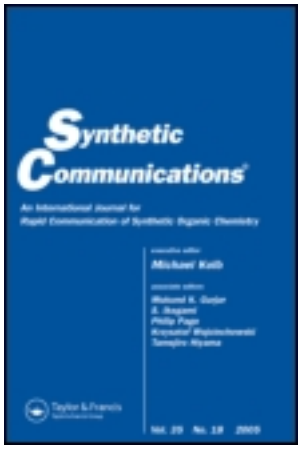

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Novel One Pot Regioselective Multicomponent Synthesis of Highly Functionlaized Spiro Pyrrolidines Through 1,3-Dipolar Cycloaddition Approach

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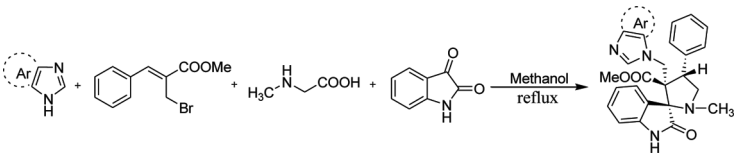
NOVEL ONE POT REGIOSELECTIVE MULTICOMPONENT SYNTHESIS OF HIGHLY FUNCTIONLAIZED SPIRO PYRROLIDINES THROUGH 1,3-DIPOLAR CYCLOADDITION APPROACH

Subban Kathiravan and Raghavachary Raghunathan
Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, India

GRAPHICAL ABSTRACT



Abstract *One-pot multicomponent synthesis of novel highly functionalized spiro pyrrolidine oxindoles has been accomplished in good yields through 1,3-dipolar cycloaddition reaction of azomethine ylide derived from sarcosine and oxindole with various benzimdazole substituted Baylis–Hillman derivatives. The regiochemical and stereochemical outcome of the multicomponent cycloaddition reaction is ascertained by spectroscopic studies, and one of the products was characterized through x-ray crystallographic analysis.*

Keywords Baylis–Hillman; benzimidazole; cycloaddition; imidazole; spirooxindoles

INTRODUCTION

Multicomponent reactions (MCRs) have attracted much attention because of their convergence, ease of execution, and good yields of products.[1] Over the past decade, greater efforts have been made to develop new MCRs, which has led to tremendous advances in generating libraries of molecules for the discovery of biologically active lead compounds and also for the optimization of potent drug candidates.[2]

Oxindole derivatives have drawn considerable attention because of their abundance in numerous natural products as well as their extensive applications in biology and pharmacology.[3] A great number of compounds that carry oxindole moieties are reported to possess significant antibacterial, antiprotozoal, anti-inflammatory, and antitumor properties,[4] and they have been widely employed as potential synthons for the synthesis of alkaloids and clinical pharmaceuticals (Fig. 1).[5] In particular,

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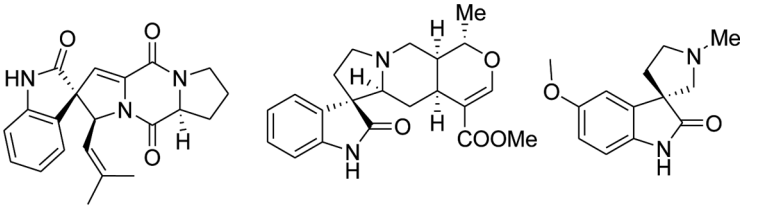


Figure 1. Some typical oxindole derivatives.

compounds containing the spirooxindole ring systems have been reported to behave as aldose reductase, poliovirus, and rhinovirus 3C-proteinase inhibitors,[6] so great efforts have been devoted to the expeditious synthesis of these structural frameworks.

The Baylis–Hillman reaction is well known as one of the powerful carbon–carbon bond-forming methods in organic synthesis.[7] The adducts of the reactions, 3-hydroxy-2-methylidene-alkanoates (derived from acrylate esters), have been utilized as important precursors for stereoselective synthesis of different multifunctional molecules.[8] Among these transformations, the employment of corresponding Baylis–Hillman halides was quite limited except for their use in the synthesis of α-methyledene-γ-butryolactone, α-alkyledene-β-lactam, and flavanoids.[9]

Intermolecular [3 + 2] cycloaddition of azomethine ylides with various dipolarophiles have been used in an efficient and convenient protocol for the construction of highly substituted five-membered pyrrolidine units that possess significant biological

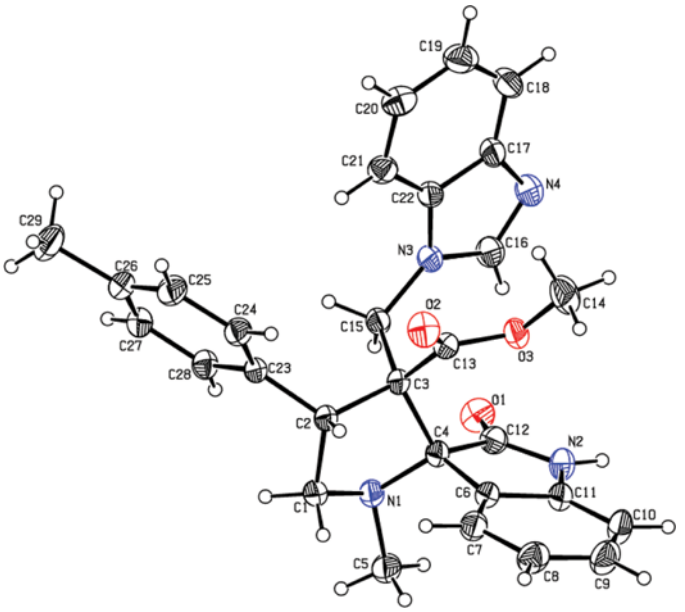


Figure 2. ORTEP diagram of **17**. (Figure is provided in color online.)

