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Efficient, two-step synthesis of N-substituted nortropinone derivatives

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Abstract—We describe a novel strategy for the synthesis of N-substituted nortropinone derivatives starting from tropinone. The key step of our synthesis is a reactivity umpolung of tropinone, which yields 8,8-dimethyl-3-oxo-8-azonia-bicyclo[3.2.1]octane iodide (IDABO) as a stable and convenient synthetic equivalent of cycloheptadienone.

Tropane alkaloids, containing the 8-azabicyclo[3.2.1]-octane scaffold, are commonly found in plants belonging to three families: *Solanaceae*, *Erythroxylaceae* and *Convolvulaceae*. Due to the unique pharmacophoric properties of this constrained nitrogen heterocycle, tropane derivatives including atropine and cocaine have found widespread uses in therapeutics. For the same reasons, this structure has been employed by medicinal chemist to produce non natural compounds binding to monoamine receptors such as 5-HT_3 receptor antagonists tropisetron and zatosetron.[1] Given the wide range of activities displayed by these molecules, there is a reasonable expectation that synthetic libraries based on this framework would be endowed of interesting pharmacological properties. Our aim was to find an easy way to introduce a large variety of substituents on the nitrogen atom, a possibility that has not been systematically explored, at the difference with the related piperidine heterocycle.[2] Three different disconnection strategies (Fig. 1) have been reported for the synthesis of tropinone and, possibly its analogues.

The first reported synthesis of tropinone was proposed as early as 1917 by Robinson[3a] and is still considered as a landmark in biomimetic chemistry. It involves a tandem sequence in which succindialdehyde, methylamine and acetonedicarboxylic acid react together to afford tropinone in a simple one-pot procedure. This procedure was improved many years later by Schöpf.[3b] However, due to low yields and purification difficulties, this strategy is not suitable for the rapid and systematic preparation of diverse N-substituted analogues.[4,5] The second synthetic approach involves tropinone N-demethylation,[6] then alkylation of the resulting secondary amine using halides or aldehydes in reducing conditions. However, this approach is of limited interest for the preparation of N-arylethyl and homologous derivatives due to the low diversity of commercially available electrophilic reagents (such as aldehydes or halides) in the phenylethyl series. A third and recent approach, starting from cycloheptanol was recently proposed by Nicolaou et al. to prepare the 8-azabicyclo[3.2.1]octane scaffold and illustrated with the synthesis of tropinone.[7] Treatment of cycloheptanol with *o*-iodylbenzoic acid (IBX) followed by sequential addition of K_2CO_3 and methylamine hydrochloride, led to a 58% yield of tropinone. The presence of IBX in the reaction medium introduces a severe restriction to the diversity of the amine involved. Indeed IBX has been shown to mediate dehydrogenation of carbonyl compounds, the benzylic

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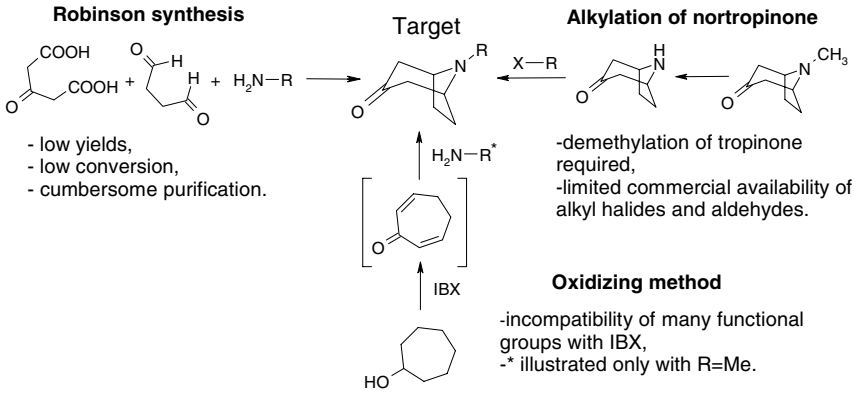


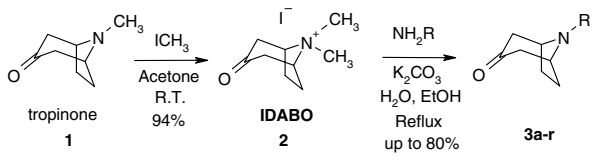
Figure 1. Known synthesis of nortropinone derivatives and limitations.

