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of Science Frontier Research: B

Chemistry

Organic Solvent Effect

Thermal Desorption Function

Highlights

Vitro Cytotoxic Evaluation

Extraction Efficiency of Cobalt (II)

Discovering Thoughts, Inventing Future

VOLUME 16 ISSUE 1 VERSION 1.0

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Synthesis, Characterization and in Vitro Cytotoxic Evaluation of Some Novel Heterocyclic Compounds Bearing Indole Ring

By Asmaa S. Salman, Naema A. Mahmoud, Anhar Abdel-Aziem, Mona A. Mohamed & Doaa M. Elsisi
Al-Azhar University, Egypt

Abstract- Reaction 1H-indole-3-carboxaldhyde 1 with thiosemicarbazide derivatives to give thiosemicarbazone derivatives 2a,b. Cyclization of thiosemicarbazone 2a with HCl, Ac_2O, phenacyl bromides and chloroacetic acid afforded the corresponding 1,2,4-triazole-3-thiol derivative 3, diacetyl derivative 4 and 1,3-thiazole derivative 5 and 1,3-thiazolidin-4-ones derivative 6 respectively. Compound 6 undergoes a series of heterocyclization reactions to give new heterocyclic compounds. The structure of the newly synthesized compounds had been confirmed by elemental analysis and spectra data. The some newly synthesized compounds were evaluated for *in vitro* cytotoxic activity against three human cancer cell lines, including human liver cancer (HepG2), human colon cancer (HT-29) and human breast cancer (MCF-7) using MTT assay.

Keywords: thiosemicarbazone, 1.3-thiazole,1, 3 thia-zoldinone, pyrazolo[3,4-d][1,3]thiazole, cytotoxic activity, MTT assay.

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Synthesis, Characterization and in Vitro Cytotoxic Evaluation of Some Novel Heterocyclic Compounds Bearing Indole Ring

Asmaa S. Salman [α], Naema A. Mahmoud [σ], Anhar Abdel-Aziem [ρ], Mona A. Mohamed [ω] & Doaa M. Elsisi [¥]

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Keywords: thiosemicarbazone, 1.3-thiazole,1,3 thiazoldinone, pyrazolo[3,4-d][1,3]thiazole, cytotoxic activity, MTT assay.

I. Introduction

Thiosemicarbazones has been used as intermediated for the preparation of many heterocyclic compounds. In the literature many researchers have reported the S/N regioselective nucleophilic completion in the synthesis of heterocyclic compounds by intramolecular cyclization reactions. Changes in reaction conditions can induce S-attack or N-attack to eventually afforded different cyclic products from a singlet starting material. Moreover, thiosemicarbazones bearing an aromatic heterocyclic moiety seem to possess enhanced biological activities[1,2]. On other hand, indoles major importance due to its therapeutic and pharmacological activities [3-7]. In view of the above and in continuation of our studies on the synthesis of heterocyclic compounds exhibiting biological activity, we report here reaction1H-indol- 3-carboxaldehyde with thiosemicarbazide derivatives to afforded the corresponding thiosemicarbazones derivatives, then cyclization by different reagents and different conditions to give some novel heterocyclic compounds bearing indole moiety.

II. Result and Discussion

a) Chemistry

The synthetic procedures adopted to obtain the target compounds are outlined in Schemes 1-3. The key intermediate 1-[1H-indol-3-ylmethylene] thiosemicarbazone derivatives 2a,b were prepared by reaction*1H*-indole-3-carboxaldehyde 1 with thiosemicarbazide derivatives such as 4-(4-methylphenyl) thiosemicarbazide or 4-(4-phenyl-1,3-thiazol-2-yl) thiosemicarbazide in refluxing ethanol containing acetic acid[8] (Scheme 1). The structure of compound **2a,b** were based on analytical and spectral data. The 1H-NMR spectra of 2a displayed D_2O- exchangeable signals at **δ** 10.01,**δ** 11.46,**δ** 11.99 ppm of three NH protons and singlet signal at **δ** 2.32 ppm for CH_3 proton.

Cyclizing of thiosemicarbazone derivative **2a** depended on cyclizing agent and conditions of reaction. Thus, Thiosemicarbazones derivative 2a which may undergo to ring closure by acid medium[9] afforded 5-[1H-indol-3-yl]-4H-1,2,4-triazole-3-thiol derivative 3 (Scheme 1).1H-NMR spectra of **3** displayed D_2O-exchangeable signals at **δ** 4.33 ppm and **δ** 12.05 ppm of SH and NH protons respectively.[13]C NMR spectra of **3** showed signals at **δ** 20.44,154.84,154.98 and 162.17 ppm to CH_3,2 C=N and C-S respectively.

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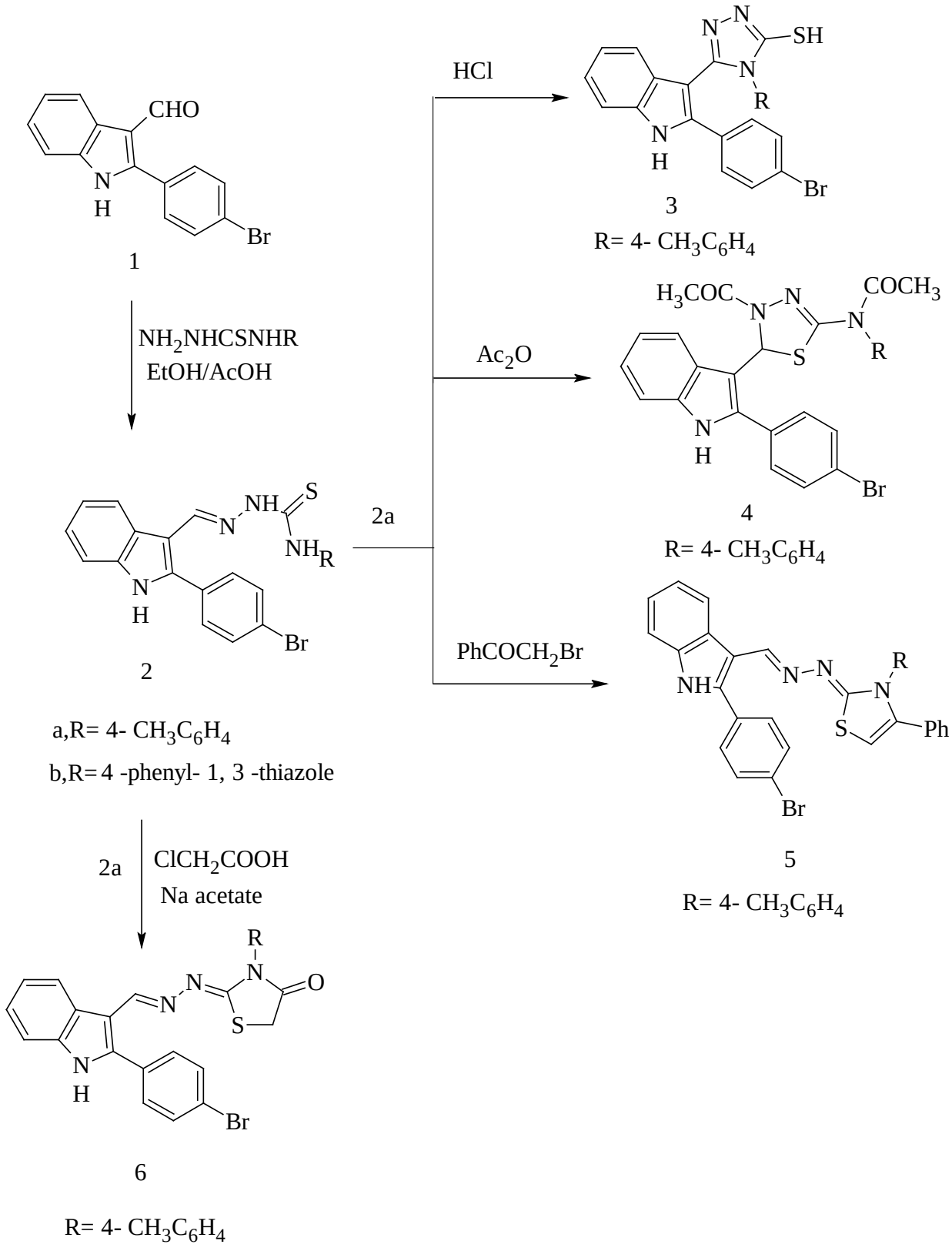
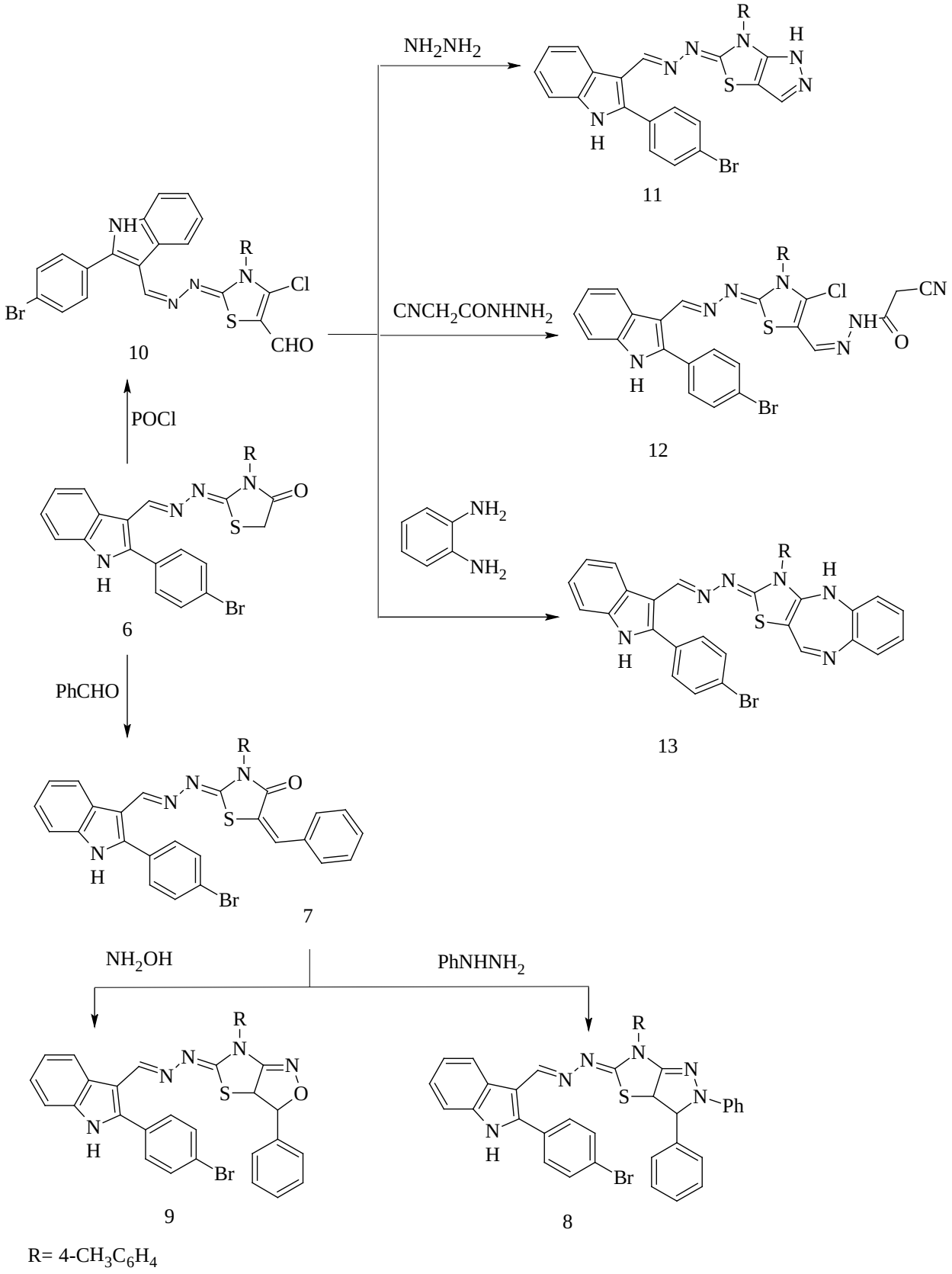
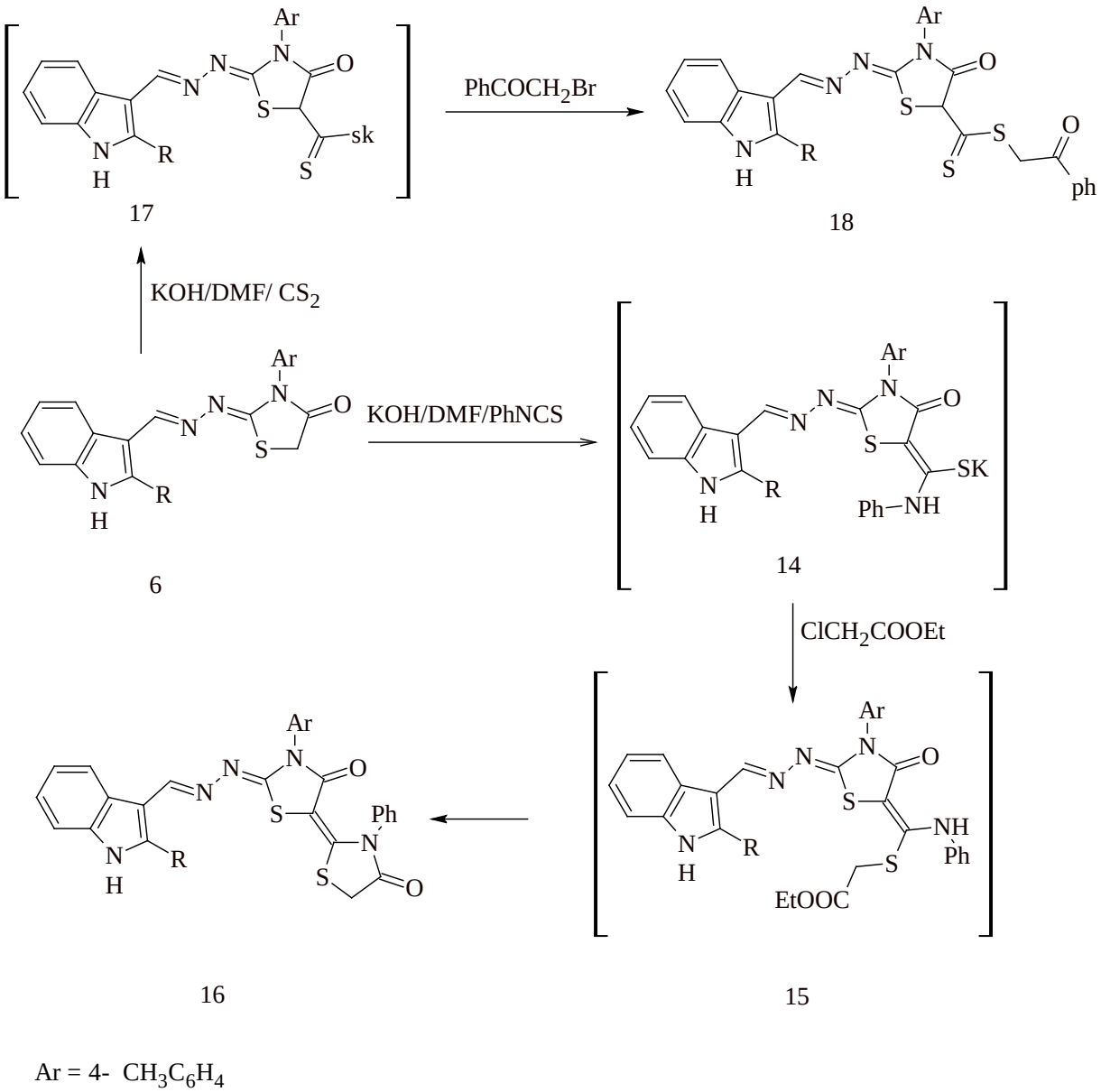


