SYNTHESIS OF SOME NEW DERIVATIVES OF ISOINDOLINE-1,3-DIONE NUCLEUS FOR ANTIHYPERGLYCEMIC EVALUATION

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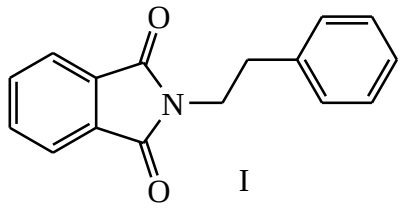
ABSTRACT:

In order to produce potent new leads for antidiabetic drugs, a new series of isoindoline-1,3-dione analogues bearing aryl sulfonylurea moieties were synthesized and screened for their antihyperglycemic activity. Some of newly synthesized compounds were identified as active antihyperglycemic agents. Compounds *N*-(cyclohexylcarbamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl) ethyl]benzenesulfon-amide**(VII_o)**,*N*-(cyclopentylcabamoyl)-4-[2-(1,3-dioxoiso- indolin-2-yl)ethyl] benzene sulfonamide **(VII_p)**, *N*-(butylcabamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfonamide**(VII_q)**,*N*-(cyclohexylcarbamoyl) -4- [(1, 3-dioxo - isoindolin- 2 – yl) methyl] benzenesulfonamide **(VII_h)** and *N*-(propylcabamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfonamide **(VII_r)** proved to be the most active members of this study, as compered to to the reference gliclazide. They showed serum glucose reduction values of 52%, 48% 45%, 44% and 44%, respectively. The detailed synthesis and biological screening data are reported.

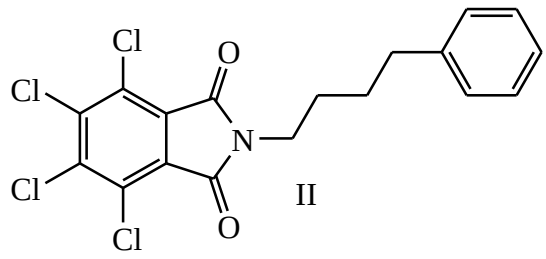
Keywords: Isoindoline-1,3-diones ; Sulfonylurea; Antihyperglycemic activity.

1. INTRODUCTION

It is clear that isoindoline-1,3-dione nucleus is the backbone of many bioactive compounds that show versatile biological and pharmacological activities **(Chan, *et al.*, 2009; Miyachi, *et al.*, 1997; Zhao, *et al.*, 2009; Yang, *et al.*, 2010; Santos, *et al.*, 2009)**. Potential activity of isoindoline-1,3-dione as antihyperglycemic is well known as compounds **I**, **II**, **III** and **IV (Mahapatra, *et al.*, 2010; Abdel-Aziz, *et al.*, 2011; Hashimoto,1998; Pascale, *et al.*, 2010; Kim, *et al.*, 2002)**.



I



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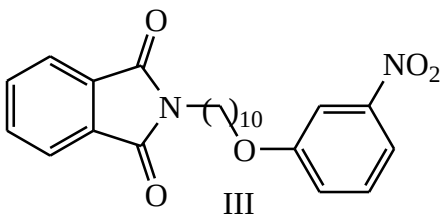
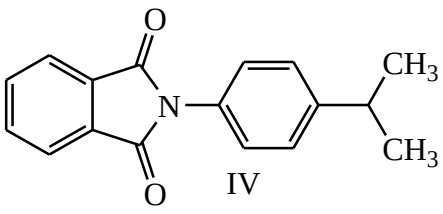


III

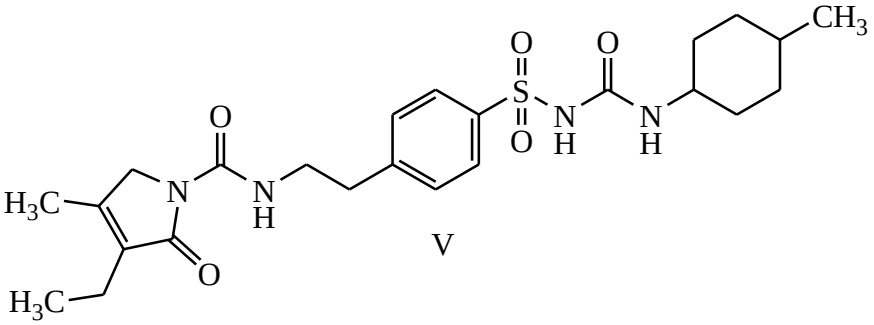


IV

WHO estimates that more than 180 million people worldwide have diabetes. The incidence of diabetes is increasing with alarming mortality and morbidity and This number is likely to more than double **(http://www. afro.who.int/en/clusters-a-programmes/dpc/non-comm unicable-diseases-managementndm/programme-components/ diabet- es-mellitus.html. 2013)**.

