Note

Inhibitory Effects on Microbial Growth Using the Derivatives of Benzyl Phenyl Sulfide

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We investigated the antimicrobial activities of twelve derivatives of benzyl phenyl sulfide by using Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) values against 10 microbial strains. These derivatives of benzyl phenyl sulfides were synthesized by means of the nucleophilic coupling reaction at our laboratory. MIC testing revealed that all synthetic derivatives of benzyl and 4-methoxybenzyl phenyl sulfides had no effect against the tested microbial strains. However, the compounds of 4-nitrobenzyl phenyl sulfide showed antimicrobial activity against many of the tested strains. Above all, 4-nitrobenzyl 4-chlorophenyl sulfide 11 exhibited the strongest and widest ranging inhibitory effects among the twelve synthetic compounds. We researched the antimicrobial activities of the coupling materials of sulfide. As a result, it was considered important for the expression of antimicrobial activities that the sulfide had a 4-nitrobenzyl group and 4-chlorophenyl group in the same molecule as in the case of benzyl phenyl sulfide.

Key words : Benzyl phenyl sulfide/Halogen group/Chemical structure/MIC/MBC.

Sulfide is an organic compound with a thioether bonding in its chemical structure. The derivatives of sulfide have special smells, and are found in plants such as garlic or onion. Medical supplies and antibacterial agents frequently contain the thioether bond in part of their molecular structure (Hsiao-C et al., 2010; Wu et al., 2004; Rattanachaikunsopon et al., 2008). For example, allyl sulfide, an important organosulfur component of garlic oil, has been reported to suppress the growth of multiple cancer cells in culture and in vivo models (Anna et al., 2008). We have hitherto researched the syntheses and function of unnatural nucleosides and nucleoside analogues (Hatano et al., 2004; 2008), and then reported their antibacterial and bactericidal activities (Hatano et al.,

2009). The benzyl sulfides were synthesized to investigate the unnatural nucleoside forming base pair reversibly and covalently using both a reducing agent and oxidizing agent. Derivatives of benzyl sulfide Bn-S-R (R: substituted group) were easily oxidized to produce the sulfoxide Bn-S(=O)-R form (Noguchi et al., 2008; Kirihaara et al., 2009). Therefore, this chemical structure and oxidized property of benzyl sulfide could perform inhibitory and controlling actions on microbial strains in industrial setting and hospitals.

In this study, we tested the antimicrobial activities of twelve benzyl phenyl sulfide derivatives R-Bn-S-Ph-X (R: functional group, X: halogen atom or hydrogen atom, Table 1) against 10 kinds of microbes. These compounds were classified into three groups with respect to their chemical structures. Group 1 consisted of sulfides possessing the benzyl group and substituted phenyl group whose substituents

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TABLE 1. Chemical structure and substituted groups and functional groups of tested benzyl phenyl sulfides.

Compounds No.	R ₁	R ₂
1	H	H
2	H	F
3	H	Cl
4	H	Br
5	MeO	H
6	MeO	F
7	MeO	Cl
8	MeO	Br
9	NO ₂	H
10	NO ₂	F
11	NO ₂	Cl
12	NO ₂	Br

13		
14		
15		

were a hydrogen, fluorine, chlorine, or bromine atom. The sulfides of group 2 had a 4-methoxybenzyl group and a hydrogenated or halogenated phenyl group. In group 3, there were sulfide derivatives with the 4-nitrobenzyl group and phenyl group with a hydrogen or halogen atom at *para* position. These sulfides were different in a small functional group bound on the phenyl ring which was connected to the sulfur atom. These small functional groups influenced the electron density on the sulfur atom and phenyl ring because of their properties for electron-withdrawing and electron-releasing. We expected these properties would contribute to the antimicrobial activities. It is important to understand the relationship between antimicrobial activities and the structure and properties of sulfides that bound a variety of functional groups.

