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Synthesis of sulfonylurea derivatives and their α-glucosidase inhibitory activity

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Abstract:

The paper describes the preparation of new sulfonylurea derivatives from sulfonyl carbamate 6 with amino derivatives. The process for synthesis of the key compound 6 included three steps starting from compound 6-chloronicotinic acid 1, which are readily available chemicals. The compound 1 in the presence of triethylamine in anhydrous acetone solvent and ethyl chloroformate to obtain 6-chloronicotinic (ethyl carbonic) anhydride compound 3. The compound 3 were subsequently reacted with compound 4 to obtain compounds 5. The sulfonamides 5 was refluxed with ethyl chloroformate in present anhydrous potassium carbonate in dry acetone to obtain the key compounds 6. The total yield of the key intermediate compound 6 is about 81.35%, related to the starting materials. Finally, three sulfonylurea derivatives 7a-c were synthesized by condensation of 6 with various of amines in toluene. Their structures have been determined by IR, MS and ^{1}H and ^{13}C NMR spectroscopic methods, and their α-glucosidase inhibitory activity have been evaluated.

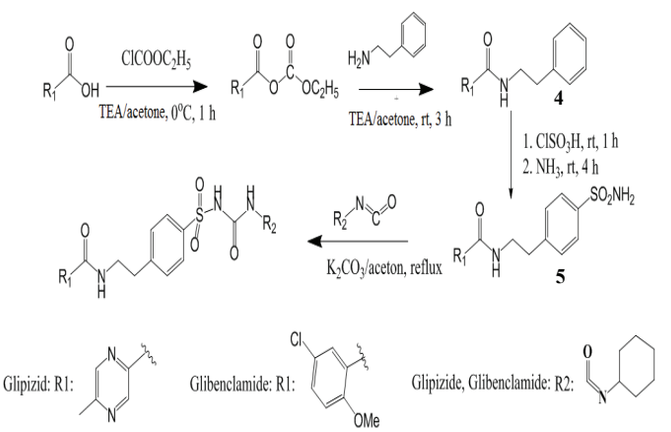
Keywords: **6-chloronicotinic acid, sulfonyl carbamate, sulfonylurea derivatives.**

Classification number: **2.2**

Introduction

Sulfonylurea derivatives are oral hypoglycemic agents used for the treatment of type II diabeties for almost eight decades [1]. These drugs act by releasing insulin from the β cells of the pancreas [2]. Along with antidiabetic activity, large numbers of sulfonylurea derivatives also exhibit a wide range of biological activity [3] such as diuretic, histamine H3 receptor antagonist, antimalarial, anticancer, and anti-inflammatory activity.

The common synthesis method of sulfonylurea derivatives is the treatment of sulfonamide with an appropriate isocyanate in the presence of a base [4]. Scheme 1 describes the synthetic route of Glipizide, Glibenclamide. The various substituted carboxylic acids were treated with 2-phenethylamine in presence of ethyl chloroformate and triethylamine in anhydrous acetone to provide the corresponding amide. The corresponding sulfonamide derivatives were prepared by reaction of 4 (see Scheme 1) with chlorosulfonation and trapped by ammoniac solution, followed by reaction with isocyanates to obtain the desired product [5].



Scheme 1. The synthetic route of Glipizide, Glibenclamide.

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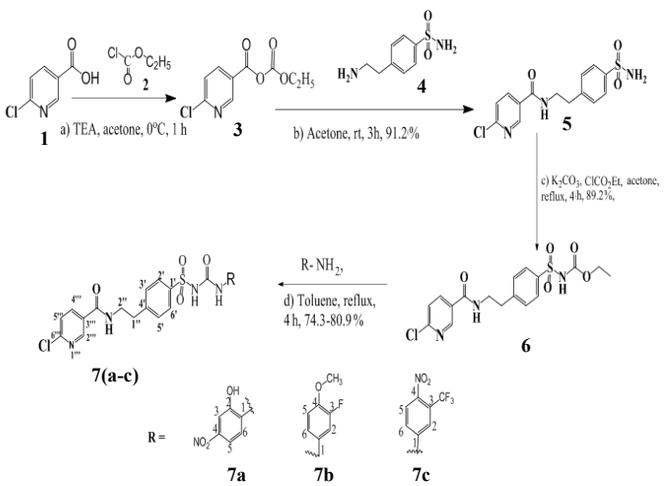
In the present paper, we report the synthesis details of new sulfonylurea derivatives. As depicted in Scheme 2 [6], compound 6-chloronicotinic acid **1** was treated with TEA and ethyl chloroformate in anhydrous acetone followed by an addition of commercially available 4-(2-aminoethyl) benzenesulfoamide to provide the product **5** (91.2%). The sulfonamide **5** was subsequently refluxed with ethyl chloroformate in the presence of anhydrous potassium carbonate to yield intermediate compound **6** (89.2%). Next, sulfonylurea derivatives **7a-c** were synthesized by the condensation of **6** with various of amines in toluene (Scheme 2). The overall yield of each compound was above 62%. The structures of the synthesized compounds were assigned on the analysis of mass spectrometry (MS) and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) data. All synthesized compounds were evaluated for α-glucosidase inhibitor activity.