There is an increasing demand of new antidiabetic products due to the drawbacks associated with insulin and oral hypoglycemic agents actually available **(Fertig, *et al.*,1995).** In response to the enormity of the growing problem, efforts to identify and develop new pharmacological agents for type II diabetes have increased dramatically in recent years **(http://diabetes manager.pbworks.com/w/page/ 17680289/Oral%20Pharmacological%20 Agents%20for%20Type%202%20Diabetes, 2013)**. These efforts have resulted in the successful introduction of several new treatment options.

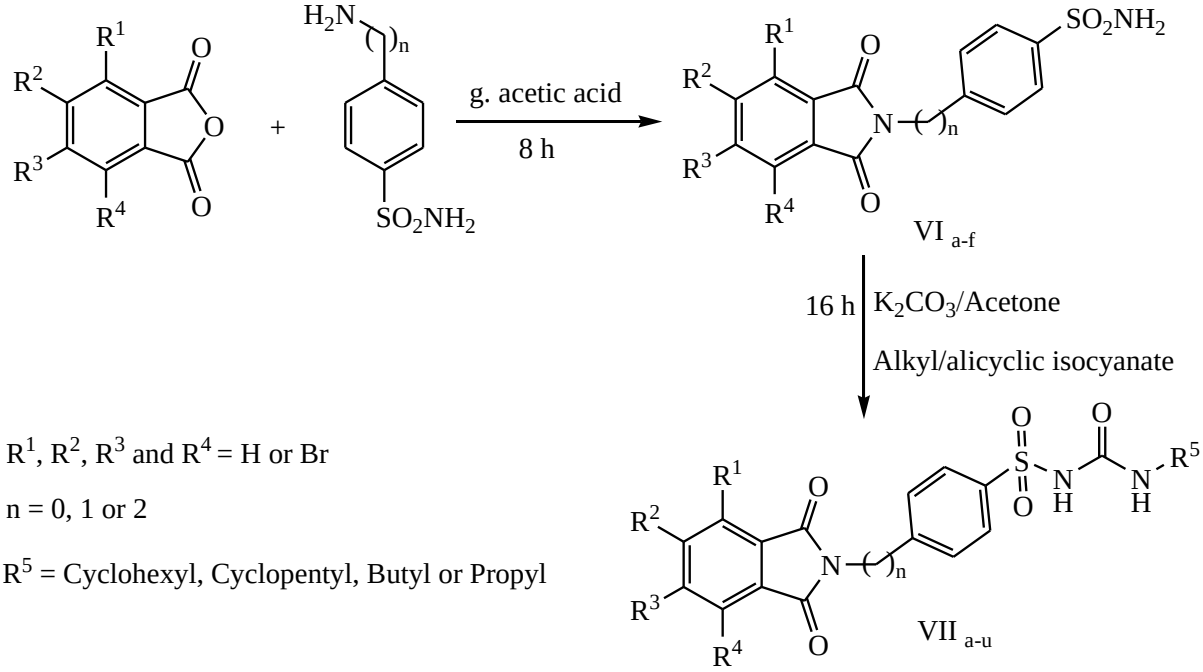
Currently, there is a very important class of oral pharmacological agents available to treat type II diabetes, sulfonylureas **(Nadendla, 2005)**. More recently, 2nd generation sulfonylureas are now widely used as an effective antihyperglycemic agents with a lower risk of adverse as compound **V (Korytkowski, 2004; Kar, 2006).**



V

From the previously mentioned findings, it was decided to synthesize some new compounds bearing both isoindoline-1,3-dione and sulfonylurea moieties hoping to obtain more effective antihyperglycemic agents.

For preparation of the newly synthesized compounds, the scheme **1** was adopted:



R^1, R^2, R^3 and R^4 = H or Br

n = 0, 1 or 2

R^5 = Cyclohexyl, Cyclopentyl, Butyl or Propyl

scheme 1: Synthesis of target compounds VII_{a-u}

2. Chemistry

Reaction of sulfonamide derivatives with phthalic anhydride derivatives in glacial acetic acid gave compounds $\mathbf{VI_{a-f}}$ that act as key compounds. The target compounds $\mathbf{VII_{a-u}}$

were obtained through the reaction of compounds V**I$_{a-f}$** with alkyl/alicyclic isocyanate derivatives in dry acetone and anhydrous potassium carbonate.

2.1. ***Experimental***

All melting points were taken on electrothermal (IA 9000 SERIS) digital melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer at Pharmaceutical analytical Unit, Faculty of Pharmacy, AlAzhar University. The ^{1}H NMR spectra were recorded in DMSO-d_6 at 300 MHz on a Varian Mercury VXR-300 NMR spectrometer at Research Services Unit, Faculty of Science, Cairo University. Chemical shifts were related to those of the solvent. Tetramethylsilane (TMS) was used as a standard. Mass spectra were recorded on Hewlett Packard 5988 spectrometer at Regional Center for Mycology and Biotechnology, Al-Azhar University. Microanalyses were carried out at Regional Center for Mycology and Biotechnology, Faculty of Science, AlAzhar University. Progresses of the reaction were monitored by TLC using TLC sheets precoated with UV fluorescent silica gel Merck 60 F254 plates and were visualized using UV lamp and dichloromethane : methanol 95:5 as mobile phase.