All tested compounds shown in Table 1 were synthesized in our laboratory based on previously reported methods (compound **1** (Alnajjar et al, 1992), **2-4** (Barry et al, 2009), **5** (Lai et al, 2002), **6** (Brookes et al, 1958), **7** (Kannan et al, 1999), **8** (Wang et al, 2003), **9** (Russell et al, 1979), **11** (Bandgar et al, 2002), **12** (Naso et al, 2009)). Purification of the synthesized compounds was carried out by recrystallization and column chromatography. Characterizations of these compounds were performed by TLC, ¹H, ¹³C, COSY NMR and elemental

analysis. 4-Halogenated phenylthiols were coupled with 4-substituted benzylchloride, and then produced the desired 4-substituted benzyl 4-halogenated phenyl sulfide. The behavior of 4-fluorophenylthiol differed from that of other halogenated phenylthiols. The nucleophilicity of phenylthiol that substituted a hydrogen atom at the *para* position of the phenyl ring to a fluorine group, such as in the case of 4-fluorophenylthiol, was very low, and this thiol did not react with 4-nitrobenzylchloride using as an electrophilic reagent under the condition of diisopropylethylamine in dichloromethane at room temperature. We tried this reaction with sodium hydride as a strong base in DMF to give the desired sulfide **10** at 86% yield. The general synthetic methods of derivatives (for example, for sulfide **7**) and the new compound **10** of benzyl phenyl sulfide were as follows.

4-Methoxybenzyl 4-chlorophenyl sulfide (7), general procedure for the preparation of derivatives of benzyl phenyl sulfide. To a solution of 4-chlorophenylthiol (0.20 g, 1.4 mmol) in dry CH₂Cl₂ at 4 °C were added dropwise diisopropylethylamine (403 mg, 537 μL, 3.1 mmol), and 4-methoxybenzylchloride (293 mg, 255 μL, 1.9 mmol) over 5 min. The mixture was stirred at room temperature for 30 min. The resulting mixture was extracted with CH₂Cl₂ and the CH₂Cl₂ solution washed with water three times. The organic solvent was dried over MgSO₄, and was evaporated *in vacuo*. The product was then recrystallized from 2-propanol to yield colorless needles of compound **7** (73%, 0.27 g). ¹H-NMR (400 MHz, CDCl₃) δ: 7.21 (4H, s), 7.18 (2H, d, *J* = 8.8 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 4.04 (2H, s), 3.79 (3H, s). ¹³C-NMR (100.6 MHz, CDCl₃) δ: 38.7, 55.2, 113.9, 128.9, 129.0, 130.0, 131.3, 132.3, 134.8, 158.8. Anal. Calcd for C₁₄H₁₃ClOS: C, 63.51; H, 4.95. Found: C, 63.43; H, 4.94.

4-Nitrobenzyl 4-fluorophenyl sulfide (10). To a suspension of NaH (0.58 g, 60% in mineral oil, 17 mmol) in dry DMF at 4 °C, 4-fluorophenylthiol (2.0 g, 16 mmol) was added dropwise over 5 min. The mixture was stirred for 20 min. 4-Nitrobenzylchloride (3.0 g, 18 mmol) was then added dropwise to this mixture over 10 min at 4 °C. The reaction mixture was allowed to warm to room temperature and was then stirred for 0.5 h. The resulting mixture was extracted with ethyl acetate, and the ethyl acetate solution was washed with water three times. The organic solvent was dried over Na₂SO₄ and was evaporated *in vacuo*. The crude residue was purified by column chromatography on silica gel, eluted with hexane-toluene (15:1), and the product was then recrystallized from 2-propanol to yield colorless needles of compound **10** (86%, 3.6

g). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.12 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.8 Hz), 7.26 (2H, dd, J = 4.4, 5.2 Hz), 6.96 (2H, t, J = 8.0 Hz), 4.06 (2H, s). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3) δ : 40.2, 116.2, 116.4, 123.7, 129.1, 129.6, 134.4, 134.5, 145.5. Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{FNO}_2\text{S}$: C, 59.30; H, 3.83; N, 5.32. Found: C, 59.28; H, 3.89; N, 5.31.

