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VIETNAM NATIONAL CHEMICAL GROUP
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SYNTHESIS AND BIOACTIVE EVALUATION OF SOME SULFONYLUREA DERIVATIVES

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DISSERTATION SUMMARY

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I. OPENING

1. The essential of the thesis

Diabetes, one of three fastest growing diseases in the world (cancer, cardiovascular disease and diabetes), is the most common of endocrine diseases. The number of worldwide people involved in diabetes in 2019 was about 463 million and expected to increase to 700 million by 2045. Vietnam also has the same situation as the world, with more than 5 million diabetic patients. Lack of controlling and treating to diabete patients can cause many dangerous complications such as damage of the small blood vessels of the heart, brain, kidneys, eyes, stroke, kidney failure, complications of the foot. These side effects may give rise twice diabetic patient's risk of death.

Structurally, sulfonylureas contain normally a central S-arylsulfonylurea unit with p-substituents on phenyl ring (R_1) and substituents at the urea's N'-terminus (R_2)] [Fig.1]. Such kind of compounds exhibit a wide range of biological activity: antidiabetic, diuretic, antitubercular, antimalerial, anticancer, antiinflammatory, thromboxane A2 receptor antagonism activity. Especially, sulfonylureas are widely used in medicine as potent blood glucose reducing agents for the treatment of diabetes. Sulfonylurea alters the plasma membrane of cells to increase their responsiveness to insulin action, by increasing the number of insulin receptor.

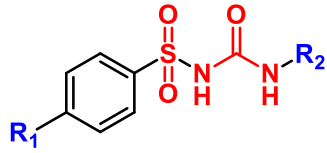


Fig.1.1: Gernaral structure of sulfonylureas

In Vietnam, until now there are still not any studies on the synthesis of sulfonylureas to develop new drugs for the treatment of diabetes, except some studies on the synthesis of generic drugs (glibenclamide, gliclazide).

Development of new sulfonylurea drugs to meet the need for treatment of type II diabetes, while reducing the side effects of drugs and having more effective treatment is an urgent and topical research direction. Therefore, based on such ideas, hence, we have chosen the research topic "Synthesis and bioactive evaluation of some sulfonylurea derivatives".

2. The research objectives of the thesis

- To synthesize and determine the structure of some new sulfonylurea derivatives with the change of substituents at the N positions of the glipizide structure by phenyl rings and heterocyclic rings containing different functional groups such as: OH, NO_2, Cl, F, I, OCH_3 ....

- To evaluate hypoglycemic activity and some other activity of synthetic products, in order to look for compounds with high biological activity and to establish as a scientific basis for further research and development of new drugs with the aim to contribute to health care for the community.

3. The main research contents of the thesis

- To synthese glipizide and intermediate sulfonamide compounds.

- To synthese and determine the structures of new sulfonylurea derivatives

- To evaluate the biological activity together with the relationship between the chemical structure and the biological activity of synthesized sulfonylurea derivarates

4. New contribution of the thesis

4. 1. Thirty sulfonylurea derivatives were synthesized, among them 22 new derivatives, such as **92(a-e), 92h, 92(m-n), 92(p-q), 94(a-i)** and **96(d, e, g).**

4. 2. *In vitro* α-glucosidase inhibition activity of synthesized sulfonylurea derivatives has been evaluated**.** Seven compounds (**92d**, **92h, 92k, 92 m, 92n, 94e and 94g**) showed the potent α- glucosidase inhibitory effect by *in vitro* method, either the similar or higher than glipizide. Among them, four compounds **92h, 92n, 92k and 94e** with IC_{50} = 5.58 µM, 79.85 µM, 226.03 µM and 213,36 µM showed stronger activity than standard drug acarbose (IC_{50} = 268.29 µM. Especially,

compound **92h** exhibited the highest activity with an IC_{50} value of 5.58 µM, 48 times much better than the standard acarbose (IC_{50} = 268.29 µM), and **92n** is 3.4 times higher than the standard acarbose.

4. 3. *In vitro* inhibition activity of nitric oxide (NO) production of ten sulfonylureas (**92c, 92d, 92l, 92m, 92n, 92h, 92k, 94e, 96h and glipizide**) have been evaluated. Compound **92c** exhibited the most potent inhibitor activity of NO production with an IC_{50} value of 73.83 µM, 2.27 times higher than glipizide (IC_{50} = 168,07 µM).

4. 4. The structural activity relationships of sulfonylurea compounds synthesized has been preliminarly concluded: The compounds having substituted hydroxyl group, especially at the para position of the phenyl ring and the compounds containing the pyrazine ring increases and play a important role in their *α*-glucosidase inhibitory activity. In addition, the introduction of the nitro group into the aromatic ring also increases the inhibitory activity of the enzyme α-glucosidase.

5. The layout of the thesis

The thesis includes 141 pages, in which the opening part (2 pages), Chapter 1: Overview (28 pages); Chapter 2: Reseach methods and experimental reseach (33 pages); Chapter 3: Results and discussion (74 pages), conclusion and suggestion (2 pages); The new contribution of the thesi**s** (1 page); The list of publications related to thesis (1 page).The references section has 116 documents in the fields related to the thesis, updated to 2018. The appendix section has 235 pages, including all the spectrum types of the synthesized sulfonylurea derivatives, results of the bioactive evaluation of sulfonylurea derivatives.

II. THE THESIS CONTENT

CHAPTER 1: OVERVIEW

1.1. Outline of diabetes

1.2. Medicines for diabetes treatment

1.3. Development of the drug based on sulfonylurea in the treatment of diabetes

1.4. Some researches on the synthesis and evaluation of hypoglycemic activity of sulfonylurea derivatives

1.5. Some researches on the other activities of sulfonylureas: anticancer, diuretic, anti-inflammation, antimalarial and antituberculosis.

CHAPTER 2: RESEARCH METHODS AND EXPERIMENTAL

2.1. Research methods

2.1.1 Chemistry Organic synthesis

Basic organic synthesis methods such as acylation, chlorosulfonylation, amidation, hydrolyzation, and condensation reaction have been used.

2.1.2 Separation and purification of products

Reagents were purchased from Aldrich and Merck with the analytical grade and used without further purification. Solvents for column chromatography were distilled before using.

2.1.3 Determination of the physical properties and the product structure

Purification of products was carried out by recrystallization or by column chromatography. Thin-layer chromatography (TLC) was performed on a pre-coated silica gel 60 F254 (Merck) and were visualized under UV light (λ max = 254 nm) and stained with a solution of 1% (w/w) vanillin in H_2SO_4. Column chromatography (CC) was performed on silica gel 300–400 mesh (Merck).

Structure of products was confirmed by means of MS, 1D (1H, 13C) and 2D (HSQC, HMBC) spectra, which were recorded on a Bruker Avance 500 MHz with TMS as the internal standard for 1H and solvent signal for 13C. IR spectra were recorded on an IMPACT 410 Nicolet spectrometer. ESI-MS spectra were measured on 1100Agilent LC/MS ion Trap. Melting points (in °C) were determined on a Thermo Mel-temp 3.0 (U.S.A).

2.1.4 Evaluation of biological activity

- *In vitro* α-glucosidase inhibition assay were tested at Institute of

Chemistry, Vietnam Academy of Science and Technology (VAST).

- Inhibitory assay of NO production was conducted at Institute of Biotechnology, VAST.

- Stability of glipizide products was assessed under rapid aging conditions at National Institute of Drug Quality Control according to USP 40.

- Acute and subchronic toxicity of products were evaluated on BALB/c albino mice, at Institute of Biotechnology, VAST.