2.1.1. General procedure for the reaction of substituted isoindoline-1,3-dione with sulfonamide derivatives VI$_{a-f}$:

A mixture of sulfonamide derivative (0.02 mol) and phthalic anhydride (0.02mol) was refluxed in glacial acetic acid (50 mL) for 10 h. The solid obtained was filtered and washed with diluted ethanol to afford V**I$_{a-f}$** .

2.1.2. 4-(1,3-dioxoisoindolin-2-yl)benzenesulfonamide (VI$_a$): **this compound has yield:** 5.10 g (84%) and m.p: 340-341 ºC as reported **(Ibrahim, 2010)**

2.1.3. 4-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)benzenesulfonamide ***(VI$_b$)****:* this compound has yield:10.50 g (85%) and m.p: 345-346 ºC as reported **(Ibrahim, 2010)**

2.1.4. 4-[(1,3-dioxoisoindolin-2-yl)methyl]benzenesulfonamide (VI$_c$):

5.20 g, (81%); mp: 230–231ºC; IR: NH_2 3356, 3257, 2CO 1705 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.84 (s, 2H, CH_2), 7.30 (s, 2H, NH) (D_2O exchangeable), 7.48–7.92(m, 8H, aromatic); Ms: m/z 316 (M^+) (5.76%), 237 (M^+-SO_2NH_2) (10.96%), 161 (M^+-$C_6H_5SO_2NH_2$) (100%). Anal. Calcd. for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86. Found: C, 56.55; H, 3.51; N, 8.45.

2.1.5. 4-[(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)methyl]benzenesulfona mide (VI$_d$):

10.40 g, (83%); mp: 338–339 ºC; IR: NH_2 3351, 3249, 2CO 1707 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.82 (s, 2H, CH_2), 7.27 (s, 2H, NH) (D_2O exchangeable), 7.43–7.87(m, 4H, aromatic); Ms: m/z 632 (M^++5) (3.54%), 549 (M^+-SO_2NH_2) (20.76%), 160 (M^+-$4BrC_6H_5SO_2NH_2$) (100%). Anal. Calcd. for $C_{15}H_8Br_4N_2O_4S$: C, 28.51; H, 1.28; N, 4.43. Found: C, 28.88; H, 1.67; N, 4.11.

2.1.6. 4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfonamide (VI$_e$):

5.41 g, (82%); mp: 224–225 ºC; IR: NH_2 3361, 3271, 2CO 1710 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.96 (t, 2H, CH_2-ph), 3.80 (t, 2H, CH_2-phthalimide), 7.25 (s, 2H, NH) (D_2O exchangeable), 7.38–7.88(m, 8H, aromatic); Ms: m/z 330 (M^+) (4.89%), 250 (M^+-SO_2NH_2) (23.49%), 160 (M^+-$CH_2C_6H_5SO_2NH_2$) (100%). Anal. Calcd. for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.45; H, 3.88; N, 8.05.

2.1.7. 4-[2-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfon- amide (VI_f):
10.78 g, (84%); mp: 280–281 ºC;IR: NH_2 3346, 3253, 2CO 1707 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.98 (t, 2H, CH_2-ph), 3.82 (t, 2H, CH_2-phthalimide), 7.28 (s, 2H, NH) (D_2O exchangeable), 7.43–7.75(m, 4H, aromatic). Anal. Calcd. for $C_{16}H_{10}Br_4N_2O_4S$: C, 29.75; H, 1.56; N, 4.34. Found: C, 29.43; H, 1.91; N, 4.75.

2.1.8. General procedure for synthesis of N-substituted bnzensulfonamide derivatives VII_{a-u}:
Reaction mixture consisting of (0.002mol.) of $\mathbf{VI_{a-f}}$ and (0.004 mol. 0.55 g) of anhydrous potassium carbonate in 150 ml of anhydrous acetone was stirred at refluxing temperature for about 1.5 h. (0.0025mol.) of the appropriate isocyanate was added dropwise to the reaction mixture. Refluxing and stirring were continued during the course of the addition and for an additional 16 hours. The acetone was removed by evaporation under reduced pressure, and about 750 ml of water were added to dissolve the resulting residue. The solution was filtered. Acidification of the filtrate with 6 N aqueous hydrochloric acid caused the precipitation of the product which was collected by filtration. Crystallization of the filter cake from 90% aqueous ethanol yielded purified sulfonylurea derivatives.

