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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME NEW ARYLSULPHONYLUREA AND THIOUREA DERIVATIVES

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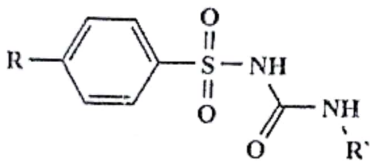
ABSTRACT

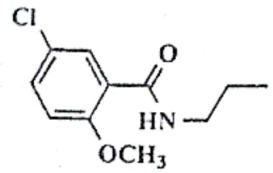
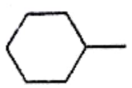
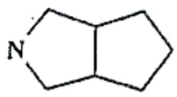
Certain arylsulphonylureas and thioureas derivatives were synthesized to be tested as hypoglycemic and antimicrobial agents in comparison with glibinclamide and sulphanilamide, respectively. The interaction of 3-chloro-2-[p-substitutedphenylamino]-N-(4-sulphamoylphenyl) maleimide (2) or its carbamate derivatives (3) with phenylisocyanate, phenylisothiocyanate or with appropriate amine afforded the target products. Some of the new compounds showed considerable hypoglycemic and antimicrobial activities.

INTRODUCTION

Arylsulphonylureas (I) are oral hypoglycemic agents have been shown to stimulate the pancreas to secrete insulin.[1] They could act on pancreas β-cells inhibiting ATP-dependent potassium (K+)-channels.[2] Despite the availability of the well known aryl-sulphonylurea derivatives (Table 1) as glibenclamide **Ia**, gliclazide **Ib**, chloropropamide **Ic**, and tolbutamide **Id**; arylsulphonylureas with extended plasma half-life[3,4] still being needed. Therefore, the goal of the present program has been directed to provide new compounds with potential antidiabetic activity and with the aim to investigate structure-activity relationship [5] . The newly suggested compounds have been designed to incorporate maleimide moiety in addition to the arylsulphonylurea or arylsulphonylthiourea structures.

Table 1: Arylsulphonylureas (I) oral hypoglycemic agents.



Compound	R	R`
I_a		
I_b	H_3C	
I_c	Cl	C_3H_7
I_d	H_3C	C_4H_9

Numerous derivatives of maleimide have also been developed as potential antimicrobial agents [6-8] . In the present work, it has been also decided to evaluate the newly synthesized maleimides for antimicrobial potencies.

CHEMISTRY

The synthesis of the designed new compounds was achieved by the route depicted in **Scheme 1.** The imidation of 2,3-dichloromaleic anhydride with 4-aminobenzenesulphonamide according to the reported procedure(9) afforded 2,3-dichloro-N-(4-sulphamoylphenyl) maleimide (1). Aminolysis of 1 with aromatic amines via Michael type reaction through activated addition elimination mechanism yielded the key intermediate (2) in reasonable yields.

Treatment of 2 with ethylchloroformate in the presence of anhydrous potassium carbonate afforded the carbamate (3). Condensation of 3 with either cyclohexylamine or propylamine gave the corresponding sulphonylureas (4a-d) and (4e,f), respectively. Alternatively, sulphonyluraes (4g-i) and sulphonylthioureas (4j-l) were obtained by condensation of 2 with phenylisocyanate or phenylisothiocyanate in refluxing acetone and dimethylformamide mixture.

Experimental :

All melting points are uncorrected. Microanalyses were performed at microanalytical center, Cairo University. Infrared spectra were carried out using Pye Unicam sp 1100 spectrophotometer. The ^{1}H-NMR spectra were recorded on Varian EM390, 90 MHz spectrometer using DMSO-d6 as a solvent and TMS as an internal standard.

2,3-Dichloro-N (4-sulphamoylphenyl) maleimide (1):

To a solution of 2,3-dichloromaleic anhydride (3.34 g, 20 mmol) in glacial acetic acid (40ml), the 4-aminobenzenesulphonamide (3.44 g, 20 mmol) in glacial acetic acid (20 ml) was dropwise added followed by refluxing the reaction mixture while stirring for 1 h. After cooling, the separated solid was filtered, washed with water, and crystallized from dioxane, yield 95%, mp > 300.

