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Research Article

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Efficient Construction of Azaspiro[4.5]trienone Libraries via Tandem Ugi 4CC/Electrophilic *ipso*-Iodocyclization in One-Pot

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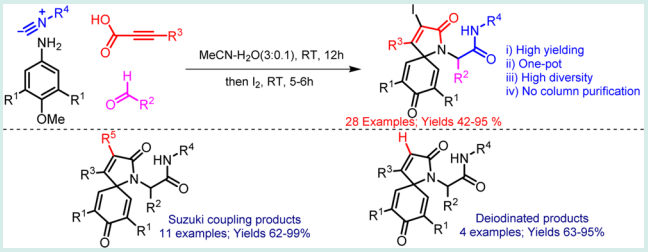
Supporting Information

ABSTRACT: A solution-phase parallel synthesis of pharmaceutically important azaspiro[4.5]trienones has been developed by performing tandem Ugi four-component condensation (U4CC), involving substituted *p*-anisidines, aldehydes, 3-alkyl/aryl-propiolic acids, and isocyanides, and iodine-mediated *ipso*-iodocyclization in one-pot. This highly atom economical process produced functionalized azaspiro[4.5]-trienones in good to excellent overall yields and products were easily isolated by precipitation followed by crystallization. These vinyl-iodide bearing azaspiro[4.5]trienones were utilized for further modifications through Suzuki coupling and deiodination reaction to demonstrate the suitability of these products for various palladium catalyzed modifications. The present method provides an easy access to highly functionalized azaspiro[4.5]trienones that can be useful in drug discovery research.



KEYWORDS: *multicomponent reaction (MCR), Ugi reaction, U4CC, ipso-iodocyclization, Suzuki coupling, Spiro compounds*

INTRODUCTION

Multicomponent reactions (MCRs) have opened a new paradigm in terms of efficient and naturally benign synthesis of small molecule libraries of significant pharmaceutical importance.[1−4] These highly functional group tolerant reactions provide an excellent beginning to the synthesis by bringing desired functionalities for further synthetic manipulations. Recent literature is full of such examples where advanced synthetic precursors or intermediates have been prepared by using MCRs to construct small molecule libraries[1−8] or to attain total synthesis of complex natural products.[9−12] Considering the utility of MCRs, chemists are developing new applications to generate novel skeletons that can be explored for drug discovery. A large number of small molecules with diverse structural components are required to identify potential hits, and therefore operationally simple and flexible synthetic methods need to be developed for the library generations.[13]

In our lab, we are developing solution phase combinatorial approaches to synthesize small molecule libraries to identify potent pharmaceuticals. Toward this direction, we have identified oxaspiro[4.5]trienone **I**[14] and azaspiro[4.5]trienone **II**[15] as constrained tamoxifen mimic with significant anticancer potential against human breast cancer cell lines MCF-7 and MDA-MB-231. The encouraging biological profile of these spiro compounds prompted us to identify an efficient method to synthesize large number of derivatives that may help in developing better structure activity relationship (SAR) to design new molecules with improved anticancer properties (Figure 1).

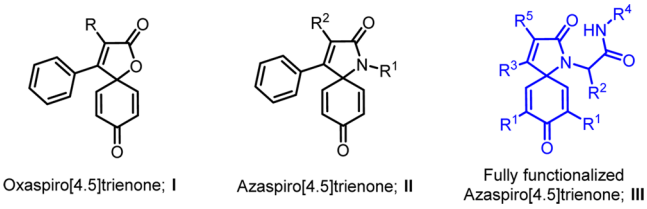


Figure 1. Recently developed cytotoxic spirotrienones from our group and designed prototype.

Literature survey shows that there are numerous methods to synthesized azaspiro[4.5]trienones (**VII**) from *N*-(4-methoxyphenyl)-*N*-alkyl-3-phenylpropiolamide (**VI**) by using various iodine sources such as molecular iodine (I_2),[16] ICl,[16] CuI,[17] or NIS[18] via electrophilic *ipso*-iodocyclization. Related substrates such as 6-methoxy-1,2,3,4-tetrahydroquinoline derived propiolamides have also been converted to spiro products by using molecular iodine.[19] Li et al. have developed *N*-halosuccinimide (NXS) mediated *ipso*-halocyclization of aniline derived propiolamides in the presence of water.[20] Apart from *ipso*-halocyclization methods, efforts have been made to obtain functionalized azaspiro[4.5]trienones by oxidative *ipso*-carboacylation/alkylation of aniline derived propiolamides.[21] Even though the reported methods for *ipso*-iodocyclization are efficient, overall yield of **VII** from *p*-anisidine (**IV**) remains