2.1.9. N- (cyclohexylcarbamoyl) – 4- (1,3- dioxoisoindolin- 2 -yl) benzenesulfon- amide (VII_a):
0.52 g, (61%); mp: 291–292 ºC;IR: 2NH 3328, CH-aliphatic 2928, 3CO 1624 cm^{-1}; ^1H NMR (DMSO-d_6): δ1.15-1.66(m, 10H, cyclohexyl group), 3.22(m, 1H, of cyclohexyl group), 5.51(s, 1H, NH-cyclohexyl) (D_2O exchangeable), 6.30(s, 1H, NH-SO_2) (D_2O exchangeable), 6.88–7.85(m, 8H, aromatic); Ms: m/z 427 (M^+) (2.19%), 302 (M^+-CONH-cyclohexyl) (100%).Anal. Calcd. for $C_{21}H_{21}N_3O_5S$: C, 59.00; H, 4.95; N, 9.83. Found: C, 59.33; H, 4.51; N, 9.45.

2.1.10. N-(cyclopentylcabamoyl)-4-(1,3-dioxoisoindolin-2-yl)benzenesulfona- mide (VII_b):
0.49 g, (59%); mp: 283–284 ºC; IR: 2NH 3330, CH-aliphatic 2927, 3CO 1619 cm^{-1}; Ms: m/z 413 (M^+) (2.50%), 302 (M^+-CONH-cyclopentyl) (100%). Anal. Calcd. for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16; Found: C, 58.44; H, 4.91; N, 4.25.

2.1.11. N-(Butylcabamoyl)-4-(1,3-dioxoisoindolin-2-yl)benzenesulfonamide (VII_c):
0.45 g, (56%); mp: 286–287 ºC;IR: 2NH 3330, CH-aliphatic 2929, 3CO 1625 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.85(t, 3H, CH_3), 1.45(m, 2H, $C\underline{H}_2CH_3$), 2.65(m, 2H, $C\underline{H}_2CH_2CH_3$), 3.15(t, 2H, $C\underline{H}_2CH_2CH_2CH_3$), 5.52(s, 1H, NH-butyl) (D_2O exchangeable), 6.58(s, 1H, NH-SO_2) (D_2O exchangeable), 7.43–7.88(m, 8H, aromatic); Ms: m/z 401 (M^+) (92.34%), 343 (M^+- H-butyl) (14.88%), 303(M^+- CONH-butyl) (29.32%), 76(100%), Anal. Calcd. for $C_{19}H_{19}N_3O_5S$: C, 56.85; H, 4.77; N, 10.47; Found: C, 56.44; H, 4.36; N, 9.99.

2.1.12. N-(Propylcabamoyl)-4-(1,3-dioxoisoindolin-2-yl)benzenesulfonamide (VII_d):
0.45 g, (58%); mp: 281–282 ºC; IR: 2NH 3283, 3130, 2CO 1709, CO 1655cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.90(t, 3H, CH_3), 1.49(m, 2H, $C\underline{H}_2CH_3$), 3.15(t, 2H, $C\underline{H}_2CH_2CH_3$), 5.51(s, 1H, NH-propyl) (D_2O exchangeable), 6.81(s, 1H, NH-SO_2) (D_2O exchangeable), 7.23–7.91(m, 8H, aromatic); Anal. Calcd. for $C_{18}H_{17}N_3O_5S$: C, 55.80; H, 4.42; N, 10.85; Found: C, 55.65; H, 4.06; N, 10.64.

2.1.13. N-(cyclohexylcarbamoyl)-4-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)benzenesulfonamide (VII_e):

0.88 g, (60%); mp: 275–276 ºC; IR: 2NH 3322, CH-aliphatic 2927, 3CO 1644 cm^{-1}; ^1H NMR (DMSO-d_6): δ1.31-1.65(m, 10H, cyclohexyl group), 3.33(m, 1H, of cyclohexyl group), 5.66(s, 1H, NH-cyclohexyl) (D_2O exchangeable), 6.80(s, 1H, NH-SO_2) (D_2O exchangeable), 7,72–8.10(m, 4H, aromatic); Anal. Calcd. for $C_{21}H_{17}Br_4N_3O_5S$: C, 33.94; H, 2.31; N, 5.66; Found: C, 33.63; H, 2.72; N, 5.21.

2.1.14. N-(butylcabamoyl)-4-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)benzenesulfonamide (VII_f):

0.84 g, (59%); mp: 281–282 ºC; IR: 2NH 3254, CH-aliphatic 2932, 3CO 1693 cm^{-1}; Ms: m/z 717 (M^++4) (2.30%), 617 (M^++4 – CONH-butyl) (11.08%), 51(100%), Anal. Calcd. for $C_{19}H_{15}Br_4N_3O_5S$: C, 31.83; H, 2.11; N, 5.86; Found: C, 31.39; H, 2.47; N, 5.54.

