Synthesis, Characterization, and Biological Activity of Some New Amino Acid Derivatives Containing Selenium

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Abstract

New derivatives of some amino acids are synthesized by two steps. Firstly, by reaction of 3,5- dinitrobenzoyl chloride in equivalent molal ratio with potassium selenide, under argon atmospher, affording 3,5- dinitrobenzoyl isoselonocyanate (A). Then by adding immediately equivalent molal ratio of selected amino acids, namely; alanine, or glycine, to (A), give amino acid derivatives [3, 5-dinitrobenzoylamino-selenomethyl] Amino Acid ***(1 & 2).*** *The new derivatives have been characterized by CHNS, IR, ^{1}HNMR, ^{13}CNMR. Compounds (1&2) have antibacterial activity against Staphylococcus aureus (NCTC6571) and Escherichia coli(NCTC5933).*

Keywords: Amino acids, dinitrobenzoyl chloride, isoselenocyanate, antibacterial activity

1. Introduction

Some amino acid derivatives and some of their metal complexes have been prepared (Kabani et al.,2005).Other derivatives have potential biological activity and had been evaluated as having antibacterial, antifungal properties (Cohan et al.2006). Little amino acid derivatives containing selenium were prepared, as we aware, in the literature. Novel amino acids derivatives,(N'-benzoyl)Hydrazide and(N'-Nicotinoyl)hydrazide, were synthesized by coupling reaction of benzoic acid and nicotinic acid hydrazides with N-protected L-amino acids; valine , leucine, phenylalanine, glutamic acid and tyrosine. The antimicrobial activity of Cu and Cd complex of the designed compounds were studied against S. aurous and E-coli (Khattab 2005).

Recently a new series of amino acid derivatives and its metal complexes based on N-[(Benzoyl amino)-Thioxomethyl)- Amino Acid (HL), [where HL; aspartic acid, glutamic acid, methionine, leucine, and tryptophan] were synthesized and characterized. All the ligands showed no biological activity, where is the complexes with Cu(II), Co(II), or Ni(II) have antibacterial activity towards E-coli and S.aureus and have no toxicity on (BALBIC) Albino mice (Al-Mudhaffar et al.,2010).

Novel derivatives of seleno-amino acids that are effective directly sources of supplemental selenium human and livestock were prepared, such as N-succinyl L- selenomethonine, L-selenomethionine isopropyleester Hydrochloride, N-Carbonyl L-selenomethionine, L-Selonomethionine hydration (Abdel-Monem et al.,2009). Benzyl selenocyanates were synthesized from benzyl bromides or chlorides in acetonitrile at room temperature (Linda et al., 2004). A series of transpiperazine compounds were reported to have significant cytotoxicity against cisplatin resistant cells (Rafique et al., 2010). Pt(II) complexes with thiourea have showed anticancer activity against leukemia cell lines. Pt(II) has also complexes with estrogen hormone and used as anticancer agent for treatment of hormone depended cancer like breast cancer (Rafique et al., 2010).

A novel Schiff-bas was synthesized by the reaction of saccharin with tryptophan and characterized by elemental analysis, FTIR, HNMR and UV- visible spectroscopy affording [C18H15O4N3S.3H2O) structure (Cakir et al., 2010).A novel sulfur and selenium containing bis-α-amino acids from hydroxyproline, wherein L-cysteine or L-selenocysteine were linked to the proline through sufur or selenium atom (Cakir & Bicer, 2010a). Novel sulfur and selenium containing bis-α-amino acids from 4-hydroxyproline were prepared (Caputo et al., 2010). 3-[(Phenylcarbonyl)seleny] propanoic acid and its ester derivatives and of 2-[(phenylcarbonyl)selenyl]acetic acid and showed moderate to significant activity against S.aureus, Salmonella typhimurium, E.coli and Bacillus subtilis (Radhakrishna et al., 2010).

