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# The indoleacetic acids in IMCRs: a three-component Ugi reaction involving TosMIC

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## ABSTRACT

Isocyanide-based MCRs (IMCRs) involving for the first time the biological and pharmaceutical active indoleacetic acids are studied. In particular, the catalytic behavior of 2-acetyl-indoleacetic acid in the Ugi three-component reaction with TosMIC is emphasized. The reaction was optimized, revealing the catalytic role of aromatic carboxylic acids as well, yielding a small library of  $\alpha$ -aminoamides. Full assignment of all  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts has been unambiguously achieved.

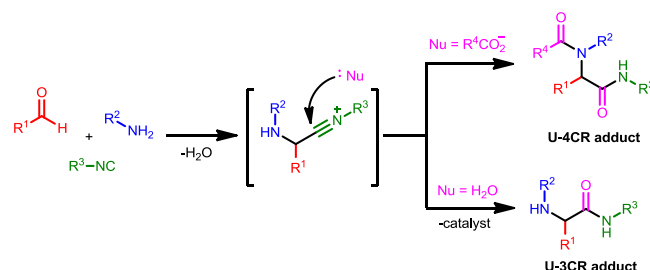
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## 1. Introduction

Multicomponent reactions (MCRs), involving at least three starting materials in a one-pot reaction, remain amongst the most efficient method of rapidly introducing molecular diversity.<sup>1,2</sup> They provide access to highly functionalized molecules in simple and straightforward one-step transformations and as such, they have found widespread use in organic and diversity-oriented synthesis.<sup>3–5</sup> Among the known MCRs to date, the most valuable reactions are those based on isocyanides. Isocyanide-based multicomponent reactions (abbreviated to IMCRs by Ugi and Dömling) have attracted much attention especially in the field of combinatorial chemistry and high throughput screening, by virtue of their synthetic potential, inherent atom efficiency, convergent nature, ease of implementation and the generation of molecular diversity.<sup>6–12</sup>

The Ugi four-component reaction (U-4CR) is one of the milestones in this field and great efforts have been devoted to the exploration of the potential of this transformation.<sup>1,13–15</sup> In recent years several modifications of the classical U-4CR have been described; these include in situ generation of isocyanides,<sup>16,17</sup> synthesis of macrocycles<sup>18–20</sup> or diverse post-modifications.<sup>21–26</sup> There has also been much interest concerning the three-

component Ugi reactions (U-3CR).<sup>27–37</sup> In this context, there are few reports of Ugi reactions in which water acts as an internal nucleophile instead of a carboxylic acid (Scheme 1), leading to the transformation of an aldehyde, a secondary amine, and an isocyanide into an  $\alpha$ -aminoamide. List et al. reported the first catalytic U-3CR with primary amines, employing phenylphosphinic acid as the best catalyst for this reaction.<sup>32</sup> Some more applications using phenylphosphinic acid as a U-3CR promoter are reported,<sup>38,39</sup> whereas Lewis acids such as  $\text{ZnCl}_2$ ,<sup>40</sup>  $\text{ZnO}$ -nanoparticle<sup>41</sup> and boric acid,<sup>42</sup> as well as  $p\text{TSA}$ <sup>43</sup> and cellulose- $\text{SO}_3\text{H}$ <sup>44</sup> were also found to catalyze U-3CR reaction among others.



Scheme 1. Ugi four and three-component reaction.

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TosMIC, a multipurpose synthon that was introduced and elaborated by van Leusen, is a unique and versatile isocyanide that leads to variety of products.<sup>45</sup> Due to its nature, it can react either from the active methylene or the isocyanide group leading to different scaffolds (Fig. 1).<sup>46</sup> The most common strategy that incorporates the active methylene functionality of TosMIC is the well-known van Leusen three component reaction (vL-3CR) yielding 1,4,5-trisubstituted imidazoles.<sup>47–51</sup> Moreover, a wide range of other heterocycles are reported such as quinoxalines, oxazolidinones, oxazoles, thiazoles, indoles, triazoles, pyrroles, benzofurans, and pyrrolopyrimidines<sup>52,53</sup> besides natural product synthesis e.g., Variolin B, Porphobilinogen and Mansouramycin B.<sup>54–56</sup> TosMIC was also utilized, through its isocyanide functionality, as a component in the classical U-4CR<sup>24,57–61</sup> or the Ugi four component-five center (U5C-4CR).<sup>62,63</sup> Nevertheless, only in few reports TosMIC has been demonstrated as a component in the U-3CR; List et al. describe one example of the U-3CR of TosMIC using phenylphosphinic acid in toluene at 80 °C<sup>32</sup> and Shaabani et al. using the biopolymer catalyst cellulose-SO<sub>3</sub>H.<sup>44</sup>

We believe that the U-3CR is of immense importance and requires more investigation in order to fully explore the scope and limitations, especially at the isocyanide part. New catalysts, which are easily accessible, cheap and with high functional group tolerance are urgently needed. Herein, we wish to report the catalytic behavior of indoleacetic and other aromatic carboxylic acids in the U-3CR involving TosMIC as isocyanide. Moreover, the incorporation of indoleacetic acid, an important bioactive molecule, as a component in other isocyanide-based MCRs is described.

## 2. Results and discussion

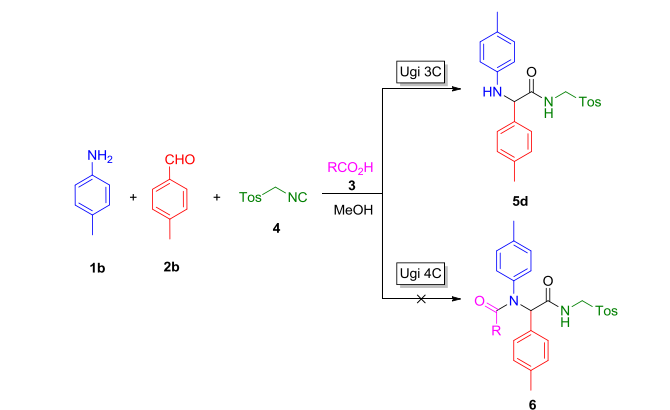
Our initial goal was to accomplish Ugi reactions involving indoleacetic acids due to their biological interest<sup>64–66</sup> and TosMIC. These reactions could be also very easily used for various post-modifications on account of the plethora of the characteristic groups available, synthesizing vast libraries with pharmaceutical interest. As a model reaction, *p*-methyl-benzaldehyde, *p*-methyl-aniline, TosMIC and indoleacetic acid (entries 6 and 7) were allowed to react in methanol at room temperature for 24 h. To our surprise, we quickly determined that compound **5d**, an U-3CR product, was isolated in 28% yield instead of the expected Ugi product **6**.

Examining the scope and limitations of this reaction (Table 1), we used the readily available 2-acetyl-indoleacetic acid, which gave the best results (57% yield, entry 1), followed by the *N*-methylated one (33% yield, entry 5). In addition, the reaction was repeated under reflux, where **5d** was isolated in a small yield (11% yield, entry 2) and with catalytic amount of 2-acetyl-indoleacetic acid

(10 mol%), where the desired compound was isolated in only 5% yield with several unidentified, mainly polymerization products (entry 3). To underscore the potential of our reaction we screened other aromatic acids as catalysts (Table 1). Benzoic acid proved to catalyze the reaction, yielding the desired compound in 39% (entry 9). Similar results were obtained using 2-phenylacetic acid as a catalyst (38% yield, entry 8), whereas in the absence of acid only the formation of the Schiff base between amine and aldehyde was observed and the reaction did not proceed any further (entry 4).