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Chart 1

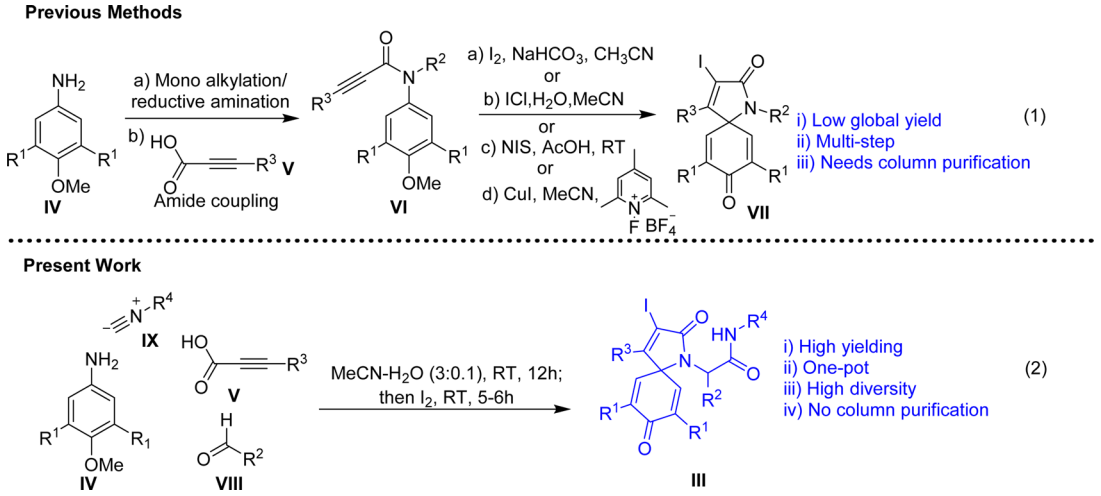
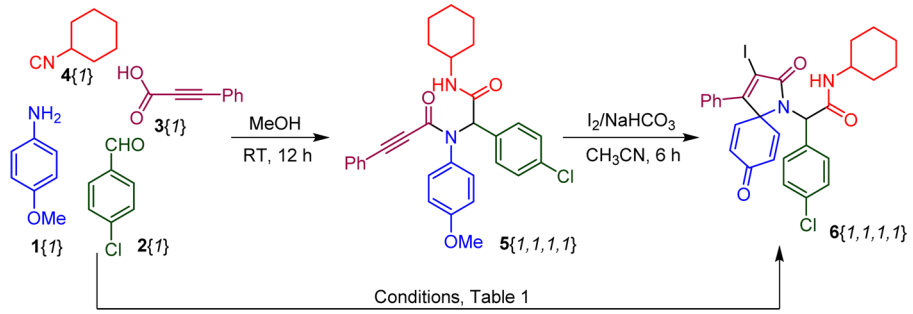


Table 1. Optimization of Conditions for One-Pot U4CC and *ipso*-Iodocyclization[a]



entry	conditions	yield (%) 5{1,1,1,1}	yield (%) 6{1,1,1,1}
1	MeOH, RT (12 h); then I_2, $NaHCO_3$, RT−reflux (24 h)	86	
2	MeOH, RT (12 h); then I_2, K_2CO_3, RT−reflux (10 h)	78	
3	(a) MeOH, RT (12 h); (b) MeCN, I_2, $NaHCO_3$, RT (6 h)		79
4	(a) MeOH, RT (12 h); (b) MeCN, I_2, $NaHCO_3$, 50 °C (1 h)		49
5	(a) MeOH, RT (12 h); (b) MeCN, I_2, K_2CO_3, RT (6 h)		39
6	(a) MeOH, RT (12 h); (b) MeCN, I_2, NaOH, RT (12 h)	54	
7	(a) MeOH, RT (12 h); (b) MeCN, I_2, NaOH, reflux (4 h)		*b*
8	MeCN, RT (24 h); then I_2, $NaHCO_3$, RT (6 h)		54
9	MeCN, RT (24 h); then I_2, RT (6 h)		63
10	MeCN−H_2O (30:1), RT (12 h); then I_2, $NaHCO_3$, RT (6 h)		76
11	MeCN−H_2O (30:1), RT (12 h); then I_2, RT (6 h)		87

[a]All the reactions were performed in open flask and progress of the reaction was monitored by TLC. Yields are global yields for both reactions and are calculated with respect to *p*-anidsidine. [b]A complex mixture of products was obtained with decomposition of Ugi adduct.

poor as it requires *N*-alkylation of *p*-anisidine followed by amide coupling with 3-alkyl/arylpropiolic acid (**V**) to synthesize precursor (**VI**) eq in Chart 1. Therefore, we envisioned to develop a one-pot process to synthesize azaspiro[4.5]trienones **III** in good overall yields via tandem Ugi four-component condensation (U4CC) and iodine mediated *ipso*-iodocyclization eq 2 in Chart 1.

We tried Ugi reaction with *p*-anisidine **1**{*1*}, 4-chlorobenzaldehyde **2**{*1*}, 3-phenylpropiolic acid **3**{*1*}, and cyclohexylisocyanide **4**{*1*} in methanol to obtain the *ipso*-iodocyclization precursor **5**{*1,1,1,1*}. The condensation product **5**{*1,1,1,1*} was isolated by precipitation and was subjected to iodine mediated *ipso*-iodocyclization in acetonitrile to obtain the desired azaspiro[4.5]trienone **6**{*1,1,1,1*} in quantitative yield.

