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Short Note

N-(2-(Benzylamino)ethyl)-4-(naphthalene-1-sulfonamido)benzamide

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Abstract: In this study, we report the synthesis of N-(2-(benzylamino)ethyl)-4-(naphthalene-1-sulfonamido)benzamide, designed on the basis of the structures of the PPARγ partial agonist SR2067 and of the commercial acetylcholinesterase inhibitor drug donepezil, aiming for a multi-target approach for the therapy of elderly diseases, such as diabetes and Alzheimer's disease. The compound was fully characterized by using ^{1}H and ^{13}C NMR, FT-IR and HRMS.

Keywords: N-(2-(benzylamino)ethyl)-4-(naphthalene-1-sulfonamido)benzamide; in vitro assays; Alzheimer's disease; diabetes

1. Introduction

The onset of Alzheimer's disease (AD) is often characterized by a comorbidity with other disorders common in the elderly, such as cardiovascular and metabolic diseases. For this reason, a joint drug therapy for the prevention and treatment of AD and type 2 diabetes (T2DM) could be successful [1].

Peroxisome proliferator-activated receptors (PPARs) are classical targets for the treatment of hyperglycaemia, obesity, hypertension and dyslipidaemia; moreover, recently, PPARγ modulators have been studied for the treatment of AD [1]. This work presents a new multi-target hybrid (**3**) containing a portion derived from the PPARγ partial agonist SR2067 [2] condensed with a portion mimicking donepezil, a drug currently used for the therapy of AD as inhibitor of cholinesterases (ChEs) [3].

SR2067 was chosen as starting compound because, differently from most PPARγ modulators, it lacks an acid group which often leads to unfavourable pharmacokinetic properties [2]. Moreover, the presence of a naphthalene-sulphonamide group and of a benzamide group allowed possible inhibitory activity against fatty acid amide hydrolase (FAAH), involved in the neuroinflammation typical of chronic elderly common diseases [1].

The central fragment included in the structure of **3**, derived from *p*-aminobenzoic acid, replaced indol-carboxylic acid of SR2067, giving the final hybrid higher flexibility. Moreover, *N*-benzyl-ethylenediamine was chosen as donepezil-like portion, to further reduce the structural rigidity.

2. Results and Discussion

Scheme 1 reports the synthesis of the final compound **3**. Commercially available α-naphthalene sulphonyl chloride was condensed with benzocaine [4]; then, the resulting ester **1** was hydrolysed in basic conditions giving the naphthalene-sulphonamide benzoic acid **2** [1]. The condensation between **2** and commercial *N*-benzyl-ethylenediamine in the presence of (2-(*1H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (TBTU) and *N*-ethyl-diisopropylamine (DIEA) as condensing agents afforded the final compound **3** [5]. None of the steps required the use of column chromatography, resulting in cost and time savings.

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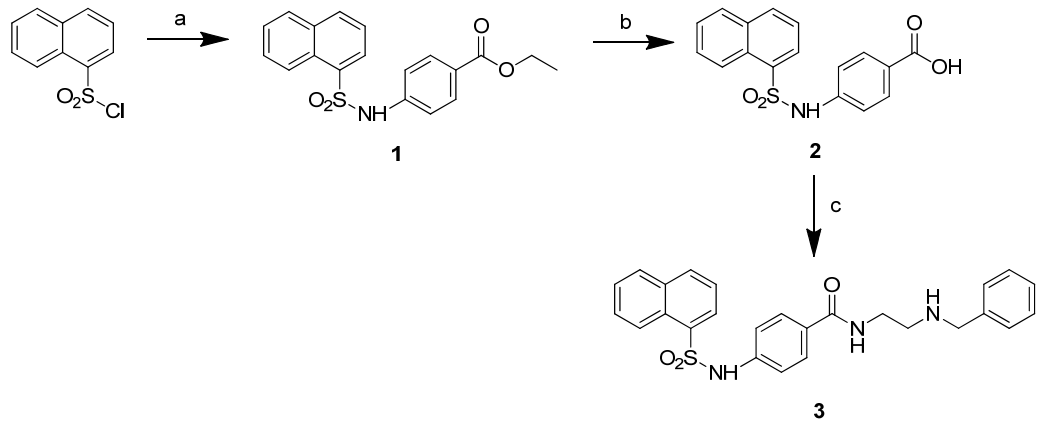

Scheme 1. Synthesis of compound **3**. (a) Benzocaine, pyridine, anhydrous CH_2Cl_2, N_2, RT, 24 h; (b) 0.25 N NaOH, THF, reflux, overnight; (c) *N*-benzyl-ethylenediamine, TBTU, DIEA, anhydrous DMF, N_2, 0 °C, 30 min RT, 3 h.

Compound **3** was tested as an inhibitor of enzymes ChEs and FAAH, using donepezil and JZL195 as reference compounds [1,3]. The hybrid resulted a moderate hAChE inhibitor (inhibition % ± SEM at 10 μM was 48 ± 2%) and PPARγ antagonist (IC_{50} ± SEM was 18.6 ± 2.6 μM) [1].

