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# Solvent-Free Michael Addition to Non-protected 3-(2-Nitrovinyl)indole by Ultrasound Activation

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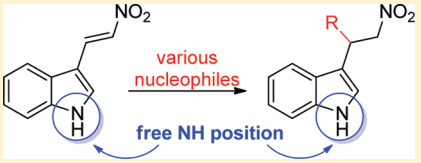
Supporting Information

**ABSTRACT:** A variety of nucleophiles provided by activated methylenes have been added on 3-(2-nitrovinyl)-1*H*-indole in very good to excellent yields, under sonication and solvent-free conditions, using solid potassium carbonate or sodium acetate as a base. Direct synthesis avoiding preliminary NH protection is reported and exemplified to 15 molecules.




The Michael addition or 1,4-addition, a powerful tool to create a C−C bond or a C−N bond (in this case, also named aza-Michael), requires two partners: a Michael donor exhibiting a nucleophilic character and a Michael acceptor, usually an $\alpha,\beta$-conjugated system.[1] This reaction has been largely studied on various conjugated acceptors, but less extension has been performed on 3-(2-nitrovinyl)-1*H*-indole. The focus onto this substrate is consistent with a large representation of the indole nucleus in natural and synthetic molecules, displaying thus a wide range of biological properties.[2] Although the nitroalkene system has been extensively studied both in racemic and enantioselective Michael addition,[3] relatively little attention has been paid to nitrovinylindole. Literature over the past decade reported the Michael addition on protected nitrovinylindoles, which represents a major drawback for efficiency (consuming time, energy, materials, increase of waste and solvents). The presence of a protecting group on the NH indole implies two additional steps in the synthesis: one step for the introduction of the protecting group and the last step-cleavage. Recent work describes the *C*-alkylation of 2-hydroxy-1,4-naphthoquinone by 3-(2-nitrovinyl)-1-phenyl-1*H*-indole.[4]

Direct asymmetric Michael addition of 2(5*H*)-furanone on *N*-Boc-3-indolyl nitroalkene[5] and of ethyl malonate on *N*-Tos-3-indolyl nitroalkene[6] were recently described. Also, the addition of *N*-Boc-L-methyl pyroglutamate to *N*-Boc-protected nitrovinylindole in the presence of the strong base LiHMDS[7] and the access to 1,3-dinitro compounds via Michael addition of nitromethane on *N*-ethyl-nitrovinylindole[8] have been reported.

To our knowledge, the Michael addition of 3-unsubstituted indoles under solvent-free conditions and at room temperature to give 2,2-bis(indolyl)nitroethane[9] and of 3-indole methylacetates in THF and in the presence of LDA at low temperature[10] are the sole examples of Michael additions on a nonprotected 3-(2-nitrovinyl)indole.

In this article, we wish to report an efficient solvent-free method to functionalize nonprotected nitrovinylindole substrate with various Michael donors. The 3-(2-nitrovinyl)indole substrate **1** was investigated to optimize the reaction conditions to perform the Michael addition in good yields. Synthesis of compound **1** was performed by a two-step procedure with 62% global yield: (i) formylation of commercially available indole ($POCl_3$ in DMF followed by treatment with sodium hydroxide) and (ii) Henry reaction on intermediate indole 3-carboxaldehyde ($AcONH_4$ in nitromethane).[11]

Previously in the laboratory, Michael addition conditions of nitroethane on benzylacrylate were screened to assess the experimental procedure in the framework of the synthesis of natural and synthetic indolizidine derivatives.[12]

The Michael addition on nonprotected 3-(2-nitrovinyl)-indole **1** was carried out with $MeNO_2$ as Michael donor, defining the scope and influence of the following criteria: nature of the base, solvent, and method of activation (thermal or sonochemical).

On the basis of the previous results, nitroalkene **1** was heated in toluene for 24 h in the presence of $K_2CO_3$ (0.6 equiv) and a quaternary ammonium salt (0.6 equiv), but these conditions led to complete degradation of the reaction mixture (Table 1, entry 1). The expected dinitro compound **2a** was however obtained with a modest yield of 34% by using tetramethylammonium hydroxide (Table 1, entry 2). These unsatisfactory results prompted us to turn our attention to sonochemical activation. As expected, the reaction rate was significantly improved in comparison with thermal activation, which highlights the potential of sonochemistry in improving the efficacy of a reaction (Table 1, entry 3). Running the reaction in solvent-free conditions opened some promising results. Both quaternary salts such as $Me_4NOH$ or benzyltrimethylammonium hydroxide (Triton B) were efficient (Table 1, entries 4 and 5) but required longer reaction times to reach complete conversion

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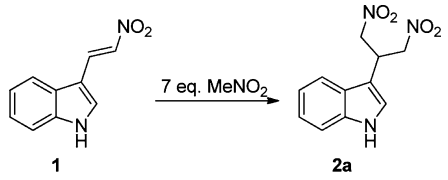
**Table 1. Optimization of the Reaction Conditions**




1 2a

| entry | solvent | conditions[a] | activation | yield (%) |
|---|---|---|---|---|
| 1 | toluene [2.6 M] | $Me_3NBnCl/K_2CO_3$ | 110 °C, 24 h | *b* |
| 2 | toluene [2.6 M] | $Me_4NOH{\cdot}5H_2O$ | 110 °C, 24 h | 34 |
| 3 | toluene [2.6 M] | $Me_4NOH$ 5% MeOH | sonication,[c] 1 h | 70 |
| 4 | | $Me_4NOH$ 5% MeOH | sonication,[c] 25 min | 59 |
| 5 | | Triton B 40% MeOH | sonication,[c] 30 min | 59 |
| 6 | | Triton B 40% MeOH | sonication,[c] 1 h | 94 |
| 7 | | $K_2CO_3$ | sonication,[c] 1 h | **95** |

[a]Reactions were performed on 0.5 mmol of nitrovinylindole with 0.6 equiv of additives. [b]Only degradation products were observed. [c]The ultrasonic bath temperature rose to 30 °C in 1 h.