Scheme 1 : Synthesis of compounds 2-6



Scheme 2 : Synthesis of compounds 7-13

While, heterocyclization of thiosemicarbazone derivative 2a in the presence of acetic anhydride gives N-[4-acetyl-5-(1H-indol-3-yl)-1,3,4-thiadiazol-2-yl] acetamide **4** (Scheme 1). Suggest that the mechanism of the reaction compound 2a with acetic anhydride follows Figure 1. Reaction compound 2a with acetic anhydride, the resonance effects between NH and the phenyl group may reduce the nucleophilicity of NH and the steric effect of phenyl group on the NH retards nucleophilic substitution with acetic anhydride. Therefore, the initial monoacetyl-substituted products are gradually converted to diacetyl substituted thiadiazoline[10]4.1H-NMR spectrum of compound 4 showed a signal at **δ** 2.16, **δ** 2.19, **δ** 2.26 ppm corresponding to three CH_3 groups and multiplet signal at **δ** 6.93-7.28 ppm for the aromatic protons and CH-5 of1,3,4-thiadiazoline ring. The mass spectrum of compound 4 showed the molecular ion peak at m/z 547 corresponding to the molecular formula $C_{27}H_{23}Br\ N_4O_2S$.



Scheme 3 : Synthesis of compounds 16 and 18

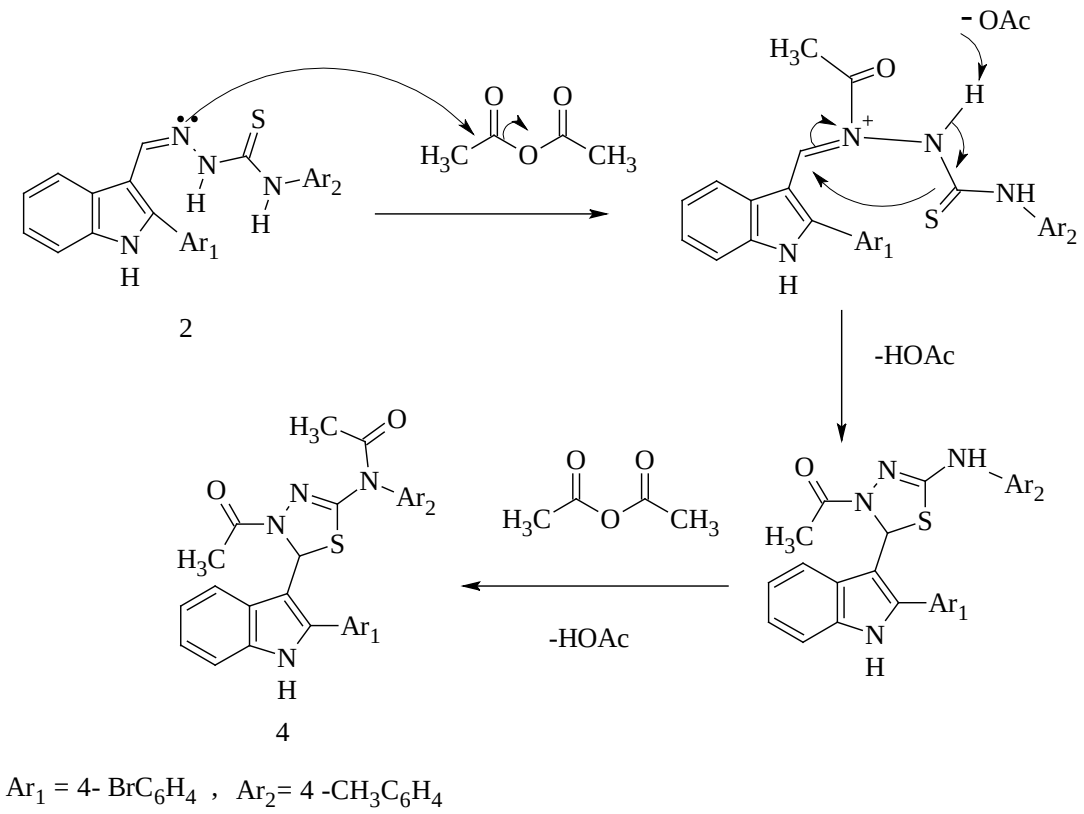
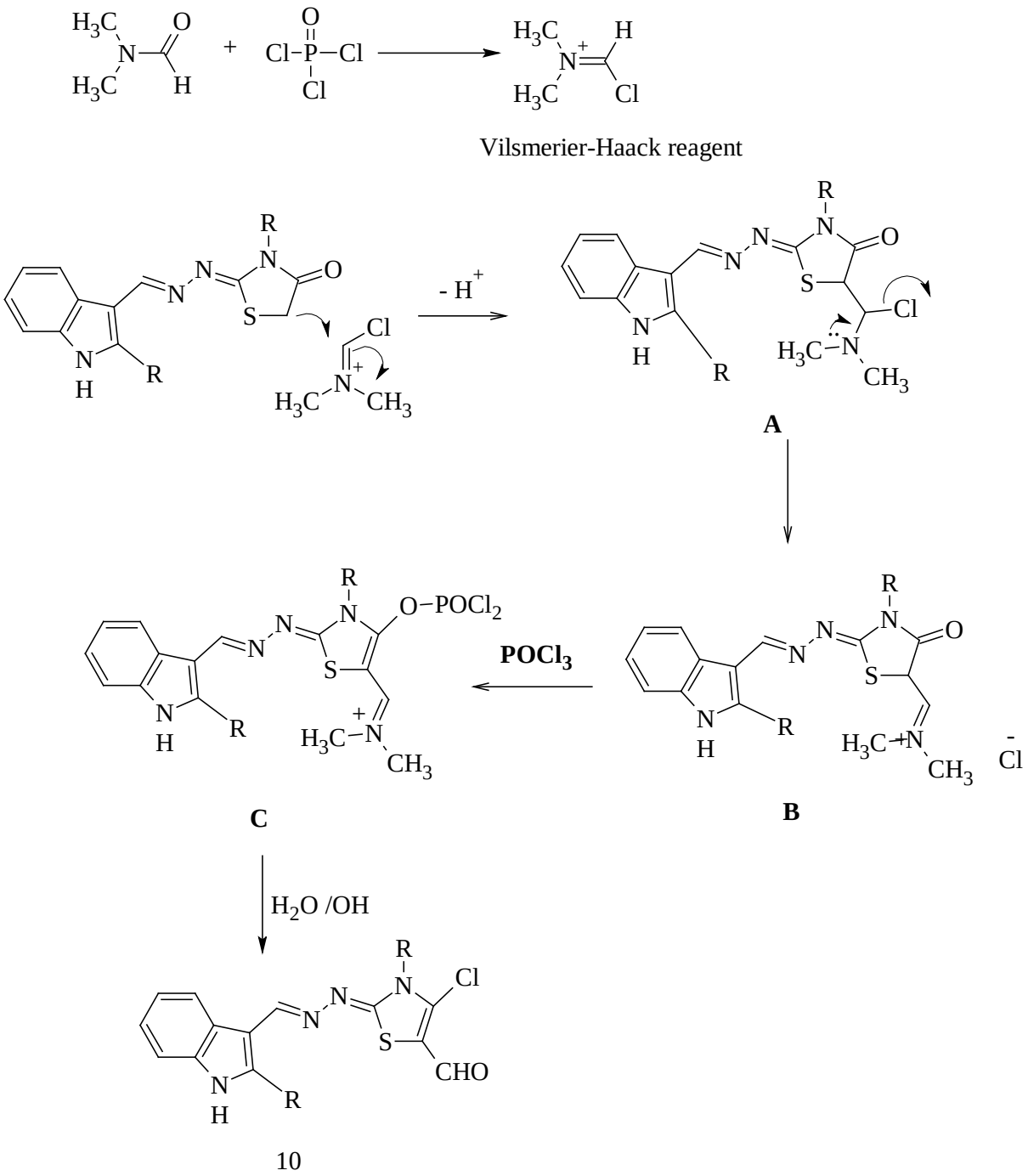


Figure 1 : Proposed mechanism formation of compound 4

Furthermore, treatment of thiosemicarbazone derivative **2a** with phenacyl bromides in boiling ethanol in the presence of anhydrous sodium acetate[11] yielded the corresponding 3-[1,3-thiazol-2(3H)-ylidene]hydrazonomethyl-1*H*-indole derivative **5**.1H-NMR spectrum of **5** showed a signal at δ 6.58 ppm corresponding to CH-5 of thiazole ring and signal at δ 8.30 ppm for an N=CH proton .The mass spectrum of compound **5** showed the molecular ion peak at *m/z* 563 corresponding to the molecular formula $C_{31}H_{23}BrN_4S$. Refluxing thiosemicarbazone derivative **2a** with chloroacetic acid in the presence of anhydrous sodium acetate in glacial acetic acid[12] afforded 1,3-thiazolidin-4-one derivative **6** (Scheme 1). IR spectra of **6** showed the disappearance of NH bands of substituted thiosemicarbazone moiety and the presence of a new band at 1703 cm^{-1} attributed to a carbonyl group of thiazolidin-4-one. The 1H-NMR spectra of **6** showed a new signal at 4.09 ppm attributed to CH_2 protone of thiazolidinone ring .[13]C NMR spectra of **6** showed signals at δ 20.65, 32.16, 152, 162 and 172 ppm to CH_3, CH_2, N=CH, C=N and C=O respectively.

Condensation1,3-thiazolidin-4-one derivative **6** with benzaldehyde in the presence of freshly fused sodium acetate in boiling glacial acetic acid yielded the corresponding arylidene derivatives[13]**7** (Scheme 2). The analytical and spectral data of compound **7** was consistent with the proposed structure.Thus,1H-NMR spectrum of compound **7** showed absence of thiazolo-methylene protons, and showed a multiplet signal at δ 7.25-7.32 for the aromatic protons and olefinic CH= proton. [13]C NMR spectra of **7** showed signals at δ 20.68, 142, 153, 156 and 165 ppm to CH_3 ,C=CH, N=CH, N=C and C=O respectively.

Compound **7** was used as starting material for further syntheses of other heterocyclic compounds. Thus, reaction compound **7** with phenyl hydrazine[14] afforded 3-(pyrazolo[3,4-d]1,3-thiazol-5-ylidene) hydrazonomethyl-1*H*-indole **8**. The 1H-NMR spectrum of **8** showed a doublet signals at δ 4.09 and δ 6.67 due to 2CH protons of pyrazoline. The mass spectrum of compound **8** showed the molecular ion peak at *m/z* 681 corresponding to the molecular formula $C_{38}H_{29}BrN_6S$.On the other hand, cyclocondensation of **7** with hydroxylamine hydrochloride in presence of sodium acetate[15] afforded 3-[1,3-thiazolo[4,5-c]isoxazol-5-ylidene]hydrazonomethyl-1*H*-indole **9**(Scheme 2). The 1H- NMR spectrum of **9** showed a doublet signals at δ 4.53 and δ 6.67 due to 2CH protons of isoxazole. The mass spectrum of compound **9** showed the molcular ion peak at *m/z* 606 corresponding to the molecular formula $C_{32}H_{24}BrN_5OS$.



