Turk J Chem
32 (2008) , 755 – 763.

Synthesis and Biological Activity of Allosteric Modulators of $GABA_B$ Receptors. Part 4. Synthesis of Potentially Fluorescent Acridines and Conformationally Restricted *N*-(arylpropyl)-1-arylethylamines*

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Received 19.06.2008

A series of 8 new derivatives of fendiline was prepared for evaluation as allosteric modulators of $GABA_B$ receptors: 4 based on acridine and 4 with restricted distance between the 2 aryl moieties.

Key Words: Fendiline analogues, acridines, acridones, aminotetralins, aminoindanes, GABA.

Introduction

In Part 1 of this series[1] we reported the synthesis of a number of *N*-(phenylpropyl)-1-arylethylamines (**1**) and their activity as positive modulators of GABA (**2**) at $GABA_B$ receptors. The most active of these compounds, the analogue **3**, had no activity of its own in the central nervous system (CNS), but at 10 nM strongly potentiated the activity of baclofen (**4**) in its hyperpolarisation at $GABA_B$ post-synaptic receptors and in reducing electrically evoked release of GABA at presynaptic receptors.

GABA is one of the major inhibitory neurotransmitters that regulates synaptic transmission and neuronal excitability in the mammalian central and peripheral nervous system,[2−4] and defects in GABA-ergic transmission can cause a variety of neurological and psychiatric diseases such as spasticity,[5] epilepsy,[6] Huntington's disease,[7] and Parkinson's disease.[8] $GABA_B$ receptors are also implicated in drug addiction related to alcohol[9,10] and cocaine.[11] Accordingly, we considered it important to investigate further analogues of the structure **1**.

*Part 3 Kerr, D.I.B.; Khalafy, J.; Ong, J.; Prager, R.H.; Rimaz, M., *J. Brazil. Chem. Soc.* **2007**, *18*, 721.
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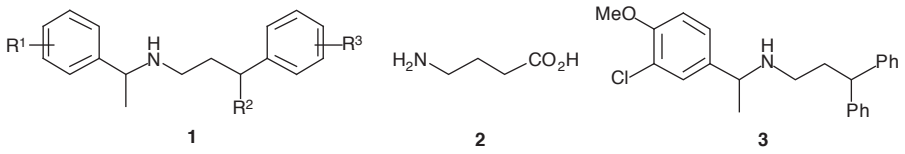
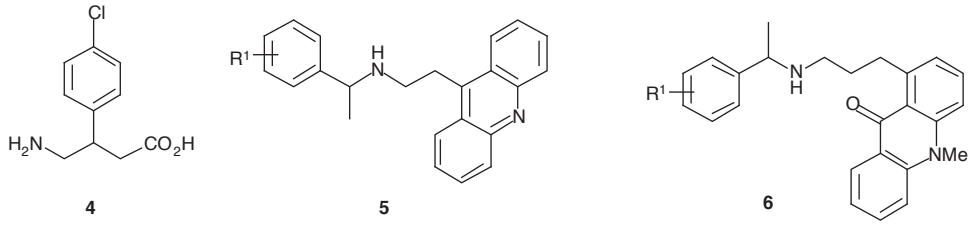


Acridines and acridinium salts are highly fluorescent,[12] and this has been utilised in chemiluminescence assays for determining glucose oxidase and alkaline phosphatase levels, in photoluminesence emitters, and as electron acceptors in photochemical processes.[13] In addition, acridine derivatives have found application in several antidepressive,[14] antimalarial, and antitumour agents.[15,16] We therefore thought that the synthesis of a series of acridine analogues bearing the phenylalkylamine moiety (**5**) as well as the analogous acridone (**6**) would be worthwhile. If these compounds acted as $GABA_B$ receptor modulators, they might also enable visualization of their binding sites.



In the first paper[1] we investigated the biological effects of shortening or lengthening the phenylpropyl sidechain in **1**, and found that the ideal spacing between the nitrogen and the aryl group was 3 carbons. In addition, we briefly investigated the consequence of introducing some restraints in the mobility of this chain by inserting double bonds or carbonyl groups; such strategies led to considerable reduction in activity. Our working hypothesis for the binding site of these compounds is shown in Figure 1. In this paper we report the synthesis of several analogues in which the 3 carbon chain is part of a carbocycle.

