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Synthesis Of New Compounds Derived From Dapsone And Study Their Biological Activity

Tareq K. Ibraheem*[1] and Ziad T I Alkayar[1], Mohammed A M Al-badri[2]

[1]Department of Chemistry, College of Education for Pure Science, University of Diyala/Iraq,
[2]College of Dentistry / Al-Iraqia University/Iraq
Corresponding Author: Email: tariq.phd744@gmail.com

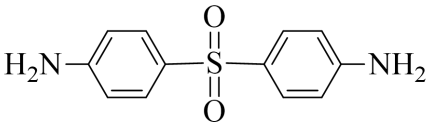
ABSTRACT
The new compounds were synthesized by treating the drug dapsone 1 with chloroacetyl chloride in the presence of base. Both amino groups are acylated to give compound 6. The symmetrical acylated product then treated with Aniline, Saccharine, p-Bromoaniline, m-Bromoaniline, p-Hydroxyaniline, m-Hydroxyaniline, o-Phenylenediamine and m-Phenylenediamine to give compounds 7(a-h). All the new compounds have scanned for their biological activities toward gram negative (Esherichia coli, Proteus mirabilis) and gram positive (Streptococcus pneumoniae, Mycobacterium tuberculosis) bacteria, the synthesized derivatives gave moderate to good activity as compared to the parent drug toward both mentioned types of bacteria.

Keywords: dapsone, symmetrical, sulfones family, Antibacterial activity

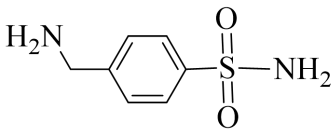
Correspondence:
Tareq K. Ibraheem
1Department of Chemistry, College of Education for Pure Science, University of Diyala/Iraq,
*Corresponding author: Tareq K. Ibraheem email-address: tariq.phd744@gmail.com

INTRODUCTION

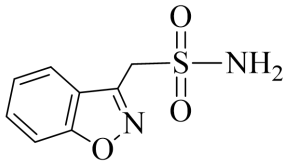
The Dapsone **1** is the drug that belongs to the sulfones family which can be used as treatment for dermatitis herpetiformis, leprosy and lepromatous disease. Figure 1 shows some examples of sulfones drugs; Mafenide **2**,[1] Zonisamide **3**,[2] Sulfadiazine **4**,[3] Probenecid **5**.[4] Sulfones are antimicrobial agents, acts as anti-metabolites for sensitive organisms.[5] The drugs modification becomes an interested branch for many research groups around the world. For the crucial role of sulfones in the medicine we focused on the synthesis of some new compounds that derived from dapsone.[6,8] Generally introducing substituted aromatic ring to the drugs might enhance the drugs activity to give better biological results.[9,10]



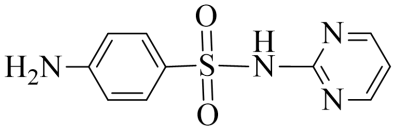
Dapsone
1



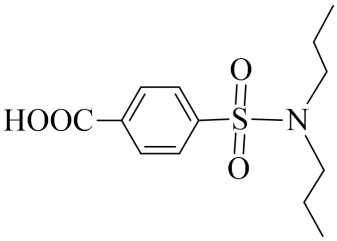
Mafenide
2



Zonisamode
3



Suladiazine
4



Probenecid
5

Figure 1 Sulfones drugs

Based on the extensive search for compounds with potential pharmacological value, it looks like these derivatives might give a good way to modify the structure of the Dapsone.[11,12] Since the literature reported the presence of Dapsone resistance.[13,14] An attempt have made to synthesize the derivative of Dapsone and to study the biological activity of the synthesized compounds.

Experimental

The reactions for the synthesis and purification of the compounds were carried out in the efficient fume cupboard. The Dapsone was obtained from SDI Company. The other material have brought from Fulka, Across Organic and Aldrich chemical companies. Solvents and reagents have purchased from markets and were of analytical grade. Spectra of FT-IR were obtained in KBr pellets from (FT-IR 8300) Shimadzu spectrophotometer in the range 4000-400 (cm^{-1}) region. All the reactions were followed by the TLC using silica plates and visualising by Ultraviolet at 254 (nm), potassium permanganate chamber was used for staining.