(Table 1, entry 6). The dinitro compound **2a** was obtained in 94% yield in 1 h. Among the screened bases, potassium carbonate provided the best isolated yield (Table 1, entry 7). Special attention was devoted to the purification of the compounds sensitive to flash column chromatography, and, when possible, simple filtration and recrystallization were done (only four molecules from the library). Flash chromatography was definitely the principal method for isolation of the products.

In a second stage, the ratio nitroalkane/nitrovinylindole **1** was optimized. Preliminary experiments described in Table 1 involved a systematic protocol of 7 equiv of nitromethane. When a 3/1 ratio of nitromethane/nitrovinylindole was employed, the isolated yield fell to 86%. The 5/1 nitromethane/nitrovinylindole ratio gave similar results as the 7/1 ratio. As a consequence, the conditions used for exemplification were the following: 1 equiv of nitrovinylindole (1 mmol), 0.6 equiv of potassium carbonate, 5 equiv of corresponding nitroalkane for 1 h in an ultrasonic bath. All the reactions were thermostatically controlled at around 25−30 °C, especially with sensitive substrates leading to accelerated retro-Michael reaction. The best balance between accelerating the rate of conversion and avoiding the retro-Michael was to run the experiment at a specific temperature, whatever the time required for complete conversion.

Scope and limitations were then explored, and different Michael donors were engaged in the defined conditions. Primary and secondary nitroalkanes led to the corresponding dinitro products **2a−c** with high isolated yield (Table 2, entries 1−3).

The presence of an additional ester function did not affect the efficiency of the reaction since the product resulting from the condensation of **1** and ethyl nitroacetate was isolated in 98% yield (Table 2, entry 4). The same procedure applied to malononitrile was unsuccessful, with total recovery of the starting material **1** observed. Replacement of potassium carbonate (method A) by the milder base sodium acetate (method B) avoided the probable self-condensation of malononitrile into 2-cyanomethyl-1,1,3,3-tetracyanopropene dimer $(NC)_2C{=}C(NH_2){-}CH_2{-}CN$ (Table 2, entry 5).

Thus, with activated methylene substrates, both methods A and B employing respectively $K_2CO_3$ and NaOAc were tested, especially when the yield was unsatisfactory under the initial conditions. This alternative was interesting in the case of ethyl acetoacetate (Table 2, entry 6) and ethyl 2-oxocyclopentanecarboxylate (Table 2, entry 7). In the latter case, the nature of the base strongly impacts the diastereoselectivity of the reaction: the best diastereoisomeric ratio was evaluated by $^1H$ NMR at 70% with method B. The major diastereoisomer obtained by method A corresponds to the minor diastereoisomer obtained by method B.

The methodology was successfully extended to seven substrates with good to excellent yields ranging from 55 to 96% (Table 2, entries 8 to 14). Dimethyl malonate (Table 2, entry 8) as well as Meldrum's acid (Table 2, entry 9) reacted efficiently with the nitrovinylindole **1** in the presence of potassium carbonate. Substituted activated methylene substrates, leading thus to the generation of a quaternary center, sensitive to retro-Michael reaction proceeded in satisfying issues (Table 2, entries 10 and 11). Two more amides **2l** and **2m** were also produced by the reaction with *N*,*N*-dimethylbarbituric acid in 84% yield (Table 2, entry 12) and with *N*,*N*-dimethylacetoacetamide (Table 2, entry 13) in 91% yield.

However, both methods A and B remained unsuccessful in the case of methyl 4,4,4-trifluoroacetoacetate and methyl methylsulfonylacetate, with no conversion with the former substrate and only 20% conversion in the latter case. Finally, the reaction performed with dimedone failed, as only degradation products were identified, while acetone was tested and afforded the desired product **2n** with a modest isolated yield. In this particular case, no conversion was observed with sodium acetate. The reaction with acetone (Table 2, entry 14) suffers also probably from self-condensation that could not be avoided by using method B.

Regarding the reactivity of the 4-hydroxycoumarin motif, this substrate could be envisioned as a $\beta$-dicarbonyl compound reacting as a nucleophile. The lack of reactivity of 4-hydroxycoumarin under the conditions of method A described in Table 1 prompted us to propose an alternative strategy. Simple stoichiometric reaction of both partners in water allowed complete conversion under sonication for 17 h (after 13 h, only 55% of expected compound **2o** was obtained; Scheme 1).

In conclusion, the Michael addition on nonprotected indole derivatives provided straightforward access, avoiding the steps of protection/deprotection. The methodology was extended to 15 substrates with good to excellent yields, which should open the way to access to non-natural tryptamine derivatives, involved in many synthetic schemes as fundamental intermediates. Retro-Michael reaction was successfully avoided by cautious regulation of the temperature. Our future work will study the enantioselective control of the reaction by means of in-house-designed organocatalysts.


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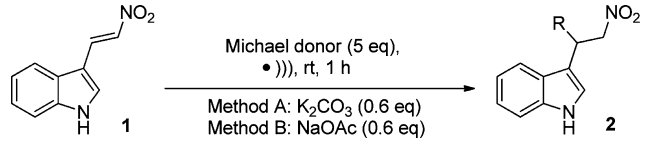
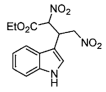
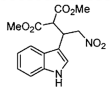
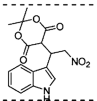
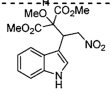
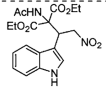
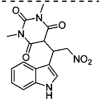
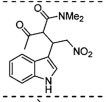
**Table 2. Study of the Michael Conditions**




| Entry | Products | Method | Isolated yield |
|---|---|---|---|
| *1* |  **2a** | A | 96% |
| *2* |  **2b** | A | 99% |
| *3* |  **2c** | A | 95% |
| *4* |  **2d** | A<br>B | 98%<br>83% |
| *5* |  **2e** | A<br>B | no conversion<br>89% |
| *6* |  **2f** | A<br>B | 79%<br>96% |
| *7* |  **2g** | A<br>B | 81%<br>>99% |
| *8* |  **2h** | A | 89% |
| *9* |  **2i** | A<br>B | 96%<br>75% |
| *10* |  **2j** | A | 69% |
| *11* |  **2k** | A | 93% |
| *12* |  **2l** | A | 84% |
| *13* |  **2m** | A | 91% |
| *14* |  **2n** | A | 55% |

