Synthesis and anti-acetylcholinesterase activity of *N*-[(indolyl)ethyl)-coumarin-yloxy)]alkanamides

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Novel coumarin–tryptamine systems attached through a linker were synthesised and evaluated *in vitro* against acetylcholinesterase by the classical Ellman's test.

Keywords: coumarin, acetylcholinesterase, Alzheimer's disease, inhibitor

Alzheimer's disease (AD) is an age-related neurodegenerative disorder of the central nervous system (CNS) and affects older people's skills, knowledge and abilities. Memory loss, cognitive impairment and language problems are some of the important symptoms of these people, making them dependent on their caregivers and relatives.[1,2] The reduced levels of acetylcholine (ACh), aggregation of β-amyloids around the neurons and also the formation of neurofibrillary tangles within the brain have been identified as the main causes of this disease.[3] Increasing the low levels of acetylcholine and inhibition of β-amyloid peptide formation which led to the enhanced cholinergic neurotransmission, have been regarded as the main treatment method for this disease.[4–6]

Targeting the acetylcholinesterase enzyme (AChE) by the action of effective inhibitors led to increased levels of acetylcholine in the brain and thus an improvement in AD symptoms. During the last decades, various AChE inhibitors have been designed and clinically approved[7] such as donepezil,[8] galantamine[9] and ensaculin.[10] Ensaculin is a drug from the coumarin family, administered for the treatment of dementia. An efficient binding of ligands to peripheral (non-catalytic) and central (catalytic) binding sites of AChE is considered the best way of inhibiting the action of this enzyme.[11] In this regard, medicinal chemists are encouraged to design compounds involving different moieties to simultaneously interact with these sites.

The coumarin skeleton is an important fused-ring system exhibiting various biological activities, therefore, various synthetic methods have been reported to date to access different coumarin derivatives.[12,13] Due to the ability of this core in binding to the peripheral anionic site (PAS) of AChE, coumarins continue to be highly investigated as a main structural feature of powerful anti-AChE molecules. Various coumarin derivatives have been known as AChE inhibitors,[14] like ensaculin, and AP2238 encompassing substitution at positions 3- or 4- and regarded as beneficial dual inhibitors.[15]

Recently, we have synthesised different series of coumarin-based compounds and evaluated their AChE inhibitory activities.[16–20] Furthermore, indole amine frameworks have been successfully utilised for the synthesis of new AChE inhibitors and multi-target agents.[21] In this context and in continuation of our recent work,[22,23] it seemed very interesting to develop coumarin carboxamide derivatives bearing an indole amine (tryptamine) scaffold to find new AChE inhibitors. Herein, we report the synthesis and anti-acetylcholinesterases activities of *N*-[(indolyl) ethyl)-coumarin-yloxy)]alkanamides **4a–i**.

Results and discussions

According to the literature, the reaction of resorcinol and ethyl acetoacetate in concentrated sulfuric acid was utilised to prepare 7-hydroxy-4-methylcoumarin.[24] Other coumarin derivatives were purchased and used without purification. The synthetic sequence was initiated by *O*-alkylation of coumarins with bromo ester derivatives and led to the corresponding alkylated products. Then, hydrolysis of the ester grouping in **2a–i** under basic conditions (aqueous sodium hydroxide solution) led to acid derivatives **3a–i**. Synthesis of these derivatives were reported previously in the literature.[18,25–29] The conversion of carboxylic acid derivatives to the corresponding acyl chlorides was carried out in refluxing thionyl chloride. Subsequent treatment with tryptamine furnished the desired products in good yields (Scheme 1). The structures of all the synthesised compounds were confirmed by analytical and spectroscopic data.

The acetylcholinesterse inhibitory activities of the synthesised compounds **4a–i** were evaluated using Ellman's protocol[30] and listed in Table 1. The results are reported as IC_{50} (μM) for active compounds and as a percentage of inhibition at 50 μM for less active ones. The biological evaluation results showed that these compounds are weak acetylcholinesterase inhibitors.

In general, 7-substituted coumarins displayed better activities compared to 4-hydroxycoumarin derivatives. Among them, those derivatives bearing a methyl group at position 4 are more active than unsubstituted analogues (**4c**,**d** *vs* **4a**,**b**). The presence of the methyl group as a substituent in a linker, led to decreased inhibitory activities compared to an unsubstituted linker. The most potent compound was **4c** in which a 7-hydroxy-4-methylcoumarin moiety was substituted with an indole through an amide linkage.