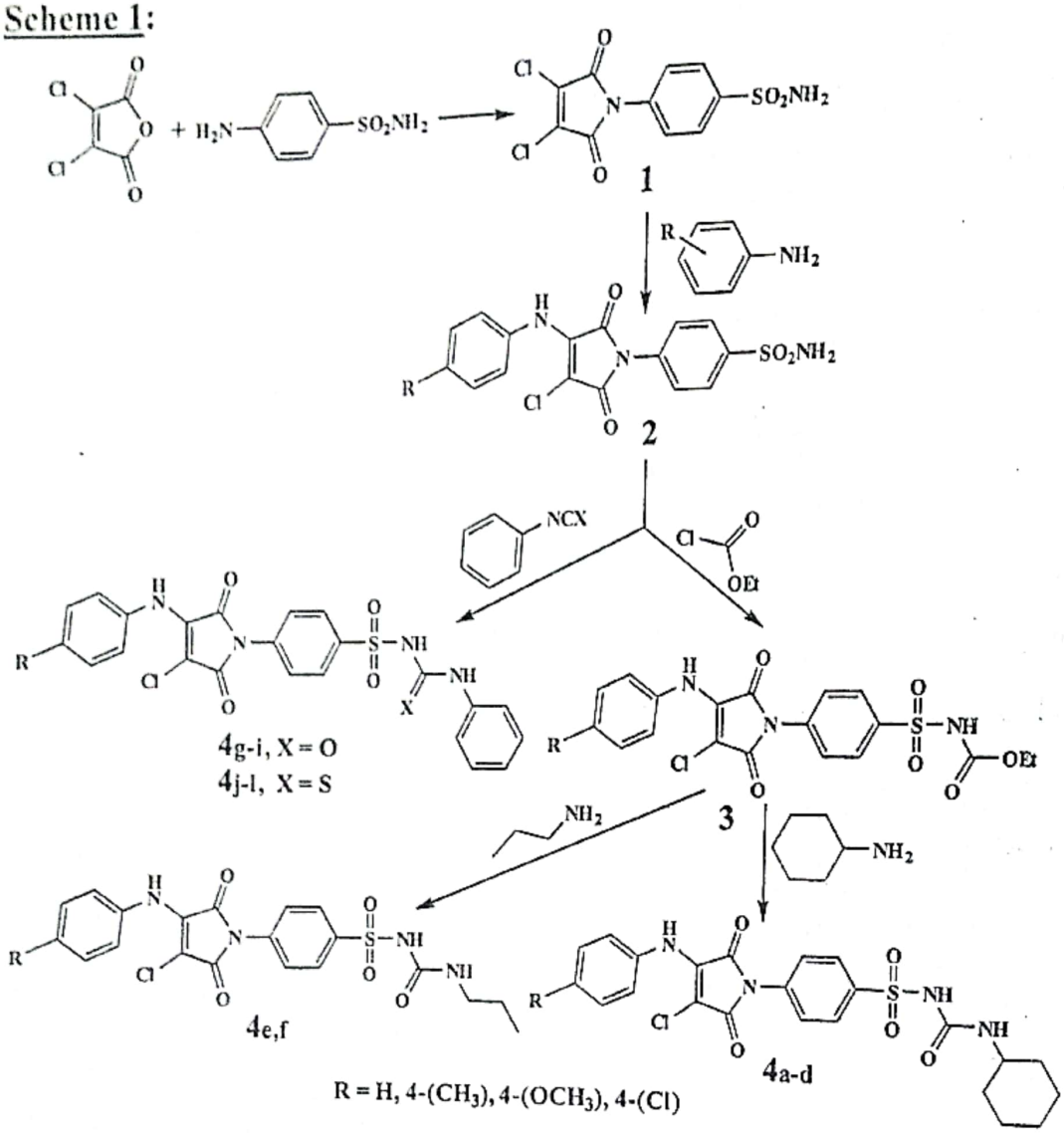
Analysis for $C_{10}H_6Cl_2N_2O_4S$ (M. Wt. = 321)

	C	H	N
Calcd	37.38	1.86	8.72
Found	37.5	1.7	8.8

3-Chloro-2- [p-substitutedphenylamino]-N-(4 sulpha - moylphenyl) - maleimide (2):

To a solution of 1 (3.21 g, 10 mmol) in dioxane (40 ml), primary aromatic amines (10 mmol) in dioxane (10 ml) were added dropwise while stirring under reflux for 1 h. The reaction mixture was then concentrated

Scheme 1:



under reduced pressure, cooled, diluted with cold water, and filtered, washed with water and crystallized from dioxane/water (Table 2).