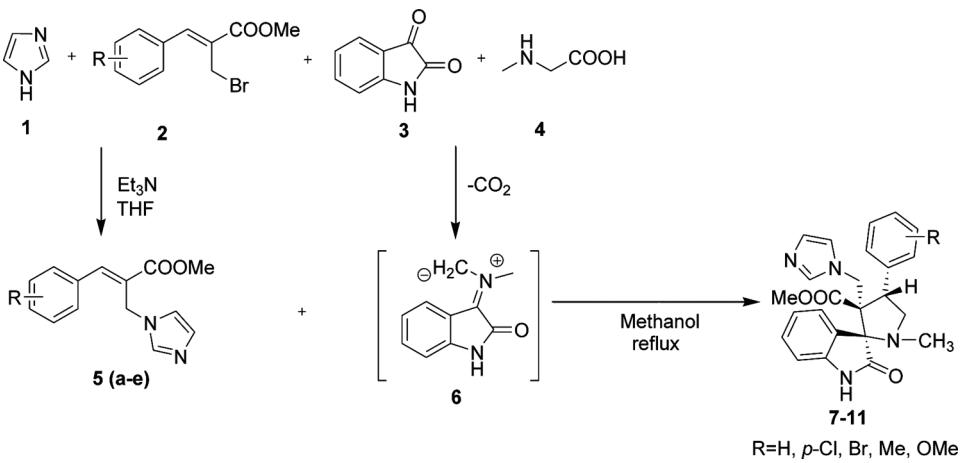
activities.[10–12] However, to the best of our knowledge, there is no report available for the synthesis of highly biologically active spiropyrrolidines having an imidazole and benzimidazole moiety attached to the pyrrolidine ring.

Imidazole, benzimidazole moiety, is usually found in numerous natural products and biologically active pharmaceuticals.[13] For example, a number of *N*-substituted imidazole derivatives, such as miconazole, ketoconazole, genaconazole, and bifonazole, have become well-established drugs for the treatment of many mycotic infections.[14]

In continuation of our studies in the area of cycloaddition reactions,[15] and with a view to synthesize a rare class of novel imidazole-grafted spiroheterocyclic derivatives, we herein report for the first time reaction of *N*-substituted imidazole derivatives by multicomponent 1,3-dipolar cycloaddition reaction for the synthesis of hitherto unknown imidazole-containing spirooxindalopyrrolidines.

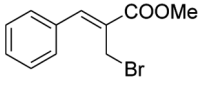
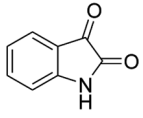
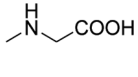
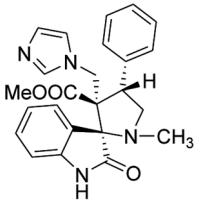
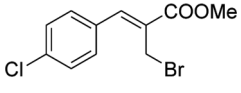
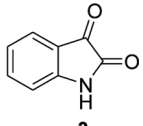
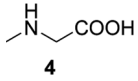
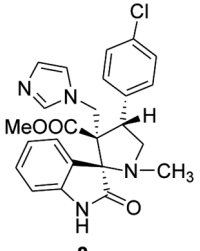
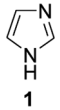
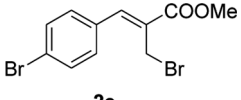
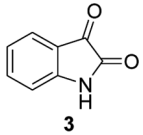
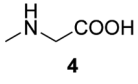
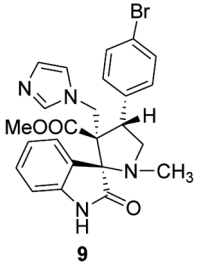
The *N*-substituted imidazole-containing spirooxindalo pyrrolidine derivatives were prepared by treating Baylis–Hillman bromide **2** with imidazole **1** in the presence of triethyl amine to give the corresponding *N*-substituted imidazoles **5 a–e** in excellent yields [formed in situ], which when reacted with azomethine ylide generated by the decarboxylative condensation of oxindole **3** with secondary amino acid sarcosine **4** in refluxing methanol gave novel 3-spiropyrrolidine oxindoles (7–11) (Scheme 1, Table 1) in good yields. The synthesis proceeded through a straightforward route and gave the anticipated products both regioselectively and stereoselectively in moderate to good yields.