**Table 1**

Screening of various catalysts and optimization conditions of the reaction

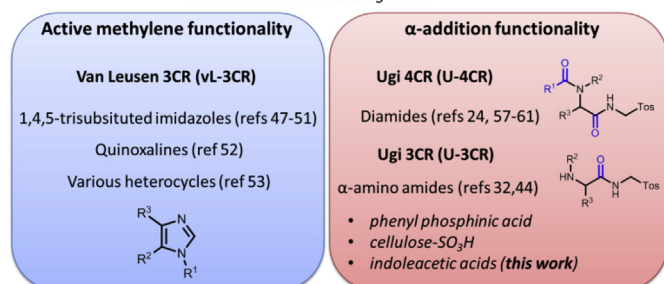
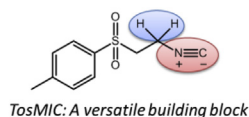


Entry	R	Conditions	Compound <b>5d</b> (yield %)
1		MeOH, rt, 24 h <sup>a</sup>	57
2		MeOH, reflux, 24 h <sup>a</sup>	11 <sup>c</sup>
3		MeOH, rt, 24 h <sup>b</sup>	>5 <sup>c</sup>
4	—	MeOH, rt, 24 h <sup>a</sup>	—
5		MeOH, rt, 24 h <sup>a</sup>	33
6		MeOH, rt, 24 h <sup>a</sup>	28
7		MeOH, rt, 24 h <sup>a</sup>	28
8		MeOH, rt, 24 h <sup>a</sup>	38
9		MeOH, rt, 24 h <sup>a</sup>	39
10		H <sub>2</sub> O, 24 h <sup>a</sup>	—
11	Me	MeOH, rt, 24 h <sup>a</sup>	7 <sup>c</sup>

<sup>a</sup> Equimolar quantities of reactants.

<sup>b</sup> Catalytical amount of acid **3**.

<sup>c</sup> Degradation and/or polymerization side products observed.

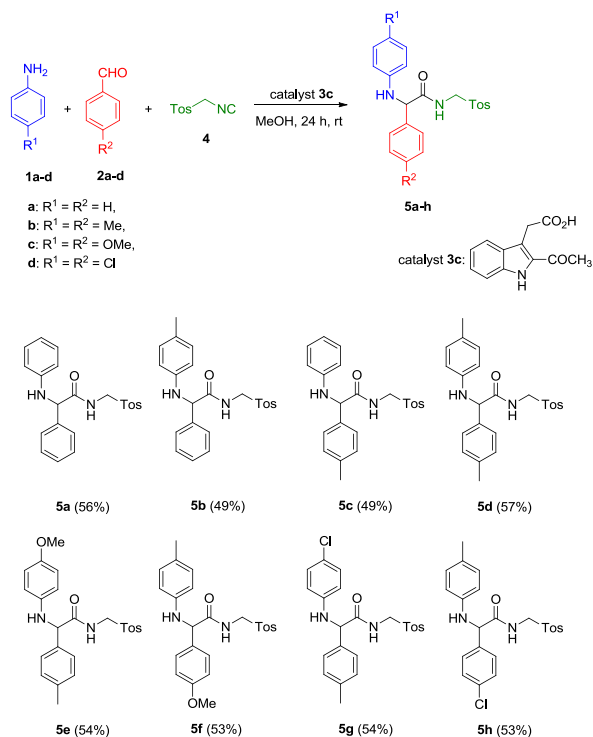


**Fig. 1.** TosMIC in MCR chemistry; the active methylene versus the α-addition functionality.



The reaction also did not progress when methanol was replaced with water (entry 10). A non-aromatic carboxylic acid as acetic acid, resulted in poor yields (7% yield, entry 11).

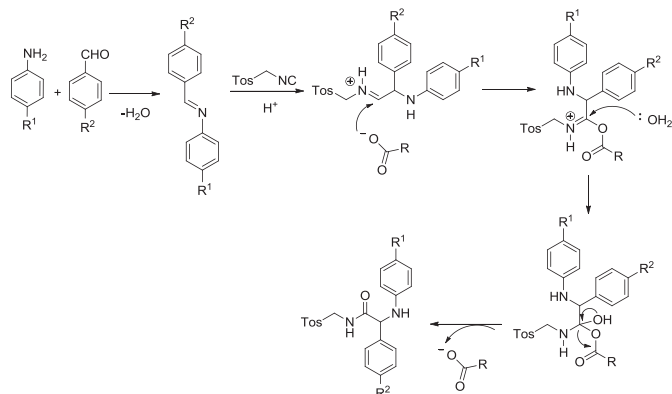
Having the optimized conditions in hand, we designed and synthesized a library of U-3C derivatives involving aromatic aldehydes, amines and TosMIC with moderate to good yields (Scheme 2,



**Scheme 2.** U-3CR catalyzed by the 2-acetyl-indoleacetic acid.

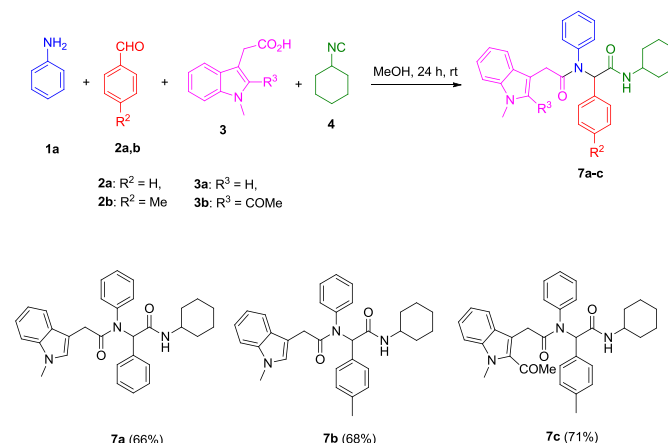
49–57%). These findings are of outmost importance, giving easy access to derivatives **5**, which can easily be subjected to post modifications. The catalysts are easily prepared<sup>67</sup> and the reaction is scalable. A plausible mechanism is given in Scheme 3. This reaction, to the best of our knowledge, is the first example of a three component Ugi reaction catalyzed by indoleacetic acids.

Next, we wanted to expand the scope of the reaction utilizing classical isocyanides. Thus, the Ugi reaction involving aniline, benzaldehyde, indoleacetic acid **3a** and cyclohexyl isocyanide was



**Scheme 3.** Plausible mechanism of the novel catalytic U-3CR.

examined whereupon after stirring in MeOH at ambient temperature for 24 h, the U-4CR products **7a,b** were isolated in 66% and 68% yield, respectively as the only reaction products (Scheme 4). An analogous reaction was observed when *N*-methyl-2-acetyl-indoleacetic acid **3b** was used, leading to formation of the Ugi product

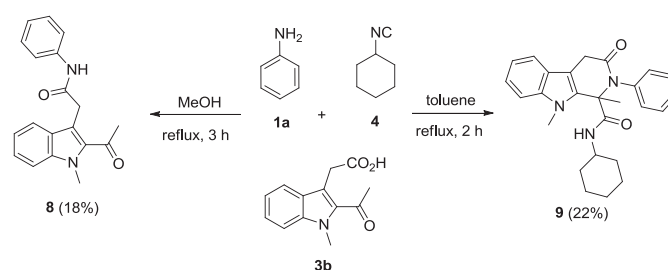


**Scheme 4.** U-4CR involving the indoleacetic moiety.

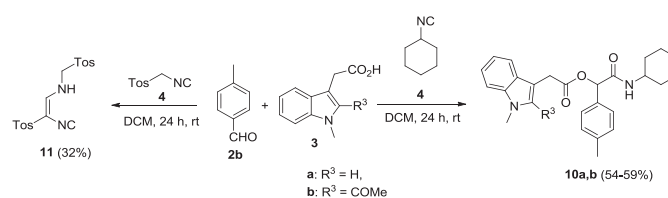
**7c** in 71% yield. It seems that the isocyanide functionality plays an important role in determining the reaction route, yielding either the U-4CR or the U-3CR adduct.

A three component, four center reaction (U-4C-3CR) was attempted by using the indoleacetic acid **3b** (as the acid and carbonyl component), aniline and cyclohexyl isocyanide, whereupon the Ugi product **9** was isolated in 22% yield under reflux in toluene. Amide **8** was isolated in low yield when the reaction performed in refluxing methanol (Scheme 5).