3-Chloro-2-[p-substitutedphenylamino]-(4-ethoxycarbonylamino -sulphonylphenyl)maleimide (3):

To a solution of 2a-d (20 mmol) in a mixture of equal volumes of dry acetone and dioxane (50 ml), finely divided anhydrous potassium carbonate (5 g) was added and the the mixture was heated under reflux for 1 h with continuous stirring. Ethyl chloroformate (20 mmol) was added dropwise. After complete addition the reaction mixture was heated under reflux for 6 h. The reaction mixture was filtered while hot; the filtrate was concentrated under reduced pressure to 20 ml, then poured into ice water (50 ml) and then acidified with acetic acid. The separated crude product was crystallized from chloroform/pet. ether (Table 3).

1-Cyclohexyl or propyl-3-[4-(3-chloro -2-p-substituted-phenylamino - N- maleimidyl) phenylsulphonyl] ureas (4a-f):

3-Chloro-2-substitutedphenylamino-N(4-ethoxy - carbonylaminosulph-onylphenyl)maleimide (3) (20 mmol) was dissolved in primary aliphatic amine (10 ml). The reaction mixture was heated under reflux for 4 h. The reaction mixture was then cooled; the separated crude product was dissolved in dry chloroform (30 ml), filtered and concentrated to 10 ml and then added petroleum ether (20 ml). The separated solid was crystallized from chloroform/pet. ether (Table 4).

1-Phenyl -3- [4 (3-chloro- 2- (p-substituted-phenylamino) N -maleimidyl) phenylsulphonyl] ureas or thioureas (4g-l):

To a solution of 2 (20 mmol) in a mixture of dry acetone (40 ml) and dimethylformamide (10 ml), finely divided anhydrous potassium carbonate (5 g) was added and the flask was dipped in an ice-bath. Phenylisocyanate or phenylisothiocyanate (20 mmol) was added dropwise over a period of 10 min. with concurrent stirring. The reaction mixture was removed from ice-bath and was then heated under reflux for 8 hours, then it was filtered while hot. The filtrate was concentrated under reduced pressure to 20 ml, poured into ice water (50 ml) and then acidified with acetic acid; the separated crude product was crystallized from DMF/water (Table 4).

BIOLOGICAL ACTIVITIES

Materials and Methods :

I) ***Hypoglycemic activity :***

Two of the newly prepared compounds 4b and 4f

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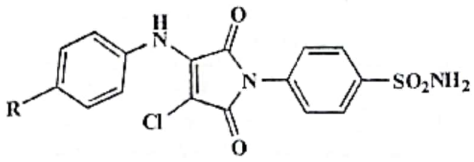
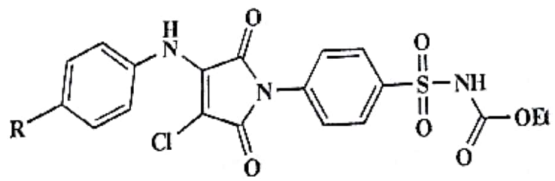
Table 2: 3-Chloro-2-[p-substitutedphenylamino] -N-(4-sulphamoylphenyl) -maleimide (2a-d).