Recently synthesis and biological activity of selenium-containing amino acid compounds by nucleophic substitution reaction of pyridineselenol and quinolineselenol derivatives with *N*-phthaloglycyl chloride followed by hydrazinolysis (Abdel-Hafez et al., 2011).

In this work, we report the synthesis, characterization, and biological activity of some new amino acid derivatives containing selenium.

2. Experimental

2.1. Materials

All D,L-amino acid were from Fluka. All solvents were from BDH and used without further purification. 3,5-Dinitrobenzoyl Chloride was from Merck. Argon gas (99.995%) was from JGC. Potassium selenocyanate was prepared as literature method (Trantelli & Pecile, 1962).

2.2. Instrumentation

IR-spectra were recorded in the range 4000-400 cm on Shimadzu FTIR-8400 spectrophotometer using KBr pellets Elemental analysis were preformed on EA 3000-A-Eurorector. ^{1}HNMR and ^{13}CNMR-spectra were recorded on Bruker Ultra shield 300MHZ using D_2O as solvent and TMS as internal standard. Melting points were determined by a Galenkamp melting point apparatus without correction.

2.3. Synthesis of amino acid derivatives(HL)(1 and 2)

2.3.1- **3,5 Dinitro benzoyl isoselonocyanate** was prepared by refluxing equivalent molal ratio of KSeCN (2.0747 g,14.4 mmol) in 20 ml acetone and 3,5-dinitro benzoyl chloride (3.7602,14.4 mmol) in 15 ml acetone, under argon atmosphere for 4hrs. The mixture solution was filtered and cooled to r.t.

2.3.2- Preperation of **3,5 dinitro-N-[(benzoyl amino) selenomethly)**-Amino Acid**s(1&2):** was carried out by adding rapidly (14.4 mmol) of appropriate amino acid in 15 ml acetone to the above solution mixture in (i) and refluxed for 20hrs. The solvent was evaporated under reduced pressure. The solid product was recrystalized twice from a mixture of (6:4) (water : ethanol) to give pure crystals of amino acid derivatives.

3,5 dinitro-N-[(benzoyl amino) selenomethly)-glycine 1 ; (DNBASG). Dark brown crystals, (55%) yield.

3,5 dinitro-N-[(benzoyl amino) selenomethly)-alanine 2 ; (DNBASA). Dark brown solid, (71%) yield,
Physical properties of the compounds **(1&2)** are given in table 1.