As both the reactions gave good yields and products were easily isolable by precipitation or crystallization, we envisaged to perform U4CC and *ipso*-iodocyclization in one-pot. Initial efforts of performing both the reactions in methanol by sequential addition of reagents did not yield any spiro product and Ugi adduct remained intact even at higher temperature [Table 1, entries 1−2]. With the above observations, it was inferred that methanol may not be suitable solvent for *ipso*-iodocyclization reaction and therefore, after completion of Ugi reaction, methanol was exchanged with acetonitrile for performing *ipso*-iodocyclization [Table 1, entries 3−7]. Among $NaHCO_3$, K_2CO_3, and NaOH, $NaHCO_3$ was found

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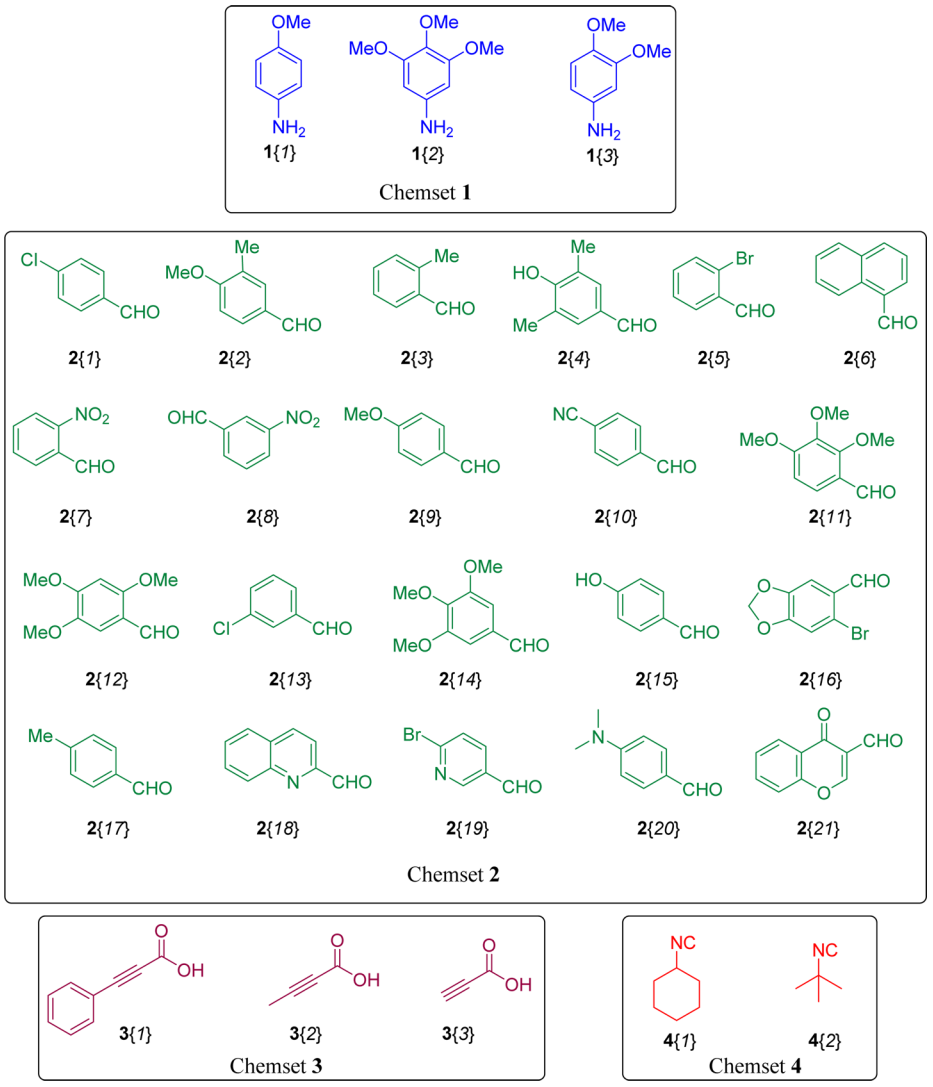

Figure 2. Chemsets: amines **1**{*1*−*2*}, aldehydes **2**{*1*−*21*}, acids **3**{*1*−*3*}, and isocyanides **4**{*1*−*2*}.

to be the most suitable base for *ipso*-iodocyclization [Table 1, entries 3−7]. In case of NaOH, *ipso*-iodocyclization did not work at room temperature and Ugi adduct **5**{*1,1,1,1*} got decomposed under reflux conditions [Table 1, entries 6−7]. To overcome the problem of exchanging solvents from MeOH to MeCN for *ipso*-iodocyclization, both the reactions were tried in acetonitrile, which was found to be low yielding with longer reaction time for Ugi reaction [Table 1, entries 8−11]. However, a mixture of acetonitrile and water was found to be compatible for performing U4CC and *ipso*-iodocyclization by sequential addition of reagents [Table 1, entries 10−11].[16] It was also observed that *ipso*-iodocyclization was faster in absence of $NaHCO_3$ [Table 1, entries 9 and 11].

With optimized reaction conditions in hand, a number of aldehydes, *p*-anisidine derivatives, isocyanides, and 3-alkyl/arylpropiolic acids were utilized to construct a library of azaspiro[4.5]trienones [Figure 2, Table 2].