All compounds were tested for antibacterial activities against *Bacillus subtilis* IFO-3134 (B.a.), *Escherichia coli* IFO-3806 (E.c.), *Klebsiella pneumoniae* IFO-3319 (K.p.), *Pseudomonas aeruginosa* IFO-12689 (P.a.), *Staphylococcus aureus* IFO-12732 (S.a.). Antifungal activities against *Aspergillus niger* IFO-6341 (A.n.), *Penicillium citrinum* IFO-6352 (P.c.), *Debaryomyces hansenii* var. *hasenii* IFO-1084 (D.h.), *Geotrichum candidum* IFO-4598 (G.c.), and *Gliocladium virens* IFO-6355 (G.v.) were also tested.

The minimum inhibitory concentration (MIC) tests of the compounds shown in Table 2 - 4 were performed by the agar dilution method of the Japan Society of Chemotherapy (Sakagami et al., 2007, Japan Society of Chemotherapy, 1993). First, all compounds were dissolved in 50 % methyl diglycol in methanol solution at a maximum concentration of 20 mg/mL (2% w/w). Sulfide compounds were added into the agar medium at the desired concentrations (1, 5, 10, 50, 100, 200, 500, 1000 $\mu\text{g/mL}$).

For the antibacterial assay, the bacteria were grown overnight at 37 °C in broth medium (a mixture of 5.0 g meat extract, 10 g peptone and 5.0 g NaCl dissolved in 1000 mL of sterilized water adjusted to pH 7.4 by using NaOH solution). After the bacterial suspensions were mixed, 100 μL of each suspension was added into 10 mL of sterile distilled water.

We applied 50 μL of a bacterial suspension (10^6 cfu/mL, *B. subtilis* vegetative cells) by a micropipette and glass spreader to a broth agar plate (containing 1.5 % agar). The plates of bacteria were incubated at 37 °C for 48 h and we determined the minimum inhibitory concentration based on the absence of colonies.

The protocol for the antifungal assay was similar to that for the antibacterial assay. Sabouraud agar plates were used for yeast, which contained 40 g glucose, 10 g peptone and 18 g agar dissolved in 1000 mL of sterilized water and adjusted to pH 5.6. The yeast was grown at 28 °C for 2 to 7 days. After a loopful was transferred to 10 mL of Sabouraud medium, the yeast culture was pre-incubated at 28 °C for 24 h. Spores were resuspended in sterilized distilled water to obtain 10^6 cfu/mL of the test yeast. Fungi were pre-incubated by growth at 28 °C for 2 to 7 days on a Sabouraud slope agar plate. 10 mL of sterilized distilled water was added to the agar plate and the resulting suspension was then filtered through sterilized gauze. This suspension, containing approximately 10^6 cfu/mL, was added to each plate for MIC.

Table 2 shows the MIC values of twelve kinds of derivatives of benzyl phenyl sulfide. MIC testing revealed that all derivatives of benzyl phenyl sulfide and 4-methoxybenzyl phenyl sulfide had no effect against any microbial strain. However, the compounds of 4-nitrobenzyl phenyl sulfide showed antimicrobial activity against many of the tested strains. 4-Nitrobenzyl phenyl sulfide **9** showed moderate effect against *B. subtilis*, *E. coli*, *D. hasenii* and *G. candidum*, and exhibited an MIC value of 200 $\mu\text{g/mL}$. This compound **9** had a weak effect against the other microbial strains (500 $\mu\text{g/mL}$). Compound **10** with a fluorine group at *p*-phenyl position had a limited effect against

TABLE 2. Antimicrobial activities (MIC, $\mu\text{g/mL}$) of benzylphenylsulfide derivatives against 10 microbial strains.

Compounds No.		R ₂	MIC (μg/mL)									
			B.s.	E.c.	K.p.	P.a.	S.a.	A.n.	P.c.	D.h.	G.c.	G.v.
1	H	>1000	>1000	>1000	1000	>1000	>1000	>1000	1000	>1000	>1000
	2	F	>1000	1000	1000	1000	>1000	>1000	>1000	1000	1000	1000
	3	Cl	>1000	>1000	>1000	1000	>1000	>1000	>1000	1000	>1000	>1000
	4	Br	>1000	>1000	>1000	1000	>1000	>1000	>1000	>1000	1000	1000
5	H	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	1000
	6	F	>1000	>1000	>1000	1000	>1000	>1000	>1000	>1000	1000	1000
	7	Cl	>1000	>1000	>1000	1000	>1000	>1000	>1000	>1000	1000	1000
	8	Br	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	1000
9	H	200	200	500	500	500	500	500	200	200	500
	10	F	200	500	1000	1000	500	1000	1000	1000	500	1000
	11	Cl	200	200	200	1000	200	200	200	200	500	500
	12	Br	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000