Figuer 2 : Proposed mechanism formation of compound 10

Moreover, chloroformylation of1,3-thiazolidin- 4-one derivative **6** using Vilsmeier–Haack reagent to 4-chloro- 1,3-thiazole-5-carboxaldehyde **10**.The most probable reaction involves initial formation of intermediate **A- C** that underwent further chlorination and hydrolysis to yield final products[16]**10(Figure 2).** The IR spectrum of compound **10** showed bands at 1675 cm^{-1} due to C=O group. The 1H-NHR revealed a new signal at δ 9.95 ppm assigned to CHO proton and disappearance signal at δ 4.09 ppm attributed to CH_2 thiazolidinone.[13]C-NMR spectra of **7** showed new signal at δ135.89 ppm assigned for C- Cl group.

Reaction 4-chloro-1,3-thiazole-5-carboxaldehyde **10** with hydrazine hydrate[17] afforded the corresponding pyrazolo[3,4-d]1,3-thiazole derivative **11** (Scheme 2). The chemical structure of the compound **11** was elucidated on the basis of elemental analysis and spectral data.IR spectrum of compound **11** was characterized by the presence of a strong band at 3380, 3176 cm^{-1} due to two NH proton. The mass spectrum of

compound **11** showed the molecular ion peak at *m/z* 547 corresponding to the molecular formula $C_{26}H_{19}BrN_6S$.

Furthermore, reaction 4-chloro-1,3-thiazole-5-carboxaldehyde **10** with a cyanoacetic acid hydrazide afforded the corresponding cyanoacetohydrazide derivative **12** [18]. 1H-NMR of compound **12** showed D_2O -exchangeable signal at δ11.33, 11.49 ppm due to 2NH protons and singlet signals at δ 8.29, 8.36 ppm and 4.22 ppm due to 2CH=N and CH_2 protons respectively. Reaction 4-chloro-1,3-thiazole-5-carbaldehyde **10** with *o*-phenylenediamine in ethanol solution containing triethylamine (TEA) as catalyst afforded 1,3-thiazolo[4,5-b]1,5-benzodiazepine derivative **13** (Scheme 2). The 1H-NMR spectrum of compound **13** showed D_2O-exchangeable signal at δ 12.03 and 12.31 ppm due to 2NH protons. The mass spectrum of compound **13** showed the molecular ion peak at *m/z* 603 corresponding to the molecular formula $C_{32}H_{23}BrN_6S$.

The active methylene in 1,3-thiazolidin-4-one derivative **6** was allowed to react with phenyl isothiocyanate in dry *N, N*-dimethylformamide (DMF) containing catalytic amount of potassium hydroxide to give the non-isolable potassium salt **14** and then ethylchloroacetate[19] was added afforded 2'-[1*H*-indol-3-ylmethylenehydrazono]-2,5'-bi-1,3-thiazolidin-2'-ylidene-4,4'-dione **16 (Scheme 3).** Probably, the reaction mechanism is assumed to proceed *via* S-alkylation to give the intermediate **15** which was cyclized to **16**. Elemental analyses and spectral data were in favor of these proposed 1,3-thiazolidinone structures. The 1H-NMR spectrum of compound **16** showed singlet signal at *δ* 4.09 ppm corresponding to CH_2 protons of the thiazolidinone ring.[13]C NMR spectra of **16** showed signals at δ 20.75,32.16,152.65,157.15 and 162.38 and 164.72 ppm to CH_3, CH_2, N=CH, C=N and 2 C=O respectively.

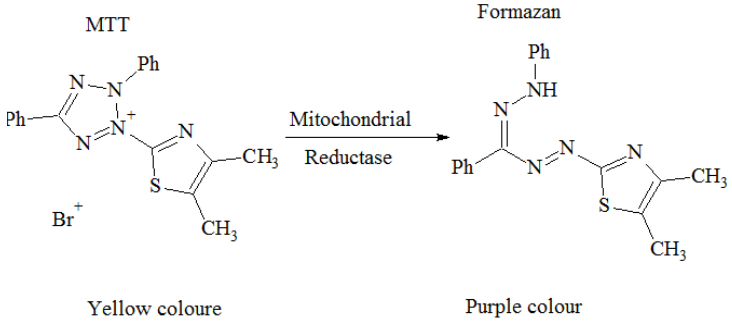
Furthermore, the reaction 1,3-thiazolidin-4-one derivative **6** with carbon disulfide in boiling DMF containing catalytic amount of potassium hydroxide afforded non-isolable intermediate potassium sulfide salts **17** then phenacyl bromide was added [20] afforded 2-oxo-2-phenylethyl {2-[1*H*-indol-3-ylmethylenehydrazono]}-1,3-thiazolidine-5-carbodithioate**18 (Scheme 3).** The chemical structure of the compounds **18** was elucidated on the basis of elemental analysis and spectral data. Compound **18** was characterized by the presence of a strong band at 1241 cm^{-1} (C=S) in the IR spectrum. 1 H NMR spectrum of **18** showed a singlet at δ 4.09 ppm corresponding to CH_2 and a singlet signal at δ 4.76 ppm for an H-5 thiazolidinone proton. [13]C NMR spectra of **18** showed signals at 10.36, 30.01,147.39,150.43,164.36, 164.73 and 185.40 ppm to CH_3, CH_2, CH=N, C=N, 2C=O, C=S respectively.

b) In Vitro Cytotoxicity Activity

The newly synthesized compounds 1, 2a, 6 and 11 were evaluated for their in vitro cytotoxic effects against human liver cancer (Hep G2),human colon cancer (HT-29) and human breast cancer (MCF-7) cell lines by the standard MTT (3-(4,5-l-2-yl)- dimethylthiazo-2,5-diphenyl tetrazolium bromide) assay21,22.

The method is based on the ability of a mitochondrial dehydrogenase from viable cells to cleave the tetrazolium rings of the pale yellow MTT and form purple formazan crystals which are impermeable to cell membranes (Scheme 4). The crystals can be solubilized by detergents. The number of living cells is directly proportional to the level of formed formazan which can be quantified photometrically. When the amount of purple formazan produced by cells treated with an agent is compared with the amount of formazan produced by untreated control cells, the effectiveness of the agent in causing death of cells can be deduced (see Figure 3).

MTT assay to determine the drug concentration required to inhibit the growth of human cancer cells by 50% (IC_{50}).The results of the MTT assay percentage viability cell and IC_{50} values are shown in Tables 1 and 2 and Figs.4 – 7.



Scheme 4 : Principle of MTT assay

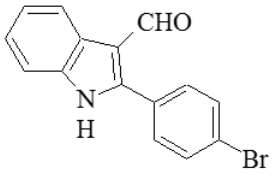
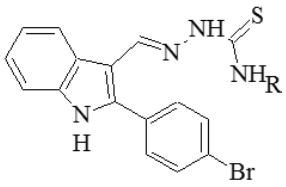
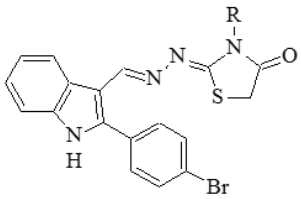
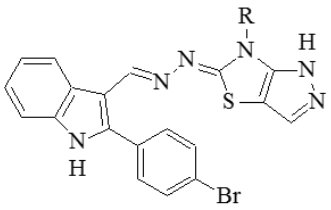
In order to investigate the structure activity relationship the intact indole ring was reserved for a different substituted to position 3. The obtained results from value of IC_{50} (Table 2 and Figure 7) revealed that :

1. Compound 1 having CHO at position-3 of indole ring more active cytotoxic agent against human liver can-cer (HepG2) and human breast cancer (MCF-7) cell line while week cytotoxic agent against colon cancer (HT -29) cell line.
2. Compounds 2a having thiosemicarbazone group at position-3 of indole ring more active cytotoxic agent against human liver cancer (HepG2) while week cyto-toxic agent against colon cancer (HT-29) and human breast cancer (MCF-7) cell line.
3. Compound 6 having 1,3-thiazolidine ring at position-3 of indole ring more active cytotoxic agent against hu-man breast cancer (MCF-7) cell line but week cyto-toxic agent against human liver cancer (HepG2) and human colon cancer (HT- 29) cell line.
4. Compound 11 having pyrazolo[3,4-d] [1,3]thiazol at position-3 of indole ring a more active cytotoxic agent against all three cancer cell.; human liver cancer (HepG2) line, human colon cancer (HT-29) line and human breast cancer (MCF-7) cell line.

Table 1 : In vitro cell viability % of test compounds 1,2,6 and 11 with different concentrations (mg/ml) by MTT assay

Comp. No.	Dilution	Cell viability%		
	(mg/ml)	Hep G2	HT29	MCF-7
1	1.00000	15.05	13.72	17.35
	0.10000	21.14	19.28	22.64
	0.01000	31.54	28.75	30.56
	0.00100	32.25	55.88	36.22
	0.00010	56.63	84.31	64.15
	0.00001	76.34	100	87.92
2a	1.00000	21.14	19.28	20
	0.10000	21.86	21.24	29.05
	0.01000	28.67	27.77	42.26
	0.00100	33.69	62.09	62.26
	0.00010	58.87	84.31	89.81
	0.00001	81.72	98.03	100
6	1.00000	17.56	16.66	18.86
	0.10000	26.52	22.54	28.3
	0.01000	30.82	31.37	35.47
	0.00100	48.39	55.55	43.77
	0.00010	93.19	84.96	86.03
	0.00001	100	97.38	94.71
11	1.00000	21.86	19.93	17.35
	0.10000	26.88	25.49	21.5
	0.01000	28.32	30.06	26.41
	0.00100	35.12	39.86	35.47
	0.00010	72.04	65.68	50.56
	0.00001	100	96.07	72.07

Table 2 : IC_{50} values (mg/ml) of the tested compounds 1,2,6 and 11

Compd. No.	Structure	IC_{50} (mg/ml)		
		Hep G2	HT29	MCF-7
1		$8.83x10^{-5}$	$8.95x10^{-4}$	$7.79x10^{-5}$
2a		$8.49x10^{-5}$	$8.05x10^{-4}$	$8.03x10^{-4}$
6		$1.03x10^{-3}$	$9x10^{-4}$	$5.81x10^{-5}$
11		$6.94x10^{-5}$	$7.61x10^{-5}$	$9.89x10^{-5}$

IC_{50} : Concentration that causes a 50 % reduction of the cell growth.

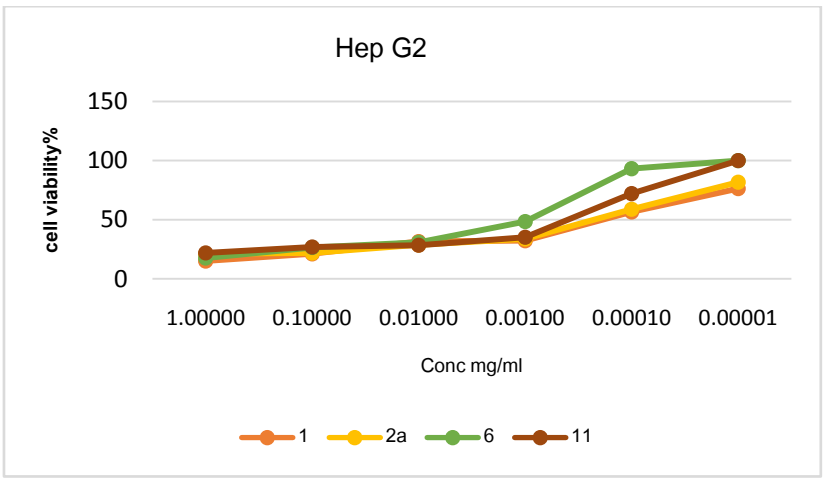


Fig. 3 : Cell viability % of Hep G2 with different concentrations of the tested compounds

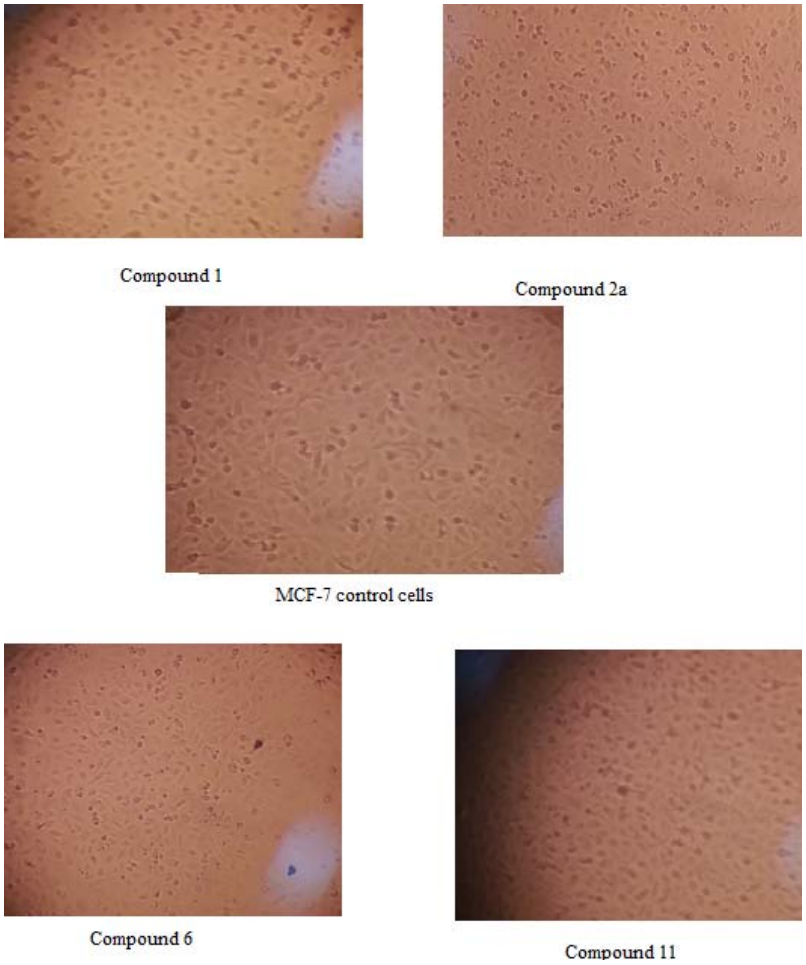


Fig. 4 : Pictoral view change in MCF 7 cell morphology after exposure to MTT

Order activity of synthesis compound against human breast cancer cell (MCF-7) line 6 > 1 > 11 > 2a