We thought that it would be also quite interesting to explore the Passerini reaction (P-3CR) with the indoleacetic acids. So, the reaction with *p*-methyl-benzaldehyde, indoleacetic acid **3a** and cyclohexyl isocyanide proceeded smoothly to give after stirring in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature for 24 h the Passerini product **10a** in 59% yield as the only reaction product (Scheme 6). The reaction



**Scheme 5.** Example of the U-4C-3CR bearing the 2-acetyl-indole acetic acid leading to a tetrahydro-1H-pyrido[3,4-b]indole.



**Scheme 6.** Investigation of the P-3CR involving indoleacetic acids **3**.



with *N*-methyl-2-acetyl-indoleacetic acid **3b** proceeded analogously to give **10b** in 54% yield. The reaction was also repeated using TosMIC as the isocyanide component, in an attempt to isolate the classical Passerini product, but unfortunately, the only isolated product was the TosMIC dimer<sup>68</sup> compound **11** in 32% yield.

## 2.1. Structure assignments of the new compounds

The assigned molecular structures of the new compounds **5d**, **7b**, and **10a** were based on rigorous spectroscopic analysis including IR, NMR (<sup>1</sup>H, <sup>13</sup>C, H–H COSY, H–H NOESY, HMQC and HMBC), MS and elemental analysis data. The HMBC correlations of protons with carbons via <sup>2</sup>J, <sup>3</sup>J and <sup>4</sup>J coupling are depicted in Fig. 2A–C. Concerning the structure elucidation of the U-3CR adducts, the derivative **5d** was studied. In IR, a strong absorption at 811 cm<sup>−1</sup> was observed correlating to the *p*-substitution of the aromatic ring. In addition, two absorptions at 3350 cm<sup>−1</sup> and one strong at 1689 cm<sup>−1</sup> for the two amino groups and the C=O respectively, are observed. In NMR, the aromatic protons are well defined through their <sup>2</sup>J and <sup>3</sup>J COLOC correlations as depicted in Fig. 2A. The protons of the methyl group at 2.36 δ (4'-Me), show a <sup>2</sup>J correlation with the carbon at 138.6 δ (C-1') and <sup>3</sup>J with the carbon at 29.87 δ (C-3', C-5'). Furthermore, the protons of the methyl group at 2.25 δ (4''-Me) show a <sup>2</sup>J correlation with the carbon at 128.9 δ (C-4'') and <sup>3</sup>J with the carbons at 129.93 δ (C-3'', C-5''). Finally, the protons of the methyl group at 2.38 δ (4'''-Me) show a <sup>2</sup>J correlation with the carbon at 45.1 δ (C-4''') and <sup>3</sup>J with the carbon at 129.8 δ (C-3''', C-5'''). The H-2 gives a correlation with the carbons at 127.2 δ (C-2', C-6'), 135.0 δ (C-1'), 144.0 δ (C-1'') and 171.5 δ (C-1). The protons of the methylene group correlate via <sup>3</sup>J with the tertiary carbon at 171.5 δ (C-1).

Concerning compound **7b** (Fig. 2B), in <sup>1</sup>H NMR the equatorial protons of the cyclohexyl group (1.45–1.90 δ) resonate at lower field than the axial (0.85–1.37 δ). The H-4' (1.55–1.65, equatorial) gives COLOC correlations via <sup>3</sup>J with the carbons at 32.63 δ (C-2') and 32.59 δ (C-6'). The NH appears as a broad double peak at 5.84 δ, whereas the H-2 as singlet at 6.06 δ with its carbon at 65.2 δ. The 5-CH<sub>2</sub> appears as a single peak at 3.54 δ with its carbon at 31.6 δ. The

H-2 gives COLOC correlation via a <sup>2</sup>J with carbons at 131.9 δ (C-1''), 140.6 δ (C-1''') and 168.9 δ (1-CO), the H-5 via <sup>2</sup>J with carbons at 107.8 δ (C-3''') and 172.0 δ (C-4) and via <sup>3</sup>J with the carbon at 127.9 δ (C-2'''). The protons of the methyl at 3.70 δ (N–Me) show a <sup>3</sup>J correlation with the carbons at 127.9 δ (C-2''') and 136.8 δ (C-7a'''), whereas the protons of the methyl at 2.22 δ (2-Me) show a <sup>2</sup>J correlation with the carbons at 137.8 δ (C-4'') and <sup>3</sup>J with the carbons at 128.7 δ (C-3'', C-5''). The H-4''' at 7.30 δ show COLOC correlation via <sup>2</sup>J and <sup>3</sup>J with the carbons at 121.4 δ (C-5'''), 127.6 δ (C-3a''') and <sup>3</sup>J with the carbons at 107.8 δ (C-3''') and 136.8 δ (C-7a'''). The H-5''' correlates via <sup>2</sup>J with the carbons at 118.8 δ (C-4''') and 119.0 δ (C-6'''), the H-6''' at 6.99 δ correlates via <sup>2</sup>J with the carbons at 108.9 δ (C-7''') and 121.4 δ (C-5'''), the H-2''' at 6.80 δ correlates via <sup>2</sup>J with the carbon at 107.8 δ (C-3''') and <sup>3</sup>J with the carbons at 127.6 δ (C-3a''') and 136.9 δ (C-7a'''). Finally, we detect NOESY interactions between N–Me protons with the H-2''' and H-7''' and between 5-CH<sub>2</sub> protons with H-2''' and H-4'''.

Compound **10a** has similar structure to **7b** (Fig. 2C). In <sup>1</sup>H NMR the equatorial protons of the cyclohexyl group (1.36–1.49 δ) appear at lower field than the axial (0.16–1.18 δ). The NH appears as a broad double peak at 5.58 δ, H-2 as singlet at 6.03 δ with its carbon at 75.1 δ and the –CH<sub>2</sub> appears as singlet at 3.80 δ with its carbon at 31.4 δ. The two methyl groups, (N–Me) and (4''-Me), appear at 3.70 δ (carbon at 32.5 δ) and 2.30 δ (carbon at 21.1 δ), respectively. The protons H-4''' and H-7''' of the indole appear as double peaks at 7.66 and 7.32 δ, with their carbons at 118.7 δ and 109.5 δ, respectively. H-5''' and H-6''' appear as double of doublets at 7.27 and 7.18 δ, with their carbons at 122.0 δ and 119.7 δ, whereas the H-2''' appears as a singlet at 7.00 δ (carbon at 127.8 δ). In the phenyl ring, H-2'' and H-6'' appear as a triplet at 7.26 δ (carbon at 129.1 δ, 2×C) and H-3'' and H-5'' appear as triplet at 7.13 δ (carbon at 127.3 δ, 2×C).

## 3. Conclusion

In conclusion, we have investigated the role and behaviour of various indoleacetic acid derivatives in Ugi and Passerini reactions. It was also emphasized that most possibly depending on the nature

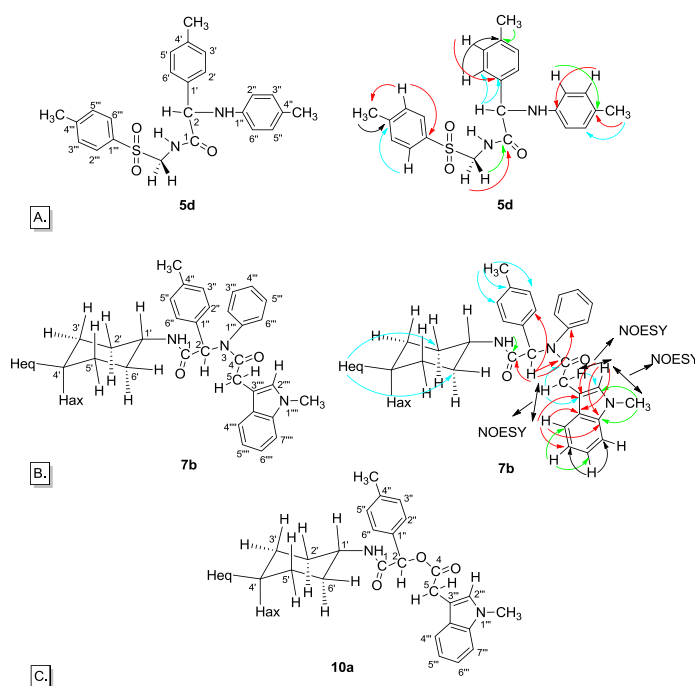


Fig. 2. Diagnostic COLOC correlations between protons and carbons (via <sup>2</sup>J<sub>C–H</sub>, <sup>3</sup>J<sub>C–H</sub> and <sup>4</sup>J<sub>C–H</sub>) observed in compounds **5d** (A), **7b** (B) and **10a** (C).



of isocyanide, indoleacetic acid derivatives could either play a catalytic role driving the reaction to an U-3CR, or being incorporated into an U-4CR and P-3CR, respectively. Useful insights to the catalyzed U-3CR by various aromatic acids were also given by synthesizing a small library. We believe that this study will add to the TosMIC chemistry and can serve as a starting point for further investigations.