oxidation and also oxidation/cyclization of unsaturated anilides. The key intermediate of the Nicolaou's synthesis is cycloheptadien-2,6-one. Despite its simplicity, this reagent has long been, a challenge for the chemist, requiring multistep procedures for its preparation.[8] Our approach to synthesize N-substituted nortropinones relies on the preparation of 8,8-dimethyl-3-oxo-8-azonia-bicyclo[3.2.1]octane iodide (IDABO), a stable synthetic equivalent of cycloheptadien-2,6-one. In this scheme, carbons of tropinone are rendered electrophilic through the quaternarization of the nitrogen.

IDABO is easily prepared on a large scale (5–100 g) by reacting iodomethane with tropinone in acetone in 92% yield.[8] It is a white, non hygroscopic, stable powder that can be stored for months at room temperature under nitrogen. In this Letter we show that refluxed under basic conditions with primary amines, IDABO yields in one-pot the corresponding *N*-alkylated nortropinone derivatives (Scheme 1).[9]

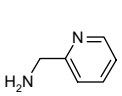
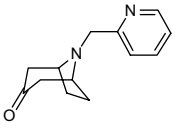
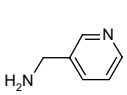
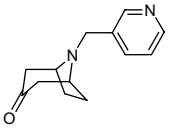
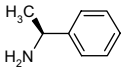
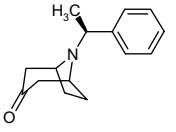
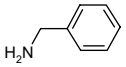
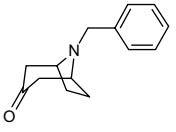
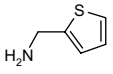
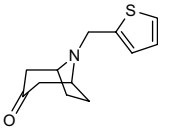
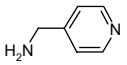
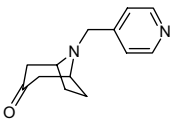
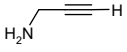
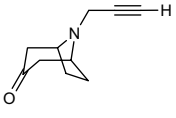
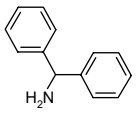
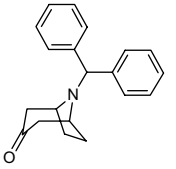
The supposed mechanism consists in the elimination of dimethylamine yielding cycloheptadien-2,6-one in situ,[10] followed by addition of primary amine to the diene to afford the desired tropinone derivative.[11] To demonstrate the scope of this reaction we engaged a variety of amines under the described conditions.

In Table 1 are reported the isolated yields of eight nortropinone derivatives using primary arylmethylamines. Although yields generally remained modest, products are isolated by flash chromatography. Only **3h** was isolated in a yield below 30%, probably due to steric hindrance. An important point was to investigate the possibility of preparing N-arylethyl derivatives that are not readily accessible by alkylation from nortropinone due to the limited availability of the corresponding aldehydes and halides.



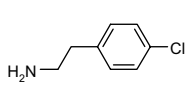
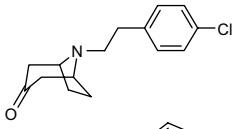
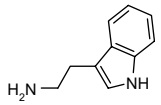
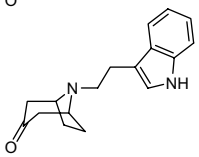
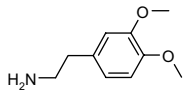
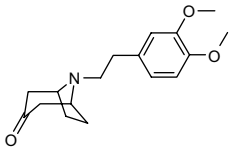
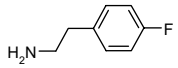
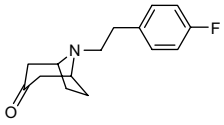
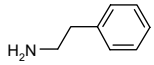
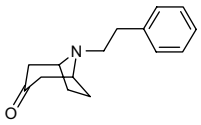
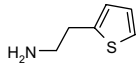
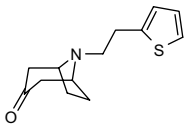
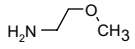
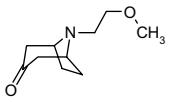
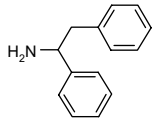
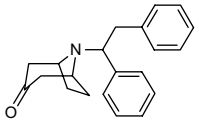
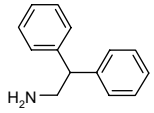
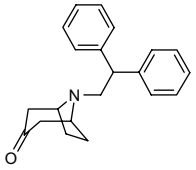
Scheme 1. One step synthesis of nortropinone analogues starting from IDABO.