2.1.15. N-(propylcabamoyl)-4-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)benzenesulfonamide (VII_g):

0.78 g, (56%); mp: 294–295 ºC; IR: 2NH 3356,3264, CH-aliphatic 2954, 3CO 1682, 1601 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.03(t, 3H, CH_3), 1.23(m, 2H, $C\underline{H}_2CH_3$), 3.45(t, 2H, $C\underline{H}_2CH_2CH_3$), 5.60(s, 1H, NH-propyl) (D_2O exchangeable), 6.43(s, 1H, NH-SO_2) (D_2O exchangeable), 7.24–8.08(m, 4H, aromatic); Anal. Calcd. for $C_{18}H_{13}Br_4N_3O_5S$: C, 30.75; H, 1.86; N, 5.98; Found: C, 30.31; H, 2.11; N, 6.33.

2.1.16. N-(cyclohexylcarbamoyl)-4-[(1,3-dioxoisoindolin-2-yl)methyl]benzenesulfonamide (VII_h):

0.50 g, (57%); mp: 183–184 ºC; IR: 2NH 3328, CH-aliphatic 2929, 3CO 1626 cm^{-1}; Ms: m/z 440 (M^+-1) (5.00%), 235 (M^+- SONHCONH-cyclohexyl) (23.49%), 56(100%), Anal. Calcd. for $C_{22}H_{23}N_3O_5S$: C, 59.85; H, 5.25; N, 9.52; Found: C, 60.19; H, 5.39; N, 9.19.

2.1.17. N-(cyclopentylcabamoyl)-4-[(1,3-dioxoisoindolin-2-yl)methyl] benzene- sulfonamide (VII_i):

0.47 g, (55%); mp: 180–181 ºC; IR: 2NH 3290, CH-aliphatic 2952, 3CO 1644, ^1H NMR (DMSO-d_6): δ1.04-1.66(m, 8H, cyclopentyl group), 3.10(m, 1H, of cyclopentyl group), 4.70(s, 2H, CH_2), 5.63(s, 1H, NH-cyclopentyl) (D_2O exchangeable), 6.40(s, 1H, NH-SO_2) (D_2O exchangeable), 7,46–8.14(m, 8H, aromatic); Anal. Calcd. for $C_{21}H_{21}N_3O_5S$: C, 59.00; H, 4.95; N, 9.83; Found: C, 59.42; H, 4.69; N, 9.52.

2.1.18. N-(butylcabamoyl)-4-[(1,3-dioxoisoindolin-2-yl)methyl]benzenesulfona- mide (VII_j):

0.46 g, (56%); mp: 186–187 ºC; IR: 2NH 3330, CH-aliphatic 2950, 3CO 1644, Ms: m/z 415 (M^+) (2.40%), 316 (M^+- CONH-butyl) (29.33%), 236(100%), Anal. Calcd. for $C_{20}H_{21}N_3O_5S$: C, 57.82; H, 5.09; N, 10.11; Found: C, 57.48; H, 5.33; N, 10.42.

2.1.19. N-(propylcabamoyl)-4-[(1,3-dioxoisoindolin-2-yl)methyl]benzenesulfon- amide (VII_k):

0.47 g, (59%); mp: 190–191 ºC; IR: 2NH 3377,3300, 3CO 1698,1651, Ms: m/z 402 (M^++1) (3.74%), 235 (M^+- SO_2NHCONH-propyl) (33.24%), 77(100%), Anal. Calcd. for $C_{19}H_{19}N_3O_5S$: C, 56.85; H, 4.77; N, 10.47;Found: C, 57.08; H, 5.10; N, 10.88.

2.1.20. N-(cyclohexylcarbamoyl)-4-[(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)methyl]benzenesulfonamide (VII_l):

0.90 g, (60%); mp: 305–306 ºC; IR: 2NH 3348, CH-aliphatic 2937, 3CO 1695, Ms: m/z 757 (M^++4) (3.14%), 115(100%), Anal. Calcd. for $C_{22}H_{19}Br_4N_3O_5S$: C C, 34.90; H, 2.53; N, 5.55; Found: C, 35.38; H, 2.95; N, 5.78.

2.1.21. N-(butylcabamoyl)-4-[(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)-methyl]benzenesulfonamide (VII_m):

0.85 g, (59%); mp: 303–304 ºC; IR: 2NH 3350, CH-aliphatic 2944, 3CO 1689 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.80(t, 3H, CH_3), 1.39(m, 2H, $C\underline{H}_2CH_3$), 2.55(m, 2H, $C\underline{H}_2CH_2CH_3$), 3.16(t, 2H, $C\underline{H}_2CH_2CH_2CH_3$), 4.71(s, 2H, CH_2-phthalimide), 5.55(s, 1H, NH-butyl) (D_2O exchangeable), 6.60(s, 1H, NH-SO_2) (D_2O exchangeable), 7.76–7.90(m, 4H, aromatic); Anal. Calcd. for $C_{20}H_{17}Br_4N_3O_5S$: C, 32.86; H, 2.34; N, 5.75; Found: C, 33.20; H, 2.87; N, 6.19.