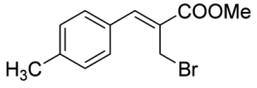
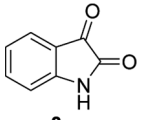
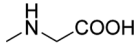
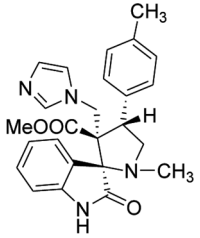
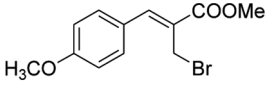
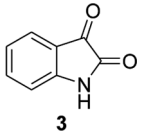
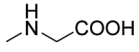
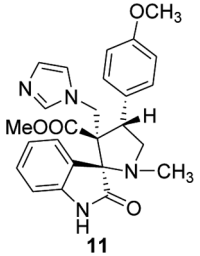
The formation of the cycloadducts was confirmed by spectral and elemental analysis. The infrared(IR) spectrum of **10** exhibited peaks at 1727.5 and 1619.3 cm^{-1} due to ester carbonyl and oxindole carbonyl groups. In the ^1H NMR spectrum of **10** the $-NCH_3$ protons of the pyrrolidine ring exhibited a singlet at δ 2.13. The ester methyl group appeared as a singlet at δ 3.36. The $-NCH_2$ protons of the pyrrolidine ring appeared as doublet of doublet at δ 3.36 and 3.80. The pyrrolidine ring proton attached to aryl unit appeared as a triplet at δ 4.67. The imidazole protons exhibited a multiplets at δ 5.99–6.6.80. The aromatic protons exhibited multiplets in the range



Scheme 1. Synthesis of functionalized spirooxindolo pyrrolidines.

Table 1. Synthesis of functionalized spiro pyrrolidines

Entry	Components				Product[a]	Time (min)	Yield (%)[b]
	1	2	3	4			
1	 **1**	 **2a**	 **3**	 **4**	 **7**	6	88
2	 **1**	 **2b**	 **3**	 **4**	 **8**	7	86
3	 **1**	 **2c**	 **3**	 **4**	 **9**	8	78

4	 **1**	 **2d**	 **3**	 **4**	 **10**	5	85
5	 **1**	 **2e**	 **3**	 **4**	 **11**	9	73

[a]Isolated products were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral analysis.
[b]Yields refer to pure isolated products after purification by slica-gel column chromatography.

Table 2. Conditions for regioselective cycloaddtion reaction for the synthesis of **7**

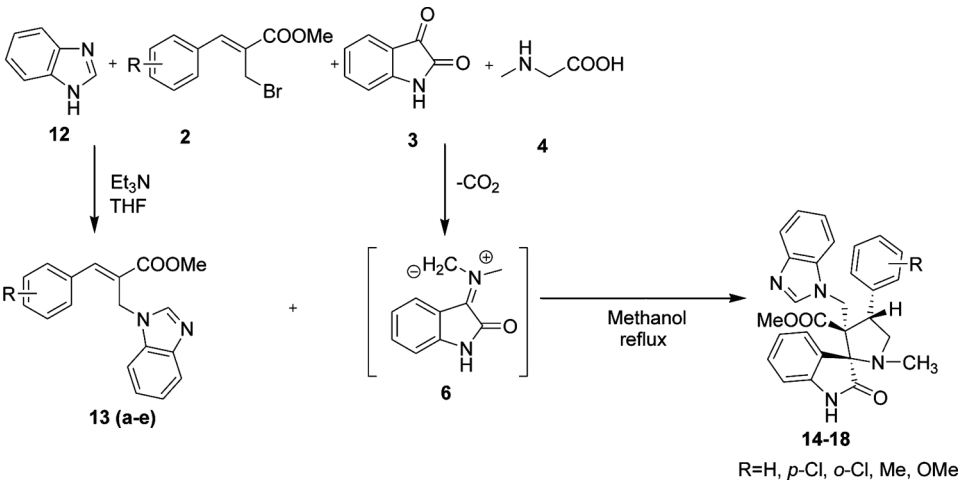
Entry	Solvent	Temperature (°C)[a]	Time (h)	Yield (%)[b]
1	THF	70	12	20
2	H_2O	100	10	5
3	Dioxane	80	12	29
4	CH_3CN	70	11	35
5	Methanol–dioxane	85	10	52
6	Methanol	70	8	88

[a]Gradually raised when the reaction was conducted.
[b]Isolated yield after column chromatography.

δ 7.01–7.52. The –NH proton of the oxindole ring appeared as a singlet at δ 9.99. The off-resonance decoupled ^{13}C NMR spectra of **8** exhibited peaks for the $-NCH_3$ and $-OCH_3$ at δ 21.1 and 58.3 ppm. The spiro carbon exhibited a peak at δ 77.83. The oxindole carbonyl and ester carbonyl resonated at δ 176.6 and 172.6 ppm. These observed chemical shift values confirmed the proposed structure of **10.** The formation of the product was also confirmed by mass spectral and elemental analysis. The mass spectrum of **10** showed a peak at m/z 430.12 (M^+). The reactions were found to be highly regioselective, leading to the formation of only one product **10**, and the formation of other possible regioisomer was not observed.