3. Material and Methods

All reagents were purchased from common suppliers and used without further purification. Reactions were monitored via TLC. High-resolution mass spectrometry (HRMS) was performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI). Mass spectra were recorded on an HP MS 6890-5973 MDS spectrometer, electron impact 70 eV, equipped with an HP ChemStation (Santa Clara, CA, USA). ^{1}H-NMR and ^{13}C-NMR spectra were recorded using the suitable deuterated solvent on a Varian Mercury 300 or 500 NMR Spectrometer (Palo Alto, CA, USA). FT-IR was recorded by using the sample as it was through Jasco FT/IR-4200 instrument (Cremella, LC, Italy). The uncorrected melting point was determined in open capillaries on a Gallenkamp electrothermal apparatus (Cambridge, UK). The purity of the compounds, on the basis of analyses performed (Figures S1–S4), was estimated as >95%.

*3.1. Preparation of Ethyl 4-(naphthalene-1-sulfonamido)benzoate (**1**)*

Benzocaine (3.03 mmol, 1 eq) was dissolved in an equal volume of anhydrous dichloromethane and pyridine (total 14 mL). Then, α-naphtalensulfonyl chloride (3.64 mmol, 1.2 eq), dissolved in anhydrous dichloromethane and pyridine (total 12 mL), was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 24 h at inert atmosphere. Then, it was washed with 2 N HCl (three times) and brine (twice) and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was treated with *n*-hexane and filtered, obtaining the title compound as a white solid. Yield 50%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 1.19 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 4.16 (q, *J* = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 7.07–7.14 (m, 2H aromatics), 7.56–7.77 (m, 5H aromatics), 7.98–8.07 (m, 1H aromatic), 8.14–8.29 (m, 2H aromatics) and 8.63–8.73 (m, 1H aromatic). GC-MS *m*/*z* (%): 355 $[M]^+$ (10), 127 (100).

*3.2. Preparation of 4-(naphthalene-1-sulfonamido)benzoic Acid (**2**)*

An amount of 0.25 N NaOH (3.75 mmol, 5 eq) was added to a solution of **1** (0.75 mmol, 1 eq) dissolved in THF (15 mL). The reaction mixture was refluxed overnight. Then, the organic solvent was removed in vacuo, and the aqueous residue was washed with ethyl acetate and acidified with 3 N HCl. The resulting acid aqueous portion was extracted with ethyl acetate (three times). The organic portions were collected and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness, affording the title

compound as a pink solid, yield 94%. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 7.10–7.15 (m, 2H aromatics), 7.62–7.79 (m, 5H aromatics), 8.05–8.10 (m, 1H aromatic), 8.21–8.33 (m, 2H aromatics), 8.70–8.73 (m, 1H aromatic) and 11.23 (bs, 1H, COOH). ESI-MS *m*/*z*: (IP: negative) 326 $[M-1]^-$.

*3.3. Preparation of N-(2-(Benzylamino)ethyl)-4-(naphthalene-1-sulfonamido)benzamide (**3**)*

To a solution of **2** (0.61 mmol, 1 eq) in anhydrous DMF (4 mL) at 0 °C and under inert atmosphere, *N*,*N*-diisopropylethylamine (DIEA, 1.83 mmol, 3 eq) was added, and the mixture was stirred at 0 °C for 10 min. Then, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU, 0.92 mmol, 1.5 eq) and a further 5 mL of anhydrous DMF were added and the reaction was stirred for 20 min at 0 °C and for 2 h at room temperature. At the end, a solution of the appropriate amine (0.92 mmol, 1.5 eq) in anhydrous DMF (4 mL) was added dropwise. The reaction was stirred under inert atmosphere at room temperature for 3 h. Then, the solvent was removed in vacuo and the resultant residue was treated with dichloromethane and filtered off, to give the final compound as a white solid, yield 32%, m.p. = 199–202 °C dec. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.80 (t, *J* = 6.3 Hz, 2H, $CH_2\underline{CH_2}NH$), 3.45–3.55 (m, 2H, $CONH\underline{CH_2}CH_2$), 3.90 (s, 2H, $NH\underline{CH_2}Ph$), 7.02–7.07 (m, 2H aromatics), 7.21–7.38 (m, 5H aromatics), 7.48–7.52 (m, 1H aromatic), 7.58–7.80 (m, 5H aromatics), 8.02–8.05 (m, 1H aromatic), 8.16–8.26 (m, 2H aromatics), 8.31–8.34 (m, 1H, $CO\underline{NH}CH_2$) and 8.70–8.74 (m, 1H aromatic). ^{13}C-NMR (125.8 MHz, DMSO-d_6) δ (ppm): 37.00, 47.12, 51.08, 110.99, 117.78, 118.87, 123.70, 124.61, 124.86, 124.96, 127.46, 127.78, 127.95, 128.68, 128.91, 129.52, 129.83, 130.57, 134.17, 134.56, 134.96, 141.26, 143.33, 166.39. FT-IR (cm^{-1}): 929 (s), 979 (m), 1100 (m), 1130 (s), 1159 (s), 1237 (m), 1298 (m), 1333 (m), 1383 (m), 1402 (m), 1504 (m), 1546 (m), 1611 (m), 1637 (m), 2360 (w), 3046 (w), 3104 (w). HRMS ($C_{26}H_{25}N_3O_3S$-H^-): calculated 458.1544 found 458.1556.

Supplementary Materials: Figure S1: ^{1}H-NMR spectrum of compound **3**; Figure S2: ^{13}C-NMR spectrum of compound **3**; Figure S3: FT-IR spectrum of compound **3**; Figure S4: HR-MS of compound **3**.

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