## ■ EXPERIMENTAL SECTION

The commercially available reagents and solvents were used without further purification. The reactions were monitored by TLC plates under a UV light. The NMR spectra of all the compounds were recorded on 300, 400, and 500 MHz spectrometers in $CDCl_3$ or in DMSO-$d_6$. Purifications were carried out by column chromatography using 230−400 mesh (40−63 $\mu$m) silica gel. The reactions were carried out in a manual thermostated (25−30 °C)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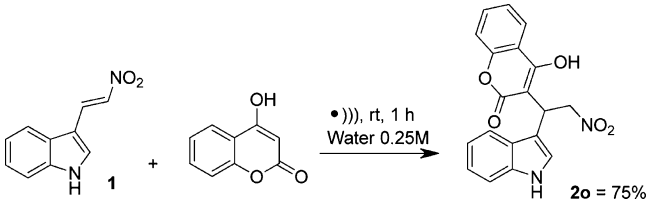
**Scheme 1. Reaction with 4-Hydroxycoumarin**




ultrasonic cleaning bath (Bransonic, Branson 2510EMT) at 42 kHz frequency.

**Representative Procedure of Michael Type Addition on Nonprotected Vinylindole.** *Procedure A.* In a round-bottom flask, a mixture of 3-(2-nitrovinyl)indole **1** (0.5 mmol, 94 mg, 1.0 equiv), $K_2CO_3$ (0.6 equiv), and the corresponding substrate (5.0 equiv) was activated by sonication at room temperature. The reaction mixture was dissolved in $CH_2Cl_2$ (100 mL) and washed with water (100 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The crude residue was purified, if necessary, by column chromatography on silica gel to give the desired compound.

*Procedure B.* $K_2CO_3$ was replaced by NaOAc

**3-[2-Nitro-1-(nitromethyl)-ethyl]-1*H*-indole (2a).** Method A: substrate, nitromethane; time, 1 h. yield = 96%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.63 (q, 1 H, $J$ = 6.6 Hz, CH), 4.86 (dd, 4 H, $J$ = 7.1 Hz, $J$ = 2.2 Hz, $CH_2NO_2$), 7.05 (d, 1 H, $J$ = 2.4 Hz, $H_{arom}$), 7.17−7.28 (m, 2 H, $H_{arom}$), 7.37 (d, 1 H, $J$ = 8.0 Hz, $H_{arom}$), 7.57 (d, 1 H, $J$ = 8.0 Hz, $H_{arom}$), 8.23 (bs, 1 H, NH). The analytical data were in accordance with literature.[13]

**3-[2-Nitro-1-(nitromethyl)-propyl]-1*H*-indole (2b).** Method A: substrate, nitroethane; time, 2 h Brown solid: yield = 99%; mp 90.2−92.2 °C (dec, $CH_2Cl_2$); IR 3411, 1553, 1534, 1341, 1233, 1128, 852, 742, 550 cm$^{-1}$; 2 diastereoisomers **a** (minor, 44%) and **b** (major, 56%); dr = 12%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.50 (d, 3 H, $J$ = 6.6 Hz, $CH_3$ $dia_a$), 1.58 (d, 3 H, $J$ = 6.8 Hz, $CH_3$ $dia_b$), 4.35 (td, $J$ = 4.7 Hz, $J$ = 9.3 Hz, CH $dia_a$), 4.44 (m, 1 H, CH $dia_b$), 4.72 (dd, 1 H, $J$ = 4.7 Hz, $J$ = 12.8 Hz, CH $dia_a$), 4.85 (dd, 1 H, $J$ = 7.5 Hz, $J$ = 13.6 Hz, CH $dia_b$), 4.90 (dd, 1 H, $J$ = 9.3 Hz, $J$ = 12.8 Hz, CH $dia_a$), 5.03 (dd, 1 H, $J$ = 6.8 Hz, $J$ = 13.6, CH $dia_b$), 5.10 (m, 1 H, CH $dia_{a+b}$), 7.03 (d, 1 H, $J$ = 2.6 Hz, CH $dia_a$), 7.10 (d, 1 H, $J$ = 2.5 Hz, CH $dia_b$), 7.17−7.26 (m, 3 $H_{arom}$, $dia_{a+b}$), 7.38 (dd, 1 H, $J$ = 3.6 Hz, $J$ = 7.7 Hz, $H_{arom}$ $dia_{a+b}$), 7.58 (dd, 1 H, $J$ = 4.4 Hz, $J$ = 7.5, $H_{arom}$ $dia_{a+b}$), 8.30 (br s, 1 H, NH $dia_{a+b}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.7 ($CH_3$ $dia_a$), 18.3 ($CH_3$ $dia_b$), 39.4 (CH $dia_b$), 40.5 (CH $dia_a$), 76.2 ($CH_2$ $dia_b$), 76.6 ($CH_2$ $dia_a$), 83.8 (CH $dia_b$), 84.4 (CH $dia_a$), 108.3 ($C_q$ $dia_b$), 108.5 ($C_q$ $dia_a$), 111.8 ($CH_{arom}$ $dia_b$), 112.0 ($CH_{arom}$ $dia_a$), 118.1 ($CH_{arom}$ $dia_b$), 118.3 ($CH_{arom}$ $dia_a$), 120.7 ($CH_{arom}$ $dia_b$), 120.7 ($CH_{arom}$ $dia_a$), 122.5 ($CH_{arom}$ $dia_b$), 123.2 ($CH_{arom}$ $dia_a$), 123.2 ($CH_{arom}$ $dia_b$), 123.5 ($CH_{arom}$ $dia_a$), 125.6 ($C_q$ $dia_a$), 126.5 ($C_q$ $dia_b$), 136.1 ($C_q$ $dia_b$), 136.5 ($C_q$ $dia_a$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{12}H_{13}N_3O_4Na$ 286.0798, found 286.0786.