Comp. No.	R	Yield %	M.P.	M. F. & M.Wt.	Analysis	
					Calcd	Found
2a	H	95	282-3	$C_{16}H_{12}ClN_3O_4S$ (377.5)	C=50.86 H= 3.17 N= 11.12	50.6 3.2 11.3
2b	CH_3	90	273- 4	$C_{17}H_{14}ClN_3O_4S$ (391.5)	C=52.10 H=3.57 N=10.72	52.0 3.5 10.6
2c	OCH_3	92	268-9	$C_{17}H_{14}ClN_3O_5S$ (407.5)	C=50.06 H=3.43 N=10.30	49.9 3.5 10.2
2d	Cl	88	292-3	$C_{16}H_{11}Cl_2N_3O_4S$ (412)	C=46.60 H=2.66 N=10.19	46.5 2.8 10.3

IR spectra of compound 2_b (cm^{-1}): 3300 and 3200 (NH), 3060-2900 (CH aromatic and aliphatic), 1710 and 1650 (C=O), 1180 (SO_2). **^{1}H-NMR** of compound 2b (DMSO-d6, ppm): 1.8 (s, 3H, CH_3), 6.8-7.8 (m, 8H, aromatic protons), 8.6 (s, 1H, NH), 10.1 (s, 2H, NH_2).

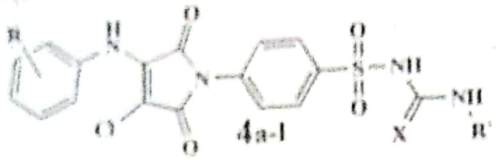
Table 3:3-Chloro -2 - [p-substitutedphenylamino] -N- (4-ethoxycarbonylaminosulphony-lphenyl) maleimide (3a-d).



Comp. No.	R	Yield %	M.P.	M. F. & M.Wt.	Analysis	
					Calcd	Found
3a	H	57	268-9	$C_{19}H_{16}ClN_3O_6S$ (449.5)	C=50.72 H= 3.55 N= 9.34	50.6 3.7 9.5
3b	CH_3	55	228-9	$C_{20}H_{18}ClN_3O_6S$ (463.5)	C=51.77 H=3.88 N=9.06	51.9 3.8 9.2
3c	OCH_3	51	192-3	$C_{20}H_{18}ClN_3O_7S$ (479.5)	C=50.05 H=3.75 N=8.75	50.2 3.6 8.9
3d	Cl	50	232-1	$C_{19}H_{15}Cl_2N_3O_6S$ (484)	C=47.1 H=3.09 N=8.67	47.0 3.2 8.6

^{1}H-NMR of compound 3c (DMSO-d6, ppm): 1.3 (3H, t, CH_3), 3.8 (3H, s, OCH_3), 4.2 (2H, q, CH_2), 6.8-7.8 (8H, m, aromatic protons), 9.1 (1H, s, NH), 10.7 (1H, s, NH)

Table (4) : 1-Alkyl or (Phenyl) -3- [4-(3-chloro-2- substitutedphenylamino -N- maleimidyl) phenyl-sulphonyl] ureas or thioureas.



4a-l

Sor No	R	R'	X	Yield %	m.p.	MF & MWt	Analysis	
							Calcd	Found
a	H		O	72	223-4	$C_{23}H_{23}ClN_4O_5S$ (502.5)	C= 54.92 H= 4.57 N= 11.14	55.0 4.7 11.3
b	p-(CH_3)		O	75	216-7	$C_{24}H_{25}ClN_4O_5S$ (516.5)	C= 55.75 H= 4.84 N= 10.84	55.7 4.7 10.9
c	p-(OCH_3)		O	78	205-6	$C_{24}H_{25}ClN_4O_6S$ (532.5)	C= 54.08 H= 4.69 N= 10.51	53.8 4.5 10.7
d	p-(Cl)		O	70	182-3	$C_{23}H_{22}Cl_2N_4O_5S$ (537)	C= 51.39 H= 4.09 N= 10.42	51.5 4.3 10.3
e	H	C_3H_7	O	65	128-9	$C_{20}H_{19}ClN_4O_5S$ (462.5)	C= 51.89 H= 4.10 N= 12.1	52.0 4.2 12.3
f	p-(CH_3)	C_3H_7	O	67	145-6	$C_{21}H_{21}ClN_4O_5S$ (476.5)	C= 52.88 H= 4.40 N= 11.75	53.0 4.3 11.9
g	H		O	82	208-9	$C_{23}H_{17}ClN_4O_5S$ (496.5)	C= 55.58 H= 3.42 N= 11.27	55.8 3.3 11.4
h	p-(CH_3)		O	75	221-2	$C_{24}H_{19}ClN_4O_5S$ (510.5)	C= 56.41 H= 3.72 N= 10.96	56.6 3.7 11.1
i	p-(OCH_3)		O	80	246-7	$C_{24}H_{19}ClN_4O_6S$ (526.5)	C= 54.70 H= 3.60 N= 10.63	54.8 3.5 10.8
j	H		S	65	211-2	$C_{23}H_{17}ClN_4O_4S_2$ (512.5)	C= 53.85 H= 3.31 N= 10.92	53.9 3.5 10.8
k	p-(CH3)		S	63	203-4	$C_{24}H_{19}ClN_4O_4S_2$ (526.5)	C= 54.70 H= 3.60 N= 10.63	54.9 3.5 10.4
l	p-(OCH3)		S	60	196-7	$C_{24}H_{19}ClN_4O_5S_2$ (542.5)	C= 53.08 H= 3.50 N= 10.32	52.8 3.7 10.4