2.2. Experiment

2.2.1 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 using

2.2.2. Synthesis of glipizide

2.2.2.1 Synthesis of 5-methyl-N-phenethylpyrazine-2-carboxamide compound **(24)**

2.2.2.2 Synthesis of 5-methyl-N-(4-sulfamoylphenethyl)pyrazine-2-carboxamide **(25)**

2.2.2.3 Synthesis of Glipizide **(26)**

2.2.3. Synthesis of Sulfonylureas 92(a-q)

2.2.3.1. Methods 1: Synthesis of sulfonylureas **92(a-e)**

2.2.3.2. Method 2: Synthesis of sulfonylureas **92(a-q)**

2.2.4. Synthesis of sulfonylureas 94(a-i)

2.2.4.1. Synthesis of **93**

2.2.4.2. Synthesis of sulfonylureas **94(a-i)**

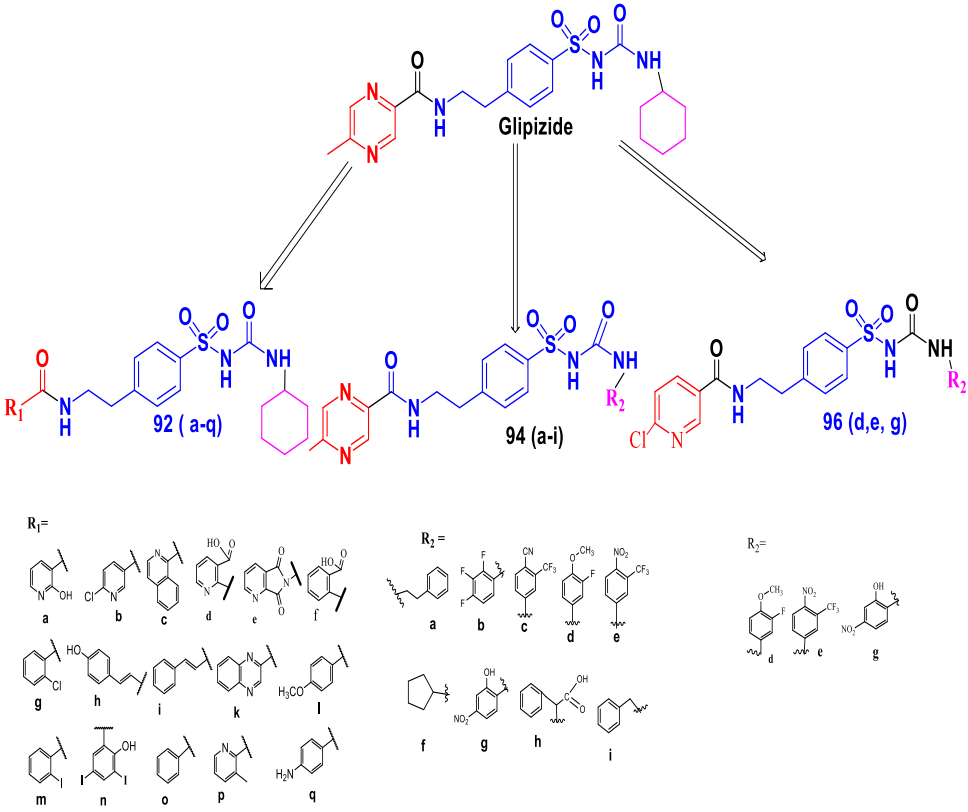
2.2.5. Synthesis of sulfonylureas 96(d, e, g)

2.2.5.1. Synthesis of ethyl ((4-(2-(6-chloronicotinamido) ethyl) phenyl) sulfonyl) carbamate **95**

2.2.5.2. Synthesis of sulfonylureas **96(d, e, g)**

CHAPTER 3. RESULTS AND DISCUSSION

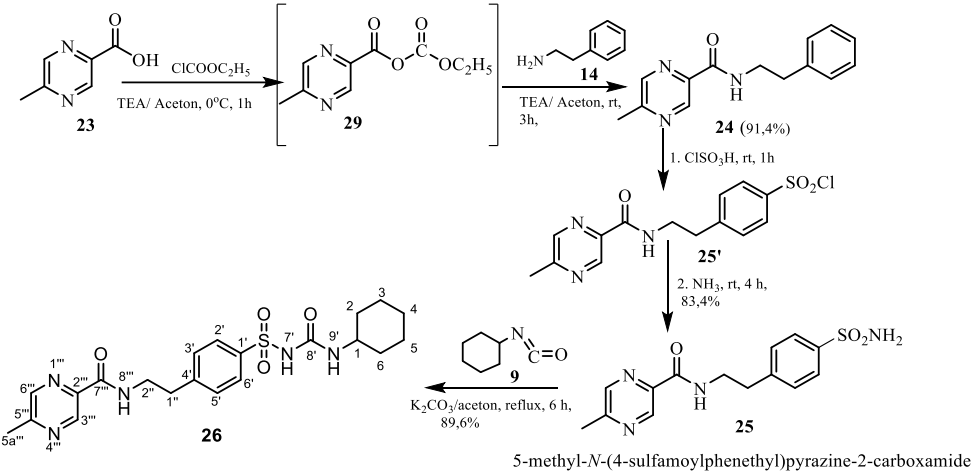
3.1 Strategy for the synthesis of sulfonylurea derivatives



Scheme 3.1: Synthetic strategy of sulfonylurea derivatives

Firstly, glipizide and intermediate sulfonamides were synthesized in order to optimize the reaction conditions. Next, from the core structure of glipizide, N-phenyl-ethylsulfamoyl, substituent groups (R_1 and R_2) which are aromatic or heterocylic compounds attached to OH, NO_2, Cl, F, I, OCH_3 groups was substituted to create the new sulfonylurea derivatives.

3.2. Synthesis of glipizide (26)



Scheme 3.2: Synthesis of glipizide.

Glipizide **(26)** was synthesized from 5-methyl pyrazin-2-carboxylic acid **23,** through 3-step reaction process as described in Scheme 3.2

3.2.1 Synthesis of compound 5-methyl-N-phenethylpyrazin-2-carboxamide (24)

5- methyl pyrazin 2-carboxylic acid **23** was coupled with 4-(2-aminoethyl)-benzenesulfonamide (**14)** in the presence of ethyl chloroformate and triethylamine in anhydrous acetone to provide the substituted 5-methyl-N-phenethylpyrazin-2-carboxamide **(24).** Instead of $SOCl_2$ or $(COCl)_2$ as reagent to activate the carboxylic acid, the ethyl chloroformate was used to avoid the formation of by-products. The synthesis procedures are presented in Figure 3.2: Firstly, stirred solution of 5- methyl-pyrazin-2-carboxylic acid (**23)** and TEA in dry acetone at 0°C and $ClCOOC_2H_5$ was added dropwise. After that the reaction was further stirred for 60 minutes to gave the intermediate anhydride **29** without puritfication, then a solution of 4-(2-aminoethyl)-benzenesulfonamide (**14)** and TEA in anhydrous acetone was added. The resulting mixture was stirred for 3 hours at the room temperature. Acetone was then removed, and the residue was acidified

with 1% HCl to pH ≈4-5. The white solid was collected and washed with distilled water. Pure product **24** was obtained by recrystallization from ethanol (91.4%).

The structures of the products were elucidated by means of ^{1}H and ^{13}C NMR, ESI-MS and IR spectroscopy. The ^{1}H NMR spectrum of compound **24** indicated the presence of two singlet signals of pyrazine protons at δ_H = 9.26 ppm (s, 1H, 3'''-H) and δ_H = 7.83 ppm (s, 1H, 6'''-H), three singlet signals of proton methyl at 2.63 (3H, s, CH_3), quartet and triplet signals of methylene protons at δ (ppm) 3.73 (q, J = 6.5 Hz, 2H) và 2.94 (t, J = 6.5 Hz, 2H), respectively. The presence of douplet signals of phenyl ring at 7.31 (2H, d, J = 7.5 Hz, H-2', H-6'), 7.23 (2H, t, J = 8.0 Hz, H-3', H-5'), multiplet signals at 7.27 (1H, m, H-1'). Especially, the appearance of the NH protons at δ_H = 8.33 ppm (t, J = 6.0 Hz, 1H, CON*H*) in the ^{1}H NMR spectrum confirmed the structure amide **24**. The ^{13}C NMR spectrum of compound **24** indicated the presence of 14 carbon atom. Especially, the appearance of the carbon signal at δ_C =163.29 ppm confirmed the C=O amide. Further, the structure of amide **24** was confirmed by its positive ESI-MS with the peak at *m/z* $[M+H]^+$= 242.0 (100%), $C_{14}H_{15}N_3O$. The IR spectrum of compound **24** was exhibited by the absorption peak at υ = 3315.73 cm^{-1} (NH), 1651.81 cm^{-1} (C=O amide), (1532.9 cm^{-1} (C=C-aromatic).