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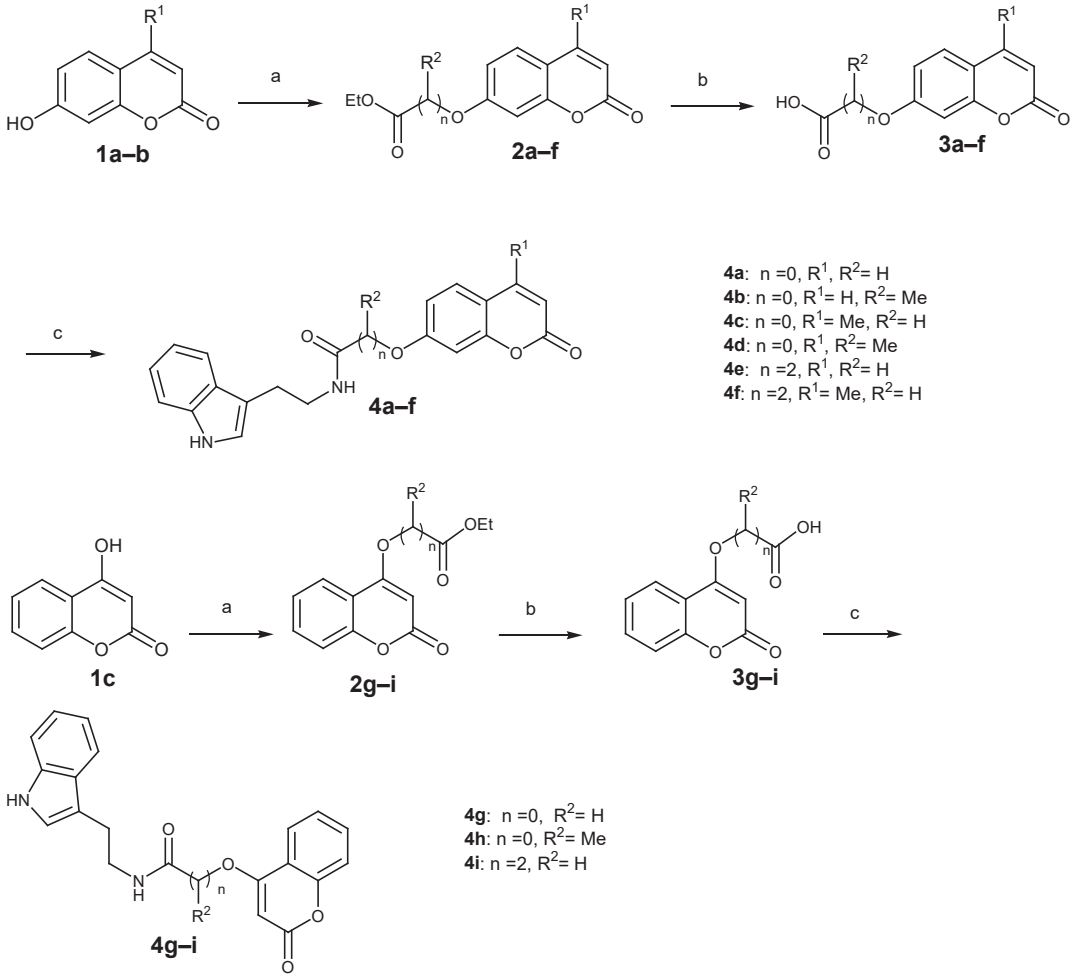

Fig. 1 Reagents and conditions: (a) $BrCH_2COOEt$ or $BrCH(CH_3)COOEt$ or $Br(CH_2)_3COOEt$, K_2CO_3, DMF, 90 °C, 5 h; (b) NaOH (5%), r.t., 12–24 h; (c) (i) $SOCl_2$, reflux, 5–6 h, (ii) K_2CO_3, tryptamine, dry toluene, reflux, 14–16 h.

Table 1 Inhibitory activities of compounds **4a–i** against AChE

Entry	Compound	AChE inhibition[a]
1	**4a**	74.6±5.2
2	**4b**	(11.1±1.3)
3	**4c**	27.3±2.7
4	**4d**	161.2±9.7
5	**4e**	(17.4±2.1)
6	**4f**	36.4±3.6
7	**4g**	(12.1±0.9)
8	**4h**	(5.7±0.6)
9	**4i**	(6.8±0.8)
10	Donepezil	0.035±0.002

[a]IC_{50} (μM) or inhibition of AChE (%) at 50 μM (in parentheses). The data are expressed as mean ± SD from three experiments.