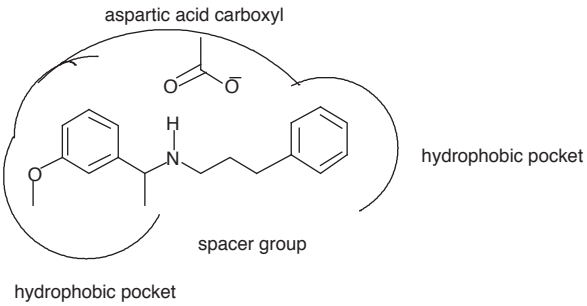
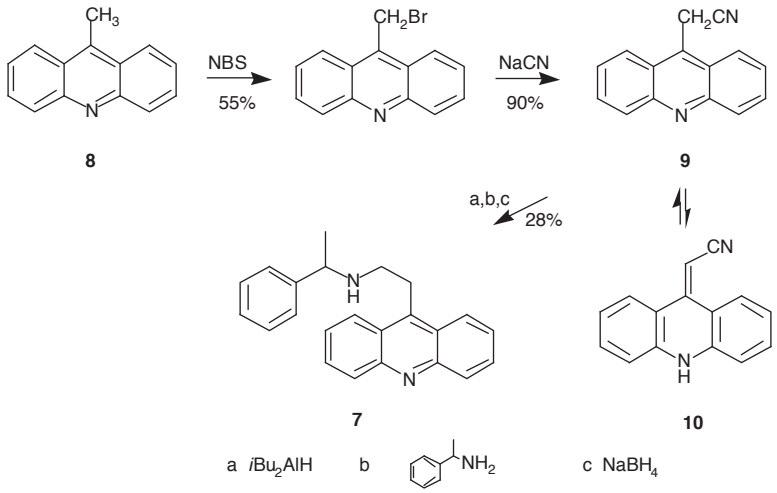


Figure 1. Proposed active site for 3-arylpropyl-α-methylbenzylamines.

Discussion

Acridine derived analogues

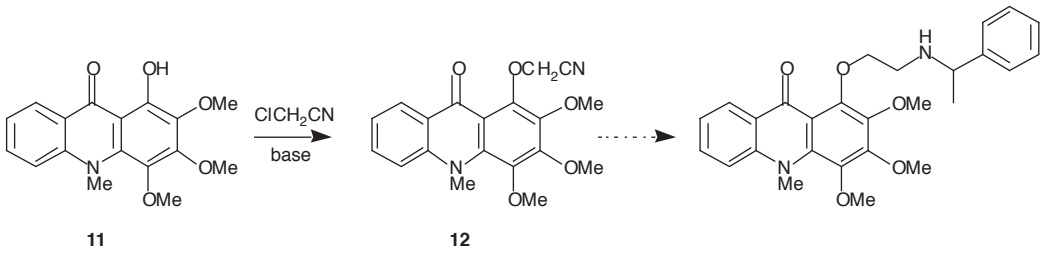
The simplest of the desired compounds (**7**) was prepared from 9-methylacridine (**8**) as shown in Scheme 1.



Scheme 1

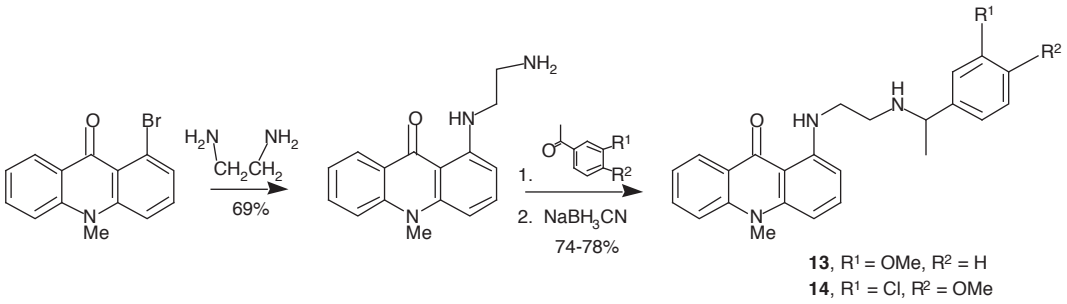
In our hands the methylation of acridine with the dimethylsulfoxide anion[17−19] to obtain **8** was not a clean reaction, and the application of the Bernthsen reaction[20,21] on diphenylamine was preferred. A comparison of the conventional procedure[21,22] with that involving a modification of the microwave irradiation procedure[23] showed that the latter was rapid and convenient. In addition, the cyanomethylacridine (**9**)[24] was generally the minor tautomeric product, the major being the cyanomethyleneacridan (**10**),[25] but either or both were suitable for reductive amination with diisobutylaluminium hydride and an α-methylbenzylamine (Scheme 1) to give the desired **7**.

