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Synthesis, characterization and crystal structure of pentyl 2-(1*H*-indole-2-carboxamido)benzoate

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Pentyl 2-(1*H*-indole-2-carboxamido)benzoate (**5**) is obtained in good yield as stable crystals by reaction of pentyl 2-amino benzoate (**6**) with indole-2-carbonyl chloride acid (**7**) in the presence of pyridine. The crystal structure of **5** confirms the presence of intramolecular hydrogen bonding (N-H…O) which produces a six-membered ring, and the molecules are linked together by intermolecular hydrogen forces (N-H…O).

1. Introduction

Heterocyclic moieties are present in a wide variety of drugs, due to their remarkable medicinal properties. Various derivatives of indole-2-carboxamide were synthesized and shown to exhibit different biological activities; examples include compounds **1** (acting against *Mycobacterium tuberculosis* (Mtb)), **2** (an antihyperlipedimic agent), **3** (a PI3Kα/EGFR inhibitor) and **4** (an anticancer agent) (**Fig. 1**).[1-4] Amide bond formation utilizes either the reaction of carboxylic acid derivatives with amines in the presence of bases, such as triethylamine or pyridine. These reactions are called indirect amidation.[5] Alternatively, direct amidation utilizes reactions of free carboxylic acid with amines through thermal direct reaction or by using a metal-catalyst.[6] In continuation of our further search for new derivatives of heterocyclic moieties,[2-4,7] we report herein the synthesis and full characterization of compound **5** (**Fig. 1**).

2. Results and Discussion

Compound **5** was prepared by reacting **6** with **7** in dry chloroform and in the presence of dry pyridine which was employed as base and catalyst, as shown in **Scheme 1**. Fischer esterification of 2-aminobenzoic acid with 1-pentanol, in the presence of sulfuric acid, afforded compound **6**. It is worthy

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to mention that the reaction of isatoic anhydride with 1-pentanol produced **6**.[8] On the other hand, compound **7** was used rather than the indole-2-carboxylic acid itself, since it is more reactive towards nucleophilic acyl substitution reaction, in particular, if the nucleophile (such as aromatic amine) is weak. Pyridine was employed in this type of reaction to trap the evolved hydrogen chloride gas by forming pyridinium chloride salt, which also helps in the conversion of **7** into more reactive species (pyridium adduct) towards nucleophilic acyl substitution reaction. This approach of synthesis has many advantages such as good yield is usually obtained and milder experimental conditions can be used. In contrast to other methodologies that used ester derivatives instead of acyl halides as reactant, strong base (e. g. sodium alkoxide) in refluxing DMF for long time is usually preferred and the yield is even low. On the other hand, coupling agent should be employed when carboxylic acid itself is acting as a starting material to form the amide group.

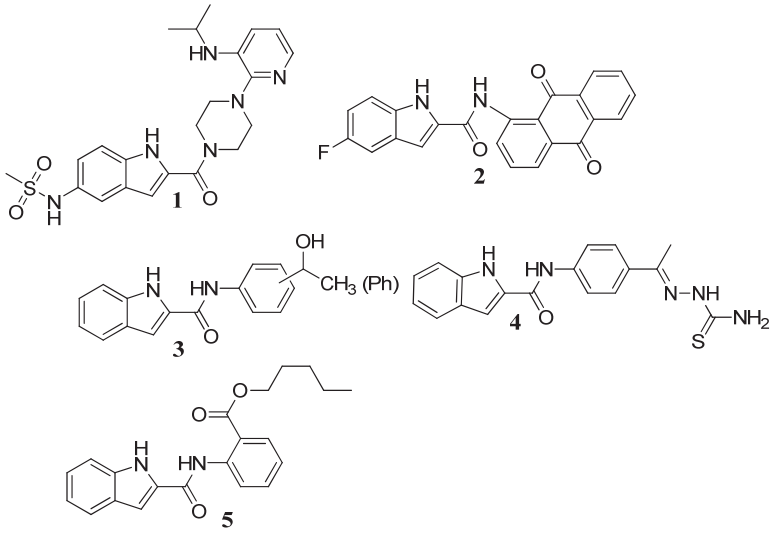
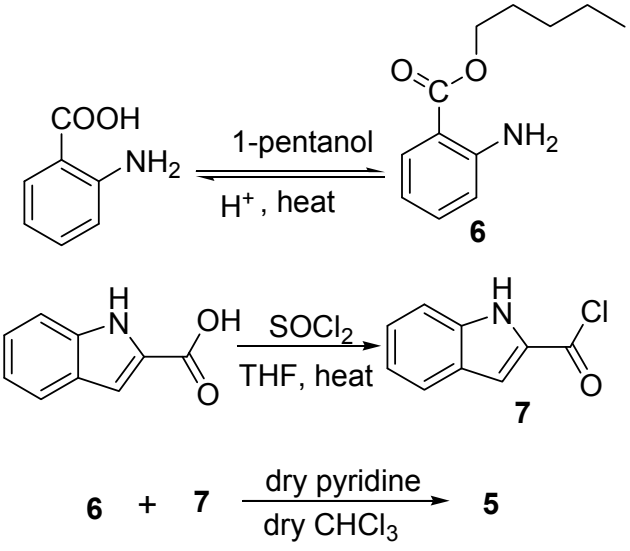