3.2.2. Synthesis of compound 5-methyl-N-(4-sulfamoylphenethyl) pyrazine-2-carboxamide (25)

Compound **24** was refluxed with $ClSO_3H$ in DCM solvent for 2 hours to obtain the intermediate compound **25'**, which subsequently treated with amoniac 30% at room temperature for 4 h to provide **25**, (83.4%). The ^{1}H and ^{13}C-NMR spectrum of compound **25**, clearly showed beside corresponding signals of compound **24,** disappeared multiplet signals at δ (ppm): 7.27 (1H, m, H-1') and appeared of the singlet protons of the SO_2NH2 group at δ (ppm): 7.27 (2H, s, H-7'), confirming the presence of SO_2NH_2.

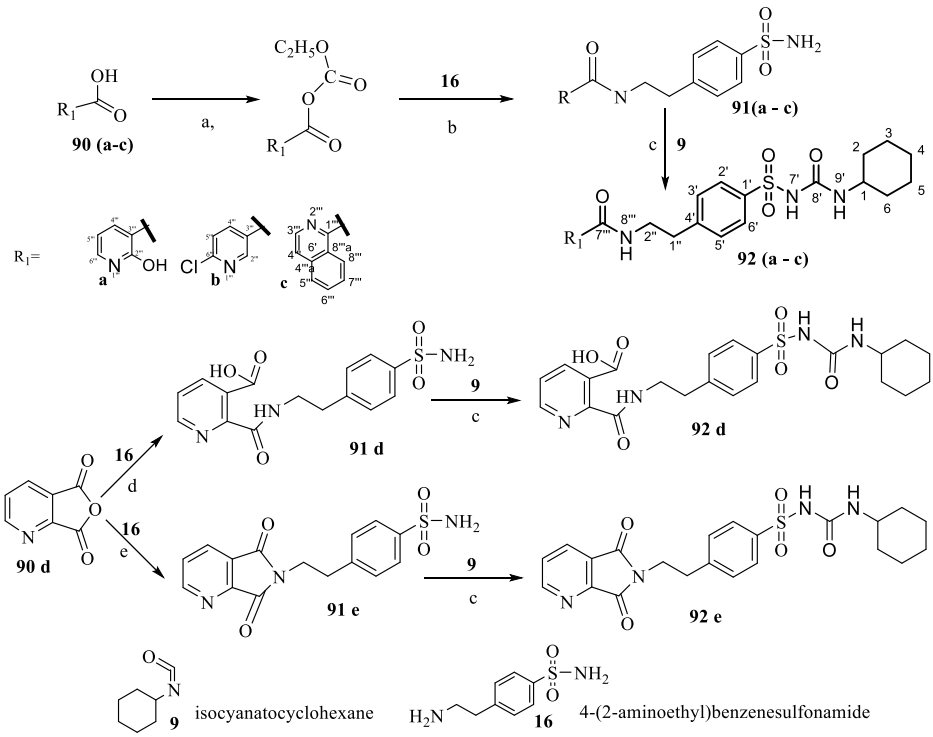
3.2.3. Synthesis of glipizide (26)

Compound **25** and K_2CO_3 was refluxed in dry acetone for 2 h followed by addition of cyclohexyl isocyanate **9**. The reaction mixture was continuously

refluxed for 6 h. The solvent was removed under reduced pressure and the residue was added water, neutralized with 1% HCl to pH=5-6. The product was collected by filtration and washed with water, pure compound **26** was obtained by recrystallization from ethanol/water (89.6 %). The **^{1}H NMR** of compound **26** was lost NH_2 proton at 7.27 ppm and exhibited additionally signals of NH proton at δ_H = 10.3 ppm (1H, br s, H-7') which was shifted to lower field. The appearance of NH douplet protons at 6.31 ppm (H-9') and the presence of multiplet signals protons of cyclohexyl ring at δ_H (ppm): 3.25 (m, H-1), 1.63-1.08 (m, 10H) in ^{1}H NMR spectra of **26** clearly confirmed the formation of product. The structure of the glipizide **26** was further confirmed by ^{13}C- NMR spectra, ESI-MS and IR spectrum. Its ^{13}C NMR showed 21 carbon signals in the structure, beside corresponding carbon signal in compound **25** was appeared carbons signals of cyclohexyl at 49.34 (C-1), 32.26 (C-2, C-6), 24.98 (C-4), 24.19 (C-3, C-5), more carbon signal of amide CONH at δ_c (ppm): 150.44 (C-8'). The ESI-MS spectrum displayed an ion molecular peak at m/z (%): 444.0 [M-H]- (100), $C_{21}H_{27}N_5O_4S$. Its IR spectrum were showed by the absortion at 3335.34 cm^{-1} and 3253.87 cm^{-1} (NH), 1688.1 and 1650.8 cm^{-1} (C=O amide).

3.3. Synthesis of sulfonylureas 92 (a-q): The synthese routes of 92 (a-q) was carried out by two methods as shown in Scheme 3.3 and 3.4. Various substituents were replaced with pyrazine moiety in glipizide, whereas the cyclohexyl ring at the other N-terminus was maintained. The desired products were synthesized by treatment of sulfonamides with appropriate isocyanides in the presence of base.

3.3.1. Method 1: *Synthesis of sulfonylureas* 92 (a-e)



*Reagents and conditions a) $ClCOOC_2H_5$, TEA, acetone, 0°C. b); TEA, acetone, (4-(2-aminoethyl)benzenesulfonamide (**16**), rt, 3 h, 70.1-72.0 %. c) K_2CO_3, acetone, **9** (cyclohexyl isocyanate), reflux, 7 h, 72.0- 75.4 %. d) Acetic acid, **16**, rt, 1 h, 82.1 %, e) Acetic acid, **16**, reflux, 7 h, 76.2 %.*

Scheme 3.3: Synthesis of compounds **92(a-e)** (method 1)

3.3.1.1. Synthesis of 91(a-c)

Various carboxylic acids **90(a-c)** were treated with $ClCOOC_2H_5$ in the presence of TEA in dry acetone to give intermediate anhydride without puritfication, which was then reacted with compound **16** for 3 hours at room temperature, Acetone was then removed, and the residue was acidified with 1% HCl to pH ≈4-5. The white solid was collected and washed with distilled water. Pure correcsponding products **91(a- c)** were obtained by recrystallization from ethanol (yields: 70.1%, 71.2 % và 72.0%, respectively).

The structures of the products **91(a-c)** were confirmed by means of ^{1}H and ^{13}C NMR IR, ESI-MS.

The ^{1}H NMR spectrum of compound **91(a-c)** indicated the presence of 2 couple douplet signals of phenyl ring protons at δ (ppm): 7.75-7.76 and 7.43-7.49ppm, quartet and triplet signals of methylene protons at δ (ppm) 3.54-3.57 (2H) and 2.93-2.99(2H), respectively. The appearance of the NH protons at δ_H = 8.84-9.83 ppm (1H, CONH), δ_H = 7.28-7.29 ppm (2H, SO_2NH_2) in the ^{1}H NMR spectrum of compound **91(a-c)** confirmed the formation of amide products. Signals ^{1}H-NMR of carboxylic acid moiety **90(a-c)** in compound **91(a-c)** are presented following: Compound **91a** showed the signals of 2- hydroxypyridine ring at δ (ppm): 12.41 (1H, OH), at δ (ppm): 8.32 (1H, d, J = 7.0 Hz, H-4’’’), 7.69 (1H, d, J = 5.5 Hz, H-6’’’) and 6.46 (1H, t, J=6.5 Hz, H-5’’’). Compound **91b** appeared the signals protons of 6 -chloropyridine ring at δ (ppm): 8.78 (1H, s, H-2’’’), 8.19 (1H, d, J = 8.0 Hz, H-4’’’) and 7.64 (1H, d, J = 8.0 Hz, H-5’’’). Compound **91c** indicated the presence of signals of isoquinoline ring protons at δ (ppm): 8.75 (1H, d, J = 9.0 Hz, H-8a’’’), 8.51 (1H, d, J = 5.5 Hz, H-3’’’), 8.03 (1H, d, J = 8.5 Hz, H-5’’’), 7.99 (1H, d, J = 5.5 Hz, H-4’’’), 7.80 (1H, m, H-7a’’’) and 7.69 (1H, m, H-6’’’).