## 4. Experimental

### 4.1. General

Column chromatography was carried out using Merck silica gel. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV<sub>254</sub> purchased from Macherey-Nagel using a 3:1 mixture of petroleum ether/ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature on a Bruker AM 300 spectrometer at 300 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C, respectively, using CDCl<sub>3</sub> as solvent. Chemical shifts are expressed in  $\delta$  values (ppm) relative to TMS as internal standard for <sup>1</sup>H and relative to TMS (0.00 ppm) or to CDCl<sub>3</sub> (77.05 ppm) for <sup>13</sup>C NMR spectra. Coupling constants <sup>n</sup>J are reported in Hz. Second order <sup>1</sup>H spectra in the aromatic region, where it was possible, were analysed by simulation.<sup>69</sup> Low-resolution electron impact mass spectra were recorded on a 6890N LC/MS system (Agilent Technology) and high resolution mass spectra were recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000  $m/z$  400. Structural assignments of the derived compounds were established by analysis of their MS and NMR spectra (<sup>1</sup>H, <sup>13</sup>C, DEPT, H–H COSY, H–H NOESY, HETCOR and COLOC).

### 4.2. General procedure for the U-3CR reaction with TosMIC

To a stirred solution of the amines **1a–d** (1.0 mmol) in methanol (8 mL), the corresponding aldehydes **2a–d** (1.0 mmol) were added and the reaction mixture stirred at rt for 1 h. Then, the catalyst **3c** (1.0 mmol) was added, the reaction mixture stirred for additional 15 min, followed by the addition of TosMIC (1.0 mmol). After 24 h at rt, the solvent was removed and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (7:1 and 3:1 for the derivatives **5a–f** and **5g–h**, respectively) as eluent affording the compounds **5a–h**.

**4.2.1. 2-Phenyl-2-(phenylamino)-N-(tosylmethyl)acetamide (5a).** Yellow crystals (0.221 g, 56% yield), mp 158–159 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.38 (s, 3H, 4''-Me), 4.55 (dd,  $J=6.5$ , 14.2 Hz, 1H, 1-CH), 4.71 (s, 1H, 2-CH), 4.79 (dd,  $J=7.3$ , 14.2 Hz, 1H, 1-CH), 6.57 (d,  $J=7.8$  Hz, 2H, H-2'', H-6''), 6.83 (t,  $J=7.3$  Hz, 1H, H-4''), 7.13–7.22 (m, 4H, H-3'', H-5'', H-3''', H-5'''), 7.33–7.41 (m, 5H, H-2', H-6', H-3', H-5', H-4'), 7.54 (d,  $J=8.3$  Hz, 2H, H-2''', H-6'''), 7.60 (br t,  $J=7.3$  Hz, 1H, 1-NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.7 (4''-Me), 60.1 (1-CH<sub>2</sub>), 64.0 (2-CH), 114.0 (C-2'', C-6''), 119.7 (C-4''), 127.3 (C-2', C-6'), 128.6 (C-2''', C-6'''), 128.9 (C-4'), 129.3 (C-3', C-5'), 129.5 (C-3'', C-5''), 129.9 (C-3''', C-5'''), 133.6 (C-1'''), 134.0 (C-1'), 145.2 (C-1''), 146.2 (C-4'''), 171.1 (1-CO). IR (Nujol) cm<sup>-1</sup> 694, 746, 1513, 1605, 1677. MS (LCMS)  $m/z$  (%) calcd for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S, M<sup>+</sup>+H: 395; found: 395 (5%, M<sup>+</sup>+H), 417 (100%, M<sup>+</sup>+Na), 433 (18%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 395.48668; found [M+H]<sup>+</sup>: 395.48625.

**4.2.2. 2-Phenyl-2-(p-tolylamino)-N-(tosylmethyl)acetamide (5b).** Yellow crystals (0.200 g, 49% yield), mp 160–162 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.26 (s, 1H, 4''-Me), 2.38 (s, 3H, 4''-Me), 4.20 (br s, 1H, 2-NH), 4.51 (dd,  $J=6.2$ , 14.3 Hz, 1H, 1-CH), 4.65 (s, 1H, 2-CH), 4.85 (dd,  $J=7.5$ , 14.3 Hz, 1H, 1-CH), 6.49 (d,  $J=8.0$  Hz, 2H, H-2'', H-6''), 7.01 (d,  $J=8.0$  Hz, 2H, H-3'', H-5''), 7.14 (d,  $J=7.8$  Hz, 2H, H-3''', H-5'''),

7.32–7.38 (m, 5H, H-2', H-6', H-3', H-5', H-4'), 7.54 (br t, 1H, 1-NH), 7.54 (d,  $J=8.0$  Hz, 2H, H-2''', H-6'''). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.5 (4''-Me), 21.7 (4''-Me), 60.1 (1-CH<sub>2</sub>), 64.5 (2-CH), 114.2 (C-2'', C-6''), 127.3 (C-2', C-6'), 128.7 (C-2''', C-6'''), 128.8 (C-4'), 129.2 (C-4''), 129.3 (C-3', C-5'), 129.9 (C-3'', C-5''), 130.0 (C-3'', C-5''), 134.0 (C-1'''), 137.9 (C-1'), 143.9 (C-1''), 145.2 (C-4'''), 171.3 (1-CO). IR (Nujol) cm<sup>-1</sup> 697, 759, 814, 1523, 1619, 1690. MS (LCMS)  $m/z$  (%) calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S, M<sup>+</sup>+H: 409; found: 409 (31%, M<sup>+</sup>+H), 431 (75%, M<sup>+</sup>+Na), 447 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 409.51326; found [M+H]<sup>+</sup>: 409.51319.

**4.2.3. 2-(Phenylamino)-2-(p-tolyl)-N-(tosylmethyl)acetamide (5c).** Brown crystals (0.200 g, 49% yield), mp 137–140 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.36 (s, 3H, 4''-Me), 2.38 (s, 3H, 4''-Me), 4.39 (br s, 1H, 2-NH), 4.53 (dd,  $J=6.5$ , 14.1 Hz, 1H, 1-CH), 4.66 (s, 1H, 2-CH), 4.75 (dd,  $J=7.2$ , 14.1 Hz, 1H, 1-CH), 6.55 (dd,  $J=0.9$ , 7.7 Hz, 2H, H-2'', H-6''), 6.82 (tt,  $J=0.8$ , 7.4 Hz, 1H, H-4''), 7.13–7.25 (m, 8H, H-2', H-6', H-3', H-5', H-3'', H-5'', H-3''', H-5'''), 7.54 (d,  $J=8.2$  Hz, 2H, H-2''', H-6'''), 7.57 (br t,  $J=6.5$  Hz, 1H, 1-NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.2 (4''-Me), 21.7 (4''-Me), 60.1 (1-CH<sub>2</sub>), 63.7 (2-CH), 114.1 (C-2'', C-6''), 119.6 (C-4''), 127.2 (C-2', C-6'), 128.7 (C-2''', C-6'''), 129.5 (C-3'', C-5''), 129.85 (C-3''', C-5'''), 129.95 (C-3', C-5'), 134.0 (C-1'''), 134.8 (C-1'), 138.7 (C-4'), 145.2 (C-1''), 146.2 (C-4'''), 171.3 (1-CO). IR (Nujol) cm<sup>-1</sup> 691, 748, 811, 1509, 1604, 1686, 3350. MS (LCMS)  $m/z$  (%) calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S, M<sup>+</sup>+H: 409; found: 409 (3%, M<sup>+</sup>+H), 431 (59%, M<sup>+</sup>+Na), 447 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 409.51326; found [M+H]<sup>+</sup>: 409.51310.

