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Thee-component, one-pot synthesis of hexahydroazepino [3,4-*b*]indole and tetrahydro-1*H*-pyrido[3,4-*b*]indole derivatives and evaluation of their cytotoxicity

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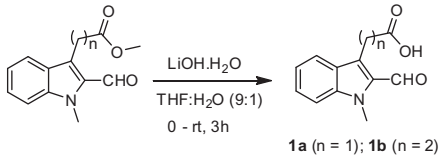
ABSTRACT

A three-component, four-center Ugi reaction has been developed to produce a novel class of 2-aryl-3-oxo-hexahydroazepino[3,4-*b*]indole and 2-aryl-3-oxo-tetrahydro-1*H*-pyrido[3,4-*b*]indole derivatives in good to high yields. A few of them exhibit moderate cytotoxicity against various cancer cell lines such as HeLa (human epithelial cervical cancer), A549 (human lung carcinoma epithelial), DU145 (human prostate carcinoma epithelial) and MCF-7 (human breast adenocarcinoma).

Multi-component reactions (MCRs) are powerful synthetic tools for the diversity-oriented synthesis (DOS) to generate combinatorial libraries.[1] They play a key role in drug discovery. MCRs are highly convergent and atom efficient generating high molecular complexity in a single-step process.[2] Among MCRs, the Ugi[3] and Passerini reactions,[4] are the most popular approaches for the combinatorial chemistry.[5,6] Recently, a new version of Ugi reaction has been developed using bifunctional substrates such as aldehydo acid or amino acid to produce a wide range of lactams with different ring sizes.[7–9] In particular, seven-membered azepinones are important structural motifs in some biologically active molecules.[10] In addition, they are very useful intermediates to the preparation of various peptides and peptidomimetic ligands for several G protein-coupled receptors.[11] However, to the best of our knowledge, there are no reports on intramolecular Ugi reaction of 2-(2-formyl-1-methyl-1*H*-indol-3-yl)acetic acid (**1a**) or 3-(2-formyl-1-methyl-1*H*-indol-3-yl)propanoic acid (**1b**), aryl amine (**2**) and isonitrile (**3**). The required starting materials **1a** and **1b** were prepared using a known procedure (Scheme 1).[12]

Following our interest on Ugi reaction for diversity oriented synthesis,[13] we herein report a novel strategy for the synthesis of



Scheme 1. Preparation of requisite starting materials.

hexahydroazepino[3,4-*b*]indole and tetrahydro-1*H*-pyrido[3,4-*b*]indole derivatives through a three-component reaction of aldehydo acid with aryl amine and isonitrile.

Initially, we attempted the coupling of 3-(2-formyl-1-methyl-1*H*-indol-3-yl)propanoic acid (**1b**) with *p*-fluoroaniline (**2**) and cyclohexyl isocyanide (**3**) in various solvents. Interestingly, the reaction proceeded well in methanol at 60 °C affording the corresponding hexahydroazepino[3,4-*b*]indole derivative **5j** in 78% yield (Table 1).

The above result provided the incentive for further study with other substrates (Table 2). Interestingly, substituted aromatic aldehydes such as *p*-bromo-, *p*-chloro-, 4-fluoro-3-chloro-, *m*-fluoro-, 2,5-dimethyl-, *p*-fluoro-derivatives participated effectively in this reaction. In all the cases, the reactions are clean affording the

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Table 1
Optimization of reaction conditions in the formation of **5j**

Entry	Solvent	T (°C)	Time (h)	Yield[a] (%)
1	Benzene	40	12	—
2	Toulene	40	12	—
3	Toulene	1110	12	<10
4	THF	66	12	20
5	Dioxane	101	12	35
6	MeOH	40	10	55
7	CH_3CN	82	10	65
8	MeOH	60	11	78

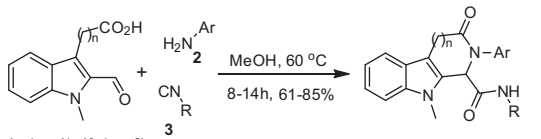
[a] Isolated yield after column chromatography.