In most of the cases, azaspiro[4.5]trienone **6** were isolated in good yields, however in some cases where heterocyclic aldehydes were used, reaction suffered in *ipso*-iodocyclization stage and a complex mixture of products were obtained [Table 2, entries 26−29]. In case of propiolic acid **3**{*3*}, diiodo product **7**{*1,1,3,2*} was isolated in moderate yield without formation of any spiro product [Table 2, entry 30]. *Ipso*-iodocyclization reactions of Ugi adducts **5**{*3,9,1,2*} and **5**{*3,17,1,2*} obtained from unsymmetrically substituted *p*-anisidine **1**{*3*}, afforded inseparable mixture of diastereomers that was observed by the ^{1}H NMR analysis of crude product [Table 2, entries 31−32, see Supporting Information for ^{1}H NMR].

To explore the reactivity of azaspiro[4.5]trienones **6** for further derivatization, Suzuki coupling of selected compounds were performed with various boronic acids by using $Pd(PPh_3)_4$ as catalyst [Scheme 1, Figures 3 and 4].[19] In addition, deiodination of selected azaspiro[4.5]trienones **6** were also performed to synthesize **10** by using $Pd(OAc)_2$ and formic acid in DMF [Scheme 2, Figure 5].

CONCLUSIONS

A straightforward method to access functionalized azaspiro[4.5]trienones has been developed by utilizing U4CC and iodine mediated electrophilic *ipso*-cyclization in one-pot. Present method is highly functional group tolerant as most of the reactions worked well with good to excellent yields. The reaction procedure is simple and product isolation can be done by precipitation to avoid time-consuming column chromatog-

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Table 2. Scope of One-Pot U4CC and *ipso*-Iodocyclization[a]

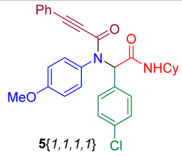
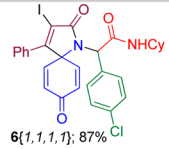
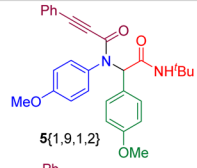
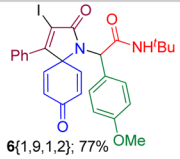
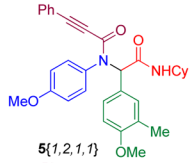
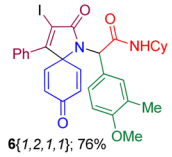
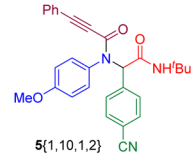
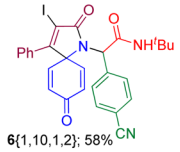
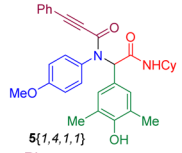
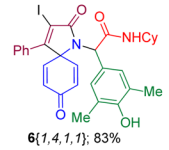
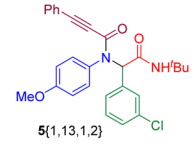
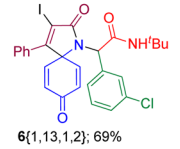
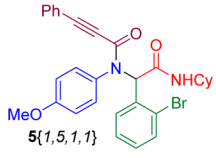
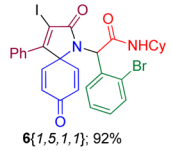
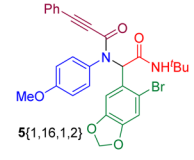
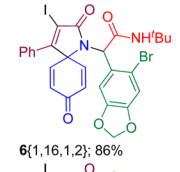
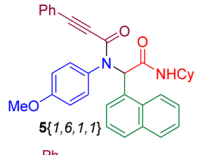
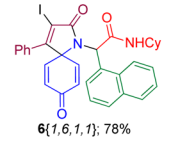
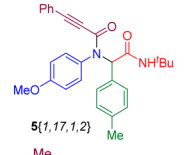
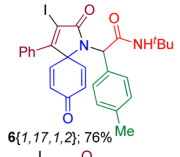
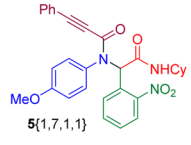
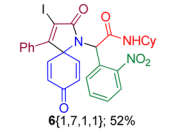
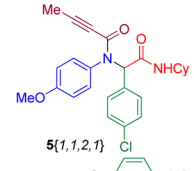
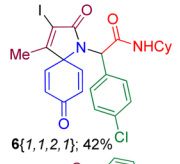
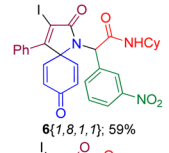
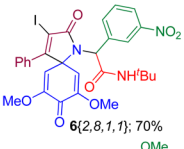
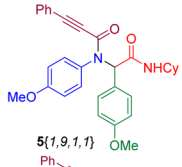
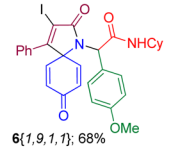
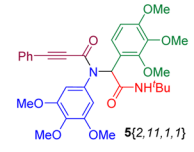
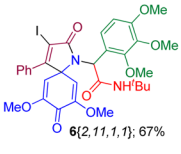
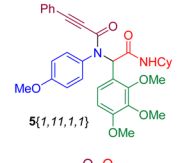
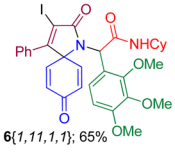
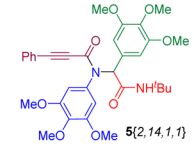
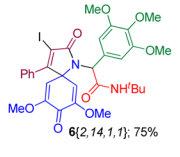
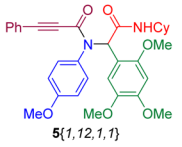
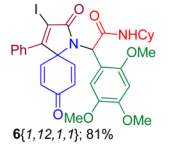
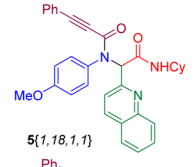
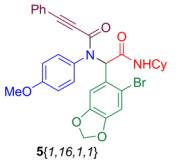
Entry	Intermediate (**5**)	Product (**6**)	Entry	Intermediate (**5**)	Product (**6**)
1	 **5**{*1,1,1,1*}	 **6**{*1,1,1,1*}; 87%	17	 **5**{1,9,1,2}	 **6**{1,9,1,2}; 77%
2	 **5**{*1,2,1,1*}	 **6**{*1,2,1,1*}; 76%	18	 **5**{1,10,1,2}	 **6**{1,10,1,2}; 58%
3	 **5**{*1,4,1,1*}	 **6**{*1,4,1,1*}; 83%	19	 **5**{1,13,1,2}	 **6**{1,13,1,2}; 69%
4	 **5**{*1,5,1,1*}	 **6**{*1,5,1,1*}; 92%	20	 **5**{1,16,1,2}	 **6**{1,16,1,2}; 86%
5	 **5**{*1,6,1,1*}	 **6**{*1,6,1,1*}; 78%	21	 **5**{*1,17,1,2*}	 **6**{*1,17,1,2*}; 76%
6	 **5**{1,7,1,1}	 **6**{1,7,1,1}; 52%	22	 **5**{*1,1,2,1*}	 **6**{*1,1,2,1*}; 42%
7	 **5**{*1,8,1,1*}	 **6**{*1,8,1,1*}; 59%	23	 **5**{*2,8,1,1*}	 **6**{*2,8,1,1*}; 70%
8	 **5**{*1,9,1,1*}	 **6**{*1,9,1,1*}; 68%	24	 **5**{*2,11,1,1*}	 **6**{*2,11,1,1*}; 67%
9	 **5**{*1,11,1,1*}	 **6**{*1,11,1,1*}; 65%	25	 **5**{*2,14,1,1*}	 **6**{*2,14,1,1*}; 75%
10	 **5**{*1,12,1,1*}	 **6**{*1,12,1,1*}; 81%	26	 **5**{*1,18,1,1*}	-------[#]
11	 **5**{*1,16,1,1*}	**6**{*1,16,1,1*}; 88%	27	**5**{*1,19,1,1*}	-------[#]