Table 1. Isolated yields starting from arylmethylamines and propargyl-amine

Entry	Amine	Product	Yield (%)
3a			68
3b			67
3c			51
3d			50
3e			50
3f			32
3g			32
3h			28

In that case (Table 2), presumably due to a better accessibility of the nitrogen atom, yields were higher than those with methylamines (average isolated yield is 58%). Compound **3j** was recrystallized from EtOH and

Table 2. Isolated yields starting from arylethylamines and 2-methoxyethylamine

Entry	Amine	Product	Yield (%)
3i			80
3j			77
3k			66
3l			64
3m			55
3n			50
3o			49
3p			45
3q			31

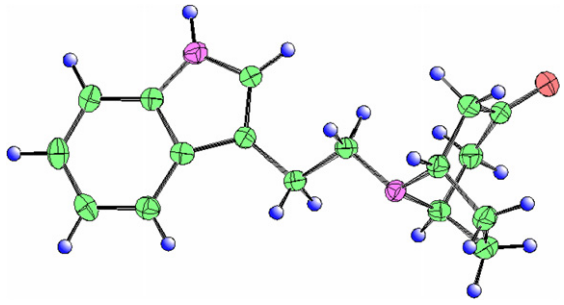
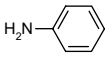
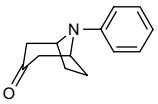
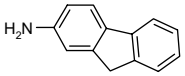
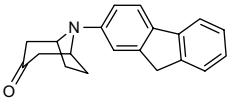
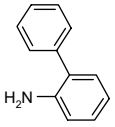
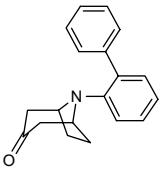


Figure 2. X-ray structure of **3j**.

Table 3. Derivatives starting from anilines

Entry	Amine	Product	Yield (%)
3r			30
3s			Not isolated
3t			Not isolated

the X-ray structure shows the expected bridged structure (Fig. 2).

Finally the reaction was also attempted with three anilines (Table 3). In agreement with their lower reactivity only one of the three aryl nortropinones (**3r**) could be isolated.

In summary, reaction of IDABO with amines is an efficient way to prepare a large variety of N-substituted nortropinone derivatives starting from tropinone. Protected from light and kept under nitrogen, IDABO is a crystalline compound that is stable for months at room temperature. It reacts readily with primary aliphatic amines under mild conditions that are required for most of the functional groups essential to medicinal chemistry. This methodology is an efficient tool for the preparation of N-substituted nortropinones that are inaccessible using alternative methods.