The ^{13}C NMR spectra of **91(a-c)** were in well agreement with the structure assigned. The appearance of two couple carbons signals of phenyl ring at δ_c (ppm): 125.72-126.98 and 128.26-129.49, two signal carbon at δ_c (ppm): 130.58-143.9, signals of CH_2 at δ (ppm): 40.00-40.84 and 34.70-34.96, amide group (CONH) appeared signal at δ_C: 162.22, 164.42 and 166.05 ppm. Signals ^{13}C-NMR of carboxylic acid moiety **90(a-c)** in compound **91(a-c)** are presented**:** In compound **91a** showed 5 signals carbons of pyridine at δ_C: 163.28, 143.62,120.24, 106.23 and 142.09 ppm, compound **91b** appeared at 152.47, 148.98, 124.48, 129.59 and 142.21ppm, isoquinoline ring of compound **91 c** showed carbon signal at δ_c (ppm): 140.76, 129.14, 126.5, 125.64, 125.60 and 123.14.

3.3.1.2. Synthesis of sulfonylureas 92(a-c)

Compounds **91(a-c)** and K_2CO_3 was refluxed in dry acetone for 2 h followed by addition of cyclohexyl isocyanate **9,** the reaction mixture was continuously refluxed for 6h. The solvent was removed and the residue was added water, neutralized with 1% HCl to pH=4-5. The product was collected by filtration and washed with water. Pure corresponding compounds **92(a-c)** were obtained by recrystallization from ethanol/water (72.9%, 75.4% and 72.0%, respectively).

The ^{1}H and ^{13}C-NMR spectrum of compound **92(a-c)** clearly showed beside corresponding signal in compound **91(a-c),** were disappeared sulfonamide singlets protons signals at δ (ppm) = 7.28-7.29 (2H, - SO_2NH_2) and appeared of the singlet protons of amide - NH at δ (ppm) = 10.27 (H-7') which was shifted to lower field. The disappearance of NH douplet protons at δ (ppm): 6.30 - 6.32ppm and the presence of multiplet signals protons of cyclohexyl ring at δ_H (ppm): 3.54-3.58 (1H) và 1.65 -1.06 (10H, m) in ^{1}H NMR spectra of **92(a-c)** clearly confirmed the formation of product.

The structures of **92(a-c)** were further confirmed by ^{13}C- NMR, ESI-MS and IR spectrum. Their ^{13}C NMR, beside corresponding carbon signal in compound **91(a-c),** was more appeared carbon signal of cyclohexyl at δ_c (ppm) = 48.02, 48.11 và 48.06 (C-1), 32.22, 32.30 và 32.33 (C-2, C-6), 24.94 và 25 (C-4), 24.12 và 24.19 (C-3, C-5), more carbonyl signal of amide CONH at δ_c (ppm): $\delta_{C\ ppm}$ =150.53, 150.61 và 151.38, respectively. The ESI-MS spectrum of compound **91(a-c)** displayed an ion molecular peak at m/z (%): $[M+H]^+$ = 447 (60%), $[M-H]^-$ = 463 (70%) và $M-H]^-$ = 479 (100), respectively. Its IR spectrum were showed by the absortion at 3351.37-32647.47-cm^{-1} (NH), 3114.91 cm^{-1} (OH), 1632.84-1669.01 cm^{-1} (C=O amide), 1308.33- 1341.38 và 1147.79-1157.25 cm^{-1} (O=S=O).

3.3.1.3. Synthesis of 91(d-e)

Compound **91d** was prepared by treatment of 2,3-pyridine dicarboxylic anhydride **90d** with compound **16** in glacial acetic acid at room temperature for 1 h (82.1%). Compound **91e** was prepared by reflux of 2,3-pyridine dicarboxylic anhydride **90d** with compound **16** in glacial acetic acid for 7 h (76.2%).

According to the literature, the reactivity of 2,3-pyridine dicarboxylic anhydride toward nitrogen nucleophiles under different conditions affords different products [111]. In our study, treatment of **16** with 2,3-pyridine dicarboxylic anhydride **90d** in glacial acetic acid at room temperature gave nicotinic acid derivative **91d**. This was compatible with the studies of Ammar YA et al. for the similar reaction [111]. It was reported that refluxing 2,3-pyridine dicarboxylic anhydride with amine in glacial acetic acid for 3 hours led to the dicarboxylation of the carboxylic acid group, providing nicotiamide as main product and nicotiimide as minor product [111]. However, in our case, nicotiimide **91e** was obtained as the main product (yield: 76.2 %), even the reaction was heated for 7 hours.

The structures of the synthesized compounds were confirmed by means of MS, 1D (^{1}H, ^{13}C) spectra.

The ^{1}H NMR spectra of **91d** indicated the additional signal of the aromatic pyridine protons at δ_H = 8.13, 8.02 and 7.28 ppm, appeared brs proton signal of NH group at 8.36 ppm (H-8’’’).

The ^{1}H NMR spectra of **91e** indicated the additional signal of the aromatic pyridine protons at δ_H = 8.96, 8.27 and 7.77 ppm. The ^{13}C NMR spectra of **91e** indicated the additional signal of the aromatic pyridine carbon at δ_c: 131.26, 127.07, 154.83, 151.29 and 127.86 ppm, together with the carbon signals at δ_C =166.03, 165.93 (*C*ONH amide) indicated the formation of the amide ring in **91e**.

3.3.1.5. Synthesis of sulfonylureas 92(d-e)

Coressponding compound **91(d,e)** and K_2CO_3 was refluxed in dry acetone for 2 h followed by addition of cyclohexyl isocyanate **9.** The reaction mixture was continuously refluxed for 6h. The solvent was removed and the residue was added water, neutralized with 1% HCl to pH=4-5. Product was collected by filtration and washed with water. Pure corresponding compound **92(d-e)** was obtained by recrystallization from ethanol/water (72.9%, 63.2% and 68.0%, respectively).

The ^{1}H-NMR spectrum of **92(d,e)** was contained signals of the ^{1}H-NMR spectrum of **91(d,e)**, beside appeared singlet proton signal of amide - NH at δ (ppm)

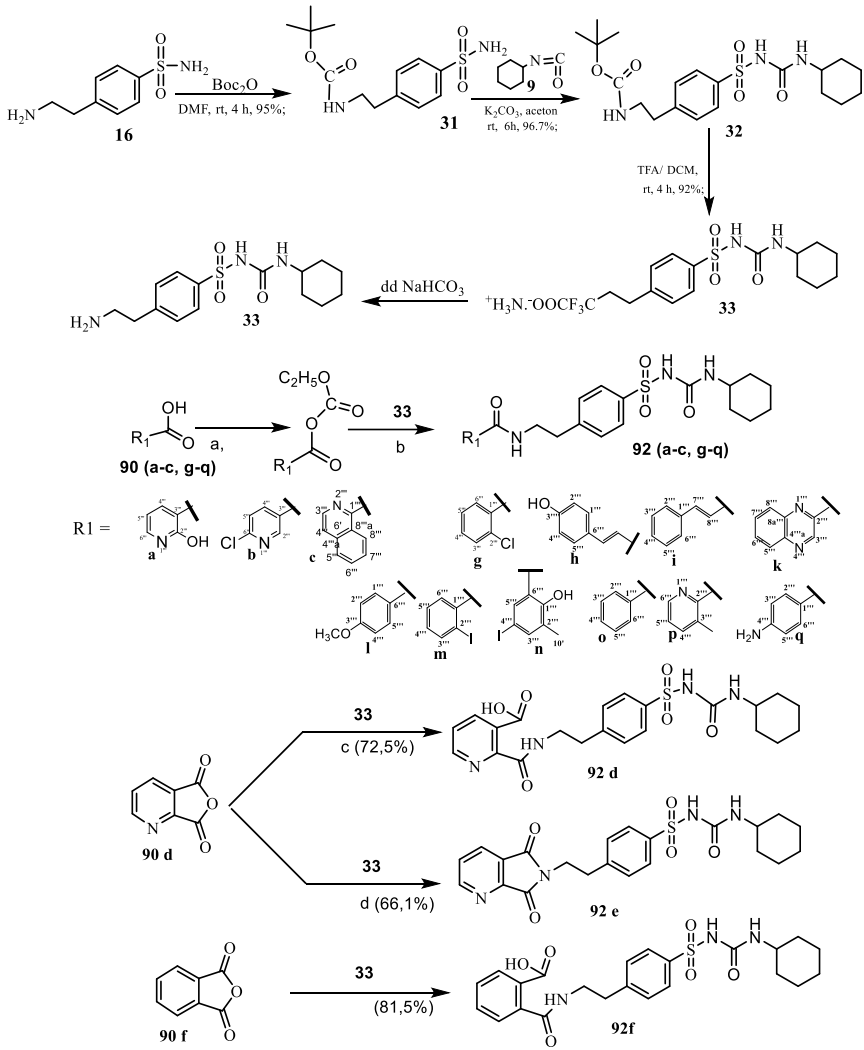
= 10.27 of compound **92e,** appeared doublet proton signal of amide - NH group of of compound **92e**, **92d** at δ (ppm): 6.36 and 6.28, respectively. Multiplet proton signals of cyclohexyl ring were appeared at δ (ppm): 3.54 và 3.03 (1H) và 1.8 -1.06 (10H, m). The ^{13}C NMR of compounds **92d** and **92e** was showed the present the new signals of amide group (C-8') at $\delta_{C\ ppm}$ =150.42 and 154.08, Appeared carbon signal of cyclohexyl ring of compound **92d** and **92e** at δ_c (ppm) = 48.02 và 48.03 (C-1), 32.20 and 32.21 (C-2, C-6), 24.92 and 24.94 (C-4), 24.08 and 24.12 (C-3, C-5), repecstively.