We next hoped to make use of the large quantities of the highly fluorescent[26] acridone alkaloids available to us from previous work.[27] Unfortunately, all attempts to alkylate a typical precursor such as normelicopicine (**11**)[28] with chloroacetonitrile, to be followed by reductive alkylations, were unsuccessful, even when using sodium hydride in dimethylsulphoxide, and only trace quantities of the desired product (**12**) were detected by NMR spectroscopy (Scheme 2).

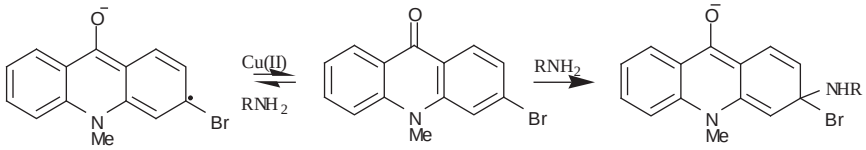


Scheme 2

However, acridones **13** and **14** were successfully prepared using our previous experience[29−31] on nucleophilic substitution of 1- and 3-bromoacridones with amines (Scheme 3). Initially we investigated the substitution of 3-bromo-10-methylacridone, but the major product on reaction with ethylenediamine was the reduction product 10-methylacridone. In the case of 1-bromo-10-methylacridone, formation of 10-methylacridone was only a minor pathway. On the assumption that this reaction probably involved initial electron transfer to form the radical anion (**15**), small amounts of Cu(II) salts were added to encourage reverse electron transfer, resulting in a considerable reduction in these byproducts (Scheme 4).



Scheme 3



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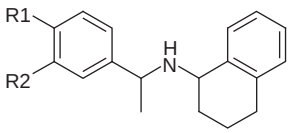
Scheme 4

Like most 1-, 3-, and 9-bromoacridones or acridines, compounds **13** and **14** were not fluorescent.



16 R^1 = H, R^2 = OMe
17 R^1 = OMe, R^2 = Cl

Analogues with restricted rotation

The above synthetic strategy was followed with 1-aminotetralin to give the analogues **16** and **17**, in which the distance between the 2 aryl moieties could be defined with some certainty.

Reductive alkylation of 1-aminotetralin with either 3-methoxyacetophenone or 3-chloro-4-methoxyacetophenone gave mixtures of the diastereoisomers of **16** and **17** respectively. In each case the ratio of isomers was close to 1:1, and the mixtures could not be separated by thin layer chromatography on silica. Further attempts to obtain the pure individual diastereoisomers were deferred until the biological screening was complete.

The biological evaluation of these compounds will be published independently.

Experimental

All solvents used were freshly distilled and dried as described by Perrin and Amarego.[32] Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Gemini Varian 300 spectrometer in deuteriochloroform with tetramethylsilane as internal standard, unless otherwise stated. Infrared spectra were recorded on a Perkin Elmer 1600 FT-infrared spectrophotometer, using fused sodium chloride cells, measured as nujol mulls or films. Reidel-de

Haen Silica gel S (pH 7, granulation 32-63 mm) was used for all column chromatography. Merck silica gel 60 F 254 aluminium backed sheets were used for analytical thin layer chromatography. GC-MS analysis was carried out with a Varian Saturn 4D instrument using a Zebron ZB-5 5% phenyl polysiloxane column (30 m, 0.25 mm ID). Electrospray ionisation mass spectra (EIMS), using a Bruker 4.7T FTMS Ultra High Resolution spectrometer, reporting the $(MH)^{+\bullet}$ and some fragmentation ions, were determined at Monash University, Melbourne, Australia.