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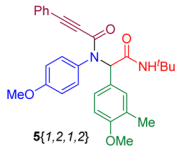
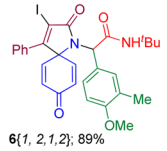
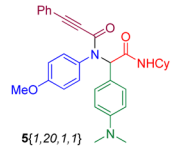
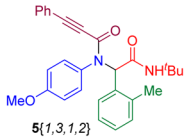
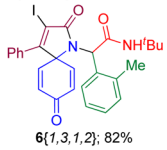
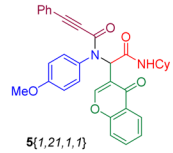
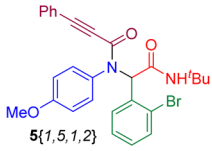
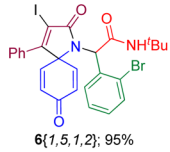
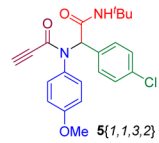
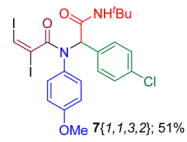
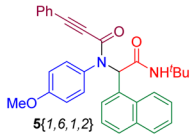
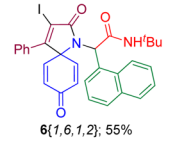
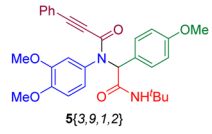
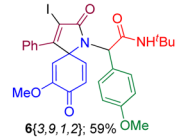
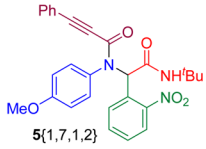
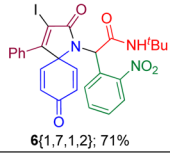
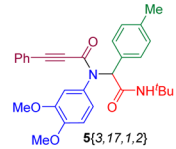
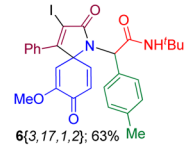
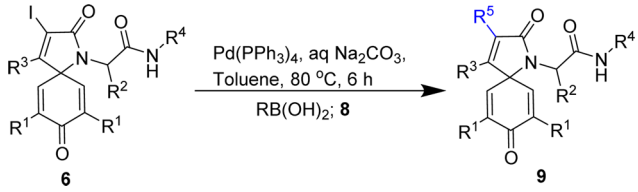
Table 2. continued