The structure of **92d** was confirmed by analysis of its 2D - NMR (HSQC, HMBC) spectrum. The correlation of δ_H = 8.05 ppm (4'''-H)/δ_C = 167.9 ppm (COOH) and δH = 8.66 ppm (6'''-H)/ δC = 165.06 ppm (CONH) was observed in HMBC spectrum of **91d**, suggesting the location of carboxylic acid and amide moiety at C-3''' and C-2''' of pyridine ring, respectively. Futhermore, the formation of the amide bond in compound **91d** was confirmed by the correlation of CONH (δH = 8.76) ppm/ C=O (δC 165.06 ppm), C-2'' (δC = 39.83 ppm).

The ESI-MS of **92d** and **92e** spectrum displayed an ion molecular peak at m/z (%): $[M-H]^-$ = 473 (20%) and $[M-H]^-$ = 455 (100), respectively. Its IR spectrum were showed by the absortions at 3320.30 - 3240.63 cm^{-1} (NH), 3742.52 cm^{-1} (OH), 1653.53-1680.00 cm^{-1} (C=O amide), 1540.62 and 1531.26 cm^{-1} (C=C-aromatic), 1319.47- 1341.06 và 1168.99-1163.47 cm^{-1} (O=S=O).

3.3.2 Method 2: Synthesis of sulfonylureas 92(a-q)

The synthetic routes of compounds **92(a-q)** are shown in Schemes 3.4. Compound **16** (4-(2-aminoethyl) benzenesulfonamide) was used as the starting material. *N*-Boc protection of **16** gave compound **31** which was then reacted with cyclohexyl isocyanate in the presence of K_2CO_3 to afford **32**. Deprotection of **32** with trifluoroacetic acid (TFA) in DCM provided the key intermediate **33**. Finally, coupling of **33** with various carboxylic acids in ethyl chloroformate and the presence of triethylamine (TEA) gave the target compounds **92(a-q).**



Reagents and conditions: *a) $ClCOOC_2H_5$, TEA, aceton, 0°C. b);TEA, aceton,* ***33****, rt, 3 h. c) Acetic acid,* ***33****, rt, 1 h, 72.5 %. d) Acetic acid,* ***33****, reflux, 7 h, 66.1 %, 81.5%.*

Scheme 3.4: synthesis of compounds **92(a-q)** (method 2).

3.3.2.1 Synthesis of 33

First, amino group of **16** was protected with *tert*-butoxycarbonyl group by the treatment with Boc_2O in the DMF at room temperature for 4 h to provide the product **31** (95%). Compound **31** was then reacted with compound cyclohexyl isocyanate **9** in presence of dry K_2CO_3 in dry acetone solvent for 6 h to afford **32** (96.7%). Subsequently, compound **32** was dissolved in DCM, cooled in an ice bath and followed by addition of TFA. The reaction mixture was stirred at room temperature for 4 h, the solvent was then removed under reduced pressure. Cool water was added to the residue and the solid was filtered, washed with distilled water, recrystallized by ethanol/ water (20/2) to give **33** (92.0%).

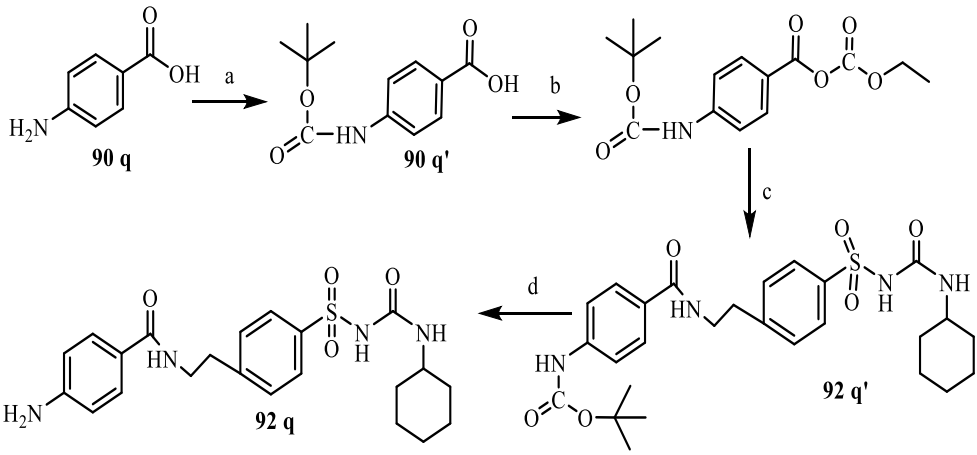
The structure of the synthesized compounds was confirmed by means of MS, 1D (^{1}H, ^{13}C) and 2D (HSQC, HMBC) spectra. The ^{1}H NMR spectra of **31** indicated the additional signal of *tert*-butyl group at δ_H = 1.36 ppm (9H, 3 × CH_3), together with the corresponding signals of **16**. The formation of urea cyclohexyl moiety in compound **32** was confirmed by the appearance of the signals at δ_H = 1.65–1.18 ppm (C_6H_{11}), 10.25 ppm (br s, 1H, SO_2NH), and at δ_C = 150.35 ppm (NH*C*ONH), 48.01–24.10 ppm (C_6H_{11}). The lack of the *tert*-butyl signal in the ^{1}H NMR of compound **33** indicated the removing of the *tert*-butyl protecting group in the structure of **33**.

The formation of the amide urea moeity in **33** was further confirmed by the correlation between CON*H*-C_6H_{11} (δ_H = 6.62 ppm)/C-8' (δ_C = 150.49 ppm), C-1 (δ_C = 48.06 ppm) and C-2, C-6 (δ_C = 32.24 ppm) in HMBC spectrum.

3.3.2.2. Synthesis of sulfonylureas 92(a-q)

The synthesis of **92(a-q)** shown in Scheme 3.4**:** Coupling of **33** with various of carboxylic acids **90(a-c, g-q)** in the presence of ethyl chloroformate and triethylamine (TEA) in dry acetone at room temperature gave the target compounds **92(a-c, g-q)**, yields (66–82%). Coupling of **33** with 2,3-pyridine dicarboxylic anhydride **90d** or phthalic anhydride **90f** in the glacial acetic acid solvent at room temperature or under or reflux affords the different target compound **92(d-e), 92f**, yield: 72.5, 66.1 and 81.5 %, respectively**.**

Because carboxylic acid **90q** contains NH_2 group which may be react with $ClCOOC_2H_5$, it was protected before using. *N*-Boc protection of **90q** gave compound **90q'** (95.5%) which was then reacted with **33** in the presence of $ClCOOC_2H_5$ and TEA in dry acetone at room temperature to afford **92q'** (85.4%). Subsequently, deprotection of **92q'** with trifluoroacetic acid (TFA) in DCM provided compound **92q** (yield: 93.5%), overall yield of 76.3%



Reagents and conditions: a) *Boc_2O, DMF, 4 h, 95.5%; b) $ClCOOC_2H_5$, aceton, TEA, 0^0C, 1 h; c)* ***33****, aceton, TEA, rt, 3 h, 85.4%; d) TFA, DCM, rt, 4 h, 93.5 %.*

Scheme 3.5: Synthesis of compound **92q**

The results of comparing yield of two synthesis method showed that the synthesis of compound **92(a-c)** by method 2 were more effective than method 1 with overall yield from 5.8% to 18.9 % higher than method 1.