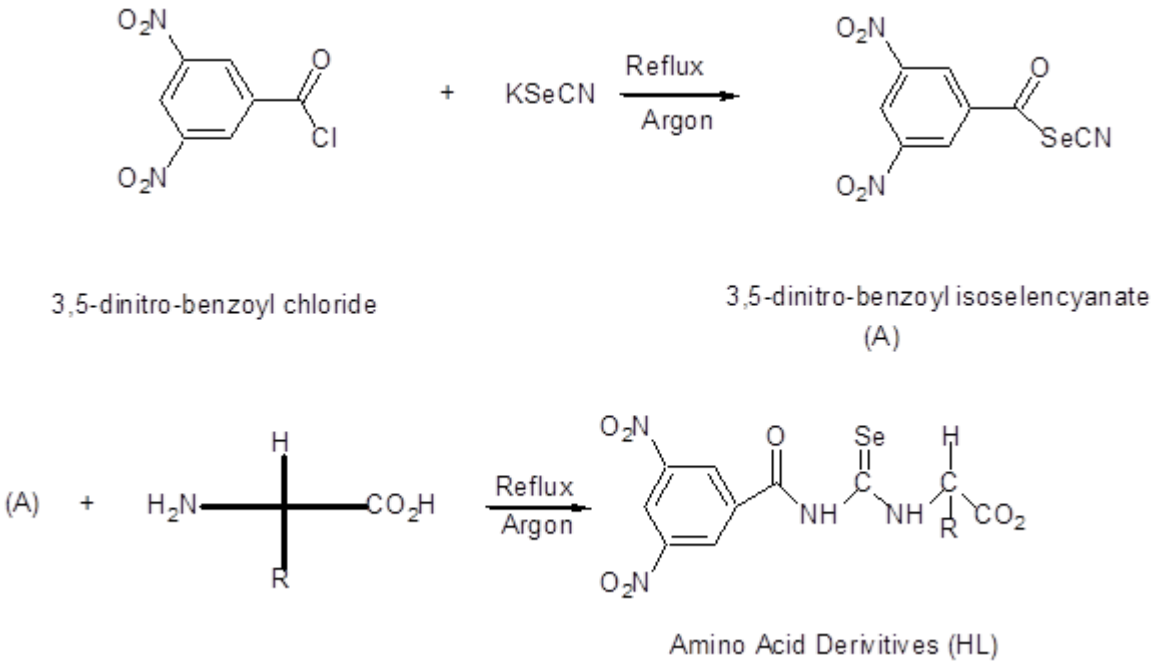
2.4- Biological activity

In vitro biological activity was accomplished by using LTF-Uni Jemp Autoclave for sterilizing and Escherichia (NCIC 5933) coli and Staphylococcus aureus (NCTC6571) for biological activity study.

3. *Results and Discussion*

3.1. Synthesis

Amino acid derivatives **(1 and 2)** were prepared, firstly by reaction of 3,5-dinitro benzoyl chloride with equivalent molal ratio of potassium selenocyanate ,under inert atmosphere, by nucleophilic addition of $SeCN^-$ to carbonyl group, to give 3,5 dinitro benzoyl isoselonocyanate (A)**,** and subsequent reactions with the respective amino acid, under reflux in acetone were carried out ,gave compounds **1** and **2** , as shown in Scheme 1.



Where(R):amino acid residue; R=H(Gly)(1), or CH3(Ala)(2)

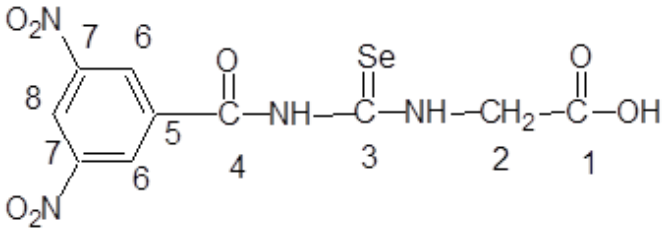
Scheme 1. Preparation of amino acid derivatives (HL)

3.2. Infrared spectra

The spectra for amino acid derivatives **(1 & 2)** show similarity in some frequencies. Aromatic C-H stretching frequencies occur in the range 3000-310 cm^{-1}, and aliphatic CH frequencies in the range (2750-2990) cm^{-1}. Bonds in the range 3250-3520 cm^{-1} are due to superimposed O-H and NH stretching bands. Carbonyl bands, υas (c=o)and υs(c=o) occurred in the range 1625-1608 cm^{-1} and 1533-1531 cm^{-1} respectively. Strong bands due to $\upsilon_{C=Se}$ occur in the range 864 cm^{-1} to 987 cm^{-1}. In selenosemicarbazones (Wiles et al., 1967), the C=Se bands occurred in the range 800-775 cm^{-1}. Details of infrared frequencies for compounds **(1 & 2)** are given in Table 2.