Synthesis of N,N'-(Sulfonylbis(4,1-phenylene))bis(2-chloroacetamide) 6

To Dapsone **1** (0.5 g, 2.0136 mmol), potassium carbonate (0.55 gm, 4.027 mmol) in DMF (10 mL), was added chloroacetyl chloride (0.32 mL, 4.027 mmol) dropwise. After 4 hours the mixture of reaction was poured into the ice. Filtration, solvent evaporation, recrystallization from EtOH gave **6** in 95% yield, as white precipitate. R_f 0.18 [petrol–EtOAc (8:2)]; IR *vmax*(film)/cm^{-1} 3314, 3110, 2987, 1684, 1534, 1302, 1107, 836 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.90 (2H, s, NH), 7.85 (4H, d, *J* 9 Hz, ArH), 7.75 (4H, d, *J* 9 Hz, ArH), 4.25 (4H, s, CH_2Cl); ^{13}C NMR (101 MHz, DMSO-d6) δ= 166.2, 143.7, 136.5, 129.3, 120.2, 44.4.

General method for alkylation

To a mixture of compound **6** (4.0 gm, 10 mmol) and NaOH (0.5 gm, 10 mmol) in ethanol (20 mL), was added amine **7(a-h)** (20 mmol). The reaction heated under reflux; after 5 h the reaction was cooled to room temperature and water (15 mL) was added. Extraction from ether (2 × 4 mL) and the organic layer were combined, dried ($MgSO_4$), filtered and concentrated under vacuum pressure.

Synthesis of compounds 8a-h

Column chromatography was used for the purification, eluting with CH_2Cl_2–MeOH (9:1) and recrystallization from MeOH gave **9a**; IR ν_{max}(film)/cm^{-1} 3330, 3320, 3110, 2987, 1684, 1534, 1302, 1107, 836 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.50 (1H, s, NH), 8.90 (2H, s, NH), 7.75-7.20 (18H, m, ArH), 3.60 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 169.4, 140.6, 137.6, 128.4, 127.5, 126.5, 122.0, 65.1. **9b**; IR ν_{max}(film)/cm^{-1} 3398, 3305, 3112, 2986, 1674, 1529, 1306, 1104, 829 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.60 (2H, s, NH), 7.91-7.23 (16H, m, ArH), 3.62 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 170.5, 160.4, 146.2, 138.9, 129.2, 128.7, 128.0, 121.1, 66.7. **9c**; IR ν_{max}(film)/cm^{-1} 3350, 3308, 3114, 2988, 1676, 1532, 1308, 1107, 832 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.20 (H, s, NH), 8.74 (2H, s, NH), 7.86-7.29 (16H, m, ArH), 3.65 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 171.2, 161.5, 146.25, 138.6, 135.2, 131.0, 128.8, 126.3, 67.3. **9d**; IR ν_{max}(film)/cm^{-1} 3397, 3306, 3112, 2985, 1670, 1531, 1305, 1107, 730 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.50 (H, s, NH), 8.80 (2H, s, NH), 7.90-7.25 (16H, m, ArH), 3.62 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 170.1, 165.2, 134.8, 139.6, 137.8, 130.7, 128.9, 126.8, 68.2. **9e**; IR ν_{max}(film)/cm^{-1} 3388, 3321, 3115, 2989, 1677, 1535, 1316, 1111, 848 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.42 (H, s, NH), 8.95 (2H, s, NH), 7.95-7.32 (16H, m, ArH), 3.79 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 178.1, 164.1, 150.8, 143.6, 134.8, 133.7, 128.8, 66.6. **9f**; IR ν_{max}(film)/cm^{-1} 3390, 3327, 3119, 2990, 1678, 1537, 1319, 1117, 800 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.90 (H, s, NH), 8.89 (2H, s, NH), 7.85-7.35 (16H, m, ArH), 3.81 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 180.1, 166.0, 142.3, 140.9, 138.6, 136.7, 129.7, 68.6. **9g**; IR ν_{max}(film)/cm^{-1} 3450, 3390, 3327, 3115, 2980, 1678, 1537, 1319, 1117, 800 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.80 (H, s, NH), 8.80 (2H, s, NH), 7.91-7.30 (16H, m, ArH), 4.67 (2H, s, NH_2), 3.81 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 175.1, 162.9, 143.3, 141.9, 135.6, 134.7, 129.9, 65.6. **9h**; IR ν_{max}(film)/cm^{-1} 3469, 3385, 3327, 3121, 2991, 1675, 1537, 1319, 1117, 810 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.80 (H, s, NH), 8.85 (2H, s, NH), 7.85-7.20 (16H, m, ArH), 4.70 (2H, s, NH_2), 3.73 (4H, s, CH_2N); ^{13}C NMR (101 MHz, DMSO-d6) δ= 170.1, 163.0, 141.3, 140.9, 137.6, 135.7, 130.7, 65.6.