9-Methylacridine (8)

(i) By the conventional Bernthsen method.[20] A mixture of diphenylamine (20 g, 0.116 mol), acetic acid (70 g, 1.16 mol), and dry zinc chloride (76 g, 0.52 mol) was heated with stirring at 200 °C for 48 h. Then 20% sulphuric acid (250 mL) was added and the mixture was refluxed for 4 h. After cooling, the mixture was neutralised by adding 25% ammonia (400 mL) with stirring and a light brown solid was collected by filtration; a black sticky product remained in the flask. The solid then was washed with water until the filtrate was neutral and then dried (6.70 g). ^{1}H-NMR analysis suggested that the product obtained was mainly 9-methylacridine (70%) with unreacted diphenylamine (30%). The crude product was dissolved in ether with stirring, and washed with 1 M HCl (3 × 20 mL). The aqueous layer was neutralised with 1 M NaOH, extracted with dichloromethane, and the extract dried over $MgSO_4$ and evaporated to yield 9-methylacridine (4.72 g, 21%), mp 110-112 °C, lit.[19] 115-117 °C. ^{1}H-NMR δ 3.13, s, 3H; 7.57, t, J 8.2 Hz, 2H; 7.79, t, J 8.8 Hz, 2H; 8.26, d, J 8.8 Hz, 4 H. ^{13}C-NMR δ 13.6, CH_3; 124.5, C; 124.7, CH; 125.4, 2xC; 127.4, CH; 129.9, CH; 148.1, 2xC.

Shorter reaction times resulted in the formation of intermediate products.

(ii) Using microwave irradiation.[22] A mixture of diphenylamine (1.69 g, 10 mmol), acetic acid (6.0 g, 100 mmol), and crushed dry zinc chloride (5.45 g, 40 mmol) was heated in a test tube with stirring until a homogeneous solution was obtained, and then was irradiated at 30% (700 W) in a microwave reactor for a total of 5 min, intermitting at 2 and 4 min to calm the vigorous reaction. After cooling, the green mixture was neutralised by adding 25% ammonia with stirring and the yellow solid was dissolved in ether, and the ether extract was washed with 1 M HCl (3 × 20 mL). The aqueous layer was neutralised with 1 M NaOH (50 mL), extracted with dichloromethane, and the extracts dried and evaporated to yield 9-methylacridine as an orange solid (0.98 g, 50%), mp 110-112 °C (lit.[19] 115-117 °C).

9-Cyanomethylacridine (9)

A mixture of 9-bromomethylacridine[33] (0.3 g, 1.08 mmol) and sodium cyanide (0.10 g, 2.16 mmol) in dimethylformamide (20 mL) was stirred at room temperature overnight. The mixture was poured onto ice-water, extracted with ethyl acetate, and the extract dried over $MgSO_4$ and concentrated to yield a yellow liquid. The product was subjected to flash silica gel column chromatography using dichloromethane as eluent to give a yellow solid (0.21 g, 90%), mp 230-232 °C (lit.[25] mp 230-231.5 °C). ^{1}H-NMR analysis suggested the product was a mixture of 9-cyanomethylacridine (**9**, 10%) and 9-cyanomethylenecridan (**10**, 90%). ^{1}H-NMR for **10** δ 5.47, s, 1H; 6.70-7.04, m, 2H; 7.10-7.20, m, 2H; 7.38-7.45, m, 2H; 7.23, d, J 8.6 Hz, 1H; 8.78, d, J 8.2 Hz, 1H; NH unsighted. ^{13}C-NMR δ 115.4, CH; 115.6, CN; 121.5, CH; 122.1, CH; 124.1, 2xCH; 127.0, C; 131.2, C; 131.6, 2xC. ν_{max} 3281, 2183, 1627 cm^{-1}.

When the reaction was carried out at 80 °C, or if CuCN was used as reagent, ^{1}H-NMR analysis showed the product was totally **10**.