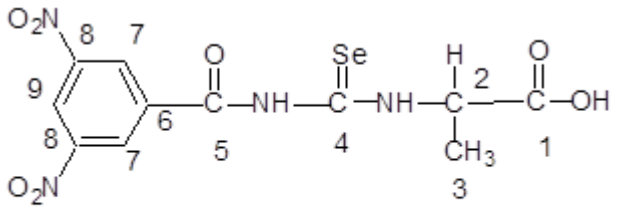
3.3. ^{1}HNMR and ^{13}CNMR spectra

^{1}H NMR spectrum of [3,5-dinitrobenzoyl amino selenomethyl] glycine(DNBASG) **1** shows singlet band at 1.93 ppm for α-CH_2.Two singlet bands at 8.97 ppm and 9.13 ppm for aromatic protons(C_6:C_8), in 2:1 ratio. C(Se)NH proton occurs as multiplet at 1.45 ppm. Carboxylic protons which may occur around 11 ppm, but not observed in the range, this may be due to deuterium exchange with acidic proton, as found in the literature (Cakir, 2010). Whereas, ^{13}C NMR shows the carboxylic carbon (C_1) at 176.43 ppm, which occur at 174.9 ppm for free glycine. α-Carbon (C_2) occur at 43.26 ppm, which for free glycine occurs at 45 ppm., C_3(C=Se) appears at 173.3 ppm as shown in Figs.(1a,1b) and Table 3.



DNBASG(1)

Compound(2);(DNBASA) shows β-CH_3 as multiplet at about 2.71 ppm. NH- amide proton appears at about 8.4 ppm, and it occured at 8.66 ppm in selenourea derivative; PhC(O)NHC(Se)NPhMe (Molter et al., 2011). C(Se)NH proton occurs at 1.37 ppm. ^{13}C NMR shows carboxylic carbon(C_1) at 173.5 ppm, and methylic carbon (C_3) at 23.43 ppm ,



DNBASA (2)

α-C(C_2) at 38.9 ppm, C-NO_2(C_8) at 148.2 ppm, C-NO_2 occurred at about 148 ppm in N-dodecyl-3,5-dinitrobenzamide (Du et al., 2011), and C_9 at 120.8 ppm. ^{1}H NMR and ^{13}CNMR spectra are shown in Figs.(1a, 2a,& 2a,2b). Detailed data are given in Table.3

From elemental analysis, and spectral measurements, we suggest the structures which are indicated above for DNBASG **1**, and DNBASA **2**.

3.4. Biological activity

Antibacterial activity of amino acid derivatives (1-2) has been studied in vitro against Escherichia coli(NCTC5933) and Staphylococcus aureus (NCTC6571) by using agar diffusion method (Shank et al., 1979; Larry et al., 1981). The prepared derivatives **1 & 2** have antibacterial activity with inhibition areas shown in table (4). Compund **2** has more antibacterial activity against E.Coli than compound **2**. In contrast to our previous work, all the ligands that contain sulfur atom in N-[(benzoylamino)-thioxomethyl] HL showed no antibacterial activity against same two bacteria (Al-Mudhaffar et al., 2010).

4. Conclusion

The prepared compounds **1** and **2** have antibacterial activity whereas analogues sulphur compounds have no such activity (Al-Mudhaffar et al., 2010). . This may encourage us to do antitumor activity for them in future work.