Conclusion

In conclusion, we have reported a multi-step strategy for the synthesis of a coumarin linked to a tryptamine moiety and evaluated the acetylcholineasterase inhibitory activities of the target compounds. The obtained results showed poor activity of the synthesised compounds against AChE. This finding showed that these coumarin derivatives require further modification to achieve promising results.

Experimental

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectrum was recorded on Bruker FT-500, using TMS as an internal standard. The elemental analysis was performed with an Elementar Analysen system GmbH VarioEL CHNS mode. Mass spectra were determined on an Agilent Technology (HP) mass spectrometer operating at an ionisation potential of 70 eV. All reagents and solvents were purchased from Aldrich and Merck, and used without any purification.

Cholinesterase inhibition assay

Acetylcholinesterase (AChE, E.C. 3.1.1.7, Type VeS, lyophilised powder, from electric eel, 1000 unit) was provided from Sigma-Aldrich. 5,50-Dithiobis-(2-nitrobenzoic acid) (DTNB), potassium dihydrogen phosphate, dipotassium hydrogen phosphate, potassium hydroxide, sodium hydrogen carbonate, and acetylthiocholine iodide (ATCh) were purchased from Fluka. The stock solutions of the target compounds were prepared in a mixture of DMSO (1 mL) and ethanol (9 mL) and diluted with 0.1 MKH_2PO_4/K_2HPO_4 buffer (pH ¼ 8.0) to obtain final concentrations. 20 mL of substrate (acetylthiocholine iodide 0.075 M) was added to the test solution to obtain the final concentration of 466 mM. All experiments were performed based on the previously described method.[30] Spectrophotometric measurements were performed on a UV Unico Double Beam Spectrophotometer.

Synthesis of coumarin esters (**2a–i**)*; general procedure*

The appropriate hydroxycoumarin derivative (5 mmol) and potassium carbonate (5.5 mmol) were dissolved in DMF (5 mL). The solution was stirred at room temperature for 20 min and then ethyl bromoacetate, or ethyl 2-bromopropionate or ethyl 4-bromobutanoate (5.2 mmol) was added dropwise to the mixture. The solution was heated at 90 °C for 5 h. Upon completion, determined by thin layer chromatography, the mixture was cooled and diluted with ice. The resultant precipitate was filtered, washed and used without further purifications.

Synthesis of coumarin acids (**3a–i**)*; general procedure*

An aqueous solution of NaOH (25 mL, 5%) was added to ester derivatives (**2a–i**) and stirred at room temperature for 12–24 h. Upon completion, the mixture was neutralised by the addition of hydrochloric acid solution (5%). The resultant white precipitate was isolated by filtration, washed and dried.

Synthesis of coumarin amides (**4a–i**)*;general procedure*

Compounds (**3a–i**) (1 mmol) were added to thionyl chloride (5 mL) and the mixture was refluxed for 5–6 h. Upon completion, thionyl chloride was removed under reduced pressure to afford the corresponding coumarin-3-carbonyl chlorides. The crude product was dissolved in dry toluene (15 mL) followed by the addition of tryptamine (1 mmol) and potassium carbonate (2 mmol) into the solution and heated at reflux temperature under nitrogen atmosphere for 14–16 h. After this time, the solvent was removed under reduced pressure and the product was filtered and dried under vacuum.

N-*[2-(1*H-*Indol-3-yl)ethyl]-2-(2-oxo-2*H-*chromen-7-yloxy) acetamide* (**4a**): Pale brown solid; yield 91%; m.p. 180–184 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.89 (s, 1H), 8.33 (t, *J* = 7.8 Hz, 1H, CONH), 8.05 (d, *J* = 9.3 Hz, 1H), 7.71–7.68 (m, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.07–6.99 (m, 3H), 6.37 (d, *J* = 9.3 Hz, 1H), 4.66 (s, 2H, CH_2), 3.48 (t, *J* = 7.5 Hz, 2H, CH_2), 2.92 (t, *J* = 7.5 Hz, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 167.3, 161.2, 160.7, 155.6, 144.7, 136.7, 130.0, 127.6, 123.1, 121.4, 118.7 (2C), 113.4, 113.3, 113.1, 112.0, 111.9, 102.2, 67.7, 39.1, 25.6. Anal. calcd for $C_{21}H_{18}N_2O_4$ (362.38): C, 69.60; H, 5.01; N, 7.73; found: C, 69.46; H, 4.89; N, 7.43%.