**3-(3-Methyl-1,3-dinitrobutan-2-yl)-1*H*-indole (2c).** Method A: substrate, 2-nitropropane; time, 50 min. Brown solid: yield = 95%; mp 108.1−111.0 °C ($CH_2Cl_2$); IR 3411, 1545, 1457, 1423, 1380, 1357, 1102, 741 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.64 (s, 3 H), 1.69 (s, 3 H), 4.54 (dd, 1 H, $J$ = 4.5 Hz, $J$ = 10.6 Hz, CH), 4.89 (dd, 1 H, $J$ = 4.5 Hz, $J$ = 13.0 Hz, $CHNO_2$), 5.00 (dd, 1 H, $J$ = 10.6 Hz, $J$ = 13.0 Hz, $CHNO_2$), 7.08 (d, 1 H, $J$ = 2.7, $H_{arom}$), 7.20 (m, 2 H, $H_{arom}$), 7.37 (d, 1 H, $J$ = 7.3 Hz, $H_{arom}$), 7.62 (d, 1 H, $J$ = 7.5 Hz, $H_{arom}$), 8.25 (br s, 1H, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 23.2 ($CH_3$), 26.4 ($CH_3$), 43.5 (CH), 76.9 ($CH_2$), 90.9 ($C_q$), 109.0 ($C_q$), 111.7 ($CH_{arom}$), 118.6 ($CH_{arom}$), 120.5 ($CH_{arom}$), 122.8 ($CH_{arom}$), 123.0 ($CH_{arom}$), 127.3 ($C_q$), 135.9 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{13}H_{15}N_3O_4Na$ 300.0955, found 300.0951.

**Ethyl 3-(1*H*-Indol-3-yl)-2,4-dinitrobutanoate (2d).** Method A: substrate, ethyl nitroacetate; time, 1h 20 min; flash chromatography EtOAc/cyclohexane, 2/8 to 100% EtOAc. Yellow oil: yield = 98%; 2 diastereoisomers **a** (minor, 45%) and **b** (major, 55%); dr = 10%; IR 3419, 1743, 1552, 1423, 1375, 1187, 1103, 1012, 856, 742 cm$^{-1}$ ; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.08 (t, 3 H, $J$ = 7.0 Hz, $CH_3$ $dia_b$), 1.25 (t, 3 H, $J$ = 7.0 Hz, $dia_a$), 4.13 (q, 2 H, $J$ = 7.0 Hz, $CH_2CH_3$ $dia_b$), 4.22−4.32 (m, 2 H, $CH_2CH_3$ $dia_a$), 4.86−4.91 (m, 1 H, CH $dia_{a+b}$), 4.94−5.01 (m, 1 H, CH $dia_{a+b}$), 5.04−5.10 (m, 1 H, CH $dia_{a+b}$), 5.71 (d, 1 H, $J$ = 7.3 Hz, CH $dia_b$), 5.78 (d, 1 H, $J$ = 8.6 Hz, CH $dia_a$), 7.07 (d, 1 H, $J$ = 2.5 Hz, $H_{arom}$ $dia_b$), 7.13 (d, 1 H, $J$ = 2.5 Hz, $H_{arom}$ $dia_a$), 7.17−7.24 (m, 2 H, $H_{arom}$ $dia_{a+b}$), 7.34 (dd, 1 H, $J$ = 2.8 Hz, $J$ = 8.1 Hz, $H_{arom}$ $dia_{a+b}$), 7.60 (d, 1 H, $J$ = 7.6 Hz, $H_{arom}$ $dia_{a+b}$), 8.30 (br s, 1 H, NH $dia_{a+b}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 13.6 ($CH_3$ $dia_b$), 13.8 ($CH_3$ $dia_a$), 36.1 (CH $dia_b$), 36.3 (CH $dia_a$), 63.8 ($CH_2$ $dia_b$), 63.9 ($CH_2$ $dia_a$), 75.8 ($CH_2$ $dia_a$), 76.0 ($CH_2$ $dia_b$), 88.5 (CH $dia_a$), 88.9 (CH $dia_b$), 107.4 ($C_q$ $dia_b$), 107.7 ($C_q$ $dia_a$), 111.9 ($CH_{arom}$ $dia_b$), 111.9 ($CH_{arom}$ $dia_a$), 117.9 ($CH_{arom}$ $dia_a$), 117.9 ($CH_{arom}$ $dia_b$), 120.7 ($CH_{arom}$ $dia_a$), 120.7 ($CH_{arom}$ $dia_b$), 123.2 ($CH_{arom}$ $dia_b$), 123.2 ($CH_{arom}$ $dia_a$), 123.4 ($CH_{arom}$ $dia_b$), 123.6 ($CH_{arom}$ $dia_a$), 125.5 ($C_q$ $dia_a$), 125.6 ($C_q$ $dia_b$), 136.0 ($C_q$ $dia_a$), 136.1 ($C_q$ $dia_b$), 162.8 ($C_q$ $dia_b$), 163.2 ($C_q$ $dia_a$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{14}H_{15}N_3O_6Na$ 344.0853, found 344.0864.