Entry	Intermediate (**5**)	Product (**6**)	Entry	Intermediate (**5**)	Product (**6**)
12	 **5**{*1,2,1,2*}	 **6**{*1, 2,1,2*}; 89%	28	 **5**{*1,20,1,1*}	-------[#]
13	 **5**{*1,3,1,2*}	 **6**{*1,3,1,2*}; 82%	29	 **5**{*1,21,1,1*}	-------[#]
14	 **5**{*1,5,1,2*}	 **6**{*1,5,1,2*}; 95%	30	 **5**{*1,1,3,2*}	 **7**{*1,1,3,2*}; 51%
15	 **5**{*1,6,1,2*}	 **6**{*1,6,1,2*}; 55%	31	 **5**{*3,9,1,2*}	 **6**{*3,9,1,2*}; 59%
16	 **5**{*1,7,1,2*}	 **6**{*1,7,1,2*}; 71%	32	 **5**{*3,17,1,2*}	 **6**{*3,17,1,2*}; 63%

[a]Yields for compound **6** are global yields and were calculated with respect to amine **1**. [#]The TLC shows a complex mixture of products.

Scheme 1. Suzuki Coupling of Iodo Products

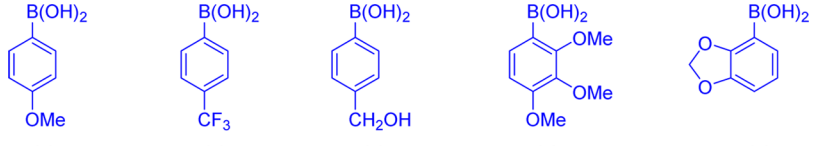


raphy. The method reduces the number of steps and provides a general procedure to synthesize large number of azaspiro[4.5]-trienone derivatives. Successful Suzuki reactions and deiodination of these compounds showed that the substrate is suitable for analogue generation. Considering the feasible combinations a large number of new azaspiro[4.5]trienones can be synthesized for the development of pharmaceuticals. A computational study to identify virtual hits among possible azaspiro[4.5]trienones is currently underway.

EXPERIMENTAL PROCEDURES

General. All reagents and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on 300, 400, and 500 MHz spectrometers using tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double douplet), t (triplet), q (quartet), and m (multiplet). Coupling constant (J) values are reported in hertz (Hz). Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60F254 (0.5 mm) aluminum plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates into ethanolic ninhydrin solution or to ethanolic anisaldehyde solution and heating the plates to 120 °C. Column chromatography was performed using silica gel of 100−200 mesh size. HPLC analysis was performed by using acetonitrile and water (buffer ammonium acetate PH 4.4) 75:25, flow rate 0.7 mL/min, column; (Phenomenex) Luna 5u C-18 size (250*4.60 mm), column oven temp 27 °C, detector; PDA (wavelength 254 nm).

General Procedure for Tandem U4CC/ipso-Iodocyclization to Synthesize Compound ***6****.* To a solution of *p*-anisidine **1**{*1*} (1 equiv) in MeCN (3 mL) and water (0.1 mL), aldehyde **2**{*1*}



Chemset **8**

Figure 3. Boronic acids **8**{*1*−*5*} used for Suzuki coupling.

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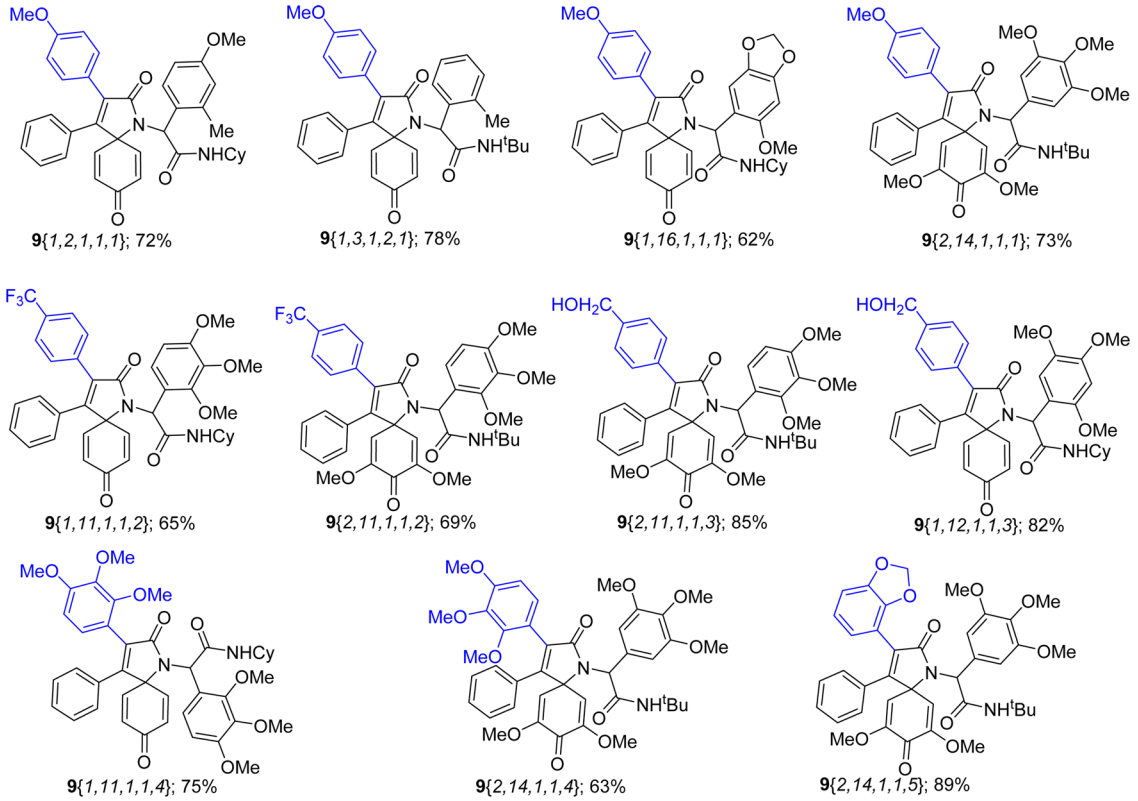
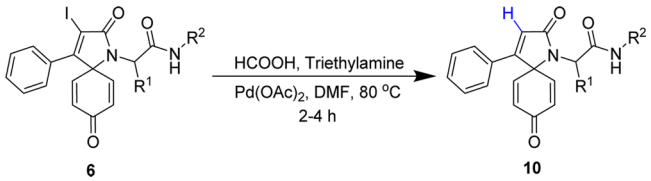