**4.2.4. 2-(p-Tolyl)-2-(p-tolylamino)-N-(tosylmethyl)acetamide (5d).** Yellow crystals (0.241 g, 57% yield), mp 171–173 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.25 (s, 3H, 4''-Me), 2.36 (s, 3H, 4''-Me), 2.38 (s, 3H, 4''-Me), 4.22 (br s, 1H, 2-NH), 4.51 (dd,  $J=6.4$ , 14.2 Hz, 1H, 1-CH), 4.62 (s, 1H, 2-CH), 4.78 (dd,  $J=7.3$ , 14.2 Hz, 1H, 1-CH), 6.47 (d,  $J=8.2$  Hz, 2H, H-2'', H-6''), 6.99 (d,  $J=8.2$  Hz, 2H, H-3'', H-5''), 7.13 (d,  $J=8.1$  Hz, 2H, H-3''', H-5'''), 7.15 (d,  $J=8.3$  Hz, 2H, H-3', H-5'), 7.20 (d,  $J=8.3$  Hz, 2H, H-2', H-6'), 7.54 (d,  $J=8.1$  Hz, 2H, H-2''', H-6'''), 7.54 (br t,  $J=7.2$  Hz, 1H, 1-NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.4 (4''-Me), 21.2 (4''-Me), 21.7 (4''-Me), 60.1 (1-CH<sub>2</sub>), 64.0 (2-CH), 114.1 (C-2'', C-6''), 127.2 (C-2', C-6'), 128.7 (C-2''', C-6'''), 128.9 (C-4'), 129.8 (C-3''', C-5'''), 129.87 (C-3', C-5'), 129.93 (C-3'', C-5''), 134.0 (C-1'''), 135.0 (C-1'), 138.6 (C-4'), 144.0 (C-1''), 145.1 (C-4'''), 171.5 (1-CO). IR (Nujol) cm<sup>-1</sup> 811, 1524, 1619, 1689, 3350. MS (LCMS)  $m/z$  (%) calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, M<sup>+</sup>+H: 423; found: 423 (9%, M<sup>+</sup>+H), 445 (62%, M<sup>+</sup>+Na), 461 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 423.53984; found [M+H]<sup>+</sup>: 423.53955.

**4.2.5. 2-((4-Methoxyphenyl)amino)-2-(p-tolyl)-N-(tosylmethyl)acetamide (5e).** Yellow crystals (0.237 g, 54% yield), mp 135–136 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.36 (s, 3H, 4''-Me), 2.37 (s, 3H, 4''-Me), 3.73 (s, 3H, 4''-OMe), 4.17 (br s, 1H, 2-NH), 4.53 (dd,  $J=6.5$ , 14.2 Hz, 1H, 1-CH), 4.59 (s, 1H, 2-CH), 4.75 (dd,  $J=7.2$ , 14.2 Hz, 1H, 1-CH), 6.51 (d,  $J=8.9$  Hz, 2H, H-2'', H-6''), 6.76 (d,  $J=8.9$  Hz, 2H, H-3'', H-5''), 7.13 (d,  $J=8.0$  Hz, 2H, H-3''', H-5'''), 7.14 (d,  $J=8.2$  Hz, 2H, H-3', H-5'), 7.20 (d,  $J=8.2$  Hz, 2H, H-2''', H-6'''), 7.53 (d,  $J=8.2$  Hz, 2H, H-2'', H-6''), 7.60 (br t,  $J=6.7$  Hz, 1H, 1-NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.1 (4''-Me), 21.7 (4''-Me), 60.1 (1-CH<sub>2</sub>), 64.5 (2-CH), 55.7 (4''-OMe), 115.0 (C-2'', C-6''), 115.3 (C-3'', C-5''), 127.1 (C-2', C-6'), 128.6 (C-2''', C-6'''), 129.79 (C-3''', C-5'''), 129.83 (C-3', C-5'), 134.1 (C-1'''), 135.0 (C-1'), 138.5 (C-4'), 140.3 (C-1''), 145.1 (C-4'''), 153.6 (C-4''), 171.6 (1-CO). IR (Nujol) cm<sup>-1</sup> 813, 1085, 1513, 1597, 1689. MS (LCMS)  $m/z$  (%) calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S, M<sup>+</sup>+H: 439; found: 439 (13%, M<sup>+</sup>+H), 461 (55%, M<sup>+</sup>+Na), 477 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 439.53924; found [M+H]<sup>+</sup>: 439.53911.

**4.2.6. 2-(4-Methoxyphenyl)-2-(p-tolylamino)-N-(tosylmethyl)acetamide (5f).** Yellow crystals (0.232 g, 53% yield), mp 174–176 °C; <sup>1</sup>H



NMR (CDCl<sub>3</sub>)  $\delta$  2.24 (s, 3H, 4''-Me), 2.37 (s, 3H, 4'''-Me), 3.79 (s, 3H, 4'-OMe), 4.22 (br s, 1H, 2-NH), 4.49 (dd,  $J$ =6.4, 14.1 Hz, 1H, 1-CH), 4.62 (s, 1H, 2-CH), 4.75 (dd,  $J$ =7.2, 14.1 Hz, 1H, 1-CH), 6.46 (d,  $J$ =8.3 Hz, 2H, H-2'', H-6''), 6.85 (d,  $J$ =8.7 Hz, 2H, H-3'', H-5''), 6.97 (d,  $J$ =8.0 Hz, 2H, H-3', H-5'), 7.13 (d,  $J$ =8.1 Hz, 2H, H-3''', H-5'''), 7.22 (d,  $J$ =8.6 Hz, 2H, H-2', H-6'), 7.54 (d,  $J$ =8.3 Hz, 2H, H-2''', H-6'''), 7.59 (br t, 1H, 1-NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.4 (4''-Me), 21.6 (4'''-Me), 55.3 (4'-OMe), 60.2 (1-CH<sub>2</sub>), 63.6 (2-CH), 114.1 (C-2'', C-6''), 114.6 (C-3', C-5'), 171.7 (1-CO), 128.5 (C-2', C-6'), 128.8 (C-4''), 129.8 (C-3'', C-5''), 129.9 (C-3'', C-5''), 130.1 (C-1'''), 134.2 (C-1'), 144.0 (C-1''), 160.0 (C-4'), 128.7 (C-2'', C-6''), 145.1 (C-4'''). IR (Nujol) cm<sup>-1</sup> 812, 1085, 1510, 1618, 1686. MS (LCMS)  $m/z$  (%) calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S, M<sup>+</sup>+H: 439; found 439 (4%, M<sup>+</sup>+H), 461 (41%, M<sup>+</sup>+Na), 477 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 439.53924; found [M+H]<sup>+</sup>: 439.53922.