Acknowledgments

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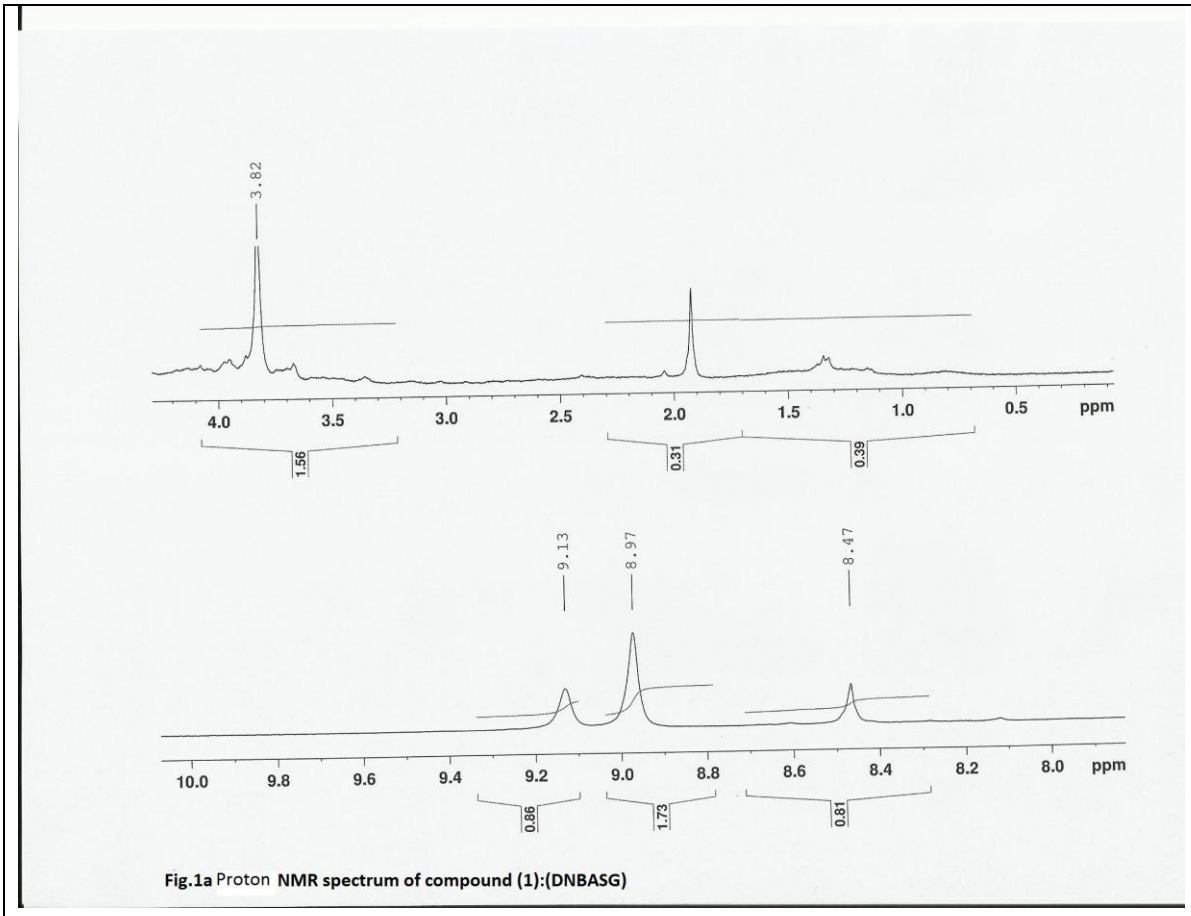