Acknowledgements

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References and notes

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8. General procedure for the synthesis of 'IDABO': 8,8-Dimethyl-3-oxo-8-azonia-bicyclo[3.2.1]octane iodide 'IDABO' (2): Tropinone (5.2 g, 37.4 mmol, 1 equiv) is dissolved in 37 mL of acetone under stirring. Methyl iodine (2.5 mL, 41.2 mmol, 1.1 equiv) is added dropwise for 45 min. The reaction is stirred at room temperature for a further 1 h. The precipitate is filtered and washed with acetone and with pentane/ethyl acetate solution. The resulting solid is dried on P_2O_5 to give 5.61 g (92%) of a white powder. LCMS: $[M^+] = 154$ (100%); ^{1}H NMR (DMSO-d_6, 300 MHz): 4.17 (m, 2H), 3.39 (s, 3H), 3.19 (s, 3H), 2.50 (m, 2H), 1.95 (m, 2H); ^{13}C NMR (DMSO-d_6; 75 MHz): 202.80, 68.66, 50.90, 44.87, 44.53, 26.41.
9. Representative procedure for the synthesis of **3a**–**r**: 8-Pyridin-2-ylmethyl-8-aza-bicyclo[3.2.1]octan-3-one (**3a**): 2-(Aminomethyl)pyridine (1.7 mL, 16.2 mmol, 1 equiv) is dissolved in 38 mL of ethanol, K_2CO_3 (4.6 g, 34.0 mmol, 2.1 equiv) dissolved in 12 mL distilled water is added. The resulting solution is refluxed. A solution of 8,8-dimethyl-3-oxo-8-azonia-bicyclo[3.2.1]octane iodide (5.0 g, 17.8 mmol, 1.1 equiv) in 25 mL distilled water is added dropwise for 45 min. The reaction media is refluxed a further 4 h. The heating is stopped, the solution is reduced under vacuum and the organic layer is extracted with DCM (3×25 mL), washed with brine (2×15 mL), dried over $MgSO_4$ and reduced under vacuo to give a brown oil. The residue is purified by flash chromatography on silica gel using a mixture of cyclohexane/ethyl acetate (1/1) as eluent to give a yellow oil (2.2 g, 68%). $[(M+H)^+] = 217$ (100%); ^{1}H NMR ($CDCl_3$): 8.45 (d, 1H, $J = 5.49$ Hz), 7.62 (td, 1H, $J = 7.55$ Hz, $J = 1.77$ Hz), 7.51 (d, 1H, $J = 7.55$ Hz), 7.12 (t, 1H, $J = 5.49$ Hz), 3.82 (s, 2H), 3.44 (m, 2H), 2.66 (dd, 2H, $J = 16.01$ Hz, $J = 4.32$ Hz), 2.13 (d, 2H, $J = 16.01$ Hz), 2.09 (m, 2H), 1.55 (m, 2H); ^{13}C NMR ($CDCl_3$): 209.02, 158.30, 147.92, 135.63, 121.54, 121.04, 57.98, 55.96, 47.08, 26.79. Compound (**3b**): $[(M+H)^+] = 217$ (100%); ^{1}H NMR (CD_2Cl_2): 8.54 (s, 1H), 8.43 (d, 1H, $J = 3.83$ Hz), 7.71 (d, 1H, $J = 7.67$ Hz), 7.21 (dd, 1H, $J = 7.67$ Hz, $J = 4.67$ Hz), 3.65 (s, 2H), 3.39 (m, 2H), 2.60 (dd, 2H, $J = 16.01$ Hz, $J = 4.32$ Hz), 2.13 (d, 2H, $J = 16.01$ Hz), 2.09 (m, 2H), 1.57 (m, 2H); ^{13}C NMR (CD_2Cl_2): 208.79, 148.85, 147.68, 135.21, 133.83, 122.48, 57.68, 51.74, 47.31, 26.73. Compound (**3c**): $[\alpha]_D^{25}$ −30.5 (MeOH); $[(M+H)^+] = 230$ (100%); ^{1}H NMR (CD_2Cl_2): 7.34–7.13 (m, 5H), 3.69 (q, 1H, $J = 6.4$ Hz), 3.54 (m, 1H), 3.39 (m, 1H), 2.56 (m, 2H), 2.02–1.89 (m, 4H), 1.47 (m, 2H), 1.34 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (CD_2Cl_2): 209.76, 145.87, 128.46, 127.01, 56.68, 56.15, 56.03, 46.39, 28.39, 28.06, 23.10. Compound (**3d**): $[(M+H)^+] = 216$ (100%); ^{1}H NMR (CD_2Cl_2): 7.50–7.25 (m, 5H), 3.70 (s, 2H), 3.50 (m, 2H), 2.70 (dd, 2H, $J = 16.01$ Hz, $J = 4.32$ Hz), 2.15 (m, 2H), 2.10 (m, 2H), 1.55 (m, 2H); ^{13}C NMR (CD_2Cl_2): 209.67, 139.76, 128.44, 128.28, 126.97, 58.67, 55.05, 48.20, 27.79. Compound (**3e**): Hydrochloride salt: $[(M+H)^+] = 222$ (100%); ^{1}H NMR (DMSO-d_6): 12.65 and 12.08 (br s, 1H), 7.71 (d, 1H, $J = 5.07$ Hz), 7.61 (d, 1H, $J = 2.55$ Hz), 7.15 (dd, 1H, $J = 5.07$ Hz, $J = 2.55$ Hz), 4.90 and 4.52 (m, 2H), 4.04 (m, 2H), 3.40–3.10 (m, 2H), 2.47 (m, 4H), 1.87 (m, 2H); ^{13}C