(R)- 9-{-[1-(phenyl)ethylamino]ethyl}acridine (7)

To a solution of 9-cyanomethylenecridan (0.2 g, 0.91 mmol) in dry dichloromethane (2 mL) was added dropwise 1.5 M di*iso*butylaluminium hydride in toluene (0.7 mL) at –78 °C. The mixture was stirred at room temperature for 3 h and then cooled to 0 °C. $(R)-\alpha$-methylbenzylamine (0.17 mL, 1.82 mmol) then was added and the mixture was stirred for 2 h. The reaction mixture was transferred to a solution of sodium borohydride (0.052 g, 1.3 mmol) in ethanol (6 mL) and then stirred overnight. The mixture was quenched by the addition of 10% HCl and then neutralised with 1 M NaOH. The organic phase was combined with the ether extracts of the aqueous phase, washed with water, dried, and concentrated, and the product was subjected to flash silica gel column chromatography using dichloromethane:methanol (9.5:0.5) as eluent to yield **7** as a pale brown liquid (0.09 g, 28%). Found $[M+H]^+$ 327.1864. $C_{23}H_{23}N_2$ requires 327.1856. ^{1}H-NMR δ 1.40, d, J 6.6 Hz, 3H; 2.97, m, 2H; 3.76, m, 2H; 3.90, t, J 6.6 Hz, 1H; 7.26, m, 2H; 7.32, m, 5H; 7.49, td, J 1.2, 3.4 Hz, 2H; 7.74, td, J 1.2, 3.4 Hz, 2H; 8.17, t, J 9.0 Hz, 2H; NH unsighted. ^{13}C-NMR δ 24.2, CH_3; 28.3, CH_2; 47.9, CH_2; 58.2, CH; 124.2, CH; 125.1, C; 125.7, CH; 126.7, CH; 127.3, C, 128.6, CH; 129.7, CH; 130.3, CH; 143.7, C; 148.6, C.

Attempted alkylation of normelicopicine (11) with chloroacetonitrile

To a suspension of sodium hydride (0.15 g, 6 mmol) in dry DMSO (5 mL) was added normelicopicine (1 g, 3 mmol) and the mixture was stirred for 1 h. Chloroacetonitrile (0.69 g, 9 mmol) was added and the mixture was stirred at room temperature for 3 h. Water was added and the mixture was extracted with dichloromethane. The combined dichloromethane extracts were dried over $MgSO_4$ and concentrated to yield orange crystals (1 g), identical with the starting material.

The addition of sodium iodide, or heating the reaction mixture to 100 °C, did not alter the outcome.

1-(2-Aminoethylamino)-10-methylacridin-9(10H)-one

1-Bromo-10-methyl-9-acridone (864 mg, 3 mmol) was dissolved in 1,2-diaminoethane hydrate (10 mL) by heating at 130 °C for 2 h. The mixture was cooled, ice water added, and the precipitate collected and dissolved in 10% HCl (15 mL). The suspension was washed with ether (4 × 25 mL), the aqueous phase basified with 2 M NaOH, and the precipitate recrystallised from ethanol as yellow needles (553 mg, 69%), mp 135-137 °C. Found: $[M+H]^+$ 268.1448. $C_{16}H_{18}N_3O$requires 268.1450. ^{1}H-NMR δ 1.72, bs, 2H; 3.07, t, J 6 Hz, 2H; 3.35, q, J 6 Hz, 2H; 3.78, s, 3H; 6.34, d, J 8.2 Hz, 1H; 6.50, d, J 8.2 Hz, 1H; 7.23, t, J 7.4 Hz, 1H; 7.44, t, J 8.2 Hz, 2H; 7.65, td, J 7.4, 1.4 Hz, 1H; 8.44, dd, J 7.4, 1.4 Hz, 1H; 10.56, bs, 1H, NH. ^{13}C-NMR δ 34.4, 41.0, 46.1, 99.3, 100.9, 114.2, 120.9, 127.0, 133.1, 135.1, 146.4, 151.7, 152.9, 165.8, 175.4, 206.8. υ_{max} 3388, 1687, 1656, 1485 cm^{-1}. Mass spectrum m/e 267 (M), 252, 238, 237, 222.