B.s.: *Bacillus subtilis*, E.c.: *Escherichia coli*, K.p.: *Klebsiella pneumoniae*, P.a.: *Pseudomonas aeruginosa*, S.a.: *Staphylococcus aureus*, A.n.: *Aspergillus niger*, P.c.: *Penicillium citrinum*, D.h.: *Debaryomyces hansenii* var. *hasenii*, G.c.: *Geotrichum candidum*, G.v.: *Gliocladium virens*.

TABLE 3. Antimicrobial activities (MIC, $\mu\text{g/mL}$) of three coupling materials (4-halogenated phenylthiol and 4-nitrobenzyl alcohol) and the mixture of each coupling materials against 10 microbial strains.

Compounds No.	MIC ($\mu\text{g/mL}$)									
	B.s.	E.c.	K.p.	P.a.	S.a.	A.n.	P.c.	D.h.	G.c.	G.v.
13	>1000	1000	1000	1000	>1000	1000	1000	1000	1000	500
14	200	200	1000	1000	500	500	500	500	500	1000
15	50	1000	1000	1000	200	1000	1000	500	500	1000
13+14	200	200	1000	500	500	500	500	500	500	500
13+15	50	1000	1000	1000	100	1000	1000	1000	500	1000

B.s.: *Bacillus subtilis*, E.c.: *Escherichia coli*, K.p.: *Klebsiella pneumoniae*, P.a.: *Pseudomonas aeruginosa*, S.a.: *Staphylococcus aureus*, A.n.: *Aspergillus niger*, P.c.: *Penicillium citrinum*, D.h.: *Debaryomyces hansenii* var. *hansenii*, G.c.: *Geotrichum candidum*, G.v.: *Gliocladium virens*.

B. subtilis (200 $\mu\text{g/mL}$). 4-Nitrobenzyl 4-chlorophenyl sulfide **11** showed the strongest and widest ranging effects among the twelve synthetic compounds, except for *P. citrinum* (MIC was 1000 mg/mL). However, we could not observe an effective MIC against any tested strain with compound **12**, 4-nitrobenzyl 4-bromophenyl sulfide.

We performed further investigation of antimicrobial activity of 4-nitrobenzyl 4-chlorophenyl sulfide **11**. We researched the antimicrobial effect of coupling materials such as 4-nitrobenzylalcohol **13**, 4-fluorophenylthiol **14**, and 4-chlorophenylthiol **15**. As shown in Table 3, 4-nitrobenzylalcohol **13** had no effect against any microbial strain. The thiol compounds **14** and **15** inhibited the growth of a few microbes, *B. subtilis* (**14**: 200 $\mu\text{g/mL}$, **15**: 50 $\mu\text{g/mL}$), *E. coli* (**14**: 200 $\mu\text{g/mL}$), and *S. aureus* (**15**: 200 $\mu\text{g/mL}$). Table 3 also indicated the effect on MIC of 1 : 1 ratio (w/w) of mixing reagents such as 4-nitrobenzyl alcohol **14** and halogenated thiols (**14**, **15**). This result revealed that the effect of the stronger reagent could be seen in the MIC of a mixed

sample. For example, it was shown that the MIC value of a mixture of **13** and **15** demonstrated the same MIC value as that of compound **15**. From these results, it appeared that the antimicrobial effect of 4-nitrobenzyl 4-chlorophenyl sulfide **11** was derived from its chemical structure of combining the 4-nitrobenzyl group and 4-chlorophenyl group by sulfide bonding.