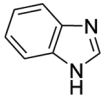
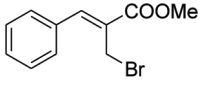
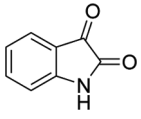
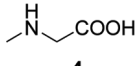
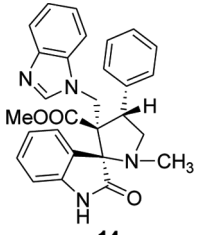
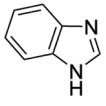
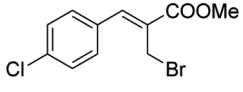
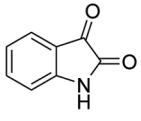
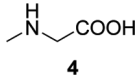
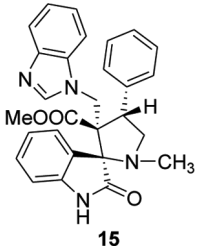
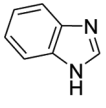
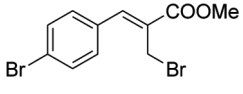
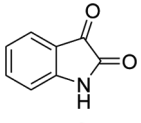
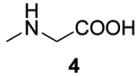
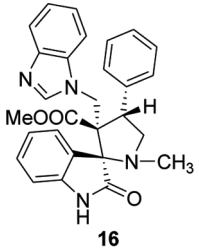
With the optimal conditions in hand, we investigated the generality of the reaction with various substitutents in the substrates (Table 1). In the multicomponent 1,3-dipolar cycloaddition, a wide range of substrates were tolerated, and the yields were good in all cases (Table 1).

We have tried the reaction with various solvents at different temperatures (Table 2), and it was observed that methanol was the best suited solvent to give good yield of the products at an optimum temperature of 80 °C.



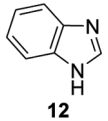
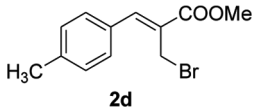
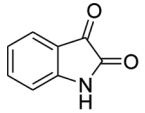
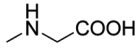
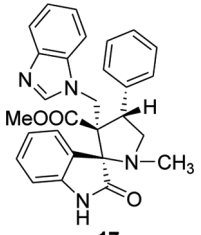
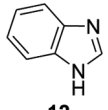
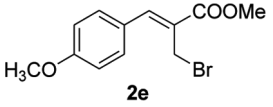
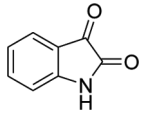
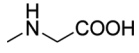
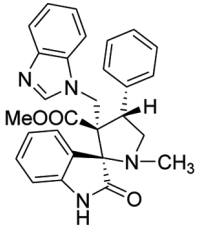
Scheme 2. Synthesis of functionalized spirooxindolo pyrrolidines.

Table 3. Synthesis of functionalized spiro pyrrolidines

Entry	Components 1	2	3	4	Product[a]	Time (min)	Yield (%)[b]
1	 **12**	 **2a**	 **3**	 **4**	 **14**	5	83
2	 **12**	 **2b**	 **3**	 **4**	 **15**	8	78
3	 **12**	 **2c**	 **3**	 **4**	 **16**	6	80

(*Continued*)

Table 3. Continued

Entry	Components				Product[a]	Time (min)	Yield (%)[b]
	1	2	3	4			
4	 **12**	 **2d**	 **3**	 **4**	 **17**	6.5	82
5	 **12**	 **2e**	 **3**	 **4**	 **18**	8	79

[a]Isolated products were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral analysis.
[b]Yields refer to pure isolated products after purification by slica-gel column chromatography.

In the next step, synthesis of *N*-substituted benzimidazole containing spiro oxindalo pyrrolidines **14–18** was accomplished in good yield (70–86%) by the reaction of benzimidazole-derived dipolarophiles **13a–e** with oxindole **3** and sarcosine **4** in refluxing methanol. The formation of the cycloadducts was evidenced by the spectral and elemental analysis and also by x-ray crystallographic analysis.[16] (Scheme 2, Table 3).

CONCLUSION

In conclusion, we have synthesized successfully a series of hitherto unknown novel imidazole- and benzimidazole-attached spirooxindalo pyrrolidines by employing multicomponent 1,3-dipolar-cycloaddition reactions of azomethine ylides. These spiro heterocycles could serve as novel and potential candidates for biological screening.

EXPERIMENTAL

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu Fouier transform FT–(IR) 8300 instrument. Mass spectra were recorded on a Jeol DX 303 HF spectrometer with Maspec System (msw/9629). ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ using tetramethylsilane (TMS) as internal standard on a Bruker spectrometer at 300 and 75 MHz, respectively. Elemental analyses were carried out on a Perkin-Elmer 2400 B instrument.

General Procedure for Synthesis of Cycloadducts

A mixture of imidazole **1** (2.5 equiv) and Baylis–Hillman bromide **2** (1 equiv) was first stirred for 10 min in the presence of triethyl amine (1.1 equiv) as base to form (*E*)-methyl-2-[(1*H*-imidazol-1-yl)methyl]-3-phenylacrylate **5a–g** (formed in situ), followed by the addition of oxindole **3** (1 equiv), and amino acid **4** (1 equiv) and the stirring was continued in refluxing methanol until the completion of reaction as evidenced by thin-layer chromatography (TLC) analysis. The solvent was removed under reduced pressure, and the crude product was subjected to column chromatography using chloroform–methanol (99:1) as eluent. The product was then recrystallized from methanol.

