Design, synthesis and *in vivo* evaluation of novel glycosylated sulfonylureas as antihyperglycemic agents

Dr. Ghadeer Suaifan

Associate Professor of Medicinal Chemistry and Pharmaceutical Instrumental analysis
Diabetes mellitus (DM) is a major degenerative disease with a serious cause of maladies in the 21st century.

DM is divided into three main types: Type I, Type II and Gestational diabetes.

Type II diabetes mellitus (T2DM) accounts for more than 90% of all diabetic cases.

Extended period of hyperglycemia causes irreversible damage to the eyes, kidneys, nerves and heart.
* 2012  1.5 million deaths were directly caused by diabetes.
* 2014  347 million diabetic cases have been diagnosed worldwide.
* 2030  Estimated to be the 7th leading cause of death.
Oral Hypoglycemic agents

Increasing insulin release from β islet cells.

Sulfonylurea

First generation
Tolbutamide

Second generation
Gliclazide

Third generation
Glimepride

Biguanides
Metformine

Reduce excessive hepatic glucose production
Side effects of sulfonyurea

- Hypoglycemia
- GIT disturbance
- Weight gain
- Hypersensetivity
Proposals:

- Must have an aromatic ring next to sulfoxide
- Should have a substituent at the para position to enhance glycemic activity
- Has some size constraints
- N-propyl to N-hexyl are most potent
CHEMISTRY

1. D-(-)+-Glucosamine hydrochloride

2. Chemical reaction with NaOH, followed by CH$_3$O-$C_6$H$_4$CHO:
   - (i) NaOH
   - (ii) CH$_3$O-$C_6$H$_4$CHO

3. Reaction with pyridine, followed by Ac$_2$O:
   - (i) pyridine
   - (ii) Ac$_2$O

4. Chemical reaction with Acetone, followed by 5M HCl:
   - (i) Acetone
   - (ii) 5M HCl

yield $= 77\%$

yield $= 80\%$

yield $= 79\%$
3rd Annual International on Pharmaceutical Sciences, 2-5 May 2015 Conference, Athens

**Chemical Structures and Reactions:**

1. **Reaction 1:**
   - Initial structure: 5
   - Reagents:
     - (i) DPC
     - (ii) DMAP
     - (iii) MeCN
   - Yield:
     - a; R=H, yield=60%
     - b; R=Cl, yield=65%
     - c; R=Me, yield=68%

2. **Reaction 2:**
   - Initial structure: 4
   - Reagents:
     - (i) NaOH
     - (ii) MeOH
     - (iii) Dowex 50WX8
   - Yield:
     - a; R=H, yield=80%
     - b; R=Cl, yield=80%
     - c; R=Me, yield=79%

3. **Reaction 3:**
   - Initial structure: 6
   - Reagents:
     - (i) MeCN
     - (ii) Et3N
   - Yield:
     - a; R=H, yield=37%
     - b; R=Cl, yield=71%
     - c; R=Me, yield=91%
In vivo evaluation

![Graph showing change in blood glucose level over time](image)

**Change in blood glucose level (%)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>8b</td>
<td>60</td>
<td>b.wt</td>
</tr>
<tr>
<td>8b</td>
<td>30</td>
<td>b.wt</td>
</tr>
<tr>
<td>8b</td>
<td>7.5</td>
<td>b.wt</td>
</tr>
<tr>
<td>Glimepride</td>
<td>1</td>
<td>b.wt</td>
</tr>
</tbody>
</table>

**Time (min)**

0 30 60 90 120 150 180

**Notes**

- Compound 8c: 60mg/kg b.wt
- Compound 8a: 60mg/kg b.wt
- Compound 8b: 60mg/kg b.wt
- Compound 8b: 30mg/kg b.wt
- Compound 8b: 15mg/kg b.wt
- Glimepride: 1mg/kg b.wt

---

3rd Annual Internationalon Pharmaceutical Sciences, 2-5 May 2015 Conference, Athens
Conclusion

- Chloro-substituted glycosylated sulfonylurea prove to be potent hypoglycemic agents. (Molecules 2015)

- Importance of these novel class as a potential antihyperglycemic agents

- Future work synthesis of more potent derivatives
Thank You

Dr Ghadeer Suaifan