Minimum bactericidal concentration (MBC) tests of the sulfide derivatives shown in Table 4 were performed by the agar dilution method against three kinds of bacteria, *E. coli*, *P. aeruginosa*, and *S. aureus*. 10 mL of the desired final concentration of each antibacterial agent solution (10, 20, 50, 100, 200, 500, 1000 $\mu\text{g/mL}$ in sterilized saline) was mixed with 50 μL of a bacterial suspension (10^8 cfu/mL), and left to stand for 0.5, 1.0, or 2.0 h, respectively. After being mixed, 50 μL of the solution was added to broth agar plates, which were then incubated at 28 °C for 48 h. We determined the minimum inhibitory concentrations based on the presence or absence of colonies. MBC values did not change by addition of an inactivator. 4-Methoxybenzyl 4-fluorophenyl sulfide **6** did not show effective MBCs against these bacteria during treatment for 1.0 h (500 $\mu\text{g/mL}$). However, it was demonstrated that **6** inhibited the growth of *P. aeruginosa* during mixing for 2.0 h with an MBC value of 200 $\mu\text{g/mL}$. Compound **14** and **15** belong to the thiol derivatives which were coupling reactant based sulfides. 4-Fluorophenylthiol **14** had a low MBC (200 $\mu\text{g/mL}$) against *E. coli* and *P. aeruginosa* during mixing for 1.0 h, however, had no MBC effect against *S. aureus* for 2.0 h. 4-Chlorophenylthiol **15** had broad antibacterial activity against three kinds of bacteria. The MBC value of **15** was 100 $\mu\text{g/mL}$ against *P. aeruginosa* for 1.0 h. Also **15** showed weak activity (200 $\mu\text{g/mL}$) against *E. coli* during treatment for 0.5 - 2.0 h and *S. aureus* during treatment for 1.0 - 2.0 h. It was found that the MBC of the other sulfide derivatives showed lower

TABLE 4. Minimum bactericidal concentration (MBC, $\mu\text{g/mL}$) of benzylphenylsulfide **6** and coupling materials **14**, **15**. Only data for the three compounds that had inhibitory effects (MIC $\leq$ 500 $\mu\text{g/mL}$) are shown.

Compounds No.	Time/h	MBC ($\mu\text{g/mL}$)		
		E.c.	P.a.	S.a.
6	0.5	1000	500	>1000
	1.0	1000	500	1000
	2.0	1000	200	500
14	0.5	500	500	1000
	1.0	200	200	1000
	2.0	200	200	1000
15	0.5	200	200	500
	1.0	200	100	200
	2.0	200	100	200

E.c.: *Escherichia coli*, P.a.: *Pseudomonas aeruginosa*, S.a.: *Staphylococcus aureus*.

effectiveness against these bacteria.

In conclusion, we determined the antimicrobial activity of synthetic benzyl phenyl sulfide derivatives against 10 microbial strains. It was clear that the 4-nitrobenzyl 4-halogenated phenyl sulfide had effective antimicrobial properties. In particular, 4-nitrobenzyl 4-chlorophenyl sulfide **11** indicated wide ranging and strong effect (MIC of 200 μ g/mL) against seven microbial strains. The coupling reactants of sulfide were investigated for their MIC and MBC against ten microbial strains. As a result, it was considered important for the expression of antimicrobial activities that the sulfide had a nitro group and chloride group in the same molecule as in the case of benzyl phenyl sulfide.