^{1}H-NMR of compound **4h** (DMSO-d_6, ppm): 1.0-2.1 (13H, m, cyclohexyl protons and CH_3), 3.2 (1H, m, N-CH of cyclohexyl), 5.6 (1H, d, NH), 6.7-7.9 (8H, m, aromatic protons), 8.7 (1H, s, NH), 10.6 (1H, s, NH).

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were screened for their hypoglycemic activity. Thirty six mature albino rats with average weight 200 gm, were used in this study. They were kept under supervision two weeks before the beginning of experiment and left on access of food and water. All rats were rendered hyperglycemic by experimental intraperitoneal injection of streptozolocin at a dose of 38 mg/kg. (18) They were divided into 6 equal groups (each of 6 rats). The first group was served as diabetic control, meanwhile, the other groups were orally administered the reference drug (glibenclamide) and the tested new compounds in a single dose as shown in the following:

Group II given glibenclamide at 0.014 mg/200 mg

Group III given compound 4b (1) at 0.016 mg/200 mg

Group IV given compound 4b (2) at 0.064 mg/200 mg

Group V given compound 4f (1) at 0.015 mg/200 mg

Group VI given compound 4f (2) at 0.06 mg/200 mg

Blood samples were withdrawn from the orbital sinus of all rats into centrifuge tubes containing sodium fluoride at 1,3, and 6 h post dosing and then centrifuged at 3000 r.p.m for 15 min for separation of plasma. The separated plasma was used for determination of blood glucose(11) and insulin levels.(12) Rats were sacrified after 6 h post dosing and the liver was removed and kept in physiological saline solution 0.9% for determination of liver glycogen.(13). The obtained data were statistically analyzed using Students "t" test (14) (Table 5).

II) ***Preliminary antimicrobial activity:***

The antimicrobial screening of the compounds 4b, 4f, 4g, 4i, and 4k against gram positive, gram negative bacteria and fungi was carried out using the disc diffusion method (15) using sulphanilamide as reference drug. The sterile discs were impregnated with different compounds (10 mg/disc). The discs were placed on the surface of the cold solid medium in petri dishes, incubated with the considered microorganisms and then incubated at 5°C for 1 h to permit good diffusion and, transferred to an incubator at 37°C for 24 h, then examined for the inhibition zones caused by the various compounds on the tested microorganisms (Table 6).

RESULTS AND DISCUSSION

I- For hypoglycemic activity:

The data obtained in this study for the newly synthesized compounds as hypoglycemic agents in rats were statistically analyzed and given in Table 5. The results showed that compound 4b in both of the applied doses (1 and 2) and the compound 4f in the used dose (1) only significantly reduced the blood glucose level up to 6 h which were relatively similar to that of glibenclamide compared with diabetic control rats. On the other hand, they elicited a variable significant increase in insulin level at 3 and 6 h after their oral administration to diabetic rats. Our finding regarding the liver glycogen revealed a highly significant increase induced by reference drug, as well as the tested compounds at 6 h after dosing.