Figure 4. Suzuki reaction products **9**.

Scheme 2. Deiodination of Azaspiro[4.5]trienones 6



(1 equiv) was added in continuous stirring at RT and allowed to stir for 4−5 min. To that mixture, 3-phenylpropiolic acid **3**{*1*} (1 equiv), followed by isocyanide **4**{*1*} (1 equiv), was added and stirred for 12−18 h. After consumption of all the substrates (based on TLC) acetonitrile was added (3 mL) to dilute the reaction mixture. To this, iodine (2 equiv) was added, and the mixture was allowed to stir for 5−6 h at RT. After completion of the reaction, reaction mixture was diluted with ethyl acetate (10 mL) and washed with sodium thiosulfate solution (10% w/v, 15 mL × 2). Aqueous layer was extracted with ethyl acetate (15 mL × 2) and the combined organic layer was dried over anhydrous sodium sulfate. After evaporation of ethyl acetate in vacuo, crude was dissolved in dichloromethane (3 mL) and was added distilled hexane (30 mL) to precipitate the product. Solid portion was filtered and dried in high vacuum to afford the desired compound **6**{*1,1,1,1*}. Yield = 87%; R_f = 0.47 (40% EtOAc in hexane). ^{1}H NMR ($CDCl_3$ + DMSO-d_6 500 MHz): δ 7.92 (s, 1H), 7.49 (d, J = 7.74 Hz, 1H), 7.37−7.33 (m, 4H), 7.22 (d, J = 8.49 Hz, 2H), 7.12 (d, J = 5.66 Hz, 2H), 7.06 (dd, J = 2.83, 10.19 Hz, 1H), 6.49 (dd, J = 2.83, 10.00 Hz, 1H), 6.17 (dd, J = 1.32, 10.19 Hz, 1H), 5.81 (dd, J = 1.32, 10.00 Hz, 1H), 5.42 (s, 1H), 3.75−3.63 (m, 1H), 1.84−1.56 (m, 5H), 1.32−1.07 (m, 5H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6 75 MHz): δ 182.3, 165.7, 157.9, 143.3, 142.9, 133.1, 131.8, 130.6, 130.0, 129.2, 128.2, 126.9, 126.7, 97.4, 70.1, 59.4, 47.4, 43.7, 31.1, 28.1, 24.0, 23.4, 23.4. HRMS (ESI): calcd for $C_{29}H_{27}ClIN_2O_3$ [M + H] $^+$613.0755, found 613.0740. IR (cm^{-1}): 3257, 2928, 2853, 1703, 1669, 1649, 1626, 1565, 1492, 1347, 1091. HPLC purity: 97.8%.

General Procedure for Suzuki Coupling to Synthesize Compound 9. Azaspiro[4.5]trienone **6**{*1,2,1,1*} (1 equiv) was dissolved in toluene (4 mL) and $Pd(PPh_3)_4$ (0.1 equiv) was added, followed by boronic acid **8**{*1*}(2 equiv) and aqueous Na_2CO_3 solution (2M, 1 mL) at RT. The mixture was stirred at 60 °C for 6 h and progress of the reaction was monitored by TLC. After complete consumption of starting material, reaction

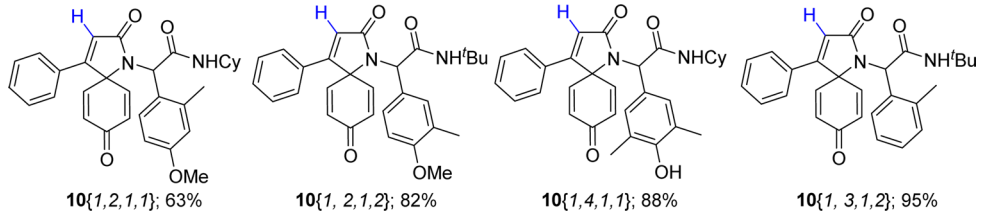


Figure 5. Deiodinated products **10**.