Fig.1a Proton **NMR spectrum of compound (1):(DNBASG)**

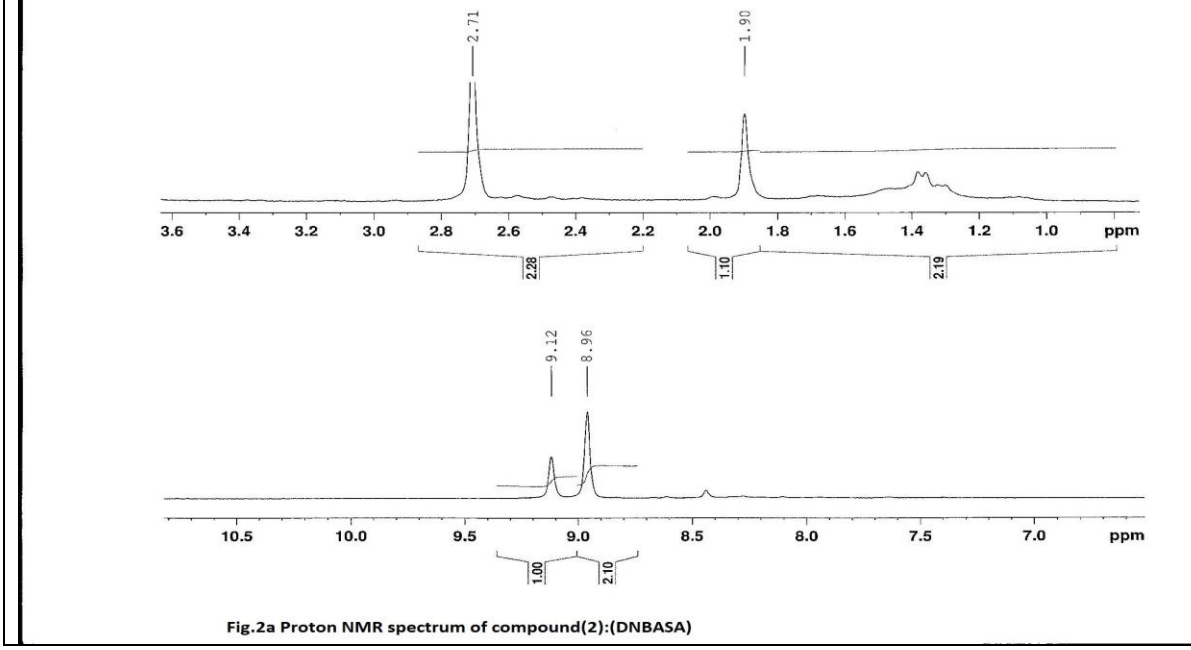

Fig.2a Proton NMR spectrum of compound(2):(DNBASA)