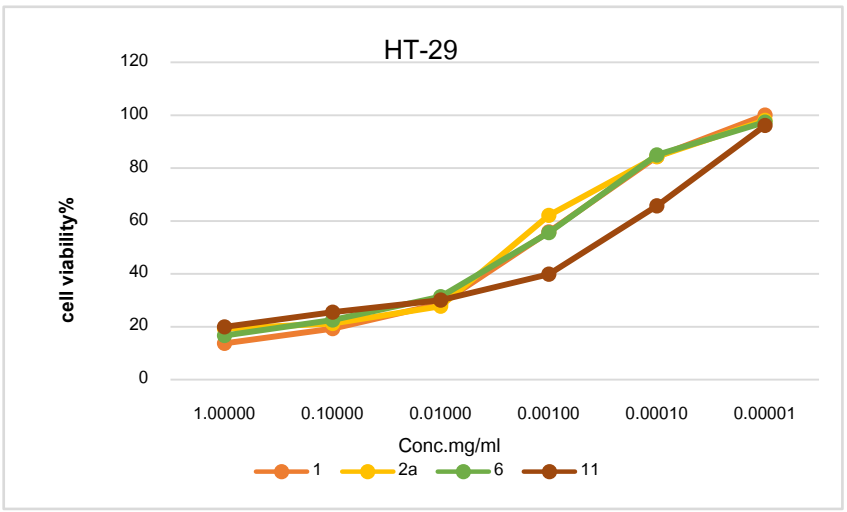


Fig.5 : Cell viability % of HT-29 with different concentrations of the tested compounds

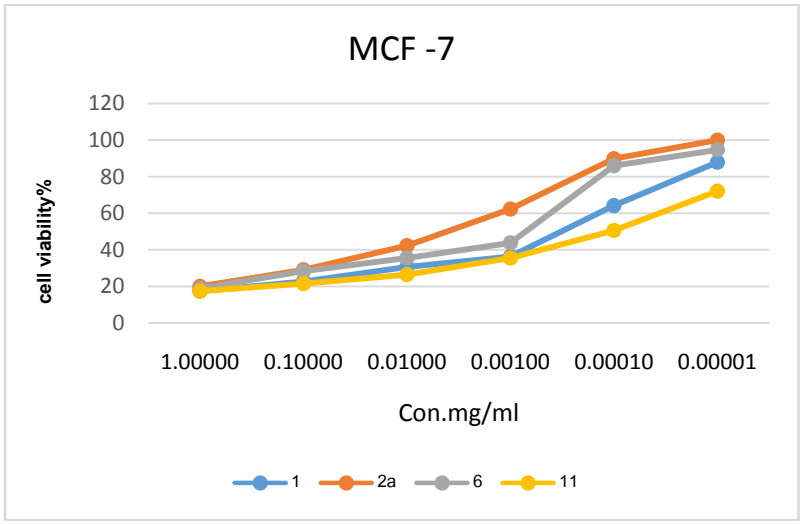


Fig. 6 : Cell viability % of MCF-7 with different concentrations of the tested compounds

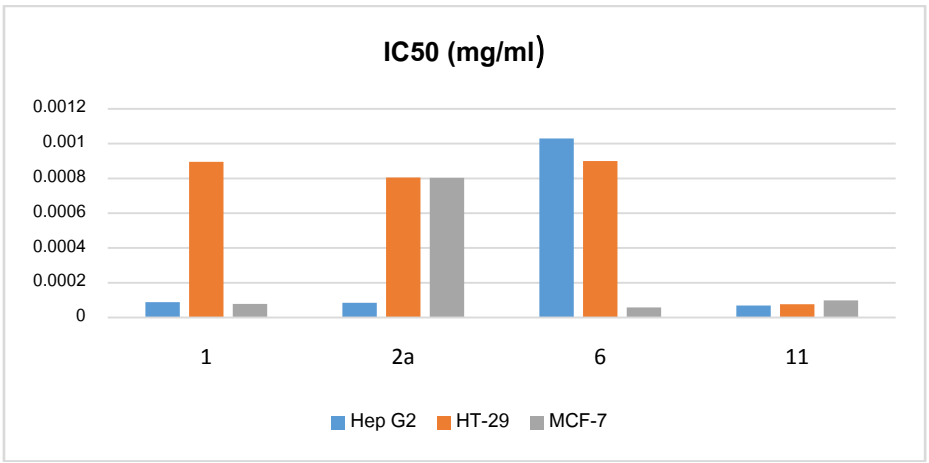


Fig. 7 : Evaluation of IC50 of test compounds

Order activity of test compounds against human liver cancer (Hep G2) cell line 11 > 2 a > 1 > 6
Order activity of test compounds against human colon cancer (HT- 29) cell line 11> 2a > 1> 6
Order activity of test compounds against human breast cancer (MCF-7) cell line 6 > 1 > 11 > 2.

III. Conclusion

In this work, variety of heterocyclic systems have been synthesized from the thiosemicarbazone derivatives .The new synthesis compounds 1,2a,6 and 11 have been evaluated for the vitro cytotoxic activity against human liver cancer (HepG2), human colon cancer l (HT-29),and human breast cancer (MCF-7) cell lines activity using MTT assay, compound 11 showed best cytotoxic activity against all the three cancer cell lines due to the presence of pyrazolo[3,4-d] [1,3]thiazol group at position-3 of indole ring. Compounds 1 also showed higher cytotoxic activities against the human liver cancer (Hep G2) and human breast cancer (MCF-7) cell line due to the presence of CHO group at position-3 of indole ring, compound 2a also showed higher cytotoxic activities against the human liver cancer (Hep G2) cell line due to the presence of thiosemicarbazone group at position-3 of indole ring and compound 6 also showed higher cytotoxic activities against the human breast cancer (MCF-7) cell line due to the presence of 1,3-thiazolidine ring at position-3 of indole ring.Hence it can be suggested that compound 1,2a,6 and 11 could be used as leads in the design and development of new anticancer drugs.

IV. Experimental

a) Chemistry

Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer (υ_{max} in cm^{-1}). The 1H-NMR and ^{13}C NMR spectra were determined in DMSO-d6 at 300 MHz on a Varian Mercury VXR- 300, NMR spectrometer using

TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 Ev. Elemental analyses were carried out at the Microanalytical center of Cairo University and main defence chemical laboratory.

i. *General procedure for the preparation of thiosemicarbazones 2a,b*

An equimolecular mixture of 2-(4-bromophenyl)-1H-indole-3-carboxaldehyde 1 and the selected thiosmi-carbazide such as 4-(4-methylphenyl) thiosemicarbazide or 4-(4-phenyl-1,3-thiazol-2-yl) thio-semicarbazide (0.01 mol) were refluxed in absolute ethanol (20 ml) in the presence of 2-3 drops of glacial acetic acid for the 3h.The reaction mixture was cooled to room temperature and separated product was filtered off, washed with cold water, dried and recrystallized from the appropriate solvent to give 2a,b .

ii. *1-[2-(4-Bromophenyl)-1H-indol-3-ylmethylene]-N-(4 methylphenyl)thiosemicarbazone 2a*

Yellow solid. Yield 80 % ,m. p.249- 250°C (ethanol- DMF).FT-IR (KBr, υ_{max} /cm $^{-1}$) : 3317, 3135 (NH), 3042, 2975, 2857 (CH),1246 (C=S) . 1H-NMR (DMSO-d6)δ ppm : 2.32 (s , 3H , CH_3), 7.17-7.28 (m, 4H, Ar-H),7.45- 7.52(m, 4H, Ar-H), 7.60 (d,1H,indole proton),7.77-7.95(m,2H,indole proton),8.33(d, 1H, indole proton),8.55 (s, 1H,=CH) 10.01 (s,1H, NH exchanged by D_2O),11.46 (s,1H,NH exchanged by D_2O), 11.99 (s,1H,NH exchanged by D_2O). MS: m/z (%):463 (M^+, 0.3), 357(1.3), 313(0.8), 298 (72.5),284 (10), 271 (100), 216 (23.3), 192 (16.3). Anal. calcd for $C_{23}H_{19}$ Br N_4S(463.39):C,59.61;H,4.13;Br,17.24;N,12.09;S,6.92 Found: C, 59.41; H,4.00 ; Br, 17.04 ; N, 12.00; S, 6.72.

iii. *1-[2-(4-Bromophenyl)-1H-indol-3-ylmethylene]-N-(4-phenyl-1,3-thiazol-2-yl)-thiosemicarbazone 2b*

Yellow solid. Yield 60 %, m.p. 140-142°C (ethanol). FT-IR (KBr, υ_{max} /cm^{-1}): 3161, 3125,3223 (NH), 3039, 2967, 2864 (CH),1237 (C=S). 1H-NMR (DMSO-d6) δ ppm : 6.95-7.30 (m, 10H, Ar-H and H-5 thiazole), 7.32(d, 1H, indole proton), 7.69-7.87 (m, 2H, indole proton), 8.19 (d, 1H, indole proton), 8.22 (s, 1H,N=CH), 8.47 (s, 1H, NH exchanged by D_2O), 8.90 (s,1H, NH exchanged by D_2O),2.44 (s ,1H,NH exhanged by D_2O). Anal.calcd for $C_{25}H_{18}BrN_5S_2$ (532.48): C, 56.39 ; H,3.41; Br,15.01; N,13.15 ; S, 12.04. Found: C, 56.19; H, 3.21 ; Br,14.89 ; N,13.00 ; S,11.89.

iv. *5-[2-(4-Bromophenyl)-1H-indol-3-yl]-4-(4-methyl phenyl)- 4H-1,2,4-triazole-3-thiol 3*

A solution of thiosemicarbazone derivative **2a** (0.01 mol) in absolute ethanol (15 ml) containing few drops of HCl was refluxed for 2 h. After cooling and dilution with water, the solid formed were filtered off, washed with water, air dried and recrystallized from ethanol to give **3** as green powder. Yield 62 %; m.p.336 – 338°C (ethanol). FT-IR (KBr,υ_{max} /cm^{-1}) : 3166 (NH), 3097, 2951, 2919 (CH), 1606 (C=N). 1H-NMR (DMSO-d6) δ ppm : 2.08 (s , 3H , CH_3) , 7.16 -7.48 (m,8H, Ar-H),7.78(d,1H,indole proton),7.65- 7.94 (m,2H, indole proton),8.43(d, 1H, indole proton), 4.33(s,1H,SH exchanged by D_2O),12.05 (s,1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6)δ ppm:20.44 (CH_3),154.84, 154.98(2C=N),162.17(C-S),106.49,111.47,120.92,121, 122.43,122.70,123.10,125.81,130.24,131.14,131.32,131. 93,136.51,141.73.Anal.calcd for $C_{23}H_{17}BrN_4S$ (461.38) :C,59.87;H,3.71;Br,17.32;N,12.14;S,6.95.Found:C, 59.57; H,3.51;Br,17.22;N,12.04 ; S,6.85.

v. *N-[4-acetyl-5-(2-(4-bromophenyl)-1H-indol-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-N-(4-methyl-phenyl) acetamide 4*

A solution of the thiosemicarbazone derivative **2a** in acetic anhydride (12 ml) was heated under reflux for 5 h. with continuous stirring and then allowed to attain room temperature. The reaction mixture was slowly added to 400 ml of ice-cooled water and then stirred at room temperature for 1h. The separated product was collected by filtration, washed with water, dried, and recrystallized from ethanol and DMF (2:1) to give **4** as orange powder, yield 55 %, m.p. 180-182°C.FT-IR (KBr,υ_{max}/cm^{-1}): 3419 (NH),3044 , 2986, 2919 (CH), 1750,1688 (2 C=O). 1H-NMR (DMSO-d6) δ ppm : 2.16 (s, 3H, CH_3),2.19 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 6.93 - 7.28 (m, 9H, Ar-H and H-5, thiadiazole ring) ,7.34(d,1H, indole proton), 7.51-7.82 (m,2H,indole proton),8.40(d, 1H, indole proton),11.55 (s, 1H,NH exchanged by D_2O). MS. m /z (%) : 547 (M^+, 0.5), 517 (0.3), 502 (0.2), 489 (1.2), 446 (0.23), 358 (79.7), 276(1.6), 271(100), 77 (80.3). Anal. calcd for $C_{27}H_{23}BrN_4O_2S$ (547.47):C, 59.23 ; H,4.23; Br,14.60;N, 10.23 ; S, 5.86. Found: C, 59.03; H,4.03 ; Br ,14.40; N, 10.03 ; S , 5.56.

vi. *2-(4-Bromophenyl)-3-[3-(4-methylphenyl)-4-phenyl-1,3-thiazol-2(3H)-ylidene]hydrazonomethyl-1H-indole 5*