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REFERENCES

- Alnajjar, M. S., and Franz, J. A. (1992) A kinetic study of the migration of a phenyl group from sulfur to a carbon radical center: rearrangement of the α -(phenylthio) benzyl radical, *J. Am. Chem. Soc.*, **114**, 1052-1058.
- Anna A. P., and Shivendra V. S. (2008) Multitargeted prevention and therapy of cancer by diallyl trisulfide and related *Allium* vegetable-derived organosulfur compounds, *Cancer Lett.*, **269**, 305-314.
- Bandgar, B. P., Pandit, S. S. and Nagargoje, S. P. (2002) Zinc-mediated simple and practical synthesis of sulfides, *Sulf. Lett.*, **25**, 247-249.
- Barry, N., Brondel, N. Lawrence, S. E., and Maguire, A. R. (2009) Synthesis of aryl benzyl NH-sulfoximines, *Tetrahedron*, **65**, 10660-10670.
- Brookes, R. F., Clark, N. G., Cranham, J. E., Greenwood, D., Marshall, J. R., and Stevenson, H. A. (1958) Toxicity of organic sulfides to the eggs and larvae of the two-spotted spider mite. IV. Benzyl phenyl sulfides substituted by halogens and other groups, *J. Sci. Food Agric.*, **9**, 111-115.
- Hatano, A., Harano, A., Takigawa, Y., Naramoto, Y., Toda, K., Nakagomi, Y., Yamada, H. (2008) Kinetic parameters and recognition of thymidine analogues substituted the functional group by thymidine phosphorylase, *Bioorg. Med. Chem.*, **16**, 3866-3870.
- Hatano, A., Makita, S., and Kiriara, M. (2004) Synthesis and characterization of a DNA analogue stabilized by mercapt C-nucleoside induced disulfide bonding, *Bioorg. Med. Chem. Lett.* **10**, 2459-2462.
- Hatano, A., Nishimura, M., and Souta, I. (2009) Impact of unnatural nucleosides on the control of microbial growth, *Biocontrol Sci.*, **14**, 55-60.
- Hsiao-C. W., Jen-H. Y., Shu-C. H., and Lee-Y. S. (2010) Allyl sulfides inhibit cell growth of skin cancer cells through induction of DNA damage mediated G₂/M arrest and apoptosis. *J. Agric. Food Chem.*, **58**, 7096-7103.
- Japan Society of Chemotherapy (1993) Methods for the determination of minimum inhibitory concentration (MIC) by microdilution method (in Japanese). *Chemotherapy* (Tokyo), **41**, 183-189.
- Kannan, P., Banu, H. S., and Pitchumani, K. (1999) Syntheses of organic benzyl sulfides from thiols using a modified clay catalyst, *Ind. Acad. Sci. Chem. Sci.*, **111**, 555-561.
- Kiriara, M., Yamamoto, J., Noguchi, T., and Hirai, Y. (2009) Selective synthesis of sulfoxides and sulfones by tantalum(V) catalyzed oxidation of sulfides with 30 % hydrogen peroxide. *Tetrahedron Lett.*, **50**, 1180-1183.
- Lai, S., and Lee, D. G. (2002) Lewis acid assisted permanganate oxidations, *Tetrahedron*, **58**, 9879-9887.
- Naso, F., Capozzi, M. A. M., Bottoni, A., Calvaresi, M., Bertolasi, V., Capitelli, F., and Cardellicchio, C. (2009) A combined theoretical and experimental investigation on the enantioselective oxidation of aryl benzyl sulfides in the presence of a chiral titanium catalyst, *Chem. Europ. J.*, **15**, 13417-13426.
- Noguchi, T., Hirai, Y., and Kiriara, M. (2008) Highly selective 30% hydrogen peroxide oxidation of sulfides to sulfoxides using micromixing, *Chem. Commun.*, **26**, 3040-3042.
- Rattanachaikunsopon P., and Phumkhachorn, P. (2008) Diallyl sulfide content and antimicrobial activity against food-borne pathogenic bacteria of chives (*Allium schoenoprasum*), *Biosci. Biotechnol. Biochem.*, **72**, 2987-2991.
- Russell, G. A., and Pecoraro, J. M. (1979) Pummerer reaction of para-substituted benzylic sulfoxides, *J. Org. Chem.* **44**, 3990-3991.
- Sakagami, Y., Sawabe, A., Komemushi, S., Ali, Z., Tanaka, T., Iliya, I., and Iinuma, M. (2007) Antibacterial activity of stilbene oligomers against vancomycin-resistant *Enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) and their synergism with antibiotics. *Biocontrol Sci.* **12**, 7-14.
- Wu, C. C., Chung, J. G., Tsai, S. J., Yang, J. H., and Sheen, L. Y. (2004) Differential effects of allyl sulfides from garlic essential oil on cell cycle regulation in human liver tumor cells. *Food Chem. Toxicol.*, **42**, 1937-1947.
- Wang, C., Batsanov, A. S., Bryce, M. R., and Sage, I. (2003) An improved synthesis and structural characterisation of 2-(4-acetylthiophenylethynyl)-4-nitro-5-phenylethynylaniline: The molecule showing high negative differential resistance (NDR), *Synthesis*, **13**, 2089-2095.