RESULTS AND DISCUSSION

The aim is to synthesis new Dapsone derivatives and to do so, the dapsone **1** was treated with two equivalents of Chloroethanoyl chloride **6** in Dimethylformamide (DMF), and anhydrous potassium carbonate. The reaction has carried out at 25 °C to give the diacylated product **7** in excellent yield,[15] the product was confirmed using IR spectrophotometer and NMR spectroscopy. The reaction was monitored by TLC silica plate and was completed after 4 hour see Scheme 1.

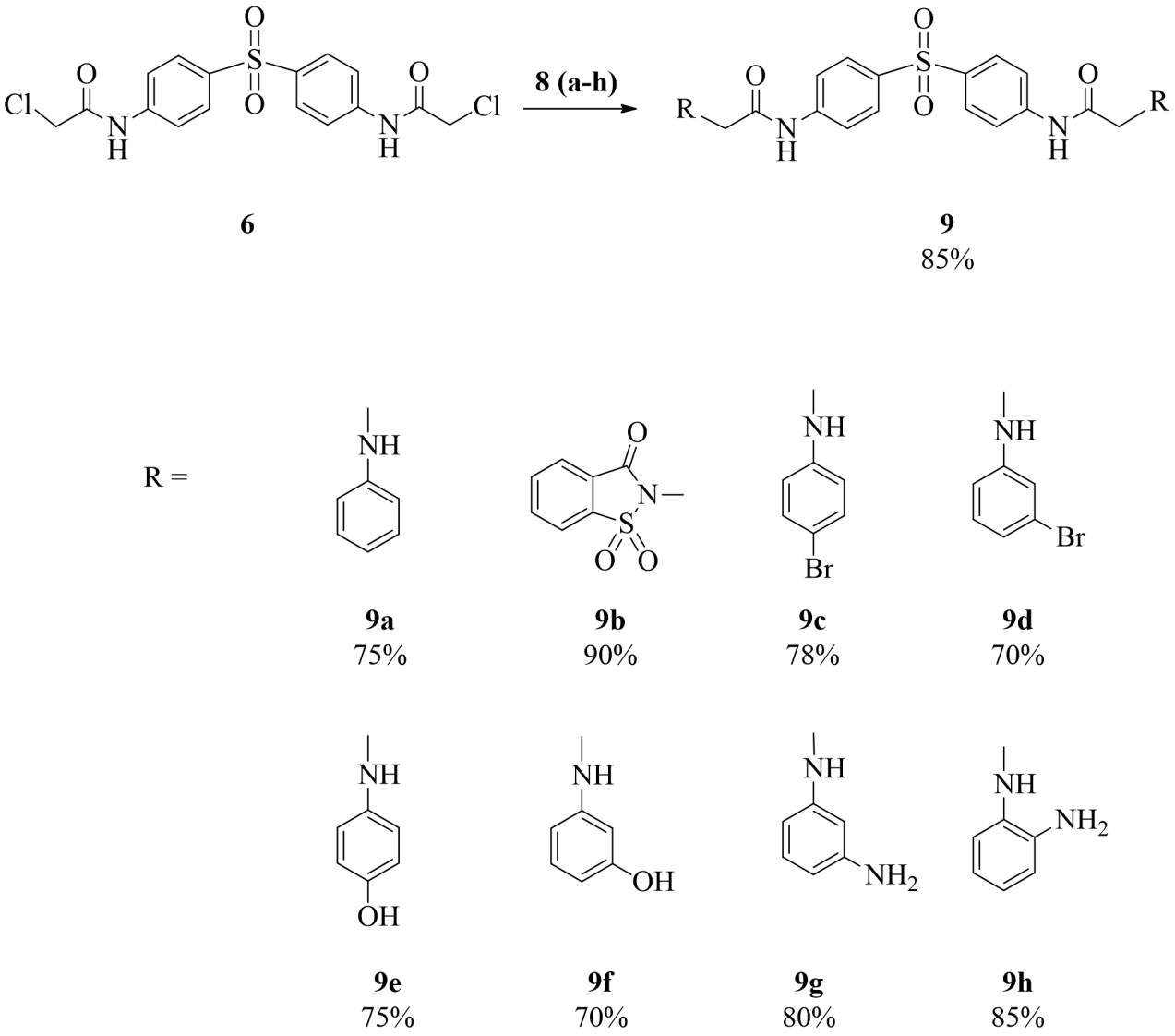
The peaks of amino (NH_2) groups of the starting material **1** were disappeared in the IR spectra and the peak at 1684 cm^{-1} was appeared instead, which is belong to amide group, indicating that the acylation step was carried out successfully.