To a solution of thiosemicarbazone derivative **2a** (0.01 mol) in absolute ethanol (20 ml) were added equimolar amounts of the phenacyl bromides and anhydrous sodium acetate. The reaction mixture was heated under reflux for 6 h with continuous stirring, then partially concentrated under reduced pressure and left to cool. The separated solid product was filtered off and recrystallized from ethanol to give **5** as yellow solid . Yield 60 %, m.p. 280-282°C. FT-IR (KBr, υ_{max}/cm^{-1}): 3122 (NH), 3028, 2947, 2826 (CH). H-NMR (DMSO-d6) δ ppm : 2.27 (s, 3H, CH_3), 6.58 (s,1H, H-5 thiazole ring), 7.14-7.28 (m,13H, Ar-H), 7.44 (d, 1H, indole proton), 7.54 -7.75 (m, 2H, indole proton), 8.41 (d,1H,indole proton),8.30(s,1H, N=CH), 11.85 (s, 1H, NH exchanged by D_2O). MS. m/z (%) : 563 (0.33), 430 (0.3), 367 (0.32), 354 (0.36), 291 (0.96), 270 (0.56), 252 (60.32), 134 (35.86), 61 (100). Anal. calcd for $C_{31}H_{23}BrN_4S$ (563.51) : C, 66.07 ; H,4.11; Br,14.18 ;

N,9.94 ; S, 5.69. Found : C, 65.97 ; H, 4.00 ; Br,14.00 ; N, 9.64 ; S,5.49 .

vii. *2-(4-Bromophenyl)-3-[3-(4-methylphenyl)-4-oxo-1,3-thia- zolidin-2-ylidene]hydrazonomethyl-1H-indole 6*

A mixture of thiosemicarbazone derivative **2a** (0.01 mol), chloroacetic acid (0.01 mol), and anhydrous sodium acetate (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 8 h with continuous stirring. The reaction mixture was left to cool and poured into ice-cold water, and the separated solid was filtered off, washed with water, dried, and recrystallized from DMF to give **6** as yellow powder. Yield 70 %, m.p. 340-342°C; FT-IR (KBr,υ_{max} cm^{-1}): 3273(NH), 3044, 2959, 2861 (CH), 1703 (C=O), 1601(C=N).1H-NMR (DMSO-d6) δ ppm : 2.36 (s, 3H, CH_3), 4.09 (s, 2 H, CH_2), 7.19 -7.31 (m, 8H, Ar-H), 7.45 (d,1H, indole proton),7.52-7.75 (m, 2H, indole proton), 7.90 (s,1H, CH=N),8.35(d, 1H, indole proton), 11.04 (s, 1H, NH exchanged by D_2O). ^{13}C NMR(DMSO-d6) δ ppm : 20.65 (CH_3),32.16 (CH_2),152 (N=CH), 162 (N=C),172(C=O), 108.37, 111.78,121.16, 122.42, 123.22, 125.76, 128.01, 129.40,129.5,129.61, 130.96, 131.13,131.85,132.51, 136.48,138.06, 141.55. Anal. calcd for $C_{25}H_{19}BrN_4OS$ (503.41): C, 59.65; H, 3.80 ; Br,15.87; N,11.13; S, 6.37.Found : C, 59.35; H ,3.50 ; Br,15.67; N ,11.00; S, 6.27.

viii. *2-(4-Bromophenyl)-3-[5-benzylidene-3-(4-methyl-phenyl)-4-oxo-1,3-thiazolidin-2-ylidene]hydrazono-methyl-1H-indole 7*

To a solution of compound **6** (0.01 mol) and anhydrous sodium acetate (0.015 mol) in glacial acetic acid (10 ml) was added the benzaldehyde (0.01 mol). The mixture was heated under reflux for 6 h with continuous stirring. The reaction mixture was left to cool and poured onto crushed ice with stirring. The separated solid was filtered off, washed with water, dried, and recrystallized from ethanol and DMF (2 : 1) to give 7 as orange powder. Yield 60 %,m.p. 210-212 °C. FT-IR (KBr) υ_{max} /cm^{-1}): 3292 (NH) ; 3029, 2942, 2842 (CH), 1683 (C=O).1H-NMR (DMSO-d6) δ ppm : 2.36 (s, 3H, CH_3), 7.25-7.32 (m,14H, Ar-H and olefinic CH=), 7.51-7.77 (m, 3H, indole proton), 8.38 (d, 1H, indole proton), 8.42 (s,1H, CH=N), 12.14 (s, 1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6) δ ppm : 20.68 (CH_3), 142 (C=CH),153(N=CH) , 156 (N=C),165 (C = O), 108.12,111.97, 122.27,122.59,125.72, 127.83, 128.09, 129.44, 129.60,129.81, 131.06, 131.25, 131.80, 132.29, 133.84, 136.53, 138.38. Anal. calcd for $C_{32}H_{23}BrN_4OS$ (591.52) : C,64.98; H,3.92; Br,13.51; N, 9.47; S,5.42. Found: C,64.68; H,3.72; Br,13.31; N, 9.27 ; S, 5.22.

ix. *2-(4-Bromophenyl)-3-[6-(4-methylphenyl)-2,3-di-phenyl-2,3,3a,6-tetrahydro-5H-pyrazolo[3,4-d]1,3-thiazol-5 ylidene]hydrazonomethyl-1H-indole 8*

A mixture of compound **7** (0.01mol) and phenyl hydrazine (0.01 mol) was refluxed in ethanol (50 ml) in present of few drops of acetic acid for 4 h. The reaction mixture was cooled, and the solid separated was filtered off, washed with water and recrystallized from aqueous ethanol to give compound **8** as orange powder. Yield 55 % yield; m.p.102-104°C. FT-IR (KBr, υ_{max}/ cm^{-1}) : 3229 (NH), 3054, 2936, 2857 (CH), 1605 (C=N). 1H-NMR (DMSO - d6) δ ppm : 2.24 (s, 3H, CH_3), 4.09 (d, 1H, CH -pyrazole), 6.67 (d,1H, CH- pyrazole), 7.08 -7.22 (m,18H, Ar-H), 7.24 -7.94(m,3H, indole proton), 8.19 (d, 1H, indole proton), 8.52 (s, 1H,CH=N), 12.20 (s, 1H,NH exchanged by D_2O). MS. m/z (%) : 681 (M^+, 0.1), 666 (0.4),510 (3.2),537(2.2), 271 (100), 165 (73.5), 77(30.9). Anal.calcd for $C_{38}H_{29}Br\ N_6S$ (681.65): C,66.96 ;H,4.29 ; Br,11.72 ; N,12.33 ; S, 4.70. Found : C,66.76; H ,4.09 ; Br,11.52 ; N, 12.03 ; S, 4.50.

x. *2-(4-Bromophenyl)-3-[3-phenyl-6-(4-methylphenyl)-3,3a-dihydro-1,3-thiazolo[4,5-c]isoxazol-5-ylidene] hydrazono- methyl-1H-indole 9*

A mixture of compound **7** (0.01 mol), hydroxylamine hydrochloride (0.012 mol), sodium acetate (0.012 mol) was refluxed in ethanol (30 ml) in present of few drops of acetic acid for 10 h., and kept overnight. Excess of solvent was distilled off under reduced pressure and the remainder was then poured into water. The solid obtained was recrystallized from ethanol to give **9** as white powder. Yield 65 % ; m.p.170 -172 °C. FT-IR (KBr, υ_{max} /cm^{-1}) : 3173(NH); 3057, 2922, 2859(CH).1H-NMR (DMSO-d6) δ ppm : 2.17 (s,3H,CH_3), 4.35 (d,1H,CH- isoxazole), 5.55 (d, 1H,CH-isoxazole), 6.65-8.27 (m, 17 H, Ar-H and indole proton), 8.38 (s, 1H, CH=N), 11.57 (s,1H, NH exchanged by D_2O). MS.m/z (%): 606.1 (M^+, 0.33), 530(0.25), 488.1 (0.34), 324.95 (26.67), 297.95 (100), 271.95 (8.89). Anal. calcd for $C_{32}H_{24}\ BrN_5OS$ (606.53) : C, 63.37; H, 3.99 ; Br,13.17; N, 11.55 ; S, 5.29. Found : C, 63.17; H, 3.79 ; Br,13.00 ; N,11.35 ; S, 5.0.

xi. *2-[2-(4-Bromophenyl)-1H-indol-3-ylmethylidene-hydrazono]-4-chloro-3-(4-methylphenyl)-2,3 dihydro-1,3-thiazole-5-carboxaldehyde 10*

To the Vilsmeier-Haack complex prepared from DMF (10 ml) and $POCl_3$ (0.02 mole) at 0°C was added the 1,3-thiazolidin-4-one derivative **6** (0.004 mol) and the reaction mixture was stirred at 60-65 °C for 4 hr. The reaction mixture was kept overnight and it was then slowly added to crushed ice. The product separated on neutralization with $NaHCO_3$ was filtered and recrystallized from ethanol to give **10** as yellow powder. Yield 70 % ; m.p. 150-152°C. FT-IR (KBr, υ_{max} / cm^{-1}) : 3216(NH), 3031, 2956, 2781 (CH), 1600 (C=N), 1675 (C=O). 1H-NMR (DMSO-d6) δ ppm :2.08 (s, 3H,CH_3), 7.19 -8.22 (m,12H, Ar-H and indole proton), 8.36 (s,1H,

CH=N), 9.95 (s,1H, CHO),12.45 (s,1H, NH exchanged by D_2O).^{13}C NMR (DMSO-d6) δ ppm : 20.56 (CH_3), 135.89(C-Cl), 151(N=CH), 156 (N=C), 164(C=O), 105.37, 121.01, 123.44. 125.71, 127.99, 129.40,129.51, 131.20,131.29,131.32,131.40,131.88. Anal. calcd for $C_{26}H_{18}BrClN_4OS$ (549.87) : C, 56.79 ; H, 3.30 ; Br, 14.53; Cl,6.45 ; N, 10.19 ; S, 5.83 Found :C,56.59 ; H, 3.00 ; Br, 14.33 ; Cl, 6.25; N, 10.00 ; S,5.53.

xii. *2-(4-Bromophenyl)-3-[6-(4-methylphenyl)-1,6-dihydro-5H-pyrazolo[3,4-d]1,3-thiazol-5-ylidene]-hydrazono- methyl-1H-indole 11*

A mixture of compound **10** (0.01mol) and hydrazine hydrate (0.01 mol) was refluxed in ethanol (50 ml) for 4 h. The reaction mixture was cooled, and the precipitate was filtered off and recrystallized from ethanol to gives **11** as yellow powder .Yield 64 %, m.p. 300-302° C.FT-IR (KBr, υ_{max} /cm^{-1}): 3380, 3176 (NH), 3052, 2966, 2864 (CH), 1604 (C=N).1H-NMR (DMSO-d6) δ ppm : 2.36 (s, 3H, CH_3), 6.93-7.24 (m ,9H, Ar-H and H-3 pyrazole),7.29 (d,1H, indole proton),7.54-7.85(m,2H, indole proton),8.41(d, 1H, indole proton), 8.90 (s,1H,CH=N),4.28 (s, 1H, NH exchanged by D_2O), 12.03 (s,1H, NH exchanged by D_2O). MS. m/z (%) : 527 (M^+, 0.95), 567 (0.99), 281(3.33), 254 (1.11), 248 (35.86),118(100). Anal. calcd for $C_{26}H_{19}BrN_6S$ (527.44): C,59.21 ; H, 3.63; Br,15.15; N,15.93; S,6.08. Found: C,59.00 ; H, 3.43; Br,15.00; N, 15.63 ; S , 6.00.

xiii. *N'-{2-[2-(4-Bromophenyl)-1H-indol-3-ylmethylene-hydra-zono]-4-chloro-3-(4-methylphenyl)-2,3-dihydro-1,3-thiazol-5-ylmethylene}-2-cyanoaceto-hydrazide 12*

An equimolar mixture of **10** (0.02 mol) and cyanoacetic acid hydrazide (0.02 mol) in absolute ethanol (30 ml) was heated under reflux for 2 h. The precipitate formed after cooling was filtered off, washed with cold ethanol, dried and recrystallized from xylene to give **12** as orange powder. Yield 50 %; m.p. 230 - 232°C. FT-IR (KBr, υ_{max} /cm^{-1}): 3327 (NH), 2920, 2853 (CH),1668 (C=O),2196 (CN).1H-NMR (DMSO-d6) δ ppm : 2.36 (s, 3H, CH_3),4.22 (s, 2H, CH_2), 7.15 -7.27 (m, 8H, Ar-H),7.38 -7.92 (m, 3H, indole proton), 8.18 (d, 1H, indole proton), 8.29 (s,1H, CH=N),8.36 (s,1H, CH=N), 11.33(s,1H, NH exchanged by D_2O), 11.49 (s, 1H, NH exchanged by D_2O). MS. m/z (%) : 630 (M^+, 0.87), 538(1.19), 383(8.04), 348 (1.32), 270(88.70), 295 (100). Anal. calcd for $C_{29}H_{21}BrClN_7OS$ (630.95) : C, 55.20 ; H, 3.35 ; Br, 12.66 ; Cl, 5.62 ; N, 15.54 ; S, 5.08. Found : C, 55.00; H,3.15 ; Br, 12.46 ; Cl,5.52 ; N,15.34; S, 5.00.

xiv. *2-[2-(4-Bromophenyl)-1H-indol-3-ylmethylenehy-drazono]-3-(4-methylphenyl)-3,4-dihydro-1,3-thiazolo [4,5-b]1,5-benzodiazepine 13*