1*N*-Methyl-3-((1*H*-imidazol-1-yl)methyl)-1-methyl-4-phenyl-2-oxindolepyrrolidine-3-carboxylate 7

Colorless solid, yield 88%, mp: 34 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H), 1.95 (s, 3H), 2.03 (s, 2H), 3.29 (s, 2H), 3.39 (t, $J = 9.6$ Hz, 1H), 3.74 (t, $J = 8.5$ Hz, Hz, 1H), 4.61–4.72 (m, 1H), 6.55 (s, 1H), 6.76–6.81 (m, 1H), 6.90–6.95 (m, 1H), 7.07–7.47 (m, 5H), 7.47 (d, $J = 6.3$ Hz, 2H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.1, 46.4, 46.9, 51.2, 57.1, 63.4, 66.5, 76.2, 109.5, 119.4, 121.4, 124.6, 124.8, 125.8, 126.9, 127.9, 128.9, 129.1, 136.6, 140.8, 171.3, 175.6; m/z 416.26 [M^+]. Anal. calc. for $C_{24}H_{24}N_4O_3$: C, 69.23; H, 5.76; N, 13.46. Found: C, 69.35; H, 5.69; N, 13.56%.

1*N*-Methyl-3-((1*H*-imidazol-1-yl)methyl)-1-methyl-4-(4-chlorophenyl)-2-oxindolepyrrolidine-3-carboxylate 8

Colorless solid, yield 86%, mp: 36 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.24 (s, 3H), 3.48 (t, $J = 9.4$ Hz, 1H), 3.59 (t, $J = 8.1$ Hz, 1H), 4.48 (d, $J = 14.7$ Hz, Hz, 1H), 4.62 (t, $J = 7.6$ Hz, 1H), 4.75 (d, $J = 14.7$ Hz, 1H), 5.99 (s, 1H); 6.42 (s, 1H); 6.56 (s, 1H), 6.88 (d, $J = 7.6$ Hz, 1H), 6.99–7.55 (m, 7H), 10.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.7, 45.8, 46.0, 51.4, 58.6, 64.1, 76.1, 109.8, 119.1, 121.2, 125.0, 125.6, 127.2, 128.0, 129.2, 131.0, 132.4, 137.1, 137.7, 141.8, 171.5, 175.6; m/z 450.12 [M^+]. Anal. calc. for $C_{24}H_{23}N_4O_3Cl$: C, 64.01; H, 5.11; N, 12.44. Found: C, 64.15; H, 5.05; N, 12.59%.

1*N*-Methyl-3-((1*H*-imidazol-1-yl)methyl)-1-methyl-4-(4-bromophenyl)-2-oxindolepyrrolidine-3-carboxylate 9

Colorless solid, yield 78%, mp: 34 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H), 3.40 (s, 3H), 3.50 (t, $J = 9.1$ Hz, 1H), 3.72 (t, $J = 8.4$ Hz, 1H), 4.30 (d, $J = 14.7$ Hz, Hz, 1H), 4.60 (s, 1H), 4.63 (d, $J = 5.7$ Hz, 1H), 6.61 (s, 1H), 6.76–6.80 (m, 1H), 7.01–7.06 (m, 1H), 7.20–7.26 (m, 4H), 7.44–7.46 (m, 4H), 8.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.1, 47.3, 47.8, 52.3, 58.6, 64.6, 76.6, 110.1, 119.8, 121.7, 122.5, 125.7, 126.2, 127.7, 129.8, 130.2, 131.7, 131.8, 137.1, 138.9, 141.4, 172.8, 176.1. Mass spectrum m/z: 495.2 (M^+); CHN anal calc. for $C_{24}H_{23}N_4O_3Br$: C, 58.18; H, 4.64; N, 11.31%. Found: C, 58.12; H, 4.61; N, 11.37%.

1*N*-Methyl-3-((1*H*-imidazol-1-yl)methyl)-1-methyl-4-(4-methylphenyl)-2-oxindolepyrrolidine-3-carboxylate 10

Colorless solid, yield 85%, mp: 35 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.36 (s, 3H), 3.36 (s, 3H), 3.46 (s, $J = 9.5$ Hz, 1H), 3.84 (t, $J = 8.5$ Hz, 1H), 4.36 (d, $J = 14.7$ Hz, 1H), 4.70 (t, $J = 16.5$ Hz, 1H), 4.81 (d, $J = 14.7$ Hz, 1H), 6.56 (s, 1H); 6.66 (s, 1H), 6.80 (d, $J = 7.5$ Hz, 1H), 7.01–7.04 (m, 1H), 7.16–7.27 (m, 4H), 7.49 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 35.2, 46.6, 48.0, 52.0, 58.3, 64.69, 77.83, 110.1, 120.1, 122.2, 125.8, 126.3, 127.4, 129.5, 129.6, 130.1, 134.7, 137.5, 139.3, 141.9, 172.6, 176.6; Mass spectrum m/z: 430.12 (M^+). CHN anal. calc. for $C_{25}H_{26}N_4O_3$: C, 69.76; H, 6.04; N, 13.02%; Found: C, 69.72; H, 5.99; N, 13.10%.