1 **6** **7**

95%

Scheme 1

The target compounds **9a-h** have obtained by treating compound **6** with different amines; Aniline **7a**, Saccharine **7b**, *p*-Bromoaniline **7c**, *m*-Bromoaniline **7d**, *p*-Hydroxyaniline **7e**, *m*-Hydroxyaniline **7f**, *m*-Phenylenediamine **7g** and *o*-Phenylenediamine **7h** see (Scheme 2).



Scheme 2

For the all obtained compounds the yield were good see Table 2, and the reactions completion was monitored using TLC silica plate.

In the ^{1}H NMR spectra of compound **6** revealed the presence of NH group as singlet at 8.90 ppm. The protons belong to CH_2Cl appeared at 4.24 ppm. ^{1}H NMR spectra of compounds **9a-h** the protons on CH_2N were at 3.60–3.60 ppm. In the ^{13}C NMR the peak of CH_2Cl at 44.4 ppm was disappeared and the peak at 65.1–68.5 ppm of CH_2N was appeared, indicating that the chloride was displaced by nitrogen.

Antibacterial activity

The big challenging problem is the treatment of infectious diseases, and this because of important factor including the resistance to the bacteria therapy. The biological effect of the synthesized compound have screened against gram –ve and gram +ve. As shown in Table 2, compared with Erythromycin and Amoxicillin, some compounds showed moderate to good antibacterial activity.

The antibacterial activities of the synthesized compounds were tested against (*Esherichia coli, Proteus mirabilis*) gram negative bacteria and (*Streptococcus pneumoniae, Mycobacterium tuberculosis*) gram positive bacteria using disc diffusion method. Here, Here dapsone **1** is tested as reference compound to compare the activity the test was done using the paper disc diffusion method.[16]

Clearly, Table 1 shows the activities of the chosen strains were dapsone derivatives have enhanced the antibacterial activity. Data exhibit that the effects of the substance under investigation towards *E. coli* and *P. mirabilis* and *S. pneumoniae* and *M. tuberculosis* better than the reference.

Comp no.	Zone of inhibition in (mm)			
	M. tuberculosis	S. pneumoniae	E. Coli	P. mirabilis
6	16	17	20	14
9a	24	22	23	25

9b	26	23	23	19
9c	20	26	19	22
9d	20	25	17	20
9e	18	32	14	15
9f	17	19	20	21
Dapsone	15	11	10	12
DMSO solvent	0	0	0	0

Table 1 Concentration of Dapsone = 10 mg/mL, Concentration of sample = 10 mg/mL

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