Fig. 1. Chemical structures of some indole-containing molecules



Scheme 1. Synthesis of the target product **5**

In ^{1}H NMR spectrum of **5**, signals of aliphatic protons have been observed in the range 0.8 - 5 ppm, while the signals of two protons in both N-H groups were highly deshielded (11-12 ppm) in deuterated DMSO solvent due to intra-hydrogen bonding with solvent molecules. On the other hand, the carbon atom of the amide group resonates, as expected, at 160.1 ppm in ^{13}C-NMR spectrum; other peaks are observed in the expected ranges. The results of DEPT experiments are in conformity with the proposed

structure, four methylene groups (CH_2) show down peaks at four different positions. Further, the mass spectrum of compound **5** displays the correct molecular ion peaks for which the measured HRMS data are in good agreement with the calculated values. Elemental analysis data assures the purity of the product.

2.1 Description of the Crystal Structure

Single X-ray crystallography measurements show that **5** crystallizes in the monoclinic system, with space group $P2_1/m$ and crystallographic data are listed in **Table 1**. The asymmetric unit of **5** (**Fig. 2**) contains one molecular unit. Crystal structure of **5** reveals the presence of intramolecular N-H…O bond [O(2)…H(2) 1.918, N(2)…H(2) 0.859 Å, N(2)-H(2)…O(2) 139.2°]. As expected, the bond length of C(10A)-O(1), in the amide group, is slightly longer than that of C(11A)-O(2), in the ester group, (1.220 compared to 1.204 Å); this is due to the resonance effect in the amide group.

Intramolecular hydrogen bonding forms six-membered ring, in which the amide NH group is considered as proton donor and the oxygen atom of the carbonyl of the ester group as proton acceptor. The indolic NH proton is involved in intermolecular hydrogen bonding to the oxygen atom (of the amide group) of an adjacent molecule leading to a polymeric chain structure (**Fig. 3**) [O(1)…H(1) 2.060, N(1)…H(1) 0.860 Å, N(1)-H(1)…O(1) 161.5°]. The molecule is almost planar and the dihedral angle is 1.98 °.

Table 1. Crystal data and structure refinement parameters for **5**

Crystal system	Monoclinic
Empirical formula	$C_{21}H_{22}N_2O_3$
Formula weight (g mol^{-1})	350.42
Temperature/K	293(2)
Space group	$P2_1/c$
a/Å	9.9711(8)
b/Å	7.8134(9)
c/Å	23.645(2)
β/°	99.208(7)
V/$Å^3$	1818.4(3)
Z	4
Density g/cm^3	1.2799
MoKα /mm^{-1}	0.086
F(000)	744.4
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.82 to 58.54
Index ranges	$–12 \leq h \leq 13$, $–9 \leq k \leq 10$, $–31 \leq l \leq 18$
Reflections collected	8789
Independent reflections	4210 [R_{int} = 0.0329, R_{sigma} = 0.0518]
Data/restraints/parameters	4210/0/236
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0945, wR_2 = 0.2290
Final R indexes [all data]	R_1 = 0.1344, wR_2 = 0.2507
Largest diff. peak/hole / e $Å^{-3}$	0.47/–0.45