hexahydroazepino[3,4-*b*]indole derivatives (**5j–r**, Table 2) in good yields. The reactions proceeded well with both cyclohexyl- and *t*-butyl-isocyanides. Inspired by above results, we further extended this process to the synthesis of 2-aryl-3-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole derivatives. Accordingly, treatment of 2-(2-formyl-1-methyl-1*H*-indol-3-yl)acetic acid (**1a**) with *p*-fluoroaniline (**2**) and cyclohexylisocyanide (**3**) afforded the corresponding tetrahydro-1*H*-pyrido[3,4-*b*]indole **4a** in 81% yield (Table 2). Similarly, various aryl amines and isonitriles reacted well with aldehydo acid (**1a**) to provide the corresponding tetrahydro-1*H*-pyrido[3,4-*b*]indole derivatives (**4a–i**, Table 2) reasonably in good yields.

All the synthesized compounds were evaluated for their anti-proliferative activity against a panel of four different human cancer cell lines; HeLa (cervical cancer), A549 (lung carcinoma), DU145 (prostate carcinoma) and MCF7 (breast adenocarcinoma). The growth inhibition values for the cells were expressed in IC_{50} (μM) and are summarized in the Table 3. The Ugi products consist of four rings (A, B, C and D) apart from different amide linkers on C-ring. In addition, the C-ring was modified as six- (**4a–i**) and seven-membered rings (**5j–r**).

To study the structure and activity relationship (SAR) for these compounds, we have modified the D-ring with different substituents like F, Cl, Br and CH_3 (Fig. 1). Based on the screening results, the compounds with seven-membered C-ring (**5j–r**) are more active than six-membered C-ring compounds (**4a–i**). Among the compounds (**5j–r**), **5l** and **5q** were found to exhibit significant growth inhibitory effect on the tested cell lines with IC_{50} values ranging from 12 μM–29 μM. The effect of **5l** and **5q** on cell viability was shown in the Figure 2 (Supporting information). In particular, the lead compound **5l** bearing cyclohexyl amide linker on C-ring and 4-chloro substituent on D-ring inhibited the growth of HeLa and DU145 cancer cells with the IC_{50} values of 12 μM and 13 μM, respectively. However, **5l** showed moderate cytotoxicity against A549 and MCF7 with IC_{50} value 27 μM and 29 μM. Furthermore, **5q** that possesses *tert*-butyl amide linker on C-ring and 4-chloro group on the D-ring showed potential antiproliferative activity against HeLa cells with an IC_{50} value 13 μM. In addition, **5q** showed significant cytotoxic effect towards A549 (18 μM), DU145 (21 μM) and MCF7 (18 μM) cells. The compounds **4d** and **4f** that possess six-membered C-ring and fluoro substituted D-ring have shown moderate cytotoxicity against HeLa cells with an IC_{50} value 25 μM and 26 μM, respectively. Interestingly, **4a** with 4-fluoro substituent on the D-ring inhibited the growth of Hela cells with the IC_{50} value 11 μM and also showed moderate cytotoxicity on other cell lines investigated in this study. Therefore, the lead compounds **5l**, **5q**, **4a**, **4d** and **4f** showed significant cytotoxic efficacy on cervical cancer cells. Overall, the structure activity relationship with respect to their anticancer activity reveals that chloro substituted seven-membered lactams (azepinones) (**5l**, **5q** and **5r**) are more active than chloro substituted six-membered lactams (**4c**, **4g**, and **4h**). In particular, **5l** showed better activity compared to its six-membered counterpart (**4c**). Similarly, seven-membered lactam **5q** displayed better activity than six-membered lactam **4g**. On the other hand, six-membered lactams (**4a–i**), fluoro

Table 2
Synthesis of tetrahydro-1*H*-pyrido[3,4-*b*]indole and hexahydroazepino[3,4-*b*]indole derivatives



1a (n = 1); **1b** (n = 2) — **4** (n = 1)(a-i); **5** (n = 2)(j-r)