An equimolar mixture of compound **10** (0.02 mol), *o*-phenylenediamine (0.02 mol) and 0.2 ml TEA in absolute ethanol (30 ml) was heated under reflux for 8 h. The precipitate formed after cooling was filtered off, washed with cold ethanol, dried, and recrystallized from ethanol to give **13** as orange powder. Yield 67 %; m. p.250-252°C. FT-IR (KBr,$\upsilon_{max/}$ cm^{-1}) : 3337 (NH), 3055, 2923, 2865 (CH). 1H-NMR (DMSO-d6) δ ppm : 2.27 (s, 3H, CH_3), 7.22-8.37. (m, 17 H, Ar-H and benzo-diazepine), 8.90 (s,1H, CH=N), 12.03 (s,1H, NH exchanged by D_2O),12.31(s, 1H, NH exchanged by D_2O). MS. m/z (%) : 603 (0.98) , 504 (0.32), 334 (3.89), 316(1.21), 308 (74.55), 281 (16.62), 245 (3.05),77 (100). Anal. Calcd for $C_{32}H_{23}BrN_6S$ (603.53) : C, 63.68 ; H, 3.84 ; Br,13.24 ; N,13.92 ; S, 5.31. Found : C, 63.48 ; H, 3.54 ; Br,13.14 ; N,13.62; S, 5.11.

xv. *2'-[2-(4-Bromophenyl)-1H-indol-3-ylmethylene-hydra-zono]-3'-(4-methylphenyl)-3-phenyl-2,5'-bi-1,3-thiazolidin-2'-ylidene-4,4'-dione 16*

To a stirred solution of 0.56 g KOH (0.01mol) in 20 ml DMF, 1,3-thiazolidin-4-one **6** (0.10 mol) was added. After stirring for 30 min phenyl isothiocyanate (0.01mol) was added to the resulting mixture. After complete addition, stirring of the reaction mixture at room temperature for 12 h. Then ethyl chloroacetate (0.01 mol) was added to the reaction mixture and stirred for 6 h. The reaction mixture was poured into crushed ice. The resulting precipitate was filtrated off, dried, and recrystallized from xylene to give **16** as orange powder.Yield, 60 %, m.p. 290-292°C. FT-IR (KBr, υ_{max}/cm^{-1}) : 3267 (NH), 3042, 2964, 2919 (CH), 1702 (C=O),1600 (C=N) .1H-NMR (DMSO-d6) δ ppm : 2.36 (s, 3H, CH_3), 4.09 (s,2H, CH_2), 7.07-7.32 (m, 13H, Ar-H), 7.45-7.55 (m, 2H, indole proton),7.72 (d, 1H, indole proton), 8.33 (s, 1H ,CH=N),8.35 (d, 1H, indole proton),12.02(s,1H, NH exchanged by D_2O).^{13}C NMR (DMSO-d6) δ ppm : 20.75 (CH_3), 32.16 (CH_2),152.65(CH=N),157.15(C=N),162.38(C=O),164.72(C=O), 99.43,108.37, 110.45 ,111.82 , 114.23, 122.42, 125.70,126.87,129.66,129,94, 130.66,130.74, 130.98, 131.96, 136.49, 138.06, 141.55, 149.95.Anal. Calcd for $C_{34}H_{24}BrN_5O_2S_2$ (678.62): C, 60.18 ; H ,3.56 ; Br, 11.77 ; N, 10.32; S, 9.45. Found : C,60.00 ; H, 3.36 ; Br,11.57 ; N, 10.22 ; S,9.25.

xvi. *2-Oxo-2-phenylethyl {2-[2-(4-bromophenyl)-1H indol-3-ylmethylenehydrazono]-3-(4-methylphenyl)- 4-oxo}-1,3-thiazolidine-5-carbodithioate 18*

To a stirred suspension of finely powdered potassium hydroxide (0.02 mol) in dry DMF (20 ml), 1,3-thiazolidin-4-one **6** (0.01 mol) was added. The resulted mixture was cooled at 10°C in an ice bath; then (0.01mol) carbon disulfide was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for 6 h .Then phenacyl bromide (0.01mol) was added to the mixture and stirring continued for 3 h, then the mixture was poured into crushed ice and HCl, the resulting precipitate was filtrated off, dried, and recrystallized from xylene to give **18** as red powder. Yield, 60 % ; m.p. 200-202 °C. FT-

IR (KBr,υ_{max}/cm $^{-1}$): 3274 (NH), 3056, 2967, 2861(CH), 1702 (C=O),1241 (C=S).1H-NMR (DMSO-d6) δ ppm : 2.37 (s, 3H, CH_3), 4.09 (s, 2H, CH_2), 4.76 (s,1H, H-5 thiazolidinone),7.13-7.75 (m, 13H, Ar-H), 7.39-7.97 (m, 3H, indole proton), 8.22 (d, 1H,indole proton), 8.38 (s, 1H, CH=N),12.09 (s,1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6) δ ppm : 10.36 (CH_3), 30.01 (CH_2) 147.39 (CH=N), 150.43 (C=N),164.36 (C=O), 164.73 (C=O),185.40(C=S), 107.37,110,111.22,114.03, 122.12, 124.60, 128.51, 130.52 , 130.6, 130.65,130.84,130.85, 132.92,132.08,149.01.Anal. Calcd for $C_{34}H_{25}BrN_4O_2S_2$ (665.62):C, 61.35; H,3.79; Br,12.00; N,8.42; S,9.63. Found : C, 61.15 ; H, 3.59 ; Br, 11.89 ; N,8.22 ; S, 9.43.

b) In Vitro Cytotoxic Screening (MTT assay)

In vitro cytotoxicity of newly synthesized compounds 1, 2a, 6 and 11 were evaluated against human liver cancer cell (HepG2), human colon cancer cell (HT 29) and human breast cancer cell (MCF-7) cell line using a standard MTT assay.

The monolayer cells were detached with trypsin-ethylenediaminetetraacetic acid (EDTA) to make singlet cell suspensions and viable cells were counted using a hemocytometer, then diluted with the fetal bovine serum (FBS) medium with 5% FBS to give final density of 2 × 105 cells / ml. One hundred microlitres per well of cell suspension were seeded into 96-well plates at plating density of 10,000 cells/well and incubated to allow for cell attachment at 37 0C, 5 % CO2 , 95 % air and 100% rela-tive humidity.

The synthesized samples were dissolved in 1 ml dimethylsulfoxide (DMSO) and further diluted in serum free medium to produce six concentration starting from 1mg/ml to 10-6. About 500-10,000 cells in 200 μl media per well were incubated at 37 0C and 5 % CO2 overnight to allow the cells to attach to the wells. 100 μl, from each dilution of tested samples, was added to each well, mix by shaking at 150 rpm for 5 minutes, incubate at 37 0C and 5 % CO2 for 48 hr. 20 μl of MTT (5mg/ml) in phosphate buffered saline (PBS) was added to each well plate and mix by shaking at 150 rpm for 5 minutes and incubate at 37 0C and 5 % CO2 for 5 hr to allow the MTT to be metabolized. The medium with MTT was then flicked off and the formed formazan crystals (MTT metabolic product) were solubilized in 200 μl of DMSO and then absorbance was measured at 560 nm using micro plate reader [23]. Viability of treated cells was calculated in reference to the untreated control cells by using the fol-lowing formula:

Cell viability (%) = [100 × (Sample Abs)/(Control Abs)].

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Quick Simultaneous Determination of NMP and DMAc in Synthetic Fibers by Py-GC-MS using A Thermal Desorption Function

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Abstract- The simultaneous analyses of NMP and DMAc in synthetic fibers that have been regulated recently due to their human hazard properties were studied by both a conventional GC-MS method and a thermal desorption(TD)-GC-MS method that uses Py-GC-MS instrument using the thermal desorption function. Method validation characteristics such as linearity, precision of peak area and retention time, limit of quantification on their determination using a new TD-GC-MS method were found to be acceptable according to the well-recognized method validation guidelines and the current regulation limit. Recovery ratios of DMAc from the spiked synthetic fibers were estimated to be 95.2% to 97.1% with Soxhlet extraction using methanol as measured by GC-MS. Residual amounts of NMP and DMAc in commercial meta-aramid, polyester, and spandex fibers were measured by and GC-MS and TD-GC-MS, respectively and showed a good correlation between two methods with the ratio of 85.5% to 119%. Results of this study suggested that the TD-GC-MS analysis can provide both a good screening and a quick determination of NMP and DMAc in synthetic fibers without any solvent extraction of fiber samples that is a routine and time consuming pretreatment in the conventional GC-MS analysis.

Keywords: *NMP, DMAc, solvent residues, synthetic fibers, thermal desorption, Py-GC-MS.*

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Kwang Seo Park [α], Moon Hwan Song [σ], Young Dal Cho [ρ] & Eun Kyung Choe [ω]

Abstract- The simultaneous analyses of NMP and DMAc in synthetic fibers that have been regulated recently due to their human hazard properties were studied by both a conventional GC-MS method and a thermal desorption(TD)-GC-MS method that uses Py-GC-MS instrument using the thermal desorption function. Method validation characteristics such as linearity, precision of peak area and retention time, limit of quantification on their determination using a new TD-GC-MS method were found to be acceptable according to the well-recognized method validation guidelines and the current regulation limit. Recovery ratios of DMAc from the spiked synthetic fibers were estimated to be 95.2% to 97.1% with Soxhlet extraction using methanol as measured by GC-MS. Residual amounts of NMP and DMAc in commercial meta-aramid, polyester, and spandex fibers were measured by and GC-MS and TD-GC-MS, respectively and showed a good correlation between two methods with the ratio of 85.5% to 119%. Results of this study suggested that the TD-GC-MS analysis can provide both a good screening and a quick determination of NMP and DMAc in synthetic fibers without any solvent extraction of fiber samples that is a routine and time consuming pretreatment in the conventional GC-MS analysis.

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I. Introduction

NMP(N-Methyl-2-pyrrolidinone) and DMAc(N,N-Dimethylacetamide) have enhanced its utility as a solvent or co-solvent in many synthetic reaction systems and polymeric solutions.[1-7] Due to its good solvency properties NMP has been used in many industrial applications including photoresist stripping; degreasing and coatings (polyamide, epoxy and polyurethane) in the electronics industry; agricultural formulations; consumer and industrial cleaners; an extraction solvent in lube oil processing in petrochemical industry; paint stripping; polymer solutions for fiber-spinning.[1-4] DMAc has been also commonly used as a solvent for fibers (*e.g.*, polyacrylonitrile, polyamide, spandex, meta-aramid) as well as for manufacture of agro chemicals, dyes, synthetic resins and pharmaceuticals.[1,3-7]

However, their uses are now being regulated due to their human hazard.[8,9] As classified as CMR (Carcinogenic, Mutagenic or toxic to Reproduction category) substances, the EU regulated NMP and DMAc as a candidate list of SVHC (Substances of Very High Concern) in 2011,[10] while NMP was regulated as the CHCC list (reporting list of chemicals of high concern to children) in the CSPA (Children's Safe Products Act) of the U.S. state of Washington.[11] Especially, the limit value of 0.1% (w/w) was newly set from 2012 for synthetic fibers by Oeko-tex Standard 100 that has been a global leading textile ecolabel since the middle 1990s.[12]

The most common method for the determination of these solvent residues is based on an extraction of the sample with an organic solvent and subsequent analyses by GC-MS(Gas Chromatography-Mass Spectrometry).[13] In this study, thermal desorption (TD)-GC-MS method was investigated to determine the amount of solvent residues like NMP and DMAc in synthetic fibers without the need of extraction from fibers. For this purpose, the instrument Py-GC-MS (Pyrolyzer Gas Chromatography-Mass Spectrometry) was tried only using a thermal desorption function without a usual pyrolysis.

II. Experimental

a) Instrumentation

Py-GC-MS(PY2020iD, Frontier Lab; HP 7890, MS(5975C), Agilent) and GC-MS(HP 6890, MS(5973N), 7683 Autosampler, Agilent) were used respectively, for comparison. Thermal desorption function of Py-GC-MS was used with temperature programmed from 200℃ to 340℃ for furnace avoiding the much higher temperature that are commonly used in case of pyrolysis of samples. Other detailed conditions are described in Table 2.