**2-[1-(1*H*-Indol-3-yl)-2-nitro-ethyl]-malononitrile (2e).** Method B: substrate, malononitrile; $CH_2Cl_2$/toluene (3/2) (0.250 mL) was added to the medium; time, 2 h; flash chromatography $CH_2Cl_2$/cyclohexane, 4/6. Yellow liquid: yield = 89%; IR 3411, 2916, 1552, 1459, 1424, 1379, 1339, 1230, 1107, 1011, 744 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.50−4.57 (m, 2 H), 4.94−5.05 (m, 2 H), 7.24 (t, 1 H, $J$ = 7.3 Hz, $H_{arom}$), 7.31 (t, 1 H, $J$ = 7.3 Hz, $H_{arom}$), 7.38 (d, 1 H, $J$ = 2.8 Hz, $H_{arom}$), 7.44 (d, 1 H, $J$ = 8.1 Hz, $H_{arom}$), 7.61 (d, 1 H, $J$ = 8.1 Hz, $H_{arom}$), 8.41 (bs, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 27.7 (CH), 36.7 (CH), 75.2 ($CH_2$), 107.2 ($C_q$), 111.0 ($C_q$), 111.2 ($C_q$), 121.1 ($CH_{arom}$), 117.9 ($CH_{arom}$), 121.3 ($CH_{arom}$), 122.9 ($CH_{arom}$), 123.9 ($CH_{arom}$), 125.4 ($C_q$), 136.1 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{13}H_{10}N_4O_2Na$ 277.0701, found 277.0686.

**Methyl 2-Acetyl-3-[1*H*-indol-3-yl]-4-nitrobutanoate (2f).** Method B: substrate, methyl acetoacetate; time, 3 h; flash chromatography $CH_2Cl_2$/cyclohexane, 2/8 to 100% $CH_2Cl_2$. Orange oil: yield = 96%; 2 diastereoisomers **a** (minor, 45%) and **b** (major, 55%); dr = 10%; IR 3407, 1337, 1712, 1548, 1430, 1380, 1358, 1339, 1146, 1101, 742 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.05 (s, 3 H, $CH_3$ $dia_b$), 2.26 (s, 3 H, $CH_3$ $dia_a$), 3.53 (s, 3 H, $CH_3$ $dia_a$), 3.75 (s, 3 H, $CH_3$ $dia_b$), 4.28 (d, 1 H, $J$ = 9.6 Hz, CH $dia_b$), 4.35 (d, 1 H, $J$ = 9.0 Hz, CH $dia_a$), 4.53−4.60 (m, 1 H, $dia_{a+b}$), 4.86−4.96 (m, 2 H, $dia_{a+b}$), 7.01 (d, 1 H, $J$ = 2.5 Hz, $H_{arom}$ $dia_b$), 7.04 (d, 1 H, $J$ = 2.5 Hz, $H_{arom}$ $dia_a$), 7.13−7.23 (m, 2 H, $H_{arom}$ $dia_{a+b}$), 7.32 (d, 1 H, $J$ = 8.1 Hz, $H_{arom}$ $dia_{a+b}$), 7.60 (d, 1 H, $J$ = 7.5 Hz, $H_{arom}$ $dia_{a+b}$), 8.31 (s, 1 H, NH $dia_{a+b}$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 30.1 ($CH_3$ $dia_b$), 30.6 ($CH_3$ $dia_a$), 34.2 (CH $dia_a$), 34.9 (CH $dia_b$), 52.9 (CH $dia_a$), 53.0 (CH $dia_b$), 60.9 ($CH_3$ $dia_b$), 61.3 ($CH_3$ $dia_a$), 77.5 ($CH_2$ $dia_a$), 77.8 ($CH_2$ $dia_b$), 110.5 ($C_q$ $dia_b$), 111.0 ($C_q$ $dia_a$), 111.7 ($CH_{arom}$ $dia_a$), 111.8 ($CH_{arom}$ $dia_b$), 118.2 and 118.3 ($CH_{arom}$ $dia_{a+b}$), 120.2 ($CH_{arom}$ $dia_a$), 120.3 ($CH_{arom}$ $dia_b$), 122.8 ($CH_{arom}$ $dia_{a+b}$), 123.4 ($CH_{arom}$ $dia_{a+b}$), 125.7 ($C_q$ $dia_b$), 125.9 ($C_q$ $dia_a$), 136.1 ($C_q$ $dia_b$), 136.2 ($C_q$ $dia_a$), 168.1 ($C_q$ $dia_a$), 168.6 ($C_q$ $dia_b$), 201.3 ($C_q$ $dia_b$), 202.2 ($C_q$ $dia_a$). HMRS $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{16}N_2O_5Na$ 327.0951, found 327.0963.

**Ethyl-1-[1-(1*H*-indol-3-yl)-2-nitro-ethyl]-2-oxocyclopentane-carboxylate (2g).** Method A: substrate, ethyl 2-oxocyclopentane-carboxylate; time, 2 h; flash chromatography EtOAc/cyclohexane, 2/8. Yellow oil: yield = 81%; 2 diastereoisomers **a** (major, 59%) and **b** (minor, 41%); dr = 18%. Method B: time, 2 h; flash chromatography $Et_2O$/cyclohexane, 1/1 to 100%. Yellow oil: yield = quantitative; 2 diastereoisomers **a** (minor, 15%) and **b** (major, 85%); dr = 70%; IR 3435, 1738, 1719, 1551, 1382, 1242, 1228, 1144, 1107, 1009, 859, 751 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.25 (t, 3 H, $J$ = 7.2 Hz, $CH_3$ $dia_{a+b}$), 1.46−1.53 (m, 1 H, CH $dia_{a+b}$), 1.74−1.96 (m, 2 H, CH $dia_{a+b}$), 2.01−2.12 (m, 1 H, CH $dia_{a+b}$), 2.31−2.45 (m, 2 H, CH $dia_{a+b}$), 4.11−4.34 (m, 2 H, $CH_2CH_3$ $dia_{a+b}$), 4.50 (dd, 1 H, $J$ = 4.3 Hz, $J$ = 10.4 Hz, CH $dia_a$), 4.59 (dd, 1 H, $J$ = 3.7 Hz, $J$ = 11.1 Hz, CH $dia_b$), 4.88 (dd, 1 H, $J$ = 3.7 Hz, $J$ = 13.0 Hz, CH $dia_b$), 5.02 (dd, 1 H, $J$ = 10.4 Hz, $J$ = 13.1 Hz, CH $dia_a$), 5.19 (dd, 1 H, $J$ = 4.3 Hz, $J$ = 13.1 Hz, CH $dia_a$), 5.39 (dd, 1 H, $J$ = 11.1 Hz, $J$ = 13.0 Hz, CH $dia_b$), 7.00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(d, 1 H, $J$ = 2.6 Hz, $H_{arom}$ $dia_{a+b}$), 7.13−7.22 (m, 2 H, $H_{arom}$ $dia_{a+b}$), 7.32 (d, 1 H, $J$ = 7.4 Hz, $H_{arom}$ $dia_{a+b}$), 7.64 (d, 1 H, $J$ = 7.2 Hz, $H_{arom}$ $dia_{a+b}$), 8.26 (br s, 1 H, NH $dia_{a+b}$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.2 ($CH_3$), 19.8 ($CH_2$), 34.2 ($CH_2$), 38.2 (CH), 39.6 ($CH_2$), 62.3 ($CH_2$), 63.1 ($C_q$), 77.6 ($CH_2$), 110.7 ($C_q$), 111.5 ($CH_{arom}$), 118.8 ($CH_{arom}$), 120.4 ($CH_{arom}$), 122.8 ($CH_{arom}$), 123.2 ($CH_{arom}$), 128.1 ($C_q$), 135.8 ($C_q$), 171.6 ($C_q$), 216.6 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{18}H_{20}N_2O_5Na$ 367.1264, found 367.1260.