2.1.22. N-(propylcabamoyl)-4-[(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)-methyl]benzenesulfonamide (VII_n):

0.83g, (58%); mp: 295–296 ºC; IR: 2NH 3373, CH-aliphatic 2933, 3CO 1665 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.83(t, 3H, CH_3), 1.14(m, 2H, $C\underline{H}_2CH_3$), 3.03(t, 2H, $C\underline{H}_2CH_2CH_3$), 4.50(s, 2H, CH_2-phthalimide), 5.50(s, 1H, NH-propyl) (D_2O exchangeable), 6.33(s, 1H, NH-SO_2) (D_2O exchangeable), 7.53–7.89(m, 4H, aromatic); Anal. Calcd. for $C_{19}H_{15}Br_4N_3O_5S$: C, 31.83; H, 2.11; N, 5.86;Found: C, 32.13; H, 2.43; N, 6.13.

2.1.23. N-(cyclohexylcarbamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzene- sulfonamide (VII_o):

0.55 g, (60%); mp: 157–159 ºC; IR: 2NH 3345, CH-aliphatic 2934, 3CO 1694, ^1H NMR (DMSO-d_6): δ1.17-1.70(m, 10H, cyclohexyl group), 2.92(t, 2H,CH_2-ph), 3.23(m, 1H, of cyclohexyl group), 3.49(t, 2H, CH_2-phthalimide), 5.54(s, 1H, NH-cyclohexyl) (D_2O exchangeable), 6.34(s, 1H, NH-SO_2) (D_2O exchangeable), 6,99–7.83(m, 8H, aromatic); Anal. Calcd. for $C_{23}H_{25}N_3O_5S$: C, 60.64; H, 5.53; N, 9.22; Found: C, 60.22; H, 5.89; N, 9.65.

2.1.24. N-(cyclopentylcabamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzene- sulfonamide (VII_p):

0.50 g, (57%); mp: 163–164 ºC; IR: 2NH 3333, CH-aliphatic 2940, 3CO 1694, Ms: m/z 442 (M^++1) (38.08%), 328(M^+- CONH-cyclopentyl) (23.64%), 160(M^+- $CH_2C_6H_4SO_2NHCONH$-cyclopentyl) (12%), 29(100%), Anal. Calcd. for $C_{22}H_{23}N_3O_5S$: C, 59.85; H, 5.25; N, 9.52; Found: C, 60.13; H, 5.57; N, 9.81.

2.1.25. N-(butylcabamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfona- mide (VII_q):

0.47 g, (55%); mp: 186–187 ºC; IR: 2NH 3422, 3322, CH-aliphatic 2945, 3CO 1680, Ms: m/z 429 (M^+) (2.49%), 160(M^+- $CH_2C_6H_4SO_2NHCONH$-butyl) (10.11%), 77(100%), Anal. Calcd. for $C_{21}H_{23}N_3O_5S$: C, 58.73; H, 5.40; N, 9.78; Found: C, 59.11; H, 5.89; N, 10.11.

2.1.26. N-(propylcabamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfo- namide (VII_r):

0.46 g, (55%); mp: 213–214 ºC; IR: 2NH 3329, CH-aliphatic 2925, 3CO 1616 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.80(t, 3H, CH_3), 1.10(m, 2H, $C\underline{H}_2CH_3$), 2.90(t, 2H,CH_2-ph), 3.01(t, 2H, $C\underline{H}_2CH_2CH_3$), 3.87(t, 2H, CH_2-phthalimide), 5.55(s, 1H, NH-propyl) (D_2O exchangeable), 6.23(s, 1H, NH-SO_2) (D_2O exchangeable), 7.80–8.33(m, 8H, aromatic); Anal. Calcd. for $C_{20}H_{21}N_3O_5S$: C, 57.82; H, 5.09; N, 10.11;Found: C, 57.53; H, 5.33; N, 10.46.

2.1.27. N-(cyclohexylcarbamoyl)-4-[2-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfonamide (VII_s):

0.88 g, (57%); mp: 246–247 ºC; IR: 2NH 3324, CH-aliphatic 2928, 3CO 1656, ^{1}H NMR (DMSO-d_6): δ1.02-1.61(m, 10H, cyclohexyl group), 2.90(t, 2H,CH_2-ph), 3.16(m, 1H, of cyclohexyl group), 3.66(t, 2H, CH_2-phthalimide), 5.60(s, 1H, NH-cyclohexyl) (D_2O exchangeable), 6.44(s, 1H, NH-SO_2) (D_2O exchangeable), 7,44–7.76(m, 4H, aromatic); Anal. Calcd. for $C_{23}H_{21}Br_4N_3O_5S$: C, 35.82; H, 2.74; N, 5.45; Found: C, 35.65; H, 2.73; N, 5.87.