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mixture was cooled and diluted by ethyl acetate (10 mL) followed by washing with water (10 mL × 2). The organic layer was concentrated in vacuo and crude was redissolved in dichloromethane (3 mL) followed by addition of distilled hexane (15 mL) to afford the product **9**{*1,2,1,1,1*} as precipitate that was collected by filtration. Yield = 72%; R_f = 0.70 (50% EtOAc in hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 (d, J = 8.68 Hz, 2H), 7.32−7.14 (m, 5H), 7.05 (d, J = 6.79 Hz, 2H), 6.75 (d, J = 8.68 Hz, 3H), 6.68 (dd, J = 2.83, 10.00 Hz, 1H), 6.22 (t, J = 10.76 Hz, 2H), 5.72 (d, J = 8.12 Hz, 2H), 4.88 (s, 1H), 3.82 (s, 3H), 3.82−3.78 (m, 1H), 3.75 (s, 3H), 2.17 (s, 3H), 1.94 (d, J = 11.70 Hz, 1H), 1.85 (d, J = 10.95 Hz, 1H), 1.70−1.54 (m, 3H), 1.41−1.28, (m, 2H), 1.15−1.03 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 184.5, 169.8, 167.7, 159.6, 158.2, 148.6, 146.1, 146.0, 144.3, 134.7, 131.9, 131.8, 131.6, 130.8, 128.9, 128.6, 128.4, 127.8, 127.1, 126.8, 122.8, 113.4, 109.8, 68.0, 61.4, 55.3, 55.1, 48.9, 32.7, 32.6, 25.4, 24.7, 24.6, 16.2. HRMS (ESI): calcd for $C_{38}H_{38}N_2NaO_5$ $[M + Na]^+$ 625.2678, found 625.2683. IR (cm^{-1}): 3257, 2927, 2853, 1690, 1666, 1647, 1623, 1609, 1513, 1367, 1252, 1178. HPLC purity: 87.0%.

*General Procedure for Deiodination of **6** to Synthesize Compound **10**.* Azaspiro[4.5]trienone **6**{*1,2,1,1*} (1 equiv) was dissolved in DMF (4 mL) and was added $Pd(OAc)_2$ (0.1 equiv), followed by triethylamine (1.2 equiv) and formic acid (1.2 equiv). The reaction mixture was stirred at RT for 15 min and at 80 °C for 4 h. After complete consumption of the starting material, reaction mixture was poured in to crushed ice. The mixture was extracted by ethyl acetate (10 mL × 3) and the combined organic layer was washed with aqueous $NaHCO_3$ (20%, 5 mL), and dried over anhydrous sodium sulfate. The organic layer was concentrated in vacuo and crude was redissolved in dichloromethane (3 mL), followed by addition of distilled hexane (15 mL) to afford the product **10**{*1,2,1,1*} as precipitate that was collected by filtration. Yield = 63%; R_f = 0.26 (40% EtOAc in hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.28 (m, 5H), 7.23−7.19 (m 2H), 6.82 (dd, J = 2.83, 10.00 Hz, 1H), 6.75 (d, J = 8.30 Hz, 1H), 6.61 (s, 1H), 6.56 (dd, J = 2.83, 10.00 Hz, 1H), 6.43 (d, J = 10.00 Hz, 1H), 6.35 (dd, J = 1.32, 10.00 Hz, 1H), 5.75 (d, J = 7.93 Hz, 1H), 4.66 (s, 1H), 3.82 (s, 3H), 3.78−3.72 (m, 1H), 2.17 (s, 3H), 1.92 (d, J = 11.14 Hz, 1H), 1.79 (d, J = 10.57 Hz, 1H), 1.65−1.53 (m, 3H), 1.34−1.28 (m, 2H), 1.15−1.02 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 184.4, 170.0, 167.6, 158.0, 156.6, 146.2, 145.9, 132.1, 131.8, 131.4, 130.9, 130.4, 128.8, 128.0, 127.2, 127.0, 126.7, 124.7, 109.9, 68.3, 60.7, 55.3, 48.8, 32.6, 32.5, 25.4, 24.6, 24.5, 16.2. HRMS (ESI): calcd for $C_{31}H_{32}N_2NaO_4$ $[M + Na]^+$ 519.2260, found 519.2243. IR (cm^{-1}): 3280, 2929, 2852, 1697, 1664, 1624, 1555, 1504, 1390, 1349, 1256, 1212, 1141. HPLC purity: 99.8%.

■ ASSOCIATED CONTENT

Supporting Information

Complete characterization data, ^{1}H and ^{13}C NMR spectra of all the newly synthesized compounds **6**, **7**, **9**, and **10**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00065.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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■ ABBREVIATIONS

U4CC	Ugi four-component condensation
MeOH	methanol
MeCN	acetonitrile
MCRs	multicomponent reactions
NIS	*N*-iodosuccinimide
DMF	*N,N*-dimethylformamide
RT	room temperature
TLC	thin layer chromatography

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