**2-[1-(1*H*-Indol-3-yl)-2-nitro-ethyl]-malonic Acid Dimethyl Ester (2h).** Method A: substrate, methyl malonate; time, 1 h; flash chromatography EtOAc/cyclohexane, 3/7. Yellow oil: yield = 89%; IR 3402, 1729, 1551, 1458, 1434, 1243, 1150, 1012, 742, 543 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.59 (s, 3 H), 3.72 (s, 3 H), 4.10 (d, 1 H, $J$ = 8.0 Hz, $CHCO_2Me$), 4.60 (td, 1 H, $J$ = 5.3 Hz, $J$ = 8.0 Hz), 4.97 (dd, 1 H, $J$ = 5.3 Hz, $J$ = 12.8 Hz, $CHNO_2$), 5.05 (dd, 1 H, $J$ = 8.0 Hz, $J$ = 12.8 Hz, $CHNO_2$), 7.13 (d, 1 H, $J$ = 2.5 Hz, $H_{arom}$), 7.14−7.23 (m, 2 H, $H_{arom}$), 7.34 (d, 1 H, $J$ = 7.9 Hz, $H_{arom}$), 7.61 (d, 1 H, $J$ = 7.9 Hz, $H_{arom}$), 8.17 (bs, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 34.9 (CH), 53.0 (2 $CH_3$), 54.3 (CH), 77.3 ($CH_2$), 111.0 ($C_q$), 111.6 ($CH_{arom}$), 118.4 ($CH_{arom}$), 120.3 ($CH_{arom}$), 122.8 ($CH_{arom}$), 123.0 ($CH_{arom}$), 126.0 ($C_q$), 136.1 ($C_q$), 167.9 ($C_q$), 168.4 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{16}N_2O_6Na$ 343.0901, found 343.0900.

**5-(1-(1*H*-Indol-3-yl)-2-nitroethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2i).** Method A: substrate, Meldrum's acid; $CH_2Cl_2$/toluene (3/2) (0.250 mL) was added to the medium; time, 2 h; flash chromatography EtOAc/cyclohexane, 25/75 to 100% EtOAc. Yellow solid: yield = 96%; mp 138.5−140.0 °C (dec, $CH_2Cl_2$); IR 3369, 1781, 1737, 1557, 1545, 1429, 1387, 1330, 1316, 1200, 1112, 1068, 849, 740 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.45 (s, 3 H, $CH_3$), 1.71 (s, 3 H, $CH_3$), 4.08 (d, 1 H, $J$ = 2.8 Hz, CH), 4.91 (dd, 1 H, $J$ = 6.0 Hz, $J$ = 13.4 Hz, $CHNO_2$), 5.02−5.07 (m, 1 H, CH), 5.43 (dd, 1 H, $J$ = 9.8 Hz, $J$ = 13.4 Hz, $CHNO_2$), 7.17−7.25 (m, 3 H, $H_{arom}$), 7.34 (d, 1 H, $J$ = 7.6 Hz, $H_{arom}$), 7.75 (d, 1 H, $J$ = 7.8 Hz, $H_{arom}$), 8.29 (br s, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 27.6 ($CH_3$), 28.2 ($CH_3$), 33.6 (CH), 48.5 (CH), 76.5 ($CH_2$), 105.9 ($C_q$), 110.3 ($C_q$), 111.4 ($CH_{arom}$), 119.1 ($CH_{arom}$), 120.6 ($CH_{arom}$), 123.1 ($CH_{arom}$), 124.1 ($CH_{arom}$), 126.3 ($C_q$), 135.6 ($C_q$), 164.3 ($C_q$), 165.5 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{16}N_2O_6Na$ 355.0901, found 355.0912.