2.1.28. N-(butylcabamoyl)-4-[2-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl) ethyl]benzenesulfonamide (VII_t):

0.53 g, (56%); mp: 219–220 ºC; IR: 2NH 3342, CH-aliphatic 2943, 3CO 1665 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.83(t, 3H, CH_3), 1.23(m, 2H, $C\underline{H}_2CH_3$), 1.90(m, 2H, $C\underline{H}_2CH_2CH_3$), 2.90(t, 2H,CH_2-ph), 3.20(t, 2H, $C\underline{H}_2CH_2CH_2CH_3$), 3.45(t, 2H, CH_2-phthalimide), 5.51(s, 1H, NH-butyl) (D_2O exchangeable), 6.45(s, 1H, NH-SO_2) (D_2O exchangeable), 7.28–7.77(m, 4H, aromatic); Anal. Calcd. for $C_{21}H_{19}Br_4N_3O_5S$: C, 33.85; H, 2.57; N, 5.64; Found: C, 33.50; H, 2.92; N, 6.01.

2.1.29. N-(propylcabamoyl)-4-[2-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl) ethyl]benzenesulfonamide (II_u):

0.81 g, (54%); mp: 211–212 ºC; IR: 2NH 3310, CH-aliphatic 2920, 3CO 1615 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.98(t, 3H, CH_3), 1.60(m, 2H, $C\underline{H}_2CH_3$), 2.88(t,2H, CH_2-ph), 3.17(t, 2H, $C\underline{H}_2CH_2CH_3$), 3.66(t, 2H, CH_2-phthalimide), 5.66(s, 1H, NH-propyl) (D_2O exchangeable), 6.51(s, 1H, NH-SO_2) (D_2O exchangeable), 7.44–7.77(m, 4H, aromatic); Anal. Calcd. for $C_{20}H_{17}Br_4N_3O_5S$: C, 32.86; H, 2.34; N, 5.75; Found: C, 33.10; H, 2.73; N, 6.10.

3. PHARMACOLOGY

3.1. Principle of Antihyperglycemic test

The test based on the method used by Ramsey *et al*. **(Ramsey, *et al.*, 2007)** where the compounds to be tested or the standard (gliclazide) were given by oral route to groups of hyperglycemic adult male rats. After administration by three hours, the blood glucose level was determined and compared with standard.

3.2. Materials and Methods

Adult male rats (72 ± 10 days of age, weight ranging between 100 to 150 g) were injected intraperitoneally with streptozotocin (STZ), (60 mg/kg, Sigma) dissolved in 0.9% Sodium citrate buffer (pH 4.5) **(Tanko, *et al.*, 2008).**

Blood glucose levels were measured 48-72 hrs after STZ administration and a value >350 mg/dl was considered to be diabetic. The diabetic rats were divided into three groups (i) drug treated group comprised of 12 subgroups for 12 test compounds, (ii) standard treated group and (iii) vehicle treated group. Each group as well as sub-group was comprised of 6 animals. The tested compounds as well as the standard drug were suspended in 5% gum acacia and administered by oral route at a dose of 200 mg/kg. After three hours, blood was drawn from the tail of conscious rats and the glucose content was estimated with using the (ACCU-CHEK Active) instrument and results were reported as mg/dl).

Table 1: Antihyperglycemic activity of some selected newly synthesized compounds and reference drug

Comp. No.	Serum glucose (mg/dL)	Serum glucose reduction (%)
VII_a	259	40 %
VII_d	267	38 %
VII_e	302	30 %
VII_h	146	44 %
VII_i	250	42 %
VII_l	293	32 %
VII_o	207	52 %
VII_p	224	48 %
VII_q	237	45 %
VII_r	161	44 %
VII_s	293	32 %
VII_t	289	33 %
Diabetic control	432	-
Refrence (Gliclazide)	211	51 %

4. STRUCTURE-ACTIVITY CORRELATION

Compounds belong to the unsubstituted isoindoline-1,3-dione proved to be more active than tetrabromo substituted one. Insertion of a one carbon spacer between the N-terminus of the isoindoline-1,3-dione and the phenyl moiety increased the hypoglycemic activity. Extending the spacer length to two carbons distance (as **VII_o**, **VII_p**, **VII_q** and V**II_r**) produced the most active agent in this work, with 52 %, 48 % and 45 % reduction, respectively. It seemed that two carbons distance favor the interaction with the enzymatic receptors involved. The bulky and long chain alkyl groups on the N-substitution of the sulfonamide moiety produced higher activity than the less bulky and short alkyl one(cyclohexyl and butyl groups are more active than cyclopentyl and propyl groups respectively).