**4.2.7. 2-((4-Chlorophenyl)amino)-2-(p-tolyl)-N-(tosylmethyl)acetamide (5g).** Yellow crystals (0.239 g, 54% yield), mp 166–168 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.38 (s, 3H, 4'-Me), 2.40 (s, 3H, 4'''-Me), 4.59 (dd,  $J$ =6.6, 14.2 Hz, 1H, 1-CH), 4.63 (s, 1H, 2-CH), 4.73 (dd,  $J$ =6.8, 14.2 Hz, 1H, 1-CH), 6.46 (d,  $J$ =8.7 Hz, 2H, H-2'', H-6''), 7.11 (d,  $J$ =8.7 Hz, 2H, H-3'', H-5''), 7.16 (d,  $J$ =8.1 Hz, 2H, H-3''', H-5'''), 7.19 (d,  $J$ =8.3 Hz, 2H, H-3', H-5'), 7.22 (d,  $J$ =8.3 Hz, 2H, H-2', H-6'), 7.34 (br t,  $J$ =6.6 Hz, 1H, 1-NH), 7.52 (d,  $J$ =8.2 Hz, 2H, H-2'', H-6''). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.2 (4'-Me), 21.7 (4'''-Me), 60.1 (1-CH<sub>2</sub>), 63.5 (2-CH), 115.1 (C-2'', C-6''), 124.3 (C-4''), 127.1 (C-2', C-6'), 128.6 (C-2''', C-6'''), 129.3 (C-3'', C-5''), 129.9 (C-3''', C-5'''), 130.1 (C-3', C-5'), 133.9 (C-1'''), 134.5 (C-1'), 139.0 (C-4'), 144.7 (C-1''), 145.3 (C-4'''), 170.9 (1-CO). IR (Nujol) cm<sup>-1</sup> 812, 1503, 1601, 1686. MS (LCMS)  $m/z$  (%) calcd for C<sub>23</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>S, M<sup>+</sup>+H: 443; found: 465/467 (81%, M<sup>+</sup>+Na), 481/483 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 443.95832; found [M+H]<sup>+</sup>: 443.95825.

**4.2.8. 2-(4-Chlorophenyl)-2-(p-tolylamino)-N-(tosylmethyl)acetamide (5h).** Yellow crystals (0.234 g, 53% yield), mp 179–181 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.25 (s, 3H, 4'-Me), 2.40 (s, 3H, 4'''-Me), 4.81 (dd,  $J$ =7.4, 14.2 Hz, 1H, 1-CH), 4.51 (dd,  $J$ =6.2, 14.2 Hz, 1H, 1-CH), 4.66 (s, 1H, 2-CH), 7.25 (d,  $J$ =8.7 Hz, 2H, H-2', H-6'), 7.31 (d,  $J$ =8.6 Hz, 2H, H-3', H-5'), 4.27 (br s, 1H, 2-NH), 2.25 (s, 3H, 4''-Me), 6.47 (d,  $J$ =8.3 Hz, 2H, H-2'', H-6''), 6.99 (d,  $J$ =8.1 Hz, 2H, H-3'', H-5''), 2.39 (s, 3H, 4'''-Me), 7.53 (d,  $J$ =8.2 Hz, 2H, H-2''', H-6'''), 7.15 (d,  $J$ =8.0 Hz, 2H, H-3''', H-5'''). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.4 (4''-Me), 21.7 (4'''-Me), 60.0 (1-CH<sub>2</sub>), 63.4 (2-CH), 114.1 (C-2'', C-6''), 128.57 (C-2', C-6'), 128.63 (C-2''', C-6'''), 129.2 (C-4''), 129.3 (C-3', C-5'), 129.8 (C-3''', C-5'''), 130.0 (C-3'', C-5''), 133.9 (C-1'''), 134.7 (C-1'), 136.4 (C-4'), 143.6 (C-1''), 145.3 (C-4'''), 171.0 (1-CO). IR (Nujol) cm<sup>-1</sup> 815, 1522, 1618, 1686. MS (LCMS)  $m/z$  (%) calcd for C<sub>23</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>S, M<sup>+</sup>+H: 443; found: 465/467 (53%, M<sup>+</sup>+Na), 481/483 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 443.95832; found [M+H]<sup>+</sup>: 443.95799.

### 4.3. General procedure for the U-4CR reaction with cyclohexyl isocyanide

To a stirred solution of the amine **1a** (1.0 mmol) in methanol (1 mL), the corresponding aldehydes **2a,b** (1.0 mmol) were added and the reaction mixture stirred at rt for 1 h. Then, the indole carboxylic acids **3a,b** (1.0 mmol) were added, the reaction mixture stirred for additional 10 min, followed by the addition of cyclohexyl isocyanide (1.0 mmol). After 24 h at rt, the solvent was removed and the resulting residue was washed with ether affording compounds **7a–c**.

**4.3.1. N-Cyclohexyl-2-(2-(1-methyl-1H-indol-3-yl)-N-phenyl acetamido)-2-phenylacetamide (7a).** Yellow oil (0.316 g, 66% yield); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.89–1.01 (m, 2H, H<sub>ax</sub>-2', H<sub>ax</sub>-6'), 1.04–1.15 (m, 1H, H<sub>ax</sub>-4'), 1.23–1.38 (m, 2H, H<sub>eq</sub>-3', H<sub>eq</sub>-5'), 1.24–1.38 (m, 2H, H<sub>ax</sub>-3',

H<sub>ax</sub>-5'), 1.53–1.62 (m, 1H, H<sub>eq</sub>-4'), 1.79–1.90 (m, 2H, H<sub>eq</sub>-2', H<sub>eq</sub>-6'), 3.56 (s, 2H, 5-CH<sub>2</sub>), 3.70 (s, 3H, N-Me), 3.78–3.87 (m, 1H, H<sub>ax</sub>-1'), 5.73 (br d,  $J$ =6.1 Hz, 1H, 1-NH), 6.06 (s, 1H, 2-CH), 6.83 (s, 1H, H-2'''), 6.99–7.28 (m, 13H, H-2'', H-3'', H-4'', H-5'', H-6'', H-2''', H-3''', H-4''', H-5''', H-6''', H-5''', H-6''', H-7'''), 7.32 (d,  $J$ =7.9 Hz, 1H, H-4'''). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  24.7 (C-5'), 24.8 (C-3'), 25.3 (C-4'), 31.6 (5-CH<sub>2</sub>), 32.6 (N-Me), 32.6 (C-2', C-6'), 48.5 (C-1'), 65.1 (2-CH), 107.5 (C-3'''), 108.9 (C-7'''), 118.7 (C-4'''), 118.9 (C-6'''), 121.3 (C-5'''), 127.6 (C-3a'''), 127.8 (C-4'''), 128.0 (C-2'''), 128.1 (C-3'', C-5''), 128.7 (C-1''), 129.1 (C-2'', C-6''), 130.3 (C-3''', C-5'''), 130.4 (C-2'', C-6''), 134.7 (C-7a'''), 136.6 (C-4''), 140.2 (C-1'''), 168.7 (1-CO), 172.1 (4-CO). MS (LCMS)  $m/z$  (%) calcd for C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>, M<sup>+</sup>+H: 480; found: 480 (8%, M<sup>+</sup>+H), 502 (68%, M<sup>+</sup>+Na), 518 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 480.61262; found [M+H]<sup>+</sup>: 480.61258.