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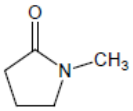
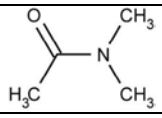
Table 1 : Current prohibitions on use of NMP and DMAc in industrial products

Substance	CAS No.	Chemical structure	Hazard classification	Global prohibition on use		
				CSPA[a]	REACH[b]	Oeko-Tex Standard 100[c]
NMP	872-50-4		CMR : Toxic to reproduction category 2	CHCC list	Candidate List of SVHC for Authorization (0.1%(w/w) in article)	Limit value of 0.1%(w/w)
DMAc	127-19-5		CMR : Toxic to reproduction category 2	-		Limit value of 0.1%(w/w)

a. CSPA(Children's Safe Product Act) in Washington State, U.S.; CHCC(Chemicals of High Concern to Children)

b. REACH(Registration, Evaluation, Authorization, and Restriction of Chemicals); SVHC(Substances of Very High Concern)

c. Globally recognized textile ecolabel

Table 2 : Instrumental conditions for TD-GC-MS analyses of NMP and DMAc

	Thermal desorption mode	Double shot analysis
Thermal desorption condition[a]	Thermal desorption time	14 min
	Furnace temperature program	-Initial : 200 ℃ (for 0 min)- 20 ℃/min to 300℃ (for 0 min)- 5 ℃/min to 340 ℃ (for 1 min)
	Interface temp.	300 ℃
	Sample amount loaded	Fiber : 1 mg Standard solutions mixed in a cup : 5 μL (NMP) + 5 μL (DMAc)
GC condition[b]	Column	HP- INNOWAX Column (30 m(L) X 0.25 mm(ID) X 0.25 m(T))
	Carrier gas	Helium with flow rate of 1 mL/min
	Injection mode	Split ratio of 20 : 1
	Temperatures	Injector 250 ℃, Detector 280 ℃
	Oven temperature program	- Initial : 50 ℃ for 1 min - 15 ℃/min to 250 ℃ (for 5 min)
MS condition (Acquisition mode)	Scan mode	Range : 25 ~ 600 amu
	SIM mode	Selected ions(Reference ions), m/z : - NMP 99 (42, 44, 98) - DMAc 87 (43, 44, 72)

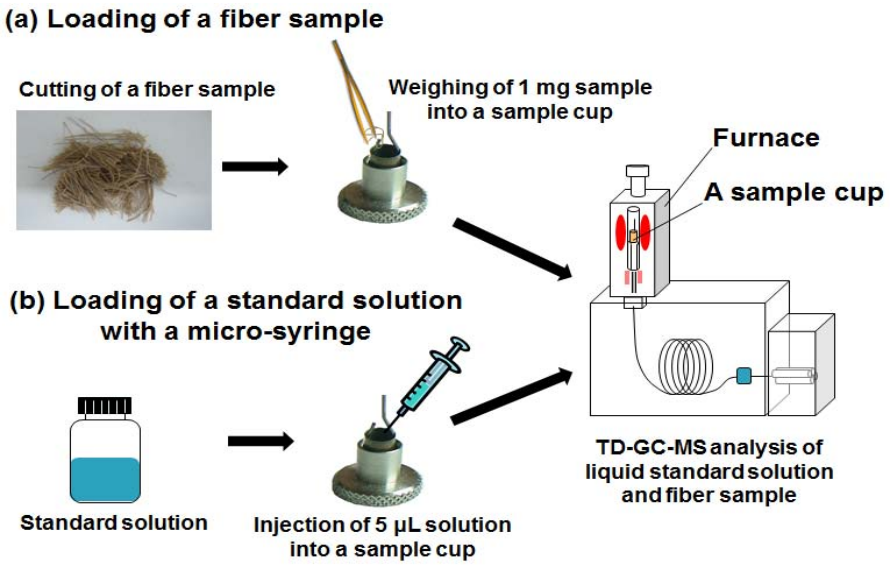


Fig.1 : Schematic diagram of TD-GC-MS analysis of synthetic fibers

b) Reagents

Methyl alcohol (HPLC grade, 99.5%, J.T.Baker) was used for preparation of standard solutions of DMAc and NMP as well as extraction of synthetic fibers. DMAc (HPLC grade, 99.0%, MACRON Chemicals) and NMP (Guaranteed reagent, 99.0%, JUNSEI) were purchased.

c) Samples

Three kinds of commercial synthetic fibers such as meta-aramid, polyester, and spandex were used as obtained in the form of yarns. Each sample was cut into short fibers (ca. 3~5 mm) to achieve homogeneity.

d) Validation data for TD-GC-MS measurement

Standard solutions of 1.25, 2.5, 5.0, 10.0 ng/μL were prepared for NMP and DMAc, respectively, by diluting their stock solutions (1,000 ng/μL) with methanol. A 5 μL portion of each standard solution with the same concentration was loaded by a micro-syringe into a cup to make a mixed standard solution of NMP and DMAc. According to the instrumental conditions described in Table 2, TD-GC-MS measurement of the mixed standard solution of each concentration was repeated 7 times. Then, relative standard deviations (RSD) of retention times and peak areas for each concentration of NMP and DMAc were calculated. Limit of detection (LOD) and limit of quantification (LOQ) of each substance were calculated using the linear equation of standard curve (Y = aX + b) according to "Eqs. (1) and (2)". [14,15]

$$LOD = 3.3 \times \sigma / S \quad (1)$$

$$LOQ = 10 \times \sigma / S \quad (2)$$

σ : Standard deviation of intercept (b) of linear equation (Y = aX + b)

S : Slope (a) of linear equation (Y = aX + b)

GC-MS measurement of DMAc standard solutions in the range of 0.3125 ~ 5 ng/μL were done in the same way for comparison according to the instrumental condition described in Table 2.

e) Calibration curves for GC-MS and TD-GC-MS analyses of fiber samples

For GC-MS analyses, five standard solutions of 0.3125, 0.625, 1.25, 2.5 and 5 ng/μL were prepared for NMP and DMAc, respectively, by diluting their stock solutions (1,000 ng/μL) with methanol and subjected to GC-MS analyses according to the condition mentioned. in Table 2. The calibration curve for each substance was built with the mean values (n=3). For TD-GC-MS analyses, standard solutions of NMP were prepared with concentrations of 2.5, 5.0, 10.0, 20.0 ng/μL and standard solutions of DMAc were prepared with concentrations of 12.5, 25.0, 50.0, 100 ng/μL. In four sample cups, 5 μL of each of NMP and DMAc standard solutions was loaded by micro-syringes (Figure 1) in the order of their concentrations so that each analyte in four cups ended up with 12.5, 25, 50, 100 ng for NMP and 62.5, 125, 250, 500 ng for DMAc. The calibration curve for each substance was built with the mean values (n=3).

f) GC-MS analyses of spiked fiber samples

To estimate the recovery efficiency of DMAc from synthetic fibers by methanol extraction, spiked fiber samples were prepared by pipetting 1 mL of DMAc standard solution of 1000 μg/mL to the exactly weighed fiber in the thimble filter.[14] The spiked sample were subjected to the Soxhlet extraction followed by GC-MS measurement mentioned in sections of pretreatment and instrumentation. Recovery ratio of DMAc was calculated by dividing the measured amount by the theoretical amount. The corresponding fiber sample was also analyzed in the same procedure to check the presence of DMAc in the sample before spiking. Three replicates were done for samples and their spiked samples.

g) GC-MS analyses of fiber samples

Each fiber sample (ca. 2 g) was weighed precisely into a thimble filter (ADVANTEC®, ID 25 mm, OD 28 mm, L 100 mm) and extracted using a Soxhlet apparatus for 6 h with 100 mL methanol. After Soxhlet extraction, methanol was evaporated by a Turbovap concentrator and the sample solution was made up by adjusting the volume exactly to 10 mL with methanol. Three replicates were done for pretreatment of each sample. A portion of 1 μL was subjected to GC-MS analysis described in Table 2.

h) TD-GC-MS analyses of fiber samples

One mg of each fiber sample was approximately loaded into the stainless steel cup (80 μL Disposable eco cup, Frontier Lab) and the exact weight was recorded. Without any sample treatment the sample cup was placed in a furnace and subjected to TD-GC-MS analysis described in Figure 1(a) and Table 2. Three replicates were done for each sample.

III. Results and Discussion

a) Validation characteristics of TD-GC-MS analysis of NMP and DMAc using Py-GC-MS using a thermal desorption function

TD-GC/MS analysis was tried with Py-GC-MS in a way that outgases were emitted (thermally desorbed) from a fiber sample in a sample cup inside the furnace (250 °C), collected into the inlet part of GC and analyzed by GC-MS. The difference from the normal TD-GC-MS to identify the major VOCs emissions in industrial sites and to control organic compounds in a clean room or in wafer surfaces is that sorbent tube sampling and the subsequent TD-GC/MS analysis are used for these purposes.[16-18] However, in this study, the chemical instrument Py-GC-MS was used with a lower temperature without using a pyrolysis condition.

To obtain the precision of retention time and peak areas of TD-GC/MS analyses of NMP and DMAc, a portion of standard solutions of four concentrations in the range of 1.25 to 10 ng/μL was loaded in a cup. In our experimental condition, NMP and DMAc were fully separated with retention times of 11.1 min and 8.8 min, respectively. NMP with higher boiling point, 204.3 °C was eluted later than DMAc with b.p of 163 °C ~ 165 °C.[8,9] When each standard solution was analyzed by TD-GC/MS seven times, precision of retention times and peak areas were evaluated by calculating RSD of retention times and peak areas. RSD of retention times were estimated to lie in 0.02% ~ 0.05% (NMP) and 0.05% ~ 0.20% (DMAc) while RSD of peak areas were 3.96% ~ 6.71% (NMP) and 2.78% ~ 6.42% (DMAc) that are acceptable (Figure 2) .[20] These values are slightly bigger than RSD of 0% for retention times and 1.12% ~ 3.16% for peak areas that were obtained by GC-MS analyses of DMAc.

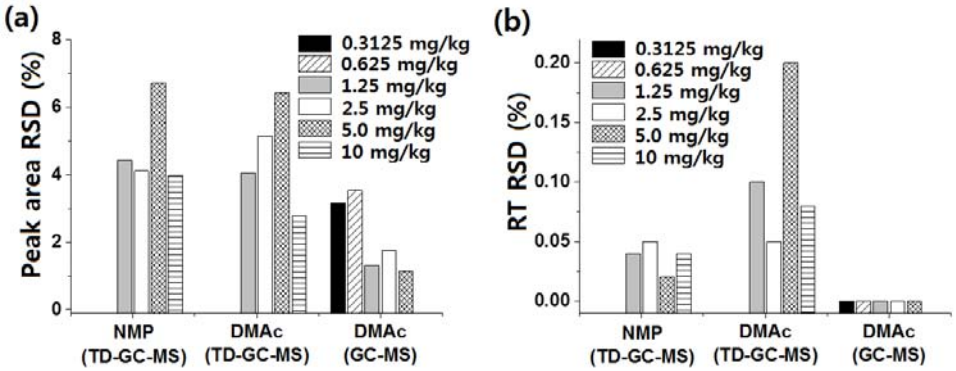


Fig. 2 : Precision of retention times and peak areas (n=7) of NMP and DMAc using the TD-GC-MS system in this study

**Concentration range(TD-GC-MS), 1.25 to 10 ng/μL; Volume loaded, 5 μL; Split ratio 1:20.*

**Concentration range(GC-MS for comparison), 0.3125 to 5 ng/μL; Volume loaded, 1 μL; Splitless.*

Linearity during TD-GC-MS measurements was also secured with R^2 of 0.9989 for NMP and R^2 of 0.9998 for DMAc from the regression line established with 5 concentrations in the range of 1.25 ng/μL ~ 10 ng/μL because R^2 of 0.99 is often used as criterion of linearity (Table 3).[15]

When a split ratio of 20:1 was used in TD-GC-MS analysis, LODs were estimated in Table 3; 0.023 ng/μL or 0.115 ng in solution for NMP; 0.266 ng/μL and 1.33 ng in solution for DMAc. When 1 mg of fiber was subjected to the TD-GC-MS measurement, LODs in measurement of NMP and DMAc in fibers were found to be 0.115 ng/mg and 1.33 ng/mg, respectively. LOQ can be further calculated as 3.03 times LOD according to Eqs. (1) and (2).

Table 3. Limit of detection in TD-GC-MS analyses of NMP and DMAc in this study

Measurement method	Substance	Range measured		Y = aX + b		R^2	LOD[c]	LOD[d]
		Conc. (ng/μL)	Conc. (ng) [a]	Slope a	Standard deviation of b		in solution	in fiber (ng/mg)
TD-GC-MS	NMP	1.25~ 10	6.25 ~ 50 (0.3125~ 2.5)[b]	23,317	160	0.9989	0.023 ng/μL 0.115 ng[a] (0.006 / 0.0180 ng)[b]	0.115 (0.006)[b]
	DMAc	1.25~ 10	6.25 ~ 50 (0.3125~ 2.5)[b]	19,204	1,547	0.9998	0.266 ng/μL 1.33 ng[a] (0.067 ng)[b]	1.33 (0.067)[b]
GC-MS for comparison	DMAc	0.3125 ~ 5	0.3125 ~ 5	538,680	1,123	0.9999	0.007 ng/μL 0.007 ng[a]	0.035

a. Volume loaded in TD- GC-MS, 5 μL, split ratio of 20:1; Volume loaded in GC-MS, 1 μL, splitless

b. Absolute amounts after considering the split ratio; for example, 0.3125 ng = 6.25 ng / 20

c. $LOD_{solution} = 3.3 \times \sigma/S$; σ, standard deviation of intercept; S, slope of linear equation; $LOQ_{solution} = 10 \times \sigma/S$

d. For TD-GC-MS, one mg of fiber was analyzed in this study; for GC-MS, $LOD_{fiber} = LOD_{solution} \times 5$ where dilution factor = 5 (2 g fiber in final volume 10 mL (methanol)) based on recovery ratio = 100 %

e. Y: peak area

GC-MS analyses of NMP and DMAc in synthetic fibers after Soxhlet extraction with methanol

The common method for the determination of solvent residues is based on an extraction of the sample with an organic solvent and subsequent analyses by gas chromatography with mass selective detection (MSD).[13] Because NMP and DMAc are polar solvents and water-miscible,[8,9] methanol was chosen to extract them from synthetic fibers.