1*N*-Methyl-3-((1*H*-imidazol-1-yl)methyl)-1-methyl-4-(4-methoxyphenyl)-2-oxindolepyrrolidine-3-carboxylate 11

Colorless solid, yield 73%, mp: 32 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.27 (s, 3H), 3.27 (s, 3H), 3.74 (t, $J = 8.5$ Hz, 1H), 4.27 (d, $J = 14.7$ Hz, 1H), 4.62 (t, $J = 8.2$ Hz, 1H), 4.74 (d, $J = 15.0$ Hz, 1H), 5.91 (s, 1H), 6.52 (d, $J = 18.6$ Hz, 1H), 6.72 (d, $J = 18.6$ Hz, 1H), 6.93 (t, $J = 7.5$ Hz, 1H), 7.08–7.44 (m, 8H), 10.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 35.2, 46.6, 47.9, 51.9, 58.4, 64.8, 77.5, 109.9, 120.0, 122.4, 125.9, 126.4, 127.6, 129.5, 129.6, 130.1, 134.7, 137.6, 139.3,

141.5, 172.5, 176.3 ppm; Mass spectrum m/z: 446.23 (M^+). CHN anal. calc. for $C_{25}H_{26}N_4O_4$: C, 67.26; H, 5.82; N, 12.55%. Found: C, 67.21; H, 5.78; N, 12.60%.

1*N*-Methyl-3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1-methyl-4-phenyl-2-oxindolepyrrolidine-3-carboxylate 14

Colorless liquid, yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.66 (s, 3H), 3.50 (t, $J = 10.0$ Hz, 1H), 3.87 (t, $J = 8.4$ Hz, 1H), 4.51 (d, $J = 15.3$ Hz, 1H), 4.95 (t, $J = 8.6$ Hz, 1H), 5.66 (d, $J = 15.3$ Hz, 1H), 6.69–7.78 (m, 14H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.4, 41.0, 48.6, 52.3, 66.7, 109.7, 120.2, 122.1, 122.8, 126.5, 128.3, 129.0, 129.1, 129.8, 134.0, 142.8, 143.0, 143.5, 144.8, 166.8 ppm; Mass spectrum m/z: 466.62 (M^+). CHN anal calc. for $C_{28}H_{26}N_4O_3$: C, 72.10; H, 5.57; N, 12.01%. Found: C, 72.05; H, 5.51; N, 12.13%.

1*N*-Methyl-3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1-methyl-4-(4-chlorophenyl)-2-oxindolepyrrolidine-3-carboxylate 15

Colorless liquid, yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.83 (s, 3H), 3.51 (t, $J = 9.9$ Hz, 1H), 3.74–3.80 (m, 1H), 4.45 (d, $J = 15.0$ Hz, 1H), 4.82–4.87 (m, 1H), 5.36 (d, $J = 15.0$ Hz, 1H), 6.68–7.62 (m, 13H), 9.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 35.4, 43.2, 47.8, 51.9, 58.0, 64.5, 110.0, 119.3, 121.9, 121.9, 122.4, 122.5, 125.82, 126.17, 128.81, 129.8, 131.5, 133.6, 136.1, 141.2, 142.0, 143.4, 171.8, 176.2; m/z: 500.09 (M^+). CHN anal. calcd. for $C_{28}H_{25}N_4O_3Cl$: C, 67.20; H, 5.00; N, 10.00%. Found: C, 67.32; H, 5.10; N, 10.11%.

1*N*-Methyl-3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1-methyl-4-(2-chlorophenyl)-2-oxindolepyrrolidine-3-carboxylate 16

Colorless liquid, yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H), 3.54 (t, $J = 9.8$ Hz, 1H), 3.75–3.92 (m, 1H), 4.43 (d, $J = 6.9$ Hz, 1H), 4.54–4.4.61 (m, 1H), 5.13 (d, $J = 6.9$ Hz, 1H), 6.62–7.81 (m, 13H), 9.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.4, 43.2, 47.8, 51.9, 58.0, 64.5, 110.0, 119.3, 121.9, 121.9, 122.4, 122.5, 125.82, 126.17, 128.81, 129.8, 131.5, 133.6, 136.1, 141.2, 142.0, 143.4, 171.8, 176.2 ppm. Mass spectrum m/z; 500.26 (M^+). CHN anal. calc. for $C_{28}H_{25}N_4O_3Cl$: C, 67.20; H, 5.00; N, 10.00%. Found: C, 67.12; H, 4.93; N, 10.15%.