1-{2-[1-(3-Methoxyphenyl)ethylamino]ethylamino}-10-methylacridin-9(10H)-one (13)

A mixture of the amino compound above (150 mg), 3-methoxyacetophenone (84 mg), and titanium tetraisopropoxide (400 mg, 2 equiv.) was stirred under nitrogen at 80 °C for 1.5 h. A solution of sodium cyanoborohydride (36 mg) in dry ethanol (2 mL) was added dropwise. The reaction mixture was stirred at rt for 16 h, water (5 mL) was added, and the mixture extracted with ether (3 × 10 mL). The extract yielded an orange oil, which was purified by chromatography on alumina, using dichloromethane as eluent, giving **13** as an orange oil (175 mg, 78%). Found: $[M+H]^+$ 402.2176. $C_{25}H_{28}N_3O_2$ requires 402.2180. ^{1}H-NMR δ 1.44, d

J 6.6 Hz, 3H; 2.73, bs, 1H, NH; 2.87, q, J 6.2 Hz, 2H; 3.40, q, J 6.2 Hz, 2H; 3.70, s, 3H; 3.82, s, 3H; 3.88, q, J 6.6 Hz, 1H; 6.47, d, J 8.2 Hz, 1H; 6.75-7.03, m, 3H; 7.18-7.27, m, 2H; 7.29, d, J 8.2 Hz, 1H; 7.38, t, J 8.2 Hz, 2H; 7.61, td, J 7.0, 1.8 Hz, 1H; 8.42, dd, J 8.0, 1.8 Hz, 1H; 10.47, bt, J 5.5 Hz, 1H, NH. ^{13}C-NMR δ 24.2, 34.3, 42.8, 46.1, 55.2, 58.3, 99.3, 100.9, 108.2, 111.8, 112.7, 114.1, 119.1, 120.8, 122.9, 126.9, 129.4, 133.0, 135.0, 141.8, 145.1, 146.5, 152.7, 159.8, 180.2; Mass spectrum m/e 401 (M), 292, 251, 237, 209, 135.

1-{2-[1-(3-Chloro-4-methoxyphenyl)ethylamino]ethylamino}-10-methylacridin-9(10H)-one (14)

A mixture of the amino compound above (267 mg), 3-chloro-4-methoxyacetophenone (185 mg), and titanium tetraisopropoxide (570 mg, 2 equiv.) was reacted as above and finally with sodium cyanoborohydride (63 mg) in dry ethanol (3 mL). After chromatography the product (**14**) was isolated as yellow oil (324 mg, 74%). Found: $[M+H]^+$ 436.1783. $C_{25}H_{27}ClN_3O_2$ requires 436.1791. ^{1}H-NMR δ 1.38, d, J 6.6 Hz, 3H; 2.38, bs, 1H, NH; 2.72-2.96, m, 2H; 3.37, q, J 6.2 Hz, 2H; 3.71, s, 3H; 3.81, q, J 6.6 Hz, 1H; 3.86, s, 3H; 6.28, d, J 8.2 Hz, 1H; 6.46, d, J 8.2 Hz, 1H; 6.87, d, J 8.6 Hz, 1H; 7.17-7.32, m, 3H; 7.39, t, J 8.2 Hz, 2H; 7.61, td, J 8.0, 1.6 Hz, 1H; 8.44, dd, J 8.0, 1.6 Hz, 1H; 10.46, bt, J 5.2 Hz, 1H, NH. ^{13}C-NMR δ 24.2, 34.3, 42.8, 46.0, 56.1, 57.3, 99.4, 100.9, 108.2, 112.0, 114.1, 120.8, 122.3, 122.9, 125.9, 127.0, 128.5, 133.0, 135.0, 138.2, 141.9, 145.1, 152.7, 153.8, 180.3. υ_{max} 3228, 2963, 2837, 1686, 1621, 1493, 1256, 1040, 726 cm^{-1}. Mass spectrum m/e 437, 435, 238, 237, 222, 169.