**2-[1-(1*H*-Indol-3-yl)-2-nitro-ethyl]-2-methoxy-malonic Acid Dimethyl Ester (2j).** Method A: substrate, dimethyl methoxymalonate; time, 1 h 30 min; flash chromatography EtOAc/cyclohexane, 3/7 to 8/2. Yellow solid: yield = 69%; mp 133.0−135.0 °C ($CH_2Cl_2$); IR 3374, 1742, 1721, 1545, 1449, 1434, 1266, 1246, 1187, 1133, 1104, 1014, 971, 742 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.33 (s, 3 H, $OCH_3$), 3.65 (s, 3 H, $CO_2CH_3$), 3.82 (s, 3 H, $CO_2CH_3$), 4.80 (m, 2 H), 5.29 (AB system, 1 H, $J$ = 9.0 Hz, $J$ = 10.2 Hz, CH), 7.09−7.15 (m, 2 H, $H_{arom}$), 7.23 (d, 1 H, $J$ = 2.4 Hz, $H_{arom}$), 7.28 (m, 1 H, $H_{arom}$), 7.63 (dd, 1 H, $J$ = 2.0 Hz, $J$ = 6.5 Hz, $H_{arom}$), 8.23 (br s, 1 H, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 40.6 (CH), 52.4 ($CH_3$), 53.0 ($CH_3$), 56.3 ($CH_3$), 77.3 ($CH_2$), 86.2 ($C_q$), 109.9 ($C_q$), 111.3 ($CH_{arom}$), 118.9 ($CH_{arom}$), 120.1 ($CH_{arom}$), 122.3 ($CH_{arom}$), 124.3 ($CH_{arom}$), 126.8 ($C_q$), 135.6 ($C_q$), 168.1 ($C_q$), 168.4 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{18}N_2O_7Na$ 373.1006, found 373.1017.

**2-[1-(1*H*-Indol-3-yl)-2-nitro-ethyl]-2-acetamido-malonic Acid Diethyl Ester (2k).** Method A: substrate, diethyl acetamidomalonate; time, 2 h; flash chromatography $Et_2O$/cyclohexane, 3/7 to 8/2. Beige solid: yield = 93%; mp 153.0−154.5 °C ($CH_2Cl_2$); IR 3382, 1734, 1672, 1554, 1490, 1368, 1301, 1258, 1213, 1114, 1027, 1011, 742 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.12 (t, 3 H, $J$ = 7.0 Hz, $CH_3$), 1.26 (t, 3 H, $J$ = 7.0 Hz, $CH_3$), 2.08 (s, 3 H, $NHCOCH_3$), 3.70−3.79 (m, 1 H, $CH_2$), 3.97−4.05 (m, 1 H, $CH_2$), 4.20−4.35 (m, 2 H, $CH_2$), 4.72 (dd, 1 H, $J$ = 12.1 Hz, $J$ = 13.1 Hz, CH), 5.10 (dd, 1 H, $J$ = 3.5 Hz, $J$ = 12.1 Hz, $CHNO_2$), 5.56 (dd, 1 H, $J$ = 3.5 Hz, $J$ = 13.1 Hz, $CHNO_2$), 6.86 (br s, 1H, NH), 7.07−7.13 (m, 2 H, $H_{arom}$), 7.16 (dd, 1 H, $J$ = 1.0 Hz, $J$ = 7.0 Hz, $H_{arom}$), 7.27 (d, 1 H, $J$ = 7.8 Hz, $H_{arom}$), 7.57 (d, 1 H, $J$ = 7.8 Hz, $H_{arom}$), 8.37 (br s, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 13.7 ($CH_3$), 14.1 ($CH_3$), 23.2 ($CH_3$), 40.9 (CH), 62.8 ($CH_2$), 63.6 ($CH_2$), 67.8 ($C_q$), 78.0 ($CH_2$), 108.8 ($C_q$), 111.6 ($CH_{arom}$), 118.9 ($CH_{arom}$), 120.1 ($CH_{arom}$), 122.6 ($CH_{arom}$), 123.3 ($CH_{arom}$), 126.7 ($C_q$), 135.9 ($C_q$), 166.2 ($C_q$), 166.9 ($C_q$), 170.4 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{23}N_3O_7Na$ 428.1428, found 428.1427.

**5-(1-(1*H*-Indol-3-yl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (2l).** Method A: substrate, 1,3-dimethylbarbituric acid; $CH_2Cl_2$/toluene (3/2) (0.250 mL) was added to the medium; time, 1 h. Brown solid: yield = 84%; mp 79.2−81.1 °C (dec, MeOH); IR 3393, 2919, 1667, 1550, 1457, 1422, 1376, 1120, 744 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.68 (s, 3 H, $NCH_3$), 2.93 (s, 3 H, $NCH_3$), 4.00 (d, 1 H, $J$ = 3.2 Hz, CH), 4.62 (ddd, 1 H, $J$ = 3.2 Hz, $J$ = 6.8 Hz, $J$ = 9.2 Hz, CH), 5.15 (dd, 1 H, $J$ = 9.2 Hz, $J$ = 13.9 Hz, $CHNO_2$), 5.45 (dd, 1 H, $J$ = 6.8 Hz, $J$ = 13.9 Hz, $CHNO_2$), 7.00 (td, $J$ = 0.8 Hz, $J$ = 7.9 Hz, $H_{arom}$), 7.08 (m, 1 H, $H_{arom}$), 7.16 (d, 1 H, $J$ = 2.5 Hz, $H_{arom}$), 7.31 (dd, 2 H, $J$ = 2.9 Hz, $J$ = 7.9 Hz, $H_{arom}$), 11.13 (br s, 1 H, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.4 ($CH_3$), 28.6 ($CH_3$), 38.1 (CH), 51.5 (CH), 76.4 (CH), 108.8 ($C_q$), 111.7 ($CH_{arom}$), 118.7 ($CH_{arom}$), 120.6 ($CH_{arom}$), 122.4 ($CH_{arom}$), 123.3 ($CH_{arom}$), 125.6 ($C_q$), 135.8 ($C_q$), 150.8 ($C_q$), 167.5 ($C_q$), 167.6 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{16}N_4O_5Na$ 367.1013, found 367.1008.