1*N*-Methyl-3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1-methyl-4-(4-methylphenyl)-2-oxindolepyrrolidine-3-carboxylate 17

Colorless liquid, yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17, (s, 1H), 2.35 (s, 3H), 2.68 (s, 3H), 3.47 (t, $J = 8.1$ Hz, 1H), 3.85 (d, $J = 7.6$ Hz, 1H), 4.51 (d, $J = 15.3$ Hz, 1H), 4.906 (t, $J = 11.7$ Hz, 1H), 5.63 (d, $J = 15.3$ Hz, 1H), 6.78–7.65 (m, 12H), 9.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.0, 35.6, 42.2, 48.0, 51.5, 57.8, 64.7, 110.2, 119.1, 121.7, 122.4, 122.7, 123.5, 125.5, 125.9, 126.2, 127.5, 128.3, 129.6, 129.7, 130.5, 134.4, 137.8, 141.3, 143.9, 171.3, 176.8; m/z: 480.51(M^+). CHN anal. calcd. for $C_{29}H_{28}N_4O_3$: C, 72.50; H, 5.83; N, 11.66%. Found: C, 72.63; H, 5.79; N, 11.60%.

1*N*-Methyl-3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1-methyl-4-(4-methoxyphenyl)-2-oxindolepyrrolidine-3-carboxylate 18

Colorless liquid, yield 79%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H), 2.34 (s, 3H), 2.67 (s, 3H), 3.47 (t, $J = 10.2$ Hz, 1H), 3.83–3.89 (m, 1H), 4.53 (d, $J = 15.3$ Hz, 1H), 4.89–4.94 (m, 1H), 5.66 (d, $J = 15.3$ Hz, 1H), 6.79–7.65 (m, 12H), 9.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.9, 35.4, 42.6, 48.5, 51.8, 57.6, 64.7, 78.2, 110.9, 111.4, 120.7.1, 121.2, 122.8, 122.0, 125.1, 129.3, 132.1, 134.0, 134.4, 137.6, 141.1, 141.7, 143.6, 171.2, 176.9 ppm; Mass spectrum m/z: 496.18 (M^+). CHN anal. calc. for $C_{29}H_{28}N_4O_4$: C, 70.16; H, 5.64; N, 11.29%. Found: C, 70.11; H, 5.59; N, 11.36%.

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REFERENCES

1. (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. Strategies for heterocyclic construction via novel multicomponent reactions based on isocyanides and nucleophilic carbenes. *Acc. Chem. Res.* **2003**, *36*, 899–907; (b) Domling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; (c) Orru, R. V. A.; de Greef, M. Recent advances in solution phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* **2003**, 1471–1499.
2. (a) Karthikeyan, K.; Perumal, P. T.; Etti, S.; Shanmugam, G. Diasteroselective synthesis of pyrazolyl isoxalidines via 1,3-dipolar cycloaddition. *Tetrahedron* **2007**, *63*, 10581–10586; (b) Domling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17–89; (c) Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. A novel three-component one-pot synthesis of pyrano[2,3-d]pyrimidines and pyrido[2,3-d]pyrimidines using microwave heating in the solid state. *Tetrahedron Lett.* **2003**, *44*, 8307–8310; (d) Feliu, L.; Vera-Luque, P.; Albericio, F.; Álvarez, M. Advances in solid-phase cycloadditions for heterocyclic synthesis. *J. Comb. Chem.* **2007**, *9*, 521–565; (e) Zhu, J. Recent developments in the isonitrile-based multicomponent synthesis of heterocycles. *Eur. J. Org. Chem.* **2003**, 1133–1144; (f) Mohammadi, A. A.; Dabiri, M.; Qaraat, H. A regioselective three-component reaction for synthesis of novel 1′*H*-spiro[isoindoline-1,2′ quinazoline]-3,4′(3′*H*)-dione derivatives. *Tetrahedron* **2009**, *65*, 3804–3808.
3. (a) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-spirooxindole natural products as inspirations for the developments of potential therapeutic agents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758; (b) Bindra, J. S. *The Alkaloids*, Vol. 14; R. H. F. Manske (Eds.); Academic Press: New York, 1973,; p. 84.
4. (a) Dandia, A.; Singh, R.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. Efficient microwave-enhanced regioselective synthesis of a series of benzimidazolyl/triazolyl spiro[indole-thiazolidinones]as potent antifungal agents and crystal structure of spiro[3*H*-indole-3,2′-thiazolidine]-3′(1,2,4-triazol-3-yl)-2,4'(1*H*)-dione. *Bioorg. Med. Chem.* **2006**, *14*, 2409–2417; (b) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J.

R.; Wang, S. Structure based design of potent non-peptide MDM2 inhibitors. *J. Am. Chem. Soc.* **2005**, *127*, 10130–10131.