Scheme 2. Synthesis 7(a-c) novel sunlfonylureas compounds.

Experimental

Materials and methods

Reagents were purchased from Aldrich and Merck with analytical grade and used without further purification. Solvents for column chromatography were distilled before use. Melting points (°C) were determined on a Thermo Mel-temp 3.0 (USA). IR spectra were recorded on an IMPACT 410 Nicolet spectrometer. Electrospray ionization mass spectrometry (ESI-MS) spectra were measured on an 1100 Agilent LC/MS ion trap. NMR spectra (^{1}H, ^{13}C) were recorded on a Bruker Avance 500 MHz with tetramethylsilane (TMS) as the internal standard for ^{1}H and solvent signal for ^{13}C. Thin-layer chromatography was performed on a pre-coated silica gel 60 F254 (Merck) and visualized under UV light (λ_{max} 254 nm) and stained with a solution of 1% (v/v) vanillin in H_2SO_4. Column chromatography was performed on silica gel 300-400 mesh (Merck).

Procedure for the preparation of 6-Chloro-N-(4-sulfamoylphenethyl)nicotinamide (5)

To a stirred solution of 6-chloronicotinic acid (0.01 mol) in anhydrous acetone (50 ml) and triethylamine (1.42 ml, 0.01 mol) at 0°C, ethyl chloroformate (0.97 ml, 0.01 mol) was added dropwise and the reaction was further stirred for 60 min. After 15 min, a solution of 4-(2-aminoethyl)-benzenesulfonamide (2.0 g, 0.01 mol) and triethylamine (1.42 ml, 0.01 mol) in anhydrous acetone was added. The resulting mixture was stirred for 3 h at room temperature. Acetone was then removed, and the residue was acidified with 5% HCl to pH≈5. The white solid was collected and washed with distilled water. Pure product was obtained by recrystallization from ethanol.

Yield: 91.20% - white powder, m.p. 236-238°C. -IR (KBr): ν=3378 (NH), 1637 (CO-amid), 1587 (C=C-aromatic), 1320 and 1158 (O=S=O) cm^{-1}. - ^{1}H NMR (500 MHz, DMSO-d_6, 25°C, TMS): δ=8.84 (1H, br s, CONH), 8.78 (1H, s, H-2'''), 8.19 (1H, d, *J*=8.0 Hz, H-4'''), 7.75 (2H, d, *J*=8.0 Hz, H-2', H-6'), 7.64 (1H, d, *J*=8.0 Hz, H-5'''), 7.43 (2H, d, *J*=8 Hz, H-3', H-5'), 7.28 (2H, s, SO_2NH_2), 3.54 (2H, q, *J*=7.0 Hz, H-2''), 2.93 (2H, t, *J*=7.0 Hz, H-1''). - ^{13}C NMR (125 MHz, DMSO-d_6, 25°C, TMS): δ=164.42 (CONH), 152.47, 148.98, 143.9, 142.21, 138.78, 129.59, 129.49 (2C), 126.05 (2C), 124.48, 40.84, 34.89.

Procedure for the preparation of Ethyl-((4-(2-(6-chloronicotinamido)ethyl)phenyl) sulfonyl) carbamate (6)

6-Chloro-N-(4-sulfamoylphenethyl)nicotinamide **5** (0.01 mol) were mixed with a solution of ethyl chloroformate (1.23 ml, 0.013 mol) and anhydrous potassium carbonate (2.0 g, 0.014 mmol) in dry acetone (300 ml). The reaction was refluxed for 4h and acetone was removed under reduced pressure. The residue was suspended in 100 ml water and neutralized with 1% HCl. The white solid was filtered and washed with distilled water to obtain the desired product.