NMR (DMSO-d_6): 204.47, 132.88, 131.58, 129.80, 128.06, 59.88, 48.04, 46.40, 25.60. Compound (**3f**): Hydrochloride salt $[(M+H)^+] = 217$ (100%); ^{1}H NMR (DMSO-d_6): 9.04 (m, 2H), 9.62 (m, 2H), 4.78 (m, 2H), 4.12 (m, 2H), 3.35 (m, 2H), 2.51–2.35 (m, 4H), 1.88 (m, 2H); ^{13}C NMR (DMSO-d_6): 203.98, 149.28, 143.15, 129.07, 66.81, 65.37, 61.00, 45.94, 25.87. Compound (**3g**): Hydrochloride salt. $[(M+H)^+] = 164$ (100%); ^{1}H NMR (DMSO-d_6): 12.81 (br s, 1H, NH), 4.30–4.00 (m, 4H), 3.85 (s, 1H), 3.50–3.20 (m, 2H), 2.50–2.20 (m, 4H), 1.88 (m, 2H); ^{13}C NMR (DMSO-d_6): 204.09, 81.09, 74.56, 60.64, 46.39, 25.53. Compound (**3h**): $[(M+H)^+] = 292$ (40%); ^{1}H NMR (CD_2Cl_2): 7.64–7.58 (m, 4H), 7.39–7.21 (m, 6H), 4.61 (s, 1H), 3.50 (m, 2H), 2.72 (dd, 2H, $J = 16.10$ Hz, $J = 4.41$ Hz), 2.15 (m, 4H), 1.60 (m, 2H); ^{13}C NMR (CD_2Cl_2): 209.95, 143.88, 128.68, 127.28, 127.19, 68.49, 56.85, 48.08, 27.71. Compound (**3i**): $[(M+H)^+] = 264$ (100%); ^{1}H NMR (CD_2Cl_2): 7.32–7.20 (m, 4H), 3.52 (m, 2H), 2.81 (m, 4H), 2.62 (dd, 2H, $J = 16.00$ Hz, $J = 4.41$ Hz), 2.14 (d, 2H, $J = 16.00$ Hz), 2.00 (m, 2H), 1.60 (m, 2H); ^{13}C NMR (CD_2Cl_2): 209.32, 139.24, 130.22, 128.27, 58.88, 52.13, 47.49, 35.24, 27.83. Compound (**3j**): **3j** was recrystallized in EtOH. Mp: 119.9–121.3 °C; $[(M+H)^+] = 269$ (100%); ^{1}H NMR (CD_2Cl_2): 8.19 (br s, 1H), 7.52 (d, 1H, $J = 8.4$ Hz), 7.29 (d, 7.9 Hz), 7.15–6.95 (m, 3H), 3.53 (m, 2H), 2.98–2.80 (m, 4H), 2.60 (dd, 2H, $J = 16{,}00$ Hz, $J = 4.41$ Hz), 2.08 (d, 2H, $J = 16.00$ Hz), 1.98 (m, 2H), 1.53 (m, 2H); ^{13}C NMR (CD_2Cl_2): 209.94, 136.35, 127.64, 121.93, 119.25, 118.76, 114.41, 111.19, 58.92, 51.19, 47.50, 28.05, 25.35. Compound (**3k**): Hydrochloride salt. $[(M+H)^+] = 290$ (100%); ^{1}H NMR (DMSO-d_6): 12.31 and 11.85 (br s, 1H, NH), 7.0–6.80 (m, 3H), 4.30–4.10 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.62 (m, 1H), 3.45–3.00 (m, 5H), 2.50–2.20 (m, 4H), 1.88 (m, 2H); ^{13}C NMR (DMSO-d_6): 204.44, 149.28, 148.17, 129.94, 121.19, 113.11, 112.48, 61.05, 56.02, 52.64, 46.46, 30.47, 26.71, 25.61. Compound (**3l**): Hydrochloride salt. LCMS: $[(M+H)^+] = 248$ (100%); ^{1}H NMR (DMSO-d_6): 12.35 and 11.95 (br s, 1H), 7.37 (m, 2H), 7.17 (m, 2H), 4.40–4.10 (m, 2H), 3.70–3.54 (m, 1H), 3.45–3.00 (m, 5H), 2.50–2.25 (m, 4H), 1.85 (m, 2H); ^{13}C NMR (DMSO-d_6): 204.41, 133.79, 131.20, 131.09, 115.94, 115.66, 61.01, 58.01, 52.33, 46.46, 42.49, 29.97, 26.72, 25.59. Compound (**3m**): Hydrochloride salt. $[(M+H)^+] = 230$ (100%); ^{1}H NMR (DMSO-d_6): 12.35 and 11.95 (br s, 1H), 7.37–7.21 (m, 5H), 4.40–4.10 (m, 2H), 3.70–3.54 (m, 1H), 3.45–3.00 (m, 5H), 2.50–2.25 (m, 4H), 1.85 (m, 2H); ^{13}C NMR (DMSO-d_6): 204.42, 137.62, 129.25, 129.07, 127.25, 61.00, 58.04, 52.36, 46.49, 42.48, 30.80, 25.59. Compound (**3n**): Hydrochloride salt. $[(M+H)^+] = 236$ (100%); ^{1}H NMR (DMSO-d_6): 12.35 and 11.95 (br s, 1H), 7.48–7.35 (m, 1H), 7.10–6.95 (m, 2H), 4.40–4.10 (m, 2H), 3.80–3.00 (m, 6H), 2.50–2.25 (m, 4H), 1.85 (m, 2H); ^{13}C NMR (DMSO-d_6): 204.38, 139.19, 127.69, 126.47, 125.25, 61.12, 58.14, 52.14, 46.44, 42.51, 26.69, 25.61, 25.15. Compound (**3o**): $[(M+H)^+] = 184$ (100%); ^{1}H NMR (DMSO-d_6): 3.52 (m, 4H), 3.26 (s, 3H), 2.74 (t, 2H, $J = 5.76$ Hz), 2.60 (dd, 2H, $J = 16.11$ Hz, $J = 4.50$ Hz), 2.01 (d, 2H, $J = 16.11$ Hz), 1.91 (m, 2H), 1.42 (m, 2H); ^{13}C NMR (DMSO-d_6): 209.53, 72.42, 59.16, 58.59, 48.99, 47.08, 28.20. Compound (**3p**): $[(M+H)^+] = 306$ (100%); ^{1}H NMR (CD_2Cl_2): 7.30–7.10 (m, 8H), 6.91–6.84 (m, 2H), 3.88 (dd, 1H, $J = 9.9$ Hz,