5. (a) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. A library of spirooxindoles based on a stereoselective three-component coupling reaction. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086; (b) Marti, C.; Carreira, E. M. Construction of spiro[pyrrolidine-3, 3′-oxindoles]-Recent applications to the synthesis of oxindole alkaloids. *Eur. J. Org. Chem.* **2003**, 2209–2219; (c) Dounary, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. Catalytic asymmetric synthesis of quaternary carbons bearing two aryl substituents: Enantioselective synthesis of 3-alkyl-3-aryl oxindoles by catalytic asymmetric intramolecular Heck reactions. *J. Am. Chem. Soc.* **2003**, *125*, 6261–6271, and references therein (d) Lin, H.; Danishefsky, S. J. Gelsemine–A thought provoking target for total synthesis. *Angew. Chem. Int. Ed.* **2003**, *42*, 36–51.
6. Skiles, J. W.; McNeil, D. Spiro indolinone β-lactams, inhibitors of poliovirus and rhinovirus 3C-proteinases. *Tetrahedron Lett.* **1990**, *31*, 7277–7280.
7. (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. Recent contributions from the Baylis–Hillman reaction to organic chemistry. *Chem. Rev.* **2010**, *110*, 5447–5674; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. The Baylis–Hillman reaction a novel carbon–carbon bond-forming reaction *Tetrahedron* **1996**, *52*, 8001–8062; (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Recent advances in the Baylis–Hillman, reaction and applications. *Chem. Rev.* **2003**, *103*, 811–892.
8. (a) Cho, C.-W.; Krische, M. J. Regio- and stereoselective construction of γ-butenolides through phosphine-catalyzed substitution of Morita–Baylis–Hillman acetates: An organocatalytic allylic alkylation. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689–6691; (b) Kabalka, F. W.; Venkataiah, B.; Dong, G. Pd-catalyzed cross-coupling of Baylis–Hillman acetate adducts with bis(pinacolato)diboron: An efficient route to functionalized allyl borates. *J. Org. Chem.* **2004**, *69*, 5807–5809.
9. (a) Hoffman, H. M. R.; Rabe, J. Synthesis and biological activity of α-methylene-γ-butyrolactones. *Angew. Chem. Int. Ed.* **1985**, *24*, 94–110; (b) *1,3-Dipolar Cycloaddition Chemistry* A. Padwa (Ed.); Wiley: New York, 1984; Vols. 1 and 2; (c) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; A. R. Katritzky (Ed.); Academic Press: San Diego, 1989; Vol. 45; pp. 231–252; (d) *Advances in Cycloaddition* R. Grigg, V. Sridharan, D. P. Curran, (Eds.); Jai Press: London, 1993; Vol. 3; pp. 161–180; (e) Kathiravan, S.; Ramesh, E. Synthesis of pyrrolo[2,3-a]pyrrolizine and pyrrolizine[2,3-a]pyrrolizine derived from allyl derivatives of Baylis–Hillman adducts through intramolecular 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2009**, *50*, 2389–2391.
10. (a) Liddel, J. R. Pyrrolizidine alkaloids. *Nat. Prod. Rep.* **1996**, *13*, 187–194.
11. (a) Hartmann, T.; Witte, L. Chemistry, biology and chemoecology of pyrrolizidine alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; S. W. Pelletier (Ed.); Pergamon Press: Oxford, 1995, Vol. 9; (b) Rajeswaran, W. G.; Labroo, R. B.; Cohen, E. A. Synthesis of 5-[(indol-2-on-3-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-diones and spirocyclopropyloxindole derivatives potential aldose reductase inhibitors. *J. Org. Chem.* **1999**, *64*, 1369–1371.
12. (a) Katritzky, A. R. C.; Rees, W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry*, Pregamon Press, Oxford, 1996, Vol. 3, p. 77; (b) Kruse, L. I.; Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*, Pregamon Press: Oxford, 1990, Vol. 2, p. 123; (c) Hai, L.; Guolan, D.; Daqing, S. Regioselective synthesis of novel spiropyrrolidines and spirothiapyrrolizidines through multicomponent 1,3-dipolar cycloaddition reaction of azomethine ylides. *J. Comb. Chem.* **2010**, *12*, 633–637.
13. White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. Resistance-modifying agents,

9: Synthesis and biological properties of benzimidazole inhibitors of the DNA repair enzyme poly(ADP-ribose)polymerase. *J. Med. Chem.* **2000**, *43*, 4084–4097.

14. (a) Jones, C. D.; Winter, M. A.; Hirsch, K. S.; Stamm, N.; Taylor, H. M.; Holden, H. E.; Davenport, J. D. Estrogen synthetase inhibitors, 2: Comparison of the invitro aromatase inhibitory activity for a variety of nitrogen heterocycles substituted with diarylmethane or diarylmethanol groups. *J. Med. Chem.* **1990**, *33*, 416–429.
15. (a) Kathiravan, S.; Raghunathan, R. A facile one-pot three-component synthesis of macrocyclic imidazolidines by [3 + 2] cycloaddition reaction of azomethine ylides. *Synlett* **2009**, 1126–1129; (b) Suresh Babu, A. R.; Raghunathan, R.; Satiskumar, B. K. A facile synthesis of ferrocene grafted N-methyl spiropyrrolidines through 1,3-dipolar cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2009**, *50*, 2818–2821; (c) Suresh Babu, A. R.; Raghunathan, R. An easy access to novel steroidal dispiropyrrolidines through 1,3-dipolar cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2008**, *49*, 4618–4620.
16. Selvanayagam, S.; Sridhar, B.; Ravikumar, K.; Kathiravan, S.; Raghunathan, R. Methyl 3-[(1*H*-benzimidazol-1-yl)methyl]-1-methyl-4-(4-methylphenyl)-2′-oxopyrrolidine-2-spiro-3′-1-benzimidazole-3-carboxylate. *Acta Cryst.* **2010**, *E66*, o2508–2509.