Entry	*n*	Ar	Ar	Product[a]	Time (h)	Yield[b] (%)
a	1	*p*-F-C_6H_4	C_6H_{11}	**4a**	9	81
b	1	*p*-Br-C_6H_4	C_6H_{11}	**4b**	8	85
c	1	*p*-Cl-C_6H_4	C_6H_{11}	**4c**	10	74
d	1	*m*-F-C_6H_4	C_6H_{11}	**4d**	11	72
e	1	2,5-Me_2-C_6H_3	C_6H_{11}	**4e**	14	65
f	1	*p*-F-C_6H_4	C_4H_9	**4f**	9	82
g	1	*p*-Cl-C_6H_4	C_4H_9	**4g**	10	79
h	1	3-Cl-4-F-C_6H_3	C_4H_9	**4h**	10	76
i	1	2,5-Me_2-C_6H_3	C_4H_9	**4i**	14	68
j	2	*p*-F-C_6H_4	C_6H_{11}	**5j**	12	78
k	2	*p*-Br-C_6H_4	C_6H_{11}	**5k**	11	81
l	2	*p*-Cl-C_6H_4	C_6H_{11}	**5l**	11	70
m	2	3-Cl-4-F-C_6H_3	C_6H_{11}	**5m**	10	65
n	2	*m*-F-C_6H_4	C_6H_{11}	**5n**	14	70
o	2	2,5-Me_2-C_6H_3	C_6H_{11}	**5o**	14	63
p	2	*p*-F-C_6H_4	C_4H_9	**5p**	11	74
q	2	*p*-Cl-C_6H_4	C_4H_9	**5q**	12	72
r	2	3-Cl-4-F-C_6H_3	C_4H_9	**5r**	14	61

[a] All products were characterized by NMR, IR and mass spectrometry.
[b] Isolated yields after column chromatography.

Table 3
Anti-proliferative activity (IC_{50} values μM[b]) of indole derivatives on HeLa, A549, DU145, MCF7

Compound[a]	HeLa	A549	DU145	MCF7
4a	11 ± 0.9	62 ± 2.4	47 ± 2.6	50 ± 2.7
4b	49 ± 2.8	>100	45 ± 2.5	52 ± 2.7
4c	55 ± 2.8	59 ± 2.5	42 ± 2.2	>100
4d	25 ± 2.5	85 ± 2.4	>100	95 ± 2.8
4e	>100	>100	>100	95 ± 2.8
4f	26 ± 2.4	>100	78 ± 3.4	61 ± 2.2
4g	83 ± 2.9	63 ± 2.8	>100	96 ± 2.1
4h	>100	80 ± 2.7	95 ± 3.5	>100
4i	95 ± 3.8	49 ± 2.9	63 ± 2.8	87 ± 2.7
5j	48 ± 2.5	59 ± 2.6	90 ± 3.2	50 ± 1.6
5k	63 ± 2.6	>100	55 ± 2.1	78 ± 3.2
5l	12 ± 1.1	27 ± 2.1	13 ± 1.6	29 ± 1.2
5m	>100	>100	82 ± 2.5	54 ± 2.4
5n	44 ± 2.5	>100	52 ± 2.8	94 ± 2.8
5o	>100	>100	>100	>100
5p	46 ± 2.2	>100	70 ± 2.6	50 ± 2.3
5q	13 ± 1.7	18 ± 1.1	21 ± 1.4	18 ± 0.8
5r	67 ± 2.8	35 ± 2.4	56 ± 2.8	>100

[a] Cell lines were treated with different concentrations of compounds for 48 h as described in experimental section.
[b] IC_{50} values are indicated as mean of three independent experiments.

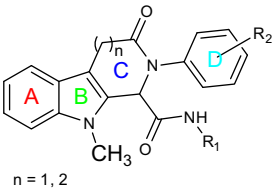


Figure 1.

substituted compounds (**4a**, **4d**, **4f**) seem to be more effective than bromo or chloro analogues (**4b**, **4c**, **4g**) in most of the cell lines. In general, halo substituted compounds are more active when compared to methyl substituted compounds.

In conclusion, we have demonstrated a novel approach for the synthesis of 2-aryl-3-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole and 2-aryl-3-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole derivatives through a Ugi four-center three-component reaction. This method is simple, convenient and catalyst-free to produce the structural diversity in a one-pot process. Of various products, five compounds (**5l**, **5q**, **4a**, **4d** and **4f**) showed moderate cytotoxicity against different cancer cell lines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.07.084.

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