**4.3.2. N-Cyclohexyl-2-(2-(1-methyl-1H-indol-3-yl)-N-phenyl acetamido)-2-(p-tolyl)acetamide (7b).** Yellow oil (0.335 g, 68% yield); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.85–1.00 (m, 2H, H<sub>ax</sub>-2', H<sub>ax</sub>-6'), 1.00–1.10 (m, 1H, H<sub>ax</sub>-4'), 1.20–1.37 (m, 2H, H<sub>ax</sub>-3', H<sub>ax</sub>-5'), 1.45–1.60 (m, 2H, H<sub>eq</sub>-3', H<sub>eq</sub>-5'), 1.55–1.65 (m, 1H, H<sub>eq</sub>-4'), 1.72–1.90 (m, 2H, H<sub>eq</sub>-2', H<sub>eq</sub>-6'), 2.22 (s, 3H, 4''-Me), 3.54 (s, 2H, 5-CH<sub>2</sub>), 3.70 (s, 3H, N-Me), 3.70–3.82 (m, 1H, H<sub>ax</sub>-1'), 5.84 (br d,  $J$ =7.4 Hz, 1H, 1-NH), 6.06 (s, 1H, 2-CH), 6.80 (s, 1H, H-2'''), 6.92 (t,  $J$ =8.0 Hz, 1H, H-4'''), 6.94 (t,  $J$ =7.0 Hz, 2H, H-3'', H-5''), 6.99 (m, 1H, H-6'''), 7.01 (t,  $J$ =8.0 Hz, 2H, H-2'', H-6''), 7.11 (m, 1H, H-5'''), 7.13 (m, 2H, H-3''', H-5'''), 7.16 (t,  $J$ =8.3 Hz, 2H, H-2''', H-6'''), 7.19 (d,  $J$ =8.2 Hz, 1H, H-7'''), 7.30 (d,  $J$ =7.9 Hz, 1H, H-4'''). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.0 (4''-Me), 24.6 (C-5'), 24.7 (C-3'), 25.5 (C-4'), 31.6 (5-CH<sub>2</sub>), 32.4 (N-Me), 32.59 (C-6'), 32.63 (C-2'), 48.5 (C-1'), 65.2 (2-CH), 107.8 (C-3'''), 108.9 (C-7'''), 118.8 (C-4'''), 119.0 (C-6'''), 121.4 (C-5'''), 127.6 (C-3a'''), 127.8 (C-4'''), 127.9 (C-2'''), 128.7 (C-3'', C-5''), 128.8 (C-2'', C-6''), 130.2 (C-3''', C-5'''), 130.5 (C-2'', C-6''), 131.9 (C-1''), 136.8 (C-7a'''), 137.8 (C-4''), 140.6 (C-1'''), 168.9 (1-CO), 172.0 (4-CO). MS (LCMS)  $m/z$  (%) calcd for C<sub>32</sub>H<sub>35</sub>N<sub>3</sub>O<sub>2</sub>, M<sup>+</sup>+H: 494; found: 494 (7%, M<sup>+</sup>+H), 516 (70%, M<sup>+</sup>+Na), 532 (100%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 494.63920; found [M+H]<sup>+</sup>: 494.63919.

**4.3.3. 2-(2-Acetyl-1-methyl-1H-indol-3-yl)-N-(2-(cyclohexylamino)-2-oxo-1-(p-tolyl)ethyl)-N-phenylacetamide (7c).** White solid (0.380 g, 71% yield), mp 225 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.91–1.05 (m, 2H, H<sub>ax</sub>-2', H<sub>ax</sub>-6'), 1.08–1.12 (m, 1H, H<sub>ax</sub>-4'), 1.24–1.34 (m, 2H, H<sub>ax</sub>-3', H<sub>ax</sub>-5'), 1.57–1.61 (m, 2H, H<sub>eq</sub>-3', H<sub>eq</sub>-5'), 1.65 (m, 1H, H<sub>eq</sub>-4'), 1.80–1.90 (m, 2H, H<sub>eq</sub>-2', H<sub>eq</sub>-6'), 2.26 (s, 3H, 2''''-Me), 2.56 (s, 3H, 4''-Me), 3.73–3.79 (m, 1H, H<sub>ax</sub>-1'), 3.81 (s, 2H, 5-CH<sub>2</sub>), 3.92 (s, 3H, N-Me), 5.60 (br d,  $J$ =7.8 Hz, 1H, 1-NH), 6.02 (s, 1H, 2-CH), 6.96 (t,  $J$ =8.3 Hz, 1H, H-4'''), 6.99 (t,  $J$ =8.2 Hz, 2H, H-3'', H-5''), 7.08 (t,  $J$ =7.9 Hz, 2H, H-2'', H-6''), 7.09 (dd,  $J$ =2.3, 8.0, 8.1 Hz, 1H, H-6'''), 7.25–7.35 (m, 6H, H-2'', H-3'', H-5'', H-6'', H-5''', H-7'''), 7.50 (d,  $J$ =8.0 Hz, 1H, H-4'''). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  15.2 (2''''-Me), 21.0 (4''-Me), 24.8 (C-3', C-5'), 25.5 (C-4'), 30.8 (N-Me), 32.7 (C-6'), 32.8 (5-CH<sub>2</sub>), 32.8 (C-2'), 48.7 (C-1'), 65.3 (2-CH), 110.2 (C-7'''), 116.1 (C-3'''), 120.2 (C-4'''), 120.6 (C-6'''), 125.6 (C-5'''), 127.1 (C-3a'''), 128.3 (C-4'''), 129.0 (C-3'', C-5''), 129.1 (C-2'', C-6''), 130.3 (C-3''', C-5'''), 130.5 (C-2'', C-6''), 131.6 (C-1''), 134.8 (C-2'''), 138.1 (C-7a'''), 138.7 (C-4''), 140.2 (C-1'''), 168.7 (1-CO), 170.5 (2-CO), 192.6 (2''''-CO). IR (Nujol) cm<sup>-1</sup> 1493, 1594, 1650. MS (LCMS)  $m/z$  (%) calcd for C<sub>34</sub>H<sub>37</sub>N<sub>3</sub>O<sub>3</sub>, M<sup>+</sup>+H: 536; found: 536 (10%, M<sup>+</sup>+H), 558 (100%, M<sup>+</sup>+Na), 574 (65%, M<sup>+</sup>+K). HRMS (ESI)  $m/z$  calcd [M+H]<sup>+</sup>: 536.67588; found [M+H]<sup>+</sup>: 536.67541.

### 4.4. Synthesis of 2-(2-acetyl-1-methyl-1H-indol-3-yl)-N-phenylacetamide (8)

To a stirred solution of the amine **1a** (1.0 mmol) in methanol (2 mL), the indole acetic acid **3b** (1.0 mmol) and cyclohexyl isocyanide (1.0 mmol) were added and the reaction mixture refluxed



for 3 h. The solvent was removed and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (5:1) affording compound **8**.

**4.4.1. 2-(2-Acetyl-1-methyl-1H-indol-3-yl)-N-phenylacetamide (8).** Yellow oil (0.055 g, 18% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.71 (s, 3H, 2-Me), 3.97 (s, 3H, N-Me), 4.02 (s, 2H, 3-CH<sub>2</sub>), 7.01 (t,  $J=7.4$  Hz, 1H, H-4'), 7.22 (m, 2H, H-2', H-6'), 7.34–7.45 (m, 5H, H-5, H-6, H-7, H-3', H-5'), 7.84 (d,  $J=8.1$  Hz, 1H, H-4), 8.54 (br s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.0 (2-Me), 33.0 (N-Me), 35.4 (3-CH<sub>2</sub>), 110.5 (C-7), 116.9 (C-3), 119.7 (C-5), 121.3 (C-2', C-6'), 121.4 (C-6), 124.0 (C-4), 126.8 (C-4'), 128.9 (C-3', C-5'), 136.0 (C-3a), 138.3 (C-1'), 138.3 (C-2), 139.2 (C-7a), 168.5 (3-CO), 193.3 (2-CO). MS (LCMS)  $m/z$  (%) calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ ,  $\text{M}^+ + \text{H}$ : 307; found: 307 (6%,  $\text{M}^+ + \text{H}$ ), 329 (100%,  $\text{M}^+ + \text{Na}$ ), 345 (94%,  $\text{M}^+ + \text{K}$ ), 361 (28%,  $\text{M}^+ + \text{Na} + \text{MeOH}$ ). HRMS (ESI)  $m/z$  calcd  $[\text{M} + \text{H}]^+$ : 307.35842; found  $[\text{M} + \text{H}]^+$ : 307.35800.

#### 4.5. Synthesis of N-cyclohexyl-1,9-dimethyl-3-oxo-2-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxamide (9)

To a stirred solution of the amine **1a** (1.0 mmol) in toluene (4 mL), the indole acetic acid **3b** (1.0 mmol) and cyclohexyl isocyanide (1.0 mmol) were added and the reaction mixture refluxed for 2 h. The solvent was removed and the resulting residue was washed with ether affording compound **9**.