$J = 4.2$ Hz), 3.82 (m, 1H), 3.58 (m, 1H), 3.40 (dd, 1H, $J = 13.2$ Hz, $J = 4.2$ Hz), 2.92 (dd, 1H, $J = 9.6$ Hz, $J = 12.9$ Hz), 2.73 (m, 2H), 2.22–1.96 (m, 4H), 1.61 (m, 2H); ^{13}C NMR (CD_2Cl_2): 209.65, 142.22, 138.79, 129.51, 128.23, 128.03, 127.91, 127.15, 125.85, 64.31, 56.50, 55.88, 46.29, 46.03, 42.83, 28.25, 28.16. Compound (**3q**): $[(M+H)^+] = 306$ (100%); ^{1}H NMR (CD_2Cl_2): 7.38–7.20 (m, 10H), 4.24 (t, 1H, $J = 7.5$ Hz), 3.52 (m, 2H), 3.28 (d, 2H, $J = 7.5$ Hz), 2.60 (dd, 2H, $J = 3.6$ Hz, $J = 12.6$ Hz), 2.14 (d, 2H, $J = 16.10$ Hz), 2.00 (m, 2H), 1.58 (m, 2H); ^{13}C NMR (CD_2Cl_2): 209.45, 144.04, 128.37, 128.17, 126.29, 59.36, 55.94, 51.27, 47.58, 27.95. Compound (**3r**): $[(M+H)^+] = 202$ (100%); ^{1}H NMR (CD_2Cl_2): 7.38–7.28 (m, 2H), 6.97–6.87 (m, 2H), 6.83 (t, 1H,7 = 7.32 Hz), 4.51 (m, 2H), 2.69 (dd, 2H, $J = 15.56$ Hz, $J = 4.47$ Hz), 2.28 (d, 2H, $J = 15.56$ Hz), 2.20 (m, 2H), 1.81 (m, 2H); ^{13}C NMR (CD_2Cl_2): 207.55, 145.40, 129.67, 118.09, 114.94, 45.45, 28.76, 26.92.

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