51 (m, 5H), 10.46 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.3, 13.2, 13.9, 19.1, 31.8, 43.4, 45.1, 58.0, 108.6, 110.5, 112.4, 114.0, 124.9, 128.5,128.7, 129.6, 130.6, 131.0, 134.0,135.1, 136.3, 142.1, 163.8, 177.8. Anal Calcd for $C_{26}H_{27}Br\ N_2O_3$: C, 63.03; H, 5.49; N, 5.65. Found: C, 62.74; H, 5.55; N, 5.58.

Ethyl 1-butyl-4-(5-methoxy-2-oxoindolin-3-yl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (8k). Off-white solid, mp. 155-157 ^oC; IR (Neat): 3175, 2980, 1692, 1621, 1543, 1338, 1251, 1144, 1079 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H), 1.11-1.20 (m, 2H), 1.47-1.57 (m, 2H), 2.60 (s, 3H), 3.74 (s, 3H), 3.78 (m, 2H), 3.89 (q, *J* = 13.8 Hz, 2H), 4.39 (s, 1H), 6.51-6.76 (m, 3H), 7.42-7.52 (m, 5H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.6, 8.2, 8.9, 14.6, 27.4, 39.0, 41.0, 50.5, 53.5, 104.1, 104.2, 105.6, 105.7, 109.1, 123.3, 125.8, 126.0, 126.2, 128.0, 129.9, 130.3, 131.8, 150.2, 159.6, 175.4. Anal Calcd for $C_{27}H_{30}\ N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.33; H, 6.65; N, 6.19.

3-(4-Acetyl-5-methyl-1-(naphthalen-1-yl)-2-phenyl-1*H*-pyrrol-3-yl)-5-bromoindolin-2-one (8o). Pale brown solid, mp. 258-260 ^oC; IR (Neat): 3281, 3054, 1721, 1632, 1473, 1405, 1367, 1206, 1104 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.18 (s, 3H), 2.29 (s, 3H), 4.29 (s, 1H), 6.78-7.29 (m, 8H), 7.58-7.76 (m, 5H), 7.90-7.99 (m, 2H), 10.46 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 13.4, 30.4, 45.3, 110.6, 112.4, 114.9,119.9, 121.9, 122.1, 124.6, 125.4, 126.8, 127.7, 128.0, 128.3, 128.5, 129.3, 129.7, 130.1, 130.3, 130.6, 130.8, 133.4, 133.5, 133.6, 137.0, 142.8, 177.3, 192.6. Anal Calcd for $C_{31}H_{23}BrN_2O_2$: C, 69.54; H, 4.33; N, 5.23. Found: C, 69.31; H, 4.28; N, 5.08.

3-(4-Benzoyl-5-methyl-1,2-diphenyl-1*H*-pyrrol-3-yl)indolin-2-one (8p). Off-white solid, mp. 151-154 ^oC; IR (Neat): 3188, 3029, 1713, 1635, 1596, 1414, 1261, 1211, 1076 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.71 (s, 3H), 4.33 (s, 1H), 6.65-6.72 (m, 2H), 6.92-7.50 (m, 17H), 10.28 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz)* δ 13.5, 44.6, 108.7, 116.6,120.3, 120.6, 122.7, 125.2, 127.1, 127.5, 128.1, 128.3, 128.4, 129.1, 129.7, 130.2, 130.6, 131.8, 134.3, 137.3, 140.0, 142.9, 178.1,192.0. Anal Calcd for $C_{32}H_{24}N_2O_2$: C, 82.03; H, 5.16; N, 5.98. Found: C, 81.79; H, 5.26; N, 5.84. *two sp^2 carbons merged with others.

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Ethyl 4-(1-benzyl-2-oxoindolin-3-yl)-2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylate (8q). Off-white solid, mp. 166-168 ^{o}C; IR (Neat): 3055, 2980, 1698, 1612, 1495, 1258, 1081 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 0.78 (t, *J* = 6.9 Hz, 3H), 2.30 (s, 3H), 3.60 (m, *J* = 6.9 Hz, 1H), 3.82 (m, *J* = 6.9 Hz, 1H), 4.52 (s, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 5.15 (d, *J* = 15.6 Hz, 1H), 6.87-6.96 (m, 4H), 7.07 (d, *J* = 7.2 Hz, 3H), 7.14-7.19 (m, 2H), 7.25-7.34 (m, 5H), 7.36-7.44 (m, 5H); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 12.6,13.9, 43.1, 44.6, 58.3, 108.2, 109.8, 115.0, 121.7, 122.5, 127.1,127.2, 127.4, 127.8, 128.2, 128.3, 128.5, 128.6, 129.1, 130.3, 130.5, 130.7, 135.8,136.8, 137.1, 137.2, 143.3, 163.8, 176.4. Anal Calcd for $C_{35}H_{30}N_2O_3$: C, 79.82; H, 5.74; N, 5.32. Found: C, 79.51; H, 5.60; N, 5.24.

Ethyl 2-methyl-4-(2-oxoindolin-3-yl)-1-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (8v). Off-white solid, mp. 126-128 ^{o}C; IR (Neat): 3231, 3091, 2935, 1700, 1618, 1484, 1216, 1088 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 0.87 (t, *J* = 6.9 Hz, 3H), 2.27 (s, 3H), 3.80 (q, *J* = 6.9 Hz, 2H), 4.46 (s, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.95-7.02 (m, 3H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.33-7.35 (m, 2H), 7.45-7.51 (m, 4H), 10.40 (s, 1H); ^{13}C NMR (DMSO-d$_6$, 75 MHz)* δ 12.5, 13.8, 45.2, 58.6, 108.7, 110.1, 117.6, 120.9, 122.7, 127.0, 127.1, 128.0, 128.5, 128.8, 129.2, 129.9, 130.8, 131.0, 136.8, 138.1, 142.8, 163.6, 177.9. Anal Calcd for $C_{26}H_{22}N_2O_3S$: C, 70.57; H, 5.01; N, 6.33; S, 7.25. Found: C, 70.39; H, 4.93; N, 6.26; S, 7.15. *one sp^2 carbon merged with others.

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An efficient three-component, catalyst-, solvent-, and column chromatography-free procedure was developed for the synthesis of 3-(1*H*-pyrrol-3-yl)indolin-2-ones