N-*[2-(1*H-*Indol-3-yl)ethyl]-2-(2-oxo-2*H-*chromen-7-yloxy) propanamide* (**4b**): Pale brown solid; yield 86%; m.p. 120–122 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.31 (brs, 1H, CONH), 7.50 (d, *J* = 9.3 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.26–7.18 (m, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.65–6.58 (m, 2H), 6.41 (m, 1H), 6.18 (d, *J* = 9.3 Hz, 1H), 4.58 (q, *J* = 6.6 Hz, 1H), 3.65–3.59 (m, 2H), 2.91–2.85 (m, 2H), 1.48 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.9, 160.0, 158.7, 154.4, 142.2, 135.4, 128.0, 126.1, 121.2, 121.1, 118.4, 117.5, 112.8, 112.4, 111.2, 111.2, 110.3, 102.1, 74.3, 38.1, 24.0, 17.6. Anal. calcd for $C_{22}H_{20}N_2O_4$ (376.41): C, 70.20; H, 5.36; N, 7.44; found: C, 69.99; H, 5.06; N, 7.26%.

N-*[2-(1*H-*Indol-3-yl)ethyl]-2-(4-methyl-2-oxo-2*H-*chromen-7-yloxy) acetamide* (**4c**): Pale brown solid; yield 80%; m.p. 166–168 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (brs, 1H, CONH), 7.52 (d, *J* =7.8 Hz, 1H), 7.39 (d, *J* =8.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.98–6.95 (m, 1H), 6.69–6.65 (m, 1H), 6.63 (s, 1H), 6.58–6.47 (m, 1H), 6.11–6.10 (m, 1H), 4.43 (s, 2H), 3.65–3.63 (m, 2H), 2.96 (t, *J* = 6.6 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.0, 159.9, 158.7, 153.9, 151.3, 135.4, 126.2, 124.9, 121.3, 121.1, 118.5, 117.5, 113.7, 111.8, 111.5, 110.4, 110.3, 101.6, 66.5, 38.3, 29.9, 21.7. Anal. calcd for $C_{22}H_{20}N_2O_4$ (376.41): C, 70.20; H, 5.36; N, 7.44; found: C, 69.98; H, 5.09; N, 7.25%.

N-*[2-(1*H-*Indol-3-yl)ethyl]-2-(4-methyl-2-oxo-2*H-*chromen-7-yloxy) propanamide* (**4d**): Pale brown solid; yield 86%; m.p. 103–105 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.41 (brs, 1H, CONH), 7.43 (d, *J* = 7.8 Hz, 1H), 7.33–7.18 (m, 2H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 6.9 Hz, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.63–6.58 (m, 2H), 6.45 (t, *J* = 5.1 Hz, 1H), 6.06–6.04 (m, 1H), 4.58 (q, *J* = 6.6 Hz, 1H), 3.61–3.45 (m, 2H), 2.94–2.89 (m, 2H), 2.26 (s, 3H), 1.47 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 160.1, 158.6, 153.8, 151.5, 135.4, 126.1, 124.8, 121.2, 121.0, 118.3, 117.4, 113.5, 111.5, 111.1, 110.8, 110.3, 102.1, 66.8, 38.1, 29.2, 24.0, 17.6. Anal. calcd for $C_{23}H_{22}N_2O_4$ (390.43): C, 70.75; H, 5.68; N, 7.17; found: C, 70.57; H, 5.47; N, 6.97%.

N-*[2-(1*H-*Indol-3-yl)ethyl]-4-(2-oxo-2*H-*chromen-7-yloxy) butanamide* (**4e**): Pale brown solid; yield 84%; m.p. 120–123 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.25 (brs, 1H, CONH), 7.65–7.40 (m, 2H), 7.35–7.20 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 6.9 Hz, 1H), 6.93 (s, 1H), 6.80–6.50 (m, 2H), 6.15 (d, *J* = 9.3 Hz, 1H), 5.63 (brs, 1H, NH), 3.90–3.89 (m, 2H), 3.55–3.53 (m, 2H), 2.89 (t, *J* = 6.0 Hz, 2H), 2.35–2.15 (m, 2H), 2.10–1.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 161.0, 160.3, 154.7, 142.5, 135.4, 127.8, 126.3, 121.2, 121.0, 118.4, 117.6, 112.0, 111.8, 111.6, 111.5, 110.3, 100.5, 66.5, 38.7, 31.6, 28.7, 24.3. Anal. calcd for $C_{23}H_{22}N_2O_4$ (390.43): C, 70.75; H, 5.68; N, 7.17; found: C, 70.55; H, 5.44; N, 6.94%.