**4.5.1. N-Cyclohexyl-1,9-dimethyl-3-oxo-2-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxamide (9).** Yellow oil (0.091 g, 22% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91–1.10 (m, 3H, H-2''<sub>ax</sub>, H-6''<sub>ax</sub>, H-4''<sub>ax</sub>), 1.23–1.35 (m, 3H, H-1''<sub>ax</sub>, H-3''<sub>ax</sub>, H-5''<sub>ax</sub>), 1.48–1.61 (m, 3H, H-3''<sub>eq</sub>, H-5''<sub>eq</sub>, H-4''<sub>eq</sub>), 1.76–1.79 (m, 2H, H-2''<sub>eq</sub>, H-6''<sub>eq</sub>), 2.63 (s, 3H, 1-Me), 2.71 (s, 2H, 4-CH<sub>2</sub>), 3.69–3.78 (m, 1H, H-1''<sub>eq</sub>), 3.97 (s, 3H, N-Me), 7.01 (t,  $J=7.2$  Hz, 1H, H-4'), 7.22 (m, 3H, H-6, H-2', H-6'), 7.41 (m, 3H, H-7, H-3', H-5'), 7.69 (d,  $J=8.1$  Hz, 1H, H-8), 7.84 (d,  $J=8.0$  Hz, 1H, H-5), 8.65 (br s, 1H, 1-NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.7 (C-3'', C-5''), 25.4 (C-4''), 31.0 (1-Me), 32.8 (4-CH<sub>2</sub>), 32.8 (C-2'', C-6''), 34.3 (N-Me), 48.3 (C-1''), 115.9 (C-1), 119.7 (C-8), 120.7 (C-5), 121.1 (C-6), 121.3 (C-7), 126.4 (C-2', C-6'), 126.7 (C-4'), 128.8 (C-3', C-5'), 139.2 (C-1'), 116.9 (C-4a), 135.1 (C-4b), 138.3 (C-9a), 168.5 (3-CO), 138.9 (C-8a), 192.6 (1-CO). MS (LCMS)  $m/z$  (%) calcd for  $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_2$ ,  $\text{M}^+ + \text{H}$ : 416; found: 438 (100%,  $\text{M}^+ + \text{Na}$ ). HRMS (ESI)  $m/z$  calcd  $[\text{M} + \text{H}]^+$ : 416.52736; found  $[\text{M} + \text{H}]^+$ : 416.52730.

#### 4.6. General procedure for the P-3CR reaction with cyclohexyl isocyanide

To a stirred solution of the aldehyde **2b** (1.0 mmol) in DCM (0.5 mL), the indole acetic acids **3a,b** (1.0 mmol) and cyclohexyl isocyanide (1.0 mmol) were added and the reaction mixture stirred at rt for 24 h. The solvent was removed and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (3:1) affording compounds **10a,b**.

**4.6.1. 2-(Cyclohexylamino)-2-oxo-1-(p-tolyl)ethyl-2-(1-methyl-1H-indol-3-yl)acetate (10a).** Yellow oil (0.226 g, 54% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.16–0.23 (m, 1H, 2'-H<sub>ax</sub>), 0.39–0.46 (m, 1H, 6'-H<sub>ax</sub>), 0.85–0.96 (m, 1H, 4'-H<sub>ax</sub>), 1.04–1.18 (m, 2H, 3'-H<sub>ax</sub>, 5'-H<sub>ax</sub>), 1.36 (m, 2H, 3'-H<sub>eq</sub>, 5'-H<sub>eq</sub>), 1.40 (m, 1H, 4'-H<sub>eq</sub>), 1.45–1.49 (m, 2H, 2'-H<sub>eq</sub>, 6'-H<sub>eq</sub>), 2.30 (s, 3H, 4''-Me), 3.42–3.52 (m, 1H, 1'-H<sub>ax</sub>), 3.70 (s, 3H, N-Me), 3.80 (q,  $J=15.2$  Hz, 2H, 5-CH<sub>2</sub>), 5.58 (d,  $J=8.6$  Hz, 1H, 1-NH), 6.03 (s, 1H, 2-CH), 7.00 (s, 1H, H-2''), 7.13 (t,  $J=8.9$  Hz, 2H, H-3', H-5''), 7.18 (ddd,  $J=1.1$ , 6.8, 8.0 Hz, 1H, H-6'''), 7.26 (t,  $J=8.1$  Hz, 2H, H-2'', H-6''), 7.27 (ddd,  $J=1.1$ , 6.7, 7.8 Hz, 1H, H-5'''), 7.32 (d,  $J=7.9$  Hz, 1H, H-7'''), 7.66 (d,  $J=7.8$  Hz, 1H, H-4''').  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.1 (s, 3H, 4''-Me), 24.48 (C-5'), 24.50 (C-3'), 25.1 (C-4'), 31.4 (5-CH<sub>2</sub>), 31.8 (C-6'), 32.1 (C-2'), 32.5 (N-Me), 47.2 (C-1'), 75.1 (2-CH), 106.0 (C-

3'''), 109.5 (C-7'''), 118.7 (C-4'''), 119.7 (C-6'''), 122.0 (C-5'''), 127.2 (C-3a'''), 127.3 (C-3'', C-5''), 127.8 (C-2''), 129.1 (C-2'', C-6''), 132.7 (C-1''), 136.9 (C-7a'''), 138.5 (C-4''), 167.0 (1-CO), 169.6 (2-CO). MS (LCMS)  $m/z$  (%) calcd for  $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_3$ ,  $\text{M}^+ + \text{H}$ : 419; found: 419 (5%,  $\text{M}^+ + \text{H}$ ), 441 (100%,  $\text{M}^+ + \text{Na}$ ), 457 (88%,  $\text{M}^+ + \text{K}$ ). HRMS (ESI)  $m/z$  calcd  $[\text{M} + \text{H}]^+$ : 419.52800; found  $[\text{M} + \text{H}]^+$ : 419.52750.

**4.6.2. 2-(Cyclohexylamino)-2-oxo-1-(p-tolyl)ethyl-2-(2-acetyl-1-methyl-1H-indol-3-yl)acetate (10b).** Yellow oil (0.271 g, 59% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.30 (s, 1H, 2''-Me), 2.63 (s, 3H, 4''-Me), 3.54–3.57 (m, 1H, H<sub>ax</sub>-1'), 3.96 (s, 3H, N-Me), 4.13 (d,  $J=2.4$  Hz, 2H, 5-CH<sub>2</sub>), 5.66 (br d,  $J=8.0$  Hz, 1H, 1-NH), 5.99 (s, 1H, 2-CH), 7.10 (t,  $J=7.9$  Hz, 2H, H-3'', H-5''), 7.19 (t,  $J=7.7$  Hz, 2H, H-2'', H-6''), 7.21 (m, 1H, H-6'''), 7.36 (m, 1H, H-5'''), 7.41 (d,  $J=8.5$  Hz, 1H, H-7'''), 7.72 (d,  $J=8.1$  Hz, 1H, H-4''').  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.0 (2''-Me), 22.7 (s, 3H, 4''-Me), 24.9 (5-CH<sub>2</sub>), 25.4 (C-4'), 31.9 (N-Me), 32.4 (C-6'), 24.7 (C-3', C-5'), 32.5 (C-2'), 47.7 (C-1'), 75.8 (2-CH), 110.6 (C-7'''), 114.0 (C-3'''), 120.6 (C-4'''), 121.2 (C-6'''), 126.3 (C-5'''), 126.6 (C-3a'''), 127.4 (C-3'', C-5''), 129.3 (C-2'', C-6''), 132.8 (C-1''), 134.8 (C-7a'''), 138.7 (C-4''), 138.8 (C-2'''), 167.0 (1-CO), 168.6 (2-CO), 192.2 (2''-CO). MS (LCMS)  $m/z$  (%) calcd for  $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4$ ,  $\text{M}^+ + \text{H}$ : 461; found: 461 (3%,  $\text{M}^+ + \text{H}$ ), 483 (100%,  $\text{M}^+ + \text{Na}$ ), 499 (50%,  $\text{M}^+ + \text{K}$ ). HRMS (ESI)  $m/z$  calcd  $[\text{M} + \text{H}]^+$ : 461.56468; found  $[\text{M} + \text{H}]^+$ : 461.56457.

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