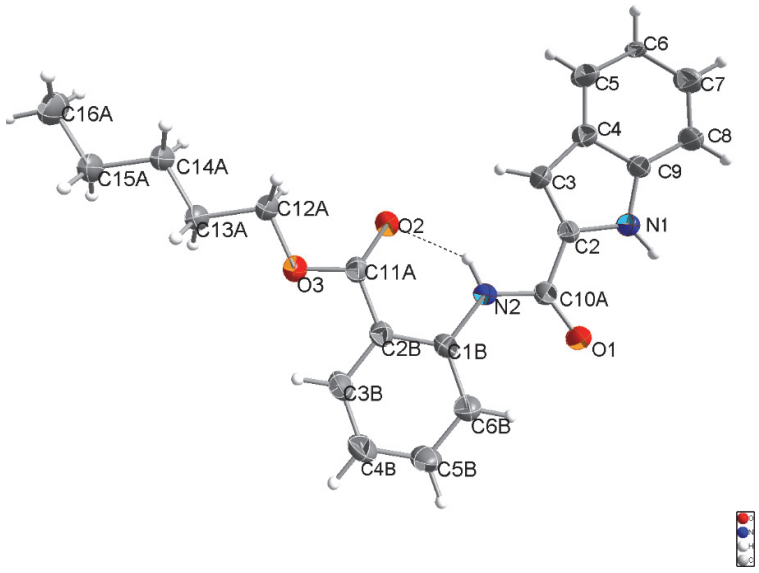


Fig. 2. Thermal ellipsoid drawing (35% probability level) of the asymmetric unit of **5**.

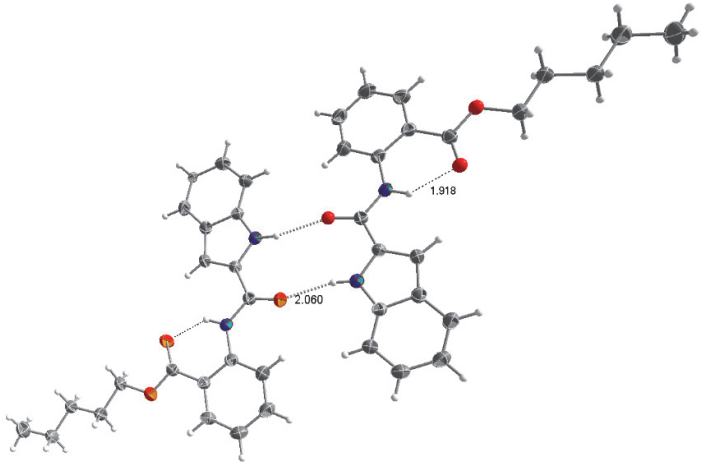


Fig. 3. View of the dimers of **5** in the crystal

3. Conclusions

The target compound **5** has been successfully prepared in reaction which follows the mechanism of nucleophilic acyl substitution of acyl chloride (**7**) and aromatic primary amine (**6**). Hydrogen-bond donor (N-H) and hydrogen-bond acceptor (C=O) functional groups were incorporated into its structure. The structure of the target product was fully characterized. Further, X-ray structural analyses of **5** shows that there are intra and inter hydrogen bonding forces.

Acknowledgments

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4. Experimental

The following chemicals were purchased and used without further purification: indole-2-carboxylic acid (Aldrich, 98%), 2-aminobenzoic acid (Aldrich, 98%), oxalyl chloride (Aldrich, 98%), N,N-dimethylformamide (DMF) (HPLC grade Tedia), pyridine (Tedia), ethyl acetate (AZ chem), 1-pentanol

(HPLC grade Acros). Compound **7** was prepared according to the published procedure.[3] Chloroform (Labchem) was purified by stirring under anhydrous sodium sulfate overnight then distilled.

NMR analysis was done using Bruker-Avance III 500 MHz spectrometers with TMS as the internal standard. Coupling constant (*J*) values are given in Hertz (Hz). High resolution mass spectra (HRMS) were measured (in positive ion mode) using electrospray ion trap (ESI) technique by collision-induced dissociation on a BrukerAPEX-4 (7 Tesla) instrument. The FT-IR measurements (500-4000 cm^{-1}) were recorded using ThermoNicolet 670 FT-IR spectrophotometer. Thin Layer Chromatography (TLC) was performed using Merck aluminum plates pre-coated with silica gel PF254; (20 x 20) cm x 0.25 mm, and detected by visualization of the plate under UV lamp (ƛ = 254 nm). Melting point was measured with an SMP 10 Stuart apparatus. Elemental analysis was obtained using Euro Vector Elemental analyzer model EUROEA3000 A, (Redavalle), Italy. Single-crystal X-ray diffraction data were collected using an Oxford Diffraction XCalibur, equipped with (Mo) X-ray Source (λ = 0.71073 Å) at 293(2) K.