Yield: 89.20% - white powder, m.p. 159-160°C. - ^{1}H NMR (500 MHz, DMSO-d_6, 25°C, TMS): δ=11.90 (1H, s, SO_2NH), 8.83 (1H, t, *J*=5.5 Hz, CONH), 8.76 (1H, d, *J*=2.0 Hz, H-2'''), 8.18 (1H, dd, *J*=2.0, 8.5 Hz, H-4'''), 7.82 (2H, d, *J*=8.0 Hz, H-2', H-6'), 7.63 (1H, d, *J*=8.0 Hz, H-5'''), 7.50 (2H, d, *J*=8.0 Hz, H-3', H-5'), 4.00 (2H, q, *J*=7.0 Hz, CH_2-carbamate), 3.55 (2H, q, *J*=7.0 Hz, H-2''), 2.96 (2H, t, *J*=7.0 Hz, H-1''), 1.08 (3H, t, *J*=7.0 Hz, CH_3). - ^{13}C NMR (125 MHz, DMSO-d_6, 25°C, TMS): δ=163.69 (CONH), 152.46 (CONH), 151.02, 148.79, 145.79, 143.51, 138.45, 137.13, 129.13 (2C), 125.69 (2C), 124.1, 56.00 (CH_2 carbamate), 40.45, 34.64, 18.51 (CH_3).

General procedure for the preparation of sulfonylurea derivatives (7a-c)

Ethyl-((4-(2-(6-chloronicotinamido)ethyl)phenyl) sulfonyl) carbamate (6) (0.01 mol) and appropriate amines (0.011 mol) in toluene was refluxed for 4 h and then allowed cool to room temperature. The solid was filtered, washed with water and recrystallized in ethanol.

6-Chloro-N-(4-(N-((2-hydroxy-4-nitrophenyl) carbamoyl)sulfamoyl)phenethyl)nico - tinamide (7a): yield 74.90% - white powder, m.p. 170-172°C**.** - MS ((-)-ESI): *m/z* (%)=520 (100). $[M-H]^-$. - IR (KBr): ν=3399 (OH), 3342 (NH), 1655 (C=O, amide), 1538 (C=C-aromatic), 1153 (C-N), 1425 and 1268 (NO_2) 1327 and 1185 (O=S=O) cm^{-1}. - ^1H NMR (500 MHz, DMSO-d_6, 25°C, TMS): δ=8.84 (1H, t, *J*=5.5 Hz, CONH), 8.78 (1H, d, *J*=2.0 Hz, H-2'''), 8.25 (1H, s, CONH), 8.18 (1H, dd, *J*=2.5, 7.5 Hz, H-4'''), 7.75-7.71 (3H, m, H-6, H-2', H-6'), 7.60 (1H, d, *J*=8.0 Hz, H-5'''), 7.59 (1H, dd, *J*=2.5, 9.0 Hz, H-5), 7.49 (1H, d, *J*=2.5 Hz, H-3), 7.27 (1H, d, *J*=8.0 Hz, H-3', H-5'), 3.52 (2H, q, *J*=6.5 Hz, H-2''), 2.88 (2H, t, *J*=7.5 Hz, H-1''). - ^{13}C NMR (125 MHz, DMSO-d_6, 25°C, TMS): δ=163.7 (CONH), 152.39 (CONH), 148.81 (2C), 143.92, 141.32, 138.44 (2C), 137.25, 129.4, 127.98 (2C), 126.75 (2C), 124.05 (2C), 117.15, 115.55, 110.13, 40.63, 34.62.