The structure of **92(g-q)** was defined by analysis of their spectral data, including ESI-MS, IR, 1D-NMR (^{1}H, ^{13}C). The ^{13}C and ^{1}H NMR of compounds **92(g-q)** contained signals of **33,** but in the ^{1}H disappeared singlet proton signal of SO_2NH at δ_H (ppm): 7.93 (2H, br s) and appeared proton signals of NH- amide were shifted to lower-filed δ_H (ppm) = 8.07 - 9.27. The formation of CONH group was confirmed by carbon new signals at δ_c (ppm): 162.25-168.79 (C-7''') in the

^{13}C NMR. Signals ^{1}H, ^{13}C-NMR of carboxylic acid moiety **90(g-q)** in compound **92(g-q)** are more presented in Table 3.1

Table 3.1: Signals ^{1}H, ^{13}C-NMR of carboxylic acid moiety **90(g-q)** in compounds **92(g-q)**

Chất	**^{1}H-NMR (**δ (ppm)	**^{13}C-NMR** δ (ppm)
92g	7.46-7.45 (1H), 7.44-7.39 (1H), 7.35 (1H), 7.30 (1H)	130.60, 129.49, 128.70, 126.99, 137.00, 129.78
92h	7.38 (2H), 6.79 (2H), 9.80 (OH), 7.32 (1H), 6.37 (1H).	129.14, 115.68, 158.78, 125.84
92i	7, 7.56 - 7.55 (3H), 7.42-7.37(3H), 7.41 (1H), 6.57 (1H).	129.36, 129.13, 128.85, 134.84
92k	9.44 (1H), 8.18 (2H), 7.98 (2H)	129.07, 127.20, 131.26, 143.63, 142.94, 139.77
92l	7.81 (2H), 6.98 (2H), 3.81(OCH3).	129.20, 113.44, 161.48, 126.71
92m	7.13-7.50 (H-bz).	129.08, 127.79, 130.54, 127.83, 143.03, 93.24
92n	8.17 (1H), 8.15 (H), 13.95 (OH).	135.11, 149.31, 150.33, 159.87, 88.82, 81.12
92o	7.82-7.78 (4H), 7.53 -7.42(5H).	131.07, 129.2, 127.26, 134.5
92p	8.41 (1H), 7.70 (1H), 7.42 (1H), 2.46 (CH_3).	140.03, 133.05, 125.28,149.24, 145.69
92q	7.53 (2H), 6.52 (2H), 5.56 (2H).	129.12, 112.48, 121.19

Structures of **92(g-q)** were further confirmed by analysis of ESI-MS and IR spectra. The ESI-MS of **92(g-q)** spectra displayed ion molecular peaks corresponding with the molecular structures. Its IR spectrum was showed by the absortions at 3301.20-3249.87 cm^{-1} (NH), 1654.59-1688.00 cm^{-1} (C=O amide,) 1529.91-1540.50 cm^{-1} (C=C-aromatic),1329.93- 1354.04 and 1158.79-1164.67 cm^{-1} (O=S=O).

On another method, compound **92d** was prepered by treatment of 2,3-pyridinedicarboxylic anhydride **90d** with compound **33** in glacial acetic acid at room temperature for 1h (yield: 72.5%), whereas compound **92e** was prepered by

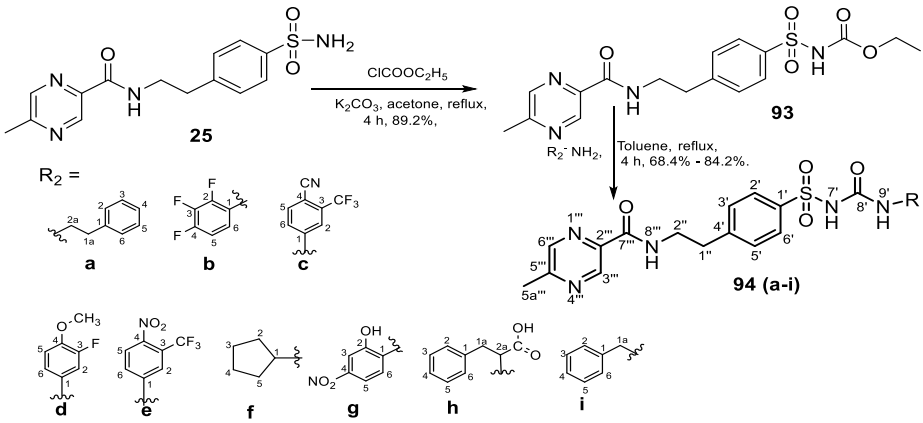
reflux of 2,3-pyridinedicarboxylic anhydride **90d** with compound **33** in glacial acetic acid for 7h (yield: 66.1%). The results showed that synthesis of **92d** and **92e** by method 2 gave higher yield than method 1 (5.8% to 18.9 %).

Synthesis of compound 92f: Phthalic anhydride **90f** was refluxed with compound **33** in glacial acetic acid for 7h and cooled to room temperature. White solid was filtered and washed with water, recrystallized in ethanol/water to obtain pure products **92f** (81.5%).

The ^{1}H NMR of compound **92f** appeared SO_2NH proton signal at low-field δ (ppm) = 10.24 (H-7'), multiplet proton signals of phthalic ring at δ (ppm) = 7.85-7.81 (4H). In the ^{13}C NMR and DEPT appeared carbon signals of CONH and COOH at δ_c (ppm): 168.55 (C-7'") and 167.60 (COOH). Six carbon signals of phthalic ring appeared at δ_c (ppm): 123.01(2C), 134.40(2C), 131.43(2C). The ESI-MS spectrum displayed an ion molecular peak at $[M-H]^-$ m/z = 471.9 (100) fit with molecular structure of **92f**. Its IR spectrum showed the absortions at ν = 3071.34 (OH), 3349.87 (NH), 1718.0 (C=O, acid), 1655.12 (C=O, amide), 1536.88 (C=C Aro), 1342.05 và 1122.79 (O=S=O) cm^{-1}.

3.4. Synthesis of sulfonylureas 94(a-i)

The synthese routes of compounds **94(a-i)** are shown in Scheme 3.6. Various substitutions such as NO_2, Cl, F, OH, OCH_3, CN, CF_3 l group were introduced at *N*-terminus of the urea moiety (R^2) to provide mimic glipizide. Sulfonamide (**25**) was refluxed with ethyl chloroformate in the presence of anhydrous potassium carbonate (K_2CO_3) to obtain the key intermediate carbamate **93**. Finally, condensation of **93** with various of amines in toluene provided sulfonylureas **94(a-i)**. The use of toluene as solvents gave the products in the best yields compared with other solvents such as dioxane or DMF.



Scheme 3.6: Synthesis of compounds **94(a-i)**

3.4.1 Synthesis of 93

Compound **25** was refluxed with dry K_2CO_3 in dry acetone for 2 h. The solution was cooled in an ice bath at room temperature and $ClCOOC_2H_5$ was added dropwise. The reaction was refluxed for 4 h and concentrated to dryness. The residue was suspended in water and neutralized with 1% HCl. White solid was collected and washed with distilled water to obtain desired product **93** (89.2%).

The ^1H and ^{13}C- NMR of compound **93** exhibited signals similar compound **25.** Disappearance of two singlets proton signals at δ(ppm): 7.27 (SO_2NH_2), beside appearance of amide (NH) proton signal at low field δ (ppm):11.88 (H-7'). Ethyl carbamate group was exhibited by proton signals at δ_H (ppm): 3.99 (2H, CH_2), 1.07 (3H, CH_3) and carbon signals at δ_C (ppm)= 61.83 và 13.88,amide carbonyl signal at δ_C (ppm) = 151.01 (C-8'). Structure of **93** was further confirmed by 2D- NMR (HSQC, HMBC) spectrum.

3.4.2. Synthesis of sulfonylureas 94(a-i)

Compound **93** was reacted with amines (R_2-NH_2) under reflux in toluene for 4 h and allowed to cool to room temperature. The solid was filtered, washed with water, extracted in EtOAC, dried over Na_2SO_4 and recrystallized in ethanol to obtain products **94(a-i) (**68.4-84.2%).