N-*[2-(1*H-*Indol-3-yl)ethyl]-4-(4-methyl-2-oxo-2*H-*chromen-7-yloxy) butanamide* (**4f**): Pale brown solid; yield 83%; m.p. 109–111 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.41 (s, 1H, CONH), 7.48 (d, *J* = 6.9 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 1.8 Hz, 1H), 6.68-6.70 (m, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.01 (d, *J* = 0.6 Hz, 1H), 5.76 (t, *J* = 5.4 Hz, 1H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.52 (t, *J* = 6.0 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H), 2.35–2.15 (m, 2H), 2.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 161.9, 161.5, 155.1, 152.8, 136.5, 127.3, 125.6, 122.2, 122.1, 119.4, 118.6, 113.6, 112.7, 112.4, 111.8, 111.4, 101.5, 67.5, 39.8, 32.7, 25.3, 24.9, 18.7. Anal. calcd for $C_{24}H_{24}N_2O_4$ (404.46): C, 71.27; H, 5.98; N, 6.93; found: C, 71.07; H, 5.77; N, 6.74% .

N-*[2-(1*H-*Indol-3-yl)ethyl]-2-(2-oxo-2*H-*chromen-4-yloxy) acetamide* (**4g**): Pale brown solid; yield 85%; m.p. 114–116 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.39 (brs, 1H, CONH), 7.80–6.60 (m, 9H), 6.48 (brs, 1H), 5.58 (s, 1H), 4.53 (s, 2H), 3.78–3.76 (m, 2H), 3.08 (t, *J* = 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.5, 163.9, 162.2, 153.2, 136.5, 132.8, 127.1, 124.1, 122.5, 122.4, 122.0, 119.6, 118.5, 116.9, 114.8, 112.1, 111.5, 91.7, 67.4, 39.2, 25.0. Anal. calcd for $C_{21}H_{18}N_2O_4$ (362.38): C, 69.60; H, 5.01; N, 7.73; found: C, 69.82; H, 5.38; N, 7.57.

N-*[2-(1*H-*Indol-2-yl)ethyl]-2-(2-oxo-2*H-*chromen-4-yloxy) propanamide* (**4h**): Pale brown solid; yield 81%; m.p. 159–161 ºC; IR (KBr) $\nu_{max/}$ cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (brs, 1H, CONH), 7.55–7.42 (m, 2H), 7.37 (d, *J* = 6.9 Hz, 1H), 7.28–7.16 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.13–6.08 (m, 1H), 5.49 (s, 1H), 4.66 (q, *J* = 6.6 Hz, 1H), 3.68–3.53 (m, 2H), 2.94–2.89 (m, 2H), 1.56 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.3, 163.7, 162.4, 153.3, 136.4, 132.7, 127.0, 124.1, 122.7, 122.4, 122.2, 119.5, 118.4, 116.8, 115.1, 112.0, 111.4, 91.9, 65.5, 39.3, 24.9, 18.3. Anal. calcd for $C_{22}H_{20}N_2O_4$ (376.41): C, 70.20; H, 5.36; N, 7.44; found: C, 70.08; H, 5.17; N, 7.23%.

N-*[2-(1*H-*Indol-3-yl)ethyl]-4-(2-oxo-2*H-*chromen-4-yloxy) butanamide* (**4i**): Pale brown solid; yield 87%; m.p. 252–254 ºC; IR (KBr) ν_{max}/cm^{-1}: 3550, 1715, 1690; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.28 (brs, 1H, CONH), 7.68 (d, *J* = 7.8 Hz, 2H), 7.55–7.40 (m, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.25–6.96 (m, 3H), 6.93 (s, 1H), 5.60 (brs, 1H), 5.51 (s, 1H), 4.05–3.90 (m, 2H), 3.65–3.40 (m, 2H), 2.90 (t, *J* = 6.0 Hz, 2H), 2.35–2.05 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 164.5, 162.1, 152.2, 135.4, 131.4, 126.3, 122.9 (2C), 122.0, 121.1, 118.4, 117.5, 115.7, 114.6, 111.7, 110.4, 89.4, 67.5, 38.8, 31.6, 28.7, 24.2. Anal. calcd for $C_{23}H_{22}N_2O_4$ (390.43): C, 70.75; H, 5.68; N, 7.17; found: C, 70.89; H, 5.87; N, 6.95%.

Acknowledgment

This work was supported and funded by Iran National Science Foundation (INSF).

Received 13 August 2016; accepted 15 January 2017
Paper 1604257 DOI: 10.3184/174751917X14859570937677
Published online: 10 February 2017

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