6-Chloro-N-(4-(N-((4-nitro-3-(trifluoromethyl)phenyl) carbamoyl)sulfamoyl)phene - thyl)-nicotinamide 7b): yield 74.30% - white powder, m.p 221-222°C. - MS ((-)-ESI): *m/z* (%) = 570 (20). $[M-H]^-$. - IR (KBr): ν=3421 (NH), 1635 (C=O, amide), 1569 (C=C-aromatic), 1141 (C-N), 1458 (NO_2), 1348 and 1153 (O=S=O) cm^{-1}. - ^1H NMR (500 MHz, DMSO-d_6, 25°C, TMS): δ=9.73 (1H, br s, SO_2NH), 8.81 (1H, br s, CONH), 8.75 (1H, br s, H-2'''), 8.16 (1H, d, *J*=6.5 Hz, H-4'''), 8.12 (1H, d, *J*=8.5 Hz, H-5), Hz, 8.01 (1H, br s, H-2), 7.91 (2H, d, *J*=7.0 Hz, H-2', H-6'), 7.81 (1H, d, *J*=7.5 Hz, H-6), 7.60 (1H, d, *J*=8.0 Hz, H -5'''), 7.51 (2H, d, *J*=7.0 Hz, H-3', H-5'), 3.55 (2H, d, *J*=5.5 Hz, H-2''), 2.96 (2H, s, H-1''). - ^{13}C NMR (125 MHz, DMSO-d_6, 25°C, TMS): δ=163.67 (CONH), 154.29, 152.43 (CONH), 148.76, 143.48, 142.09, 138.42, 133.74, 129.58, 129.33, 129.09 (2C), 127.51, 125.66 (2C), 124.15, 124.06, 123.54, 114.43, 111.67 (CF_3), 40.42, 34.54.

2-(2-(6-Chloronicotinamido)ethyl)-5-(N-((3-fluoro-4-methoxyphenyl)carbamoyl)-sulfamoyl)-benzene-1-ylium (7c): yield 80.90% - white powder, m.p 209-211°C. - MS ((-)-ESI): *m/z* (%) = 505 (100). $[M-H]^-$. - IR (KBr): ν=3409 (NH), 1673 (C=O, amide), 1539 (C=C-aromatic), 1246 (C-O), 1355 and 1170 (O=S=O) cm^{-1}. - ^1H NMR (500 MHz, DMSO-d_6, 25°C, TMS): δ=8.82-8.77 (3H, m, CONH, H-5''', H-2'''), 8.17 (1H, dd, *J*=2.5, 8.5 Hz, H-4'''), 7.88 (2H, d, *J*=8.5 Hz, H-2', H-6'), 7.59 (1H, d, *J*=8.5 Hz, H-5), 7.49 (2H, d, *J*=8.5 Hz, H-3', H-5'), 7.27 (1H, dd, *J*=2.0, 14.0 Hz, H-6), 7.07-7,01 (2H, m, H-2, CONH), 3.77 (3H, s, OCH_3), 3.57-3.53 (2H, m, H-2''), 2.95 (2H, t, *J*=7.5 Hz, H-1''). - ^{13}C NMR (125 MHz, DMSO-d_6, 25°C, TMS): δ=163.75 (CONH), 163.71 (CONH), 152.43, 148.77, 145.13, 143.50, 142.09, 138.45, 129.39 (2C), 129.12, 127.46 (2C), 125.68, 124.10, 124.05, 116.14, 115.15, 114.15, 56.18 (OCH_3), 40.00, 34.65.