Figure 3 showed that recovery ratios of DMAc from aramid, polyester and spandex fibers with spiking method[14,19] were 97.1%, 95.2% and 96.8%, respectively. These recovery ratios correspond well to the acceptable recovery percentages of 95%~105% given at the analyte concentration of 0.1%.[20,21]

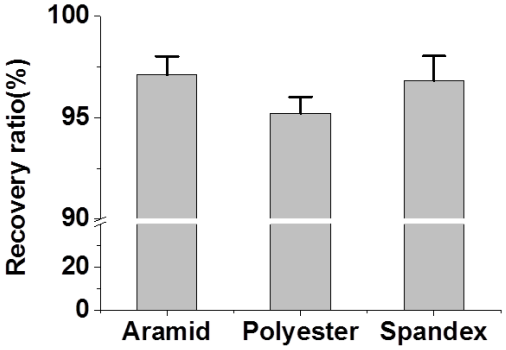


Fig. 3 : Recovery ratios of DMAc from the spiked synthetic fiber samples by Soxhlet extraction using methanol as measured by GC-MS (n=3)

**Spiked amounts of NMP and DMAc, each of 1,000 mg/kg.*

When three kinds of commercial synthetic fibers were Soxhlet-extracted with methanol and analyzed by GC-MS, DMAc and NMP were detected in the level of several tens to hundreds ng per one mg of fiber (Table 4-a). Although these amounts are under the current regulation limit, 0.1% w/w (1,000 ng/mg) (Table 1)[10-12], it seems that DMAc and NMP are still common solvents to produce synthetic fibers such as aramid, polyester and spandex fibers[1-9] and become possibly present in final products as residues. The amounts detected by GC-MS analyses were compared with those obtained by TD-GC-MS analyses.

Table 4 : Fiber Samples and Contents Of NMP and DMAc as measured by GC-MS and TD-GC-MS

Samples	Substance analyzed	Amounts measured (ng/mg)		Ratio, b/a (%)
		by GC-MS (a)	by TD-GC-MS (b)	
Aramid	NMP	62 ± 7[a]	53 ± 14	85.5
fiber	DMAc	417 ± 12	381 ± 27	91.4
Polyester	NMP	Not detected[b]	Not detected[b]	-
fiber	DMAc	158 ± 8	137 ± 6	86.7
Spandex	NMP	18 ± 5	21 ± 6	116.7
fiber	DMAc	79 ± 6	94 ± 7	119.0

a. Standard deviation (n = 3)

b. Below detection limit (0.12 ng/mg as estimated from Table 3)

TD-GC-MS analyses of NMP and DMAc in synthetic fibers without sample pretreatment

In our TD-GC-MS analyses of NMP and DMAc in synthetic fibers, thermal desorption of residual organic solvents from a fiber can occur in a sample cup that was heated from 200 °C to 340 °C. Outgases from the fiber were collected in a furnace and analyzed by GC-MS as shown in the scheme of Figure 1-a. This process that occurred in a furnace part enabled to omit the Soxhlet extraction that was necessary in the GC-MS analysis discussed in the previous section.

The amounts of NMP and DMAc in the same fiber samples detected by TD-GC-MS analyses lied in the level of several tens to hundreds ng per one mg of fiber (Table 4-b) and showed that there is a good correlation between two methods. NMP with boiling point, 204.3 °C and DMAc with b.p of 163 °C ~ 165 °C[8,9] seemed to be almost completely desorbed thermally from fibers in the scheme of Figure 1-a. Total ion and selected ion monitoring (SIM) chromatograms of a aramid fiber sample were shown in Figure 5.

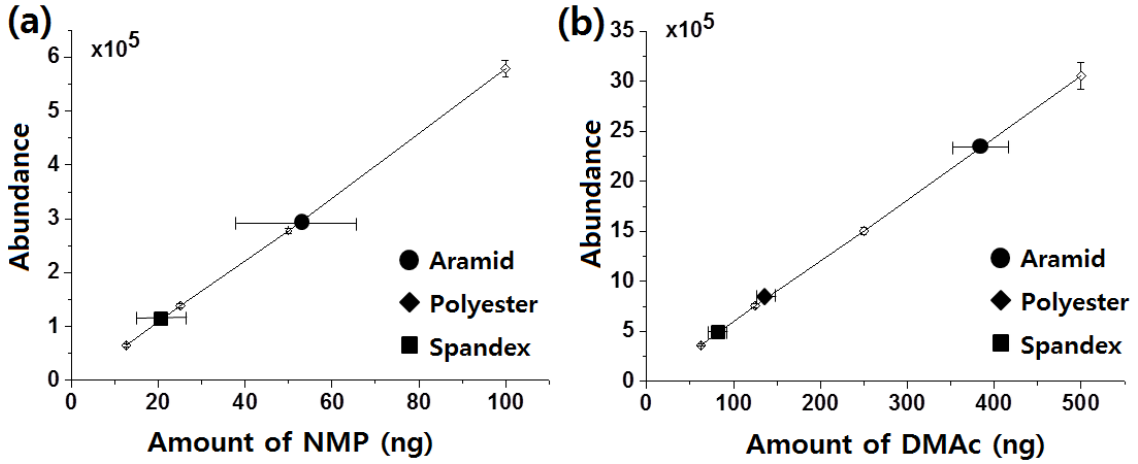


Fig. 4 : Calibration curves for simultaneous determination of NMP and DMAc by TD-GC-MS.

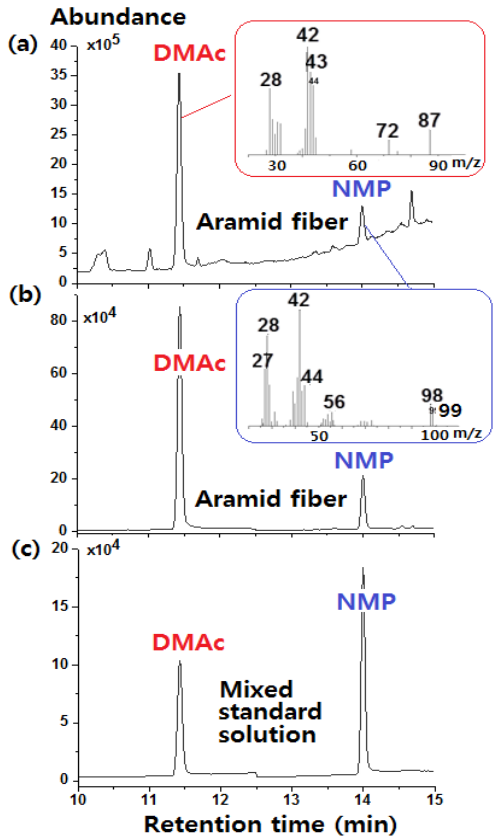


Fig. 5 : TD-GC-MS chromatograms of aramid fiber and mixed standard solution. (a) TIC chromatogram and (b) SIM chromatogram (m/z = 87, 99) of aramid fiber, (c) SIM chromatogram (m/z = 87, 99) of mixed standard solution. Fiber sample, 1 mg of aramid fiber; Mixed standard solution of 5 µL NMP (10 ng/ µL) and 5 µL DMAc (10 ng/µL)

TD-GC-MS method using a Py-GC-MS instrument can be applied for a screening of residual organic solvents in a fiber as proved in our study or possibly in other plastic products. With corresponding calibration curves of mixed standard solutions (Figs 4 and 5-c), a quick simultaneous quantitative determination of NMP and DMAc was also possible resulting in significantly correlated measured values with those determined by the conventional GC-MS (Table 4). Another successful application of TD-GC-MS method for the product analysis was previously reported as analysis of phthalate esters in PVC.[22-24] The TD-GC-MS method using a Py-GC-MS instrument developed in this study provides a convenient way without sample pretreatment to monitor residual organic solvents in fiber products with detection limit far below the current limit value of 0.1 %(w/w) (Tables 1 and 3).

IV. Conclusion

Development and validation of a fast TD-GC-MS method using a Py-GC-MS instrument for simultaneous determination of NMP and DMAc in fiber samples were carried out in this study. The acceptability of TD-GC-MS as a new convenient method to screen and determine residual organic solvents used during synthetic fiber processing was evaluated successfully by comparing data obtained by conventional GC-MS analyses. Validation characteristics of TD-GC-MS measurements including precision of retention times (RSD within 0.05 % for NMP, 0.2 % for DMAc) and peak areas (RSD within 6.71 % for NMP, 6.42 % for DMAc) and linearity (R^2 = 0.9989 for NMP, 0.9998 for DMAc in the concentration range of 1.25 ~ 10 ng/µL) were obtained. Limits of detection for NMP and DMAc were measured to be 23 ppb and 266 ppb in solution; 0.115 ppm and 1.33 ppm in fiber, respectively. With commercial aramid, polyester, and spandex fibers, residual amounts were measured by TD-GC-MS with the comparable ratio of 85.5% ~ 119% to those of GC-MS data.

V. Acknowledgements

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Organic Solvent Effect, Thermodynamic Study and Synergism Behavior for Extraction Efficiency of Cobalt (II) Complex with 1-[2-Pyridyl Azo] -2-Naphthol

By Shawket. K. Jawad, Fatimah. A. Wannas, Jihan. R. Maslim & Ibtehaj. R. Ali
Kufa University, Iraq

Abstract- After pinpoint all optimum conditions for extraction Cobalt(II) as ion pair association complex or chleated complex with complexing agent 1-[2-pyridyl azo] -2-naphthol which dimonirtrate λ_{max} for complex extracted was (446nm.) more stable complex formation was at pH= 7 and 60 μg Co(II)/5ml with 1×10^{-4} M 1-[2-pyridyl azo] -2-naphthol[PAN] dissolved in chloroform and shaking time 10 minutes. The stoichiometry of complex extracted to the organic phase was 1:1 metal : PAN $[Co(PAN)^{+}Cl^{-}]$ or $[Co(PAN)]^{+}(Cl^{-})$.Extraction method was endothermic as well as thermodynamic parameters after calculated was ΔH_{ex}= 0.0149 KJmol^{-}, ΔG_{ex}= -58.81 KJ mol^{-} and ΔS_{ex}= 176.55 J mol^{-}. Synergism study show from the slope is appear there is one molecule of TBP or MIBK participated in the structure of complex extracted to the organic phase.

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Abstract- After pinpoint all optimum conditions for extraction Cobalt(II) as ion pair association complex or chleated complex with complexing agent 1-[2-pyridyl azo] -2-naphthol which dimonirtrate λ_{max} for complex extracted was (446nm.) more stable complex formation was at pH= 7 and 60 μg Co(II)/5ml with 1×10^{-4} M 1-[2-pyridyl azo] -2-naphthol[PAN] dissolved in chloroform and shaking time 10 minutes. The stoichiometry of complex extracted to the organic phase was 1:1 metal : PAN $[Co(PAN)^{+}Cl^{-}]$ or $[Co(PAN)]^{+}(Cl^{-})$.Extraction method was endothermic as well as thermodynamic parameters after calculated was ΔH_{ex}= 0.0149 KJmol^{-}, ΔG_{ex}= -58.81 KJ mol^{-} and ΔS_{ex}= 176.55 J mol^{-}. Synergism study show from the slope is appear there is one molecule of TBP or MIBK participated in the structure of complex extracted to the organic phase.

I. Introduction

The phenomenon in which two extractants when present together, extracted species, mostly metal ionswith greater efficiency than that corresponding to their additive action is called synergism. Rather much effort has been devoted to synergistic extractions over the past two decades since the very nature of synergism offers interesting research possibilities of both the chemistry of these extractants and their potential application[1].

Functions of cobalt , enters in the composition of vitamin B12 and contributes to the metabolism of carbohydrates, proteins. Produces amino acids and creates DNA molecules. Supports the immune system and the nervous system in their work. Responsible for keep the work of the cells and the growth and development of red blood cells. High dosage of cobalt affects the heart may reduce a man's fertility. Cobalt sources, cobalt found in fruits and vegetables, but our body prefers cobalt content in vitamin B12, so it prefers to depended on this vitamin to secure our need of cobalt .Adults need2.4 micrograms of vitamin B 12 to ensure access to cobalt, and supplements should not exceed 1.4 micrograms of leafy vegetables containing 20-60 micrograms of Cobalt . While 100 grams of meat containing 15-25 micrograms of cobalt[2,3].

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Solvent extraction in an indirect separation method in general depend on thermodynamic laws, as well as from the other hand less depend on kinetic laws, and from this truth we must know all effective parameters on extraction efficiency according to this method. Kokade et al extracted Bismuth(III) by n-octyl aniline dissolved in chloroform from HCl and HBr media, and the study demonstrate the ion pair complex extracted was (RNH_3^{+}) $BiCl_5^{-2}$[4], anther researchers were perform to separation of Sn, Sb, Bi, Al, Cu, Pb and Zn from hydrochloric acid solution by solvent extraction process using TBP as an extractant[5]. A new research for extraction, determination of Manganese by using cloud point extraction, this research include formation ion pair association complex between brilliant green and MnO_4^{-} in acidic media, and this complex extracted to surfactant Triton X-100. The cloud point layer contain ion pair complex dissolved in alcohol and measure the absorbance at λ_{max} = 657nm[6]. Extraction, separation and preconcentration of Nickel (II) as chloroanion by using crown ether DB18C6 according to CPE method, and absorbance spectrum forion pair association complex extracted illustrate λ_{max}= 295nm., as well extracted good efficiency was at 0.5 M HCl and 0.25M NaCl and 1×10^{-4} DB18C6[7]. A new trend in extraction and preconcentration of chromium(VI) using laboratory made-Azo dye reagent 2-[benzene thiozolyl azo]-4-benzene naphthol (BTABN) after cloud point extraction(CPE) and its determination by spectrophotometriclly, the method involved the reaction of $Cr_2O_7^{=}$ with (BTABN) in acidic medium forming a hydrophobic ion association complex $[HBTARN^{+}][HCr_2O_7^{-}]$ which is entrapped into micelle-mediating solvent (Triton X-100) and the Cr(VI) detected spectrophotometriclly at λ_{max}=475 nm[8]. In research for extraction chloro anion complex of Cd(II) and Hg(II) used many organic agents as extractant according to liquid ion exchange method such as extractant α