**2-Acetyl-3-(1*H*-indol-3-yl)-*N*,*N*-dimethyl-4-nitrobutanamide (2m).** Method A: substrate, *N*,*N*-dimethylacetoacetamide; time, 45 min; flash chromatography $CH_2Cl_2$. Gray solid: yield = 91%; mp 163.0−164.5 °C ($CH_2Cl_2$); IR 3257, 2919, 1703, 1626, 1547, 1432, 1353, 1222, 1185, 1112, 1011, 749 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.01 (s, 3 H, $CH_3$), 3.03 (s, 3 H, $NCH_3$), 3.06 (s, 3 H, $NCH_3$), 4.52 (d, 1 H, $J$ = 10.3 Hz, CH), 4.68 (m, 1 H, CH), 4.80 (dd, 1 H, $J$ = 4.1 Hz, $J$ = 12.1 Hz, $CHNO_2$), 4.84 (dd, 1 H, $J$ = 6.1 Hz, $J$ = 12.1 Hz, $CHNO_2$), 7.02 (d, 1 H, $J$ = 2.2 Hz, $H_{arom}$), 7.15−7.25 (m, 2 H, $H_{arom}$), 7.36 (d, 1 H, $J$ = 7.4 Hz, $H_{arom}$), 7.62 (d, 1 H, $J$ = 7.8 Hz, $H_{arom}$), 8.23 (br s, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 26.7 ($CH_3$), 35.3 (CH), 36.5 ($CH_3$), 37.9 ($CH_3$), 59.7 (CH), 78.3 ($CH_2$), 110.6 ($C_q$), 111.8 ($CH_{arom}$), 118.1 ($CH_{arom}$), 120.5 ($CH_{arom}$), 123.0 ($CH_{arom}$), 123.3 ($CH_{arom}$), 126.1 ($C_q$), 136.2 ($C_q$), 166.9 ($C_q$), 203.0 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{19}N_3O_4Na$ 340.1268, found 340.1273.

**4-(1*H*-Indol-3-yl)-5-nitropentan-2-one (2n).** Method A: substrate, acetone; time, 5 h; flash chromatography $CH_2Cl_2$/cyclohexane, 1/1 to 100% $CH_2Cl_2$. Orange oil: yield = 55%; IR 3408, 1709, 1543, 1422, 1377, 1360, 1339, 1165, 1101, 740 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.13 (s, 3 H, $CH_3$), 3.06 (dd, 2 H, $J$ = 4.0 Hz, $J$ = 6.8 Hz, $CH_2$), 4.33 (quint, 1 H, $J$ = 6.8 Hz, CH), 4.77 (d, 2 H, $J$ = 6.8 Hz, $CH_2$), 7.08 (d, 1 H, $J$ = 2.5 Hz, $H_{arom}$), 7.16 (td, 1 H, $J$ = 0.8 Hz, $J$ = 7.7 Hz, $H_{arom}$), 7.23 (td, 1 H, $J$ = 0.8 Hz, $J$ = 7.7 Hz, $H_{arom}$), 7.38 (d, 1 H, $J$ = 7.7 Hz, $H_{arom}$), 7.61 (d, 1 H, $J$ = 7.7 Hz, $H_{arom}$), 8.08 (s, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 30.5 ($CH_3$), 31.4 (CH), 45.7 ($CH_2$), 79.0 ($CH_2$), 111.8 ($CH_{arom}$), 113.5 ($C_q$), 118.5 ($CH_{arom}$), 120.2 ($CH_{arom}$), 122.3 ($CH_{arom}$), 122.8 ($CH_{arom}$), 125.8 ($C_q$), 136.5 ($C_q$), 206.4 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O_3Na$ 269.0897, found 269.0890.

**4-Hydroxy-3-[1-(1*H*-indol-3-yl)-2-nitro-ethyl]-chromen-2-one (2o).** In a round-bottom flask, 3-(2-nitrovinyl)indole **1** (856 mg, 4.55 mmol, 1.0 equiv) and 4-hydroxycoumarin (738 mg, 1.0 equiv) were suspended in water (20 mL), and the reaction was activated by sonication at room temperature during 17 h. The reaction mixture was filtrated and recrystallised in $CH_2Cl_2$ (20 mL) to provide compound **2o** as a white solid (1.21 g, 75%): mp 198.3−199.2 °C ($CH_2Cl_2$); IR 3438, 3227, 1673, 1625, 1399, 1384, 1219, 1147, 1090, 745, 603 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 5.38 (dd, 1 H, $J$ = 6.9 Hz, $J$ = 12.5 Hz, $CHNO_2$), 5.51 (dd, 1 H, $J$ = 8.7 Hz, $J$ = 12.5 Hz, $CHNO_2$), 5.59 (dd, 1 H, $J$ = 6.9 Hz, $J$ = 8.7 Hz, CH), 6.98 (t, 1 H, $J$ = 7.0 Hz, $H_{arom}$), 7.06 (t, 1 H, $J$ = 7.0 Hz, $H_{arom}$), 7.32−7.38 (m, 4 H), 7.58 (td, 1 H, $J$ = 1.5 Hz, $J$ = 8.6 Hz, $H_{arom}$), 7.64 (d, 1 H, $J$ = 8.0 Hz, $H_{arom}$), 8.06 (dd, 1 H, $J$ = 1.5, $J$ = 8.3 Hz, $H_{arom}$), 11.00 (d, 1 H, $J$ = 1.0 Hz, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 30.9 (CH), 76.8 ($CH_2$), 104.1 ($C_q$), 111.2 ($C_q$), 111.6 ($CH_{arom}$), 116.0 ($C_q$), 116.3 ($CH_{arom}$), 118.2 ($CH_{arom}$), 118.7 ($CH_{arom}$), 121.2 ($CH_{arom}$), 123.3 ($CH_{arom}$), 123.6 ($CH_{arom}$), 124.0 ($CH_{arom}$), 126.4 ($C_q$), 132.3 ($CH_{arom}$), 135.8 ($C_q$), 152.2 ($C_q$), 161.5 ($C_q$), 161.6 ($C_q$); HMRS $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{14}N_2O_5Na$ 373.0795, found 373.0798.


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## ■ ASSOCIATED CONTENT

### Supporting Information

$^{1}H$ and $^{13}C$ spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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