The structures of **94(a-i)** were defined by analysis of their spectral data, including ESI-MS, IR, 1D-NMR (^{1}H, ^{13}C). The ^{13}C and ^{1}H NMR of compounds **94(a-i)** contained signals of **93,** but disappeared signals of ethyl carbamate group at δ_H (ppm) = 3.99 (2H) and 1.07 (3H) and at δ_C (ppm) = 61.83, 13.88**,** but appeared proton signals of NH- amide at δ_H (ppm) = 8.57. Signals ^{1}H, ^{13}C-NMR of amine moiety in **94(a-i)** are presented in table 3.2

Table 3.2: Signals ^{1}H, ^{13}C-NMR of amin moiety **(a-i)** in compound **94(a-i)** are presented in Table 3.2

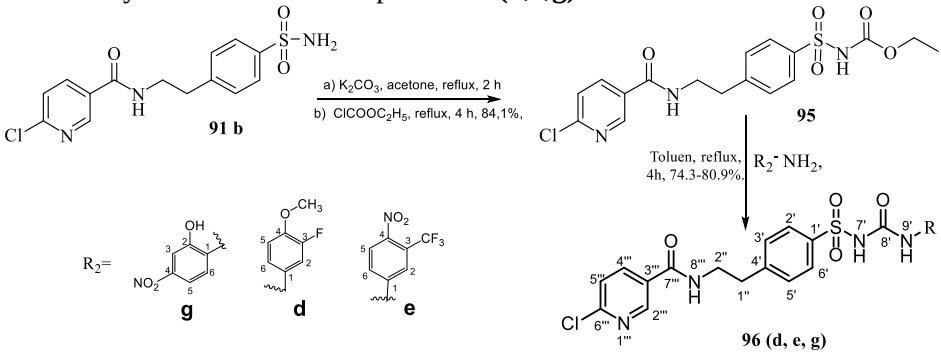
Comp	**^{1}H-NMR**	**^{13}C-NMR**
94a	7.26 - 7.10 (5H), 3.58 (2H) và 2.63 (2H).	137.27, 126.98, 126.7, 126.0, 125.67, 35.33, 33.12.
94b	7.53 (1H), 7.24 (1H).	134.62, 143.54, 139.89, 140.25, 111.47, 111.6
94c	7.84 (1H), 7.50 (1H) 7.96 (1H)	121.94, 128.49, 111.6, 128.67, 139.89, 127.7
94d	7.28 (1H), 7.05 (1H), 7.01 (1H),3.77 (OCH_3)	109.34, 111.85, 114.15, 127.47, 156.85, 116.11, 57.01 (OCH_3)
94e	8.12 (1H), 8.02 (1H), 7.80 (1H).	133.77, 127.55, 129.64, 124.92, 125.17, 114.48
94f	3.77-3.70 (1H), 1.75-1.68 (2H), 1.58-1.52 (2H), 1.49-1.42 (2H), 1.29-1.23 (2H).	32.29, 23.05, 51.00
94g	7.70 (1H), 7.62 (1H), 8.08 (1H)	118.26, 111.14, 108.62, 143.51, 142.80, 135.51
94h	7.19 (1H), 7.02 (1H), 7.28 (1H), 4.24 (1H), 3.00 - 2.94 (2H)	129.42, 128.39, 128.15, 126.68, 126.48, 136.79, 54.81, 34.74, 172.53 (COOH).
94i	7.25 (2H), 7.13 (2H), 7.19 (1H)	128.25, 127.00, 126.85, 138.18, 42.74

The ESI-MS spectra of **94(a-i)** displayed ion molecular peaks corresponding with molecular structures. IR spectrum showed by the absortions at ν = 3234.69 – 3421.78 (NH), 1635.43-1683.30 (C=O, amide), 1521.10 - 1547.06 (C = C-aromatic), 1327.51-1348.19 và 1149.02-1167.87 (O=S=O) cm^{-1}.

3.5. Synthesis of sulfonylureas 96(d, e, g)

Compounds **96(d,e,g)** were prepared by replacement of pyrizine with chloronicotinic, whereas the cyclohexyl fragment was substituted by phenyl ring containing F, NO_2, CF_3, OCH_3 and OH groups.

The synthesis route of compounds **96(d,e,g)** are showed in scheme 3.6.



Scheme 3.7: synthesis of compounds **96(d, e, g)**.

Synthesis of compound 95: Compound **91b** was refluxed with $ClCOOC_2H_5$ in presence of dry K_2CO_3 in dry acetone for 6 h to give **95** (84.1%).

The ^1H and ^{13}C- NMR of **95** exhibited signals similar **91,** beside that**,** disappeared two singlets proton signals at δ_H(ppm): 7.28 (SO_2NH_2), and appeared amide (NH) singlet proton signal at lowfield δ_H (ppm):11.90 (1H, H-7'). carbamate group were exhibited by protons signals at δ_H (ppm): 4.00 (2H, q, J = 7.0 Hz, CH_2) and 1.08 (3H, t, J = 7.0 Hz, CH_3). Carbon signals appeared at δ_C(ppm)= 56.00 and 18.5, CO-amide at δ (ppm) = 152.46 (C-8').

Synthesis of compound 96(d, e, g): Carbamate **95** and appropriate amines in toluene was refluxed for 4 h and then allowed to cool to room temperature. The solid was filtered, washed with water and recrystallized in ethanol to provide **96(d, e, g)** (yield: 80.9%, 74.3% and 74.9%).

The **^{13}C and ^1H NMR** of compounds **96(d,e,g)** showed signals of **95,** but disappeared signals of ethyl carbamate group at δ (ppm) = 4.00 (2H) and 1.08 (3H) in the ^1H,appeared proton signals of NH- amide at δ (ppm) = 7.01-8.25. Proton

signals amine moiety in **96(d,e,g)** are presented as following: **96d**: 7.59 (1H), 7.27 (1H), 7.07 - 7.01 (1H), 3.77 (3H, s, OCH_3); **96 e**: 8.12 (1H), 8.01 (1H), 7.81 (1H);**96 g**: 7.59 (1H), 7.49 (1H), 7.75-7.71

^{13}C-NMR of amine moiety in **96d**: 116.14, 115.15, 114.15, 124.05, 143.50, 142.09, 56.18 (OCH_3);**96e**: 114.43, 124.15, 123.54, 133.74, 124.06, 138.42 và 111.67 (CF_3); **96g**: 110.13, 117.15, 115.55, 129.40, 138.44.

IR (KBr) spectra appeared peak absortions at: ν = 3409.84, 3421.78 (NH), 1673.36, 1635.43 (C=O, amide), 1539.10, 1569 (C=C-aro), 1246.76 (C-O), 1355.60, 1348 và 1170.52, 1153.93 (O=S=O) cm^{-1}. The ESI-MS spectra of **96(d,e,g)** displayed an ion molecular peak corresponding with molecular structures.

3.6. Evaluation bioactivity

3.6.1 α-glucosidase inhibitory activity

Sulfonylureas are widely used in medicine as potent blood glucose-reducing agents for the treatment of diabetes. Sulfonylureas alter the plasma membrane of cells to increase their responsiveness to insulin action, by increasing the number of insulin receptors [1]. The side effect of these reagents is, however, associated with hypoglycemia, weight gain and cardiovascular risks. The combination of sulfonylureas with α-glucosidase inhibitors, an add-on therapy, have been reported to improve lipid profiles, decrease body weight, prevent macroangiopathy, reduce the hemoglobin A1c and control the glycemic level in type 2 diabetic patients [114, 115].