Pentyl 2-aminobenzoate (6). To a mixture of 2-aminobenzoic acid (0.5 g, 3.6 mmol) and 1-pentanol (6.5 mL, 60 mmol), sulfuric acid (0.8 mL, 14.7 mmol) was added dropwise at 0 °C; the resulting solution was stirred for 30 minutes at room temperature, then refluxed for 24 h. After cooling, the resulting solution was neutralized with 1 M $NaHCO_3$ (30 mL), and then the organic layer was extracted with ethyl acetate (20 mL). The organic solvent was evaporated under reduced pressure to get the desired product. Yield: 0.54 g (73%). ^{1}H NMR spectrum ($CDCl_3$), *δ,* ppm: 0.86 (t, *J* = 7.2, Hz, 3H, CH_3), 1.30-1.38 (m, 4 H, $2CH_2$), 1.73 (m, 2H, CH_2), 4.34 (t, *J* = 6.5 Hz, 2H, CH_2), 5.01 (s, 2H, NH_2), 6.34 (d, *J* = 7.9 Hz, 1H, H6), 6.91 (m, 1H, H4); 7.04 (m, 1H, H5), 7.91 (d, *J* = 8.3 Hz, 1H, H3). ^{13}C NMR spectrum ($CDCl_3$), *δ*C, ppm: 14.0 (CH_3), 21.9 (CH_2), 27.8 (CH_2), 27.9 (CH_2), 65.6 (CH_2), 127.5 (C2), 131.2 (C3), 124.7 (C4), 134.9 (C5), 120.7 (C6), 140.7 (C1), 168.1 (C=O ester). Found, %: C 69.69; H 8.41; N 6.45. $C_{12}H_{17}NO_2$. Calculated, %: C 69.54; H 8.27; N 6.76. *M* 207.

Pentyl 2-(1H-indole-2-carboxamido)benzoate (5). An exact amount of **6** (2.0 g, 9.7 mmol) in $CHCl_3$ (10 mL) was added dropwise to a solution of **7** (0.9 g, 5.0 mmol) in $CHCl_3$ (20 mL) and pyridine (5 mL) at -5 °C. The resulting solution was stirred overnight to afford the desired product as white precipitate which was filtrated off and dried under vacuum. Yield: 1.1 g (63 %), mp 183-184°C, hexane: ethyl acetate (8:2) R_f 0.75. ^{1}H NMR spectrum (DMSO-*d*$_6$), *δ*, ppm: 0.84 (t, *J* = 7.2, Hz, 3H, CH_3), 1.28-1.38 (m, 4 H, CH_2), 1.76 (m, 2H, CH_2), 4.39 (t, *J* = 6.5, 6.50 Hz, 2H, CH_2), 7.12 (t, *J* = 7.4, 7.3 Hz, 1H, H6), 7.27-7.24 (m, 2H, H7, H4`), 7.19 (s, 1H, H3), 7.41 (d, *J* = 8.2 Hz, 1H, H5), 7.68-7.77 (m, 2H, H8, H5`), 8.09 (d, *J* = 7.9 Hz, 1H, H3`), 8.49 (d, *J* = 8.3 Hz, 1H, H6`), 11.67 (s, 1H, NH-amide), 11.92 (s, 1H, N1).^{13}C NMR spectrum (DMSO-*d*$_6$), *δ*C, ppm: 14.0 (C16A), 21.9 (C15A), 27.8 (C14A), 27.9 (C13A), 65.6 (C12A), 103.5 (C8), 117.2 (C3), 127.5 (C2B), 131.2 (C3B), 124.7 (C4B), 134.9 (C5B), 120.7 (C6B), 140.7 (C1B), 121.0 (C6), 122.4 (C5), 122.4 (C7), 131.8 (C4), 137.7 (C9), 137.7 (C2), 159.8 (C10A), 168.2 (C11A). IR spectrum, *ν*, cm^{-1}: 3284 (N-H amide), 3284 (N-H indole), 1681 (C=O). HRMS ((-)-ESI): *m/z* = 349.15577 (calcd. 349.15537 for $C_{20}H_{21}N_2O_3$, [M-H]). Found, %: C 71.71; H 6.42; N 7.65. $C_{20}H_{22}N_2O_3$. Calculated, %: C 71.98; H 6.33; N 7.99. *M* 350.

Crystallographic Data

Crystals of **5** were obtained by slow evaporation of a CH_2Cl_2 solution of **5**. Data collection, reduction, and cell refinement were performed using the software package CrysAlisPro.[9] Analytical absorption corrections were applied using spherical harmonics implemented in SCALE3 (ABSPACK) scaling algorithm. Crystal structure was solved by direct methods, using the program OLEX2, followed by Fourier synthesis, and refined on F^2 with SHELXL-97.[10] Anisotropic least-squares refinement of non-H atoms was applied. All crystallographic plots were obtained using the Diamond program.[11] A summary of the crystallographic data and structure refinement parameters is given in **Table 1**.

Data Availability

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository number CCDC-1867234 (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http:// www.ccdc.cam.ac.uk).

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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