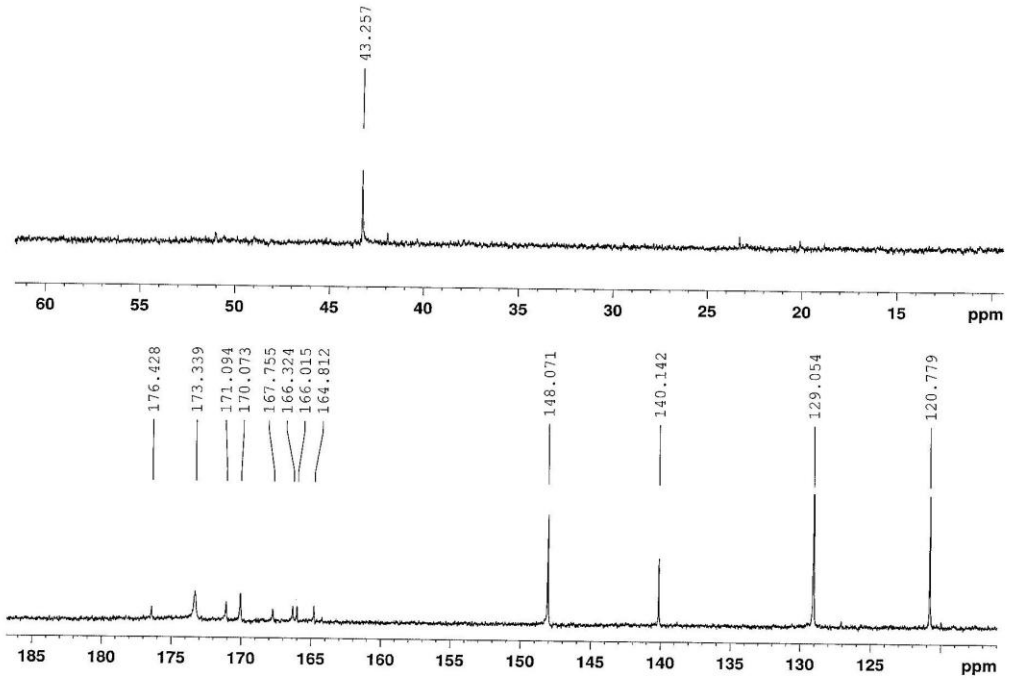

Fig.1b 13CNMR of compound (1):DNBASG

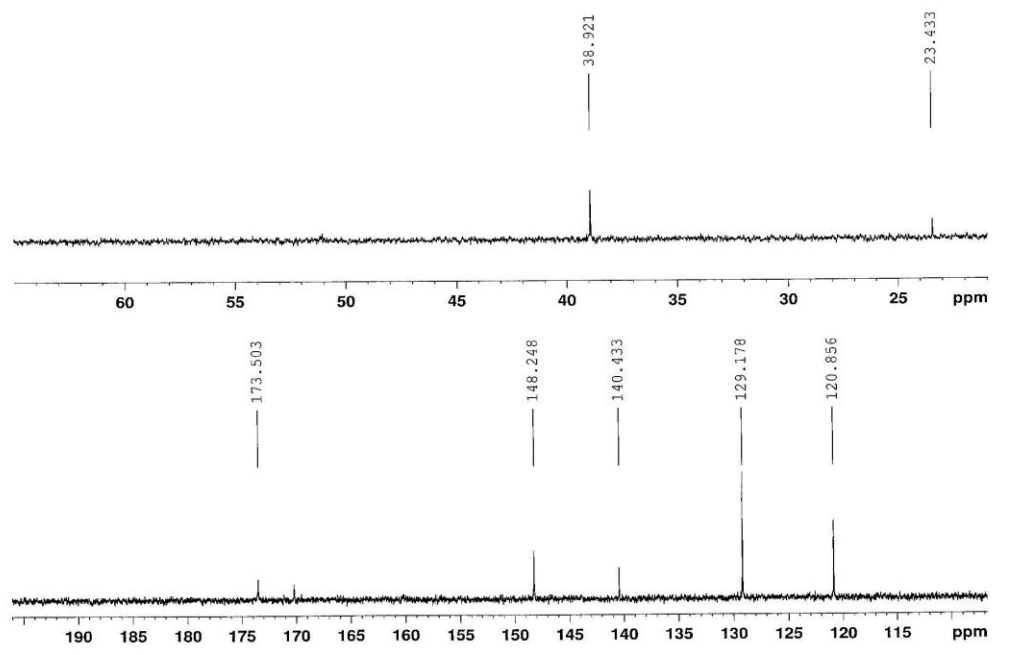

Fig.2b 13CNMR of compound(2):(DNBASA)

Table.1 Physical properties and elemental analysis of compounds (1-2)

Compound (no.)	M.p. (°C)	Color	Theoretical ratio (Experimental ratio)			
			C%	H%	N%	S%
DNBASG (1)	164(dec.)	Dark brown	32.016 (32.08)	2.149 (2.12)	14.935 (14.87)	0.000 (0.000)
DNBASA (2)	210(dec.)	Dark brown	33.95 (33.80)	2.59 (2.52)	14.40 14.03)	0.000 (0.000)

Table 2. Fundamental infrared frequencies(cm^{-1}) of compounds (1-2)

Compound (no.)	$V_{s(NH)}$	$V_{s(ar\ CH)}$	$V_{c=o}$ (carboxylic)	$V_{c=o}$ (amide)	V_{C-NO2} (arm.)	$V_{C=Se}$
DNBASG (1)	3365	3097	1714(s)	1662	1542,1348	921
DNBASA (2)	3371	3103	-----	1625	1533,1353	987

Table.3a ^{1}HNMR chemical shifts (ppm) for compounds(1-2)

Compound (no.)	Alpha(H) (CH)	H(CO-NH) (amide)	H(Se-NH)	Other
(DNBASG) (1)	1.93	8.47	1.45	Ar-H; 8.97(2H),9.13(1H)
(DNBASA) (2)	1.90	8.47	1.37	Ar-H; 8.97(2H),9.13(1H),Beta(H);CH_3:2.71

Ar = dinitrobenzoyl group

Table3b. ^{13}C NMR Chemical shifts (ppm) of compounds(1-2)

Compound (no.)	C1	C2	C3	C4	C5	C6	C7	C8	C9
(DNBASG) (1)	176.24	43.26	173.34	170.07	140.14	129.05	148.07	120.78	----
(DNBASA) (2)	173.5	38.92	23.43	-----	170.05	140.43	129.17	148.24	120.85

Table 4. Anti-bacterial activity against E. Coli & S. Aureus of compounds (1-2)

Compound (no.)	(Gram + ive St.aureus) (IZ/mm)	(Gram – ivE.Coli) (IZ/mm)
(DNBASG) (1)	9	6
(DNBASA) (2)	9	7

Inhibition zone(IZ) in mm