Resutls and discussion

Chemistry

The synthetic routes of three new *sulfonylurea derivatives* compounds are shown in Schemes 2. 6-Chloronicotinic acid was treated with ethyl chloroformate in the presence of triethylamine in anhydrous acetone solvent and to furnish 6-Chloronicotinic (ethyl carbonic) anhydride compound **3** [7]. Compound **3** was subsequently reacted with 4-(2-aminoethyl) benzenesulfonamide **4** to obtain compounds 6-chloro-N-(4-sulfamoylphenethyl) nicotinamide **5**. Refluxing of sulfonamide **5** with ethyl chloroformate in present anhydrous potassium carbonate in dry acetone obtain compound **6**. Finally, sulfonylurea derivatives **7 (a-c)** were synthesized by a reaction of **6** with various amines in toluene. The use of toluene as a solvent gives the highest product yield when compared to other solvents such as dioxane or DMF. The structures of the products were confirmed by means of ^1H and ^{13}C NMR. The ^1H NMR spectrum of compound **5** indicated the presence of three aromatic protons of the pyridine ring at δ_H 8.78 (1H, s, H-2'''), 8.19 (1H, d, *J*=8.0 Hz, H-4'''), 7.64 (1H, d, *J*=8.0 Hz, H-5'''). The appearance of the NH protons at δ_H 8.84 (1H, br s), 7.28 (2H, s, SO_2NH_2) in the ^1H NMR spectrum of compound **5** confirmed the formation of amide products. Furthermore, the ^1H NMR spectrum showed signals for benzene protons at δ_H 7.75 (2H, d, *J*=8.0 Hz, H-2', H-6'), 7.43 (2H, d, *J*=8 Hz, H-3', H-5') and the methylene protons at δ_H 3.54 (2H, q, *J*=7.0 Hz, H-2''), 2.93 (2H, t, *J*=7.0 Hz, H-1'') ppm. The ^{13}C NMR spectra of 5 was in good agreement with the structure assigned. The ^{13}C NMR spectra exhibited signals at δ_C 164,42 assignable to the amide moiety (CONH). The key intermediate **6** was characterized by ^1H NMR spectra which exhibited additional signals at δ_H 4.00 (2H, q, *J*=7.0 Hz, CH_2-carbamate) and δ_H 1.08 (3H, t, *J*=7.0 Hz, CH_3), corresponding to the ethyl ester group. The ^{13}C NMR spectra exhibited additional signals at δ_C 152.46 (CONH), δ_C 56.00 (CH_2 carbamate), and δ_C 18.51 (CH_3) assignable to the carbamate moiety ($NHCOOCH_2CH_3$). The ^1H NMR spectra of the sulfonylurea derivatives **(7a-c)** indicated the presence of two broad singlets appearing at δ_H 8.25 **(7a)**, δ_H 8.81 **(7b)**, δ_H 8.82 **(7c)**, for the NH proton of the urea moiety. Moreover, the disappearance of the ethyl ester protons and the presence of aromatic protons at δ_H 7.01-8.12 clearly confirmed the formation of urea derivatives. The ^{13}C NMR spectra of urea derivatives showed a frequency signal range observed at 152.39, 152.43, and 163.71 ppm assignable to the carbonyl carbon between the two NH groups of the urea

of compounds **7a**, **7b**, and **7c**, respectively.

α-glucosidase inhibitory activity

Three compounds were evaluated for their ability to inhibit α-glucosidase**.** Acarbose was used as standard compound and glipizide was also tested to compare with the synthesized derivatives. Compound **7c** showed moderate activity with an IC_{50} value of 329.62 µM, similar to glipizide, while compounds **7a-b** have no α-glucosidase inhibitor activity (Table 1).

Table 1. The α-glucosidase inhibitor activity of compounds 7(a-c).

Compounds	α-glucosidase inhibitory activity IC_{50} (µM)
Acarbose control	268.29
Glipizide	300.47
7a	>492.39
7b	>447.62
7c	329.62

Conclusions

We have successfully synthesized **t**hree new sulfonylurea derivatives. The structures of products were confirmed by means of ^{1}H and ^{13}C NMR. ^{1}H NMR spectrum. Newly synthesized sulfonylurea derivative **7c** exhibited promising α-glucosidase inhibitory activity, similar to that of a glipizide agent.

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

REFERENCES

[1] R. Levine (1984), "Sulfonylureas: background and development of the field", *Diabetes Care*, **7(1)**, pp.3-7.

[2] S. Seino (2012), "Cell signalling in insulin secretion: the molecular targets of ATP, cAMP and sulfonylurea", *Diabetologia*, **55(8)**, pp.2096-2108.

[3] S. Sen, Ruchika, D. Kumar, T.S. Easwari, S. Gohri (2016), "Therapeutic aspects of sulfonylureas: a brief review", *Journal of Chemical and Pharmaceutical Research*, **8(12)**, pp.121-130.

[4] WO 2001005354 A2 (2001), https://patents.google.com/patent/WO2001005354A2/sv.

[5] Thi Thoi Bui, Dai Quang Ngo, Van Loc Tran, Van Chien Tran, Thi Phuong Thao Tran (2016), "Synthesis of glipizide for the treatment of type 2 diabetes", *Vietnam Journal of Chemistry*, **54(6e2)**, pp.233-236.

[6] I.G. Rathish, et al. (2009), "Synthesis and blood glucose lowering effect of novel pyridazinone substituted benzenesulfonylurea derivatives", *European Journal of Medicinal Chemistry*, **44(8)**, pp.2673-2678.

[7] Ho Sik Rho, Heung Soo Baek, Duck Hee Kim, Ih Seop Chang (2006), "A convenient method for the preparation of alkanolamides", *Bull. Korean Chem. Soc*., **27(4)**, DOI: 10.5012/bkcs.2006.27.4.584.