5. CONCLUSION

In the present study, certain new cyclic-imides isoindoline-1,3-diones and their isosters tetrabromoisoindole-1,3- diones bearing aryl sulfonyl urea moieties were synthesized. All of the synthesized Compounds N-(cyclohexylcarbamoyl) -4-[2-(1,3-dioxoisoindolin-2-yl)ethyl]benzenesulfonamide **(VII_o)**, *N*-(cyclopentyl cabamoyl) -4- [2-(1,3-dioxoisoindolin- 2- yl) ethyl] benzenesulfonamide **(VII_p)** *N*-(butylcabamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl] benzenesulfonamide **(VII_q)**,*N*-(cyclohexylcarbamoyl)-4-[(1,3-dioxoisoindolin-2-yl)methyl] benzene sulfonamide **(VII_h)** and *N*-(propylcabamoyl)-4-[2-(1,3-dioxoisoindolin-2-yl)ethyl] benzenesulfonamide **(VII_r)** showed 52, 48, 45, 44 and 44% reduction in serum glucose level, respectively. Gliclazide showed only 51% reduction.

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REFERENCES:

Abdel-Aziz A.M., El-Azab A., Attia S.M., Al-Obaid A.M., Al-Omar M.A. and El-Subbagh H.I., (2011): European Journal of Medicinal Chemistry; **46**:4324-9.

Chan S.H., Lam K.H. , Chui C.H., Gambari R., Yuen M.C. and Wong R.S., (2009): European Journal of Medicinal Chemistry; **44**:2736–2740.

Fertig B.J., Simmon S.A. and Marten M.B., (1995): Diabetes; **95**:1468-9.

Hashimoto, Y., Curr. Med. Chem. 1998; **5**:163.

http://www.afro.who.int/en/clusters-a-programmes/dpc/non-communicable-diseases-managementndm/programme-components/diabetes-mellitus.html, Accessed 6/2013.

http://diabetesmanager.pbworks.com/w/page/17680289/Oral%20Pharmacological%20Agents%20for%20Type%202%20Diabetes, Accessed 9/ 2013.

Ibrahim M.K., Ayyad R.R., Aladl K. and Rashed M., Al-Azhar j. of pharm. Science 2010;**42**:305-322.

Kar A, (2006): Medicinal chemistry, 4th edition, 2006;678.

Kim Y., Yang H., Park K., Koh D. and Lim Y., (2002): Agric. Chem. Biotechnol.; **45(3)**: 141-6

Korytkowski M.T., (2004): Pharmacotherapy; **24**:606-620.

Mahapatra S.P., Ghode P., Jain D.K., Chaturvedi S.C., Maiti B.C. and Maity T.K., (2010): j. pharm. Sci., & Res.; **2(9)**: 567-8.

Miyachi H., Ogasawara A., Azuma A. and Hashimoto Y., (1007): Bioorganic & Medicinal Chemistry; **5**:2095-2102.

Nadendla R.R., (2005): Principle of organic medicinal chemistry, 1st edition; 274-278.

Pascale R., Carocci A., Catalano A., Lentini G. , Spagnoletta A., Cavalluzzi M. M., Santis F.D., Palma A.D., Scalera V. and Franchini C., (2010): Bioorganic & Medicinal Chemistry;**18**: 5903–5914

Ramsey D.J., Ripps H. and Qianab H., (2007): Exp Eye Res.; **85**: 413 -422.

Santos J.L., Yamasaki P.R., Chin C.M., Takashi C.H., Pavan F.R. and Leite C.F., (2009): Bioorganic & Medicinal Chemistry; **17**: 3795–9.

Tanko Y., Yerim M., Mahdi M.A., Yaro A.H., Musa K.Y. and Mohammed A., (2008): International Journal of Applied Research in Natural Products; **1**:32-6.

Yang Y.J., Yang Y.N., Jiang J.S., Feng Z.M., Liu H.Y. and Pan X.D., (2010): Chinese Chemical Letters; **21**:902– 4.

Zhao Q., Yang G., Mei X., Yuan H. and Ning J., (2009): Pesticide Biochemistry and Physiology; **95**:131– 4.

تشييد بعض المشتقات الجديدة من نواة الأيزوإندولين ١,٣- دايون لإختبارها كمضادات لزيادة السكر فى الدم

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بالبحث فى المراجع العلمية المتعددة و من أجل تشييد مركبات جديدة ذات فاعلية مضادة لزيادة نسبة السكر فى الدم وجد لبعض المشتقات الجديدة من نواة الأيزوإندولين ١,٣- دايون فاعلية عالية فى تقليل نسبة السكر فى الدم ؛ و حيث أن هذه المركبات تمثل نواة جديدة تم استحداثها فى هذا المجال، فقد تم فى هذا البحث تصميم و تشييد بعض من مركبات الأيزوإندولين ١,٣- دايون الجديدة والتى تحتوى على مجموعات السلفونيل يوريا كمواد ذات فاعلية محتملة ضد زيادة السكر فى الدم ، و قد تم إختبار تأثير بعض من هذه المركبات على زيادة نسبة السكر فى الدم ووجد أن لها مفعول إيجابى .

تم الاستعانة بعدد من المراجع العلمية القديم منها و الحديث و عددها 19 مرجعا.