Thirty synthesized sulfonylureas were evaluated α-glucosidase inhibitory activity with the hope to obtain the products with an additive potent α-glucosidase inhibitory activity to decrease their side effects. Acarbose and glipizide were used as standard compounds to compare with the synthesized derivatives. The result showed, compound **92h** (R = 4-OH-C_6H_4) was the most active compound with an IC_{50} value of 5.58 µM, 48 and 60 times much better than the standard drug acarbose

and glipizide (IC_{50} of 268.29 and 300.47 µM, respectively). The *p*-substituted hydroxyl group at *trans*-cinnamoyl moiety plays an important role of the activity. This is confirmed due to the observation that compound **92i** without the OH group (R = -C_6H_5) did not show α-glucosidase inhibition. Preliminary structure-activity relation ships (SARs) presumed that *trans*-cinnamoyl derivatives are weak intestinal α-glucosidase inhibitors [12]. However, the presence of a hydroxyl group at *para* position enhanced significantly the inhibition, probably because they may form hydrogen bonds with the polar groups (amide, guanidine, peptide, amino, and carboxyl groups) of amino acid residues in the active site of intestinal α-glucosidase enzyme [12]. Compound **92n** (R = 2-OH-3,5-di-I-C_6H_2) exhibited good activity with an IC_{50} value of 79.85 µM. Comparing the activity of **92n** with **92m** (R = 2-I-C_6H_4, IC_{50} of 278.88 µM), the installation of OH and disubstituted iodine seems to enhance the activity. Compound **92k**, **92c** and **92d** with heterocyclic substitutions (quinoxaline, isoquinoline and picolinic, respectively) showed moderate activity with IC_{50} values of 226.03, 322.49 and 312.12 µM, respectively (Table 3.3). Compound **94e** (R^1 = 3-CF_3-4-NO_2-C_6H_3) and **94g** (R^1 = 2-OH-4-NO_2-C_6H_3) exhibited good activity with an IC_{50} of 213.36 and 269.44 µM, respectively (Table 3.9, Scheme 3.28), comparing with acarbose and glipizide (IC_{50} = 268.29 and 300.47 µM, respectively. The introduction of the nitro group into the aromatic rings of the series products in Scheme 2 seems to enhance the α-glucosidase inhibitory activity.

Compound **96e** with the same R_2 substitution as compound **94e** (R_2 = 3-CF_3-4-NO_2-C_6H_3), but R_1 is 6-chloronicotinic did now show activity. That means the 5-methyl-pyrazin moiety at R_1 may play an important role in the α-glucosidase inhibitory activity. The role of 5-methyl-pyrazin at R_1 was further confirmed by the observation of the activity of compound **94g** (R_1 = 5-methyl-pyrazin, R_2 = 2-OH-4-NO_2-C_6H_3, IC_{50} of 269.44 µM, better than acarbose) and **96g** (R_1 = 6-chloronicotinic, R_2 = 2-OH-4-NO_2-C_6H_3, IC_{50} of 492.39 µM, no activity).

Compound **96d** (R_1 = 6-chloronicotinic, R_2 = 3-F-4-OCH_3-C_6H_3) showed moderate activity with an IC_{50} value of 329.62 µM.

Table 3. 3: The α- glucosidase enzyme inhibitors activity of sulfonylurea derivatives

Compound	**IC_{50}**	**Compound**	**IC_{50}**	**Compoun**	**IC_{50} (µM)**
Acabose	268.29	**92 k**	226.03	**94 c**	480.75
Glipizide	300.47	**92 l**	500	**94 d**	>500
92 a	>500	**92 m**	278.88	**94 e**	213.36
92 b	>500	**92 n**	79.85	**94 f**	>500
92 c	322.49	**92 o**	322.49	**94 g**	269.44
92 d	312.12	**92 p**	>500	**94 h**	>500
92 e	>500	**92 q**	>500	**94 i**	>500
92 f	>500	**32**	>500	**96 g**	492.39
92 g	>500	**94 a**	>500	**96 d**	329.62
92 h	5.58	**94 b**	>500	**96 e**	447.62
92 i	>500				

3.6.2 Anti-inflammatory activity

It has been known that there is an association of diabetics with chronic inflammation. The treatment of diabetics and its complication may reduce inflammation. We therefore evaluated the NO inhibitory activity of ten *α*-glucosidase inhibitory active compounds **(92c, 92d, 92l, 92m, 92n, 92h, 92k, 94e, 96h** and **glipizide).** L-NMA (N-Methyl-L-Arginine) was used as standard compound with an IC_{50} of 40.59 µM in this test. Glipizide was also tested to compare with the synthesized derivatives. Compound **92c** exhibited moderate NO inhibitory activity with an IC_{50} value of 73.83 µM**.** Compounds glipizide, **5e** and **5n** showed weak activity (IC_{50} 155.7, 167.39 and 168.07 µM, respectively). Other compounds did not show NO inhibitory activity (Table 3.4).

Table 3. 4: The NO production inhibitory activities (IC_{50}- **µM**) of the some sulfonylurea derivatives

Compound	**IC_{50}**		Compound	**IC_{50}**	
	(µg/ml)	**(µM)**		(µg/ml)	(µM)
Glipizide **(26)**	69.36±2.27	**155.7**	**92n**	NA	NA
94e	NA	NA	**92c**	**35.48±3.75**	**73.82**
96d	>100	>197.65	**92k**	**80.94±3.45**	**168.07**
92h	**78.94±2.70**	**167.39**	**92d**	>100	>210.73
92l	NA	NA	L-NMMA	**7.64±0.47**	**40.59**
92m	>100	>180.04			

CHATER 4 : CONCLUSION

Conclusion

1. Glipizide (**26**) has been synthesized to use the treatement of type 2 diabetes with high efficiency of 68.0%. The products have been assessed to meet the USP 40 standards.

2. Thirty sulfonylurea derivatives were synthesized, among them 22 are new derivatives, including **92(a-e), 92h, 92(m-n), 92(p-q), 94(a-i), 96(d, e, g).**

3. Structure of synthesized compounds were confirmed by means of ^{1}H-NMR, ^{13}C-NMR, 2D- NMR (HMBC, HSQC), ESI-MS and IR spectra.

4. *In vitro* α-glucosidase inhibitory activity of synthesized sulfonylurea derivatives has been evaluated. 7 compounds (**92d**, **92h, 92k, 92 m, 92n, 94e and 94g**) showed the significant *in vitro* α- glucosidase inhibitory effect similar or higher than glipizide, among them, four compounds (**92h, 92k, 92n and 94e)** showed activity much better than acarbose. Compound **92n** exhibited the good activity with an IC_{50} value of 79.85 µM, 3.4 times higher than the standard drug acarbose. Especially, compound **92h** has the highest activity with an IC_{50} value of 5.58 µM, 48 times higher than the standard drug acarbose (IC_{50} =268.29 µM).

5. *In vitro* inhibitory activity of nitric oxit (NO) reproduction *of* ten sulfonylurea compounds has been evaluated, from which **92c** exhibited the NO

reproduction inhibitory activity with an IC_{50} value of 73.83 µM, 2.27 times higher than glipizide (IC_{50} =168.07 µM).

6. The structural activity relationships of synthesized sulfonylurea compounds has prelimimnarly concluded: Sulfonylureas having substituted OH group, especially, the presence of OH group at *para* position of phenyl ring plays and the compounds containing the pyrazin ring increase the activity and plays an important role in *α*-glucosidase inhibitory activity. Besides, the introduction of the nitro group into the aromatic ring at *N*-ureyl unit of sulfonylureas led to increase the *α*-glucosidase inhibitory activity.

List of publications related to the thesis

1. **Thi Thoi Bui,** Van Loc Tran, Dai Quang Ngo, Van Chien Tran, Van Sung Tran and Thi Phuong Thao Tran*. *Synthesis and evaluation of α-glucosidase inhibitory activity of Sulfonylurea derivatives.* Zeitschrift für Naturforschung B, https://doi.org/10.1515/znb-2020-0134; accepted October 12, 2020; published online March 4, 2021; 76 (3-4)b: 163-171.

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

3. **Thi Thoi Bui*,** Van Loc Tran, Dai Quang Ngo, Van Chien Tran, Thị Nga Nguyen, Thi Thao Do. *Acute and subacute toxic study on mice of Glipizide synthesized in VietNam.* Vietnam journal of science and tecnology. 2019, Vol 57, No 1, 15-21.

4.**Thi Thoi Bui*,** Van Loc Tran, Dai Quang Ngo. *Synthesis of Sulfonylurea derivatives and their α-glucosidase inhibitory activity.* Vietnam Journal of Science, Technology and Engineering, 6.2020, Vol 62, No 2, 34-37.

5. **Thi Thoi Bui*,** Dai Quang Ngo, Van Loc Tran. *Synthesis of the second some sulfonylurea derivatives and evaluation of enzyme α-glucosidase inhibitory activity.* Journal of chemistry and application, 03, 2020, 5-8.

6. **Thi Thoi Bui**, Thi Kieu Dung Pham, Thi Thu Thuy Ha, Thị Bich Van Tran*. *Quality assessment and stability studies of synthesized glipizide in Vietnam.* Journal of drug quality control, 16, No 61, 2018, 28-30.