N-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1-[3-methoxyphenyl]ethylamine(16)

A mixture of 1-amino-1,2,3,4-tetrahydronaphthalene (294 mg, 2 mmol), 3-methoxyacetophenone (300 mg, 2 mmol), and titanium tetraisopropoxide (853 mg, 3 mmol) was reacted as above, and then treated with sodium cyanoborohydride (134 mg, 2 mmol) in dry ethanol (4 mL). Evaporation of the extract gave **16** as a 6:5 mixture of diastereoisomers, isolated as colourless oil (415 mg, 74%). Found: $[M+H]^+$ 282.1868. $C_{19}H_{24}NO$ requires 282.1858. ^{1}H-NMR δ 1.87, d, J 6.6 Hz, 3H (major isomer); 1.88, d, J 6.6 Hz, 3H (minor isomer); 1.60-2.05, m, 4H; 2.6-2.9, m, 2H; 3.55, t, J 4.5 Hz, 1H (major isomer); 3.72, t, J 4.5 Hz, 1H (minor isomer); 3.85, s, 3H (major isomer); 3.87, s, 3H (minor isomer); 4.04, q, J 6.6 Hz, 1H; 6.78-6.86, m, 1H: 6.98-7.36, m, 6H; 7.40, dd, J 6.8, 3.0 Hz, 1H. ^{13}C-NMR δ 18.5, 19.0, 24.7, 25.2, 27.4, 29.0, 29.4, 51.9, 53.2, 54.8, 55.2, 56.2, 112.2, 112.3, 112.4, 119.2, 119.3, 125.4, 125.7, 126.5, 126.6, 128.8, 128.9, 129.0, 129.1, 129.3, 129.4, 137.3, 159.8. υ_{max} 2929, 2859, 1600, 1585, 1486, 1451, 1254, 1046 cm^{-1}. Mass spectrum m/e 281 (M), 266, 191, 146, 136, 135, 131, 130, 115, 105, 91, 77, 55.

N-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1-[3-chloro-4-methoxyphenyl]ethylamine(17)

A mixture of 1-amino-1,2,3,4-tetrahydronaphthalene (147 mg, 1 mmol), 3-chloro-4-methoxyacetophenone (184 mg, 1 mmol), and titanium tetraisopropoxide (427 mg, 1.5 mmol) was reacted as above, and then treated with sodium cyanoborohydride (67 mg, 1 mmol) in dry ethanol (3 mL). Evaporation of the extract gave **17** as a 4:3 mixture of diastereoisomers, isolated as colourless oil (288 mg, 91%). Found: $[M+H]^+$ 316.1467. $C_{19}H_{23}ClNO$ requires 316.1468. ^{1}H-NMR δ 1.34, d, J 6.6 Hz, 3H (major isomer); 1.35, d, J 6.6 Hz, 3H (minor isomer); 1.60-2.05, m, 4H; 2.64-2.86, m, 2H; 3.52, t, J 4.6 Hz, 1H (major isomer); 3.71, t, J 4.6 Hz, 1H (minor isomer); 3.91, s, 3H (major isomer); 3.92, s, 3H (minor isomer); 3.99, q, J 6.6 Hz, 1H (major isomer); 4.01, q, J 6.6 Hz, 1H (minor isomer); 6.94, dd, J 8.4, 7.2 Hz, 1H; 7.02-7.24, m, 3H; 7.27-7.44, m, 2H; 7.49, t, J 1.8 Hz, 1H. ^{13}C-NMR δ 18.5, 19.1, 24.6, 25.4, 27.5, 28.9, 29.4, 51.7, 53.1, 53.7, 55.2, 56.1, 111.9, 112.0, 122.3, 125.5, 125.7, 125.9, 125.95, 126.5, 126.6, 128.5, 128.6, 128.7, 128.75, 128.8, 129.1, 137.1,

137.2, 139.1, 139.7, 140.0, 153.8. υ_{max} 2928, 1603, 1575, 1455, 1408, 1252, 1022, 884 cm^{-1}. Mass spectrum m/e 317, 315 (M), 302, 300, 188, 186, 171, 170, 169, 146, 131, 130, 115, 91, 77, 65.

Acknowledgments

J.K. is grateful for support from Urmia and Flinders Universities for study leave; N.M.P. is grateful to Austaid for a postgraduate scholarship.

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