The significant variation induced by the tested new compounds (4b, 4f) on both glucose and liver glycogen could be ascribed to the significant increase in insulin level, which might be due to their effect on β - cells like sulphonylureas derivatives. This would be in accordance the reported data (16-19).

II-For preliminary antimicrobial investigation:

Compounds 4f, 4i, and 4k showed potent activity against gram positive bacteria while compound 4g showed significant activity against *Escherchia coli* and *Sarcina lutea*. Compound 4b showed no activity at all. None of the tested compounds showed antifungal activity (Table 6).

Table (5) : Effect of the orally administered (single dose) newly synthesized sulphonylureas on blood glucose and insulin levels, as well as on liver glycogen of rats at different time intervals.

Parameter	Time Post dosing (h)	Group I (control) Diabetic	Group II (Daonil) 0.014 mg/200 gm	Group III [compound $4b_{(1)}$] 0.016 mg/200 gm	Group IV [compound $4b_{(2)}$] 0.064 mg/200 gm	Group V [compound $4f_{(1)}$] 0.015 mg/200 gm	Group V [compound $4f_{(2)}$] 0.060 mg/200 gm
Glucose (mg/dl)	1	239.17±13.99	152.33±14.87**	177.83±19.19*	159.18±19.29**	164.85±25.07*	187.0±26.33
	3	250.36±17.4	137.8±15.77***	151.33±24.33**	139.33±25.45**	157.0±19.61**	186.17±29.59
	6	243.17±19.46	98.33±22.98***	136.17±23.09**	133.16±21.25**	153.33±22.43**	178.18±36.76
Insulin (µu/ml)	1	4.80±0.33	8.71±1.21**	7.87±1.14	7.9±0.69**	6.38±1.41	5.18±1.17
	3	5.02±0.79	9.32±1.5**	8.73±0.96**	9.15±1.12**	7.98±1.19*	5.2±0.09
	6	4.78±0.43	9.71±1.7**	8.99±1.51**	8.83±1.36**	8.42±1.27*	5.57±1.73
Liver Glycogen (mg/100 gm)	6	456.6±27.3	1015.34±18.14****	926.44±21.23****	932.9±26.8****	753.08±32.81***	458.6±12.91

* Significant at P<0.05 ** Significant at P<0.01 *** Significant at P<0.005 **** Significant at P<0.001

Table 6: Preliminary antimicrobial activity of the newly prepared compounds.

Compound	Microorganisms*					
	1	2	3	4	5	6
4_b	-	-	-	-	-	-
4_f	-	-	-	25	20	-
4_g	30	-	-	20	-	-
4_i	-	-	-	15	10	-
4_k	-	-	10	20	20	-
Sulphanilamide	20	-	15	-	-	-

*1-*Escherichia coli* G-ve 2-*Pseudomonas aeroginosa* G-ve
3-*Staphylococcus aureus* G-ve 4-*Sarcina lutea* G+ve
5-*Bacillus subtilis* G+ve 6-*Candida albicans* Fungi

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تشييد بعض مشتقات أريل سلفونيل يوريا وثيويوريا الجديدة ذات النشاط البيولوجى

منصور أبوكل - مجدى عامر*

قسم الكيمياء الطبية - كلية الصيدلة - جامعة الزقازيق * قسم الفارماكولوجيا - كلية الطب البيطرى - جامعة المنصورة

استهدف البحث تشييد بعض مركبات أريل سلفونيل يوريا - وأريل سلفونيل ثيويوريا المشتقة من مركبات ٣ -كلورو -٣- (بارا فينيل امينو) -ن- (٤-سلفاموبل فينيل) ماليميد بهدف الحصول على مركبات جديدة ذات فاعلية فى خفض سكر الدم ويتم تناولها عن طريق الفم وكذا كمضادات للميكروبات، وقد تم التأكد من التركيب الكيميائى لهذه المركبات الجديدة بواسطة التحليل الدقيق للعناصر والاشعة تحت الحمراء وكذا الرنين المغناطيسى وقد وجد أنه لبعض المركبات المختبرة تأثير خافض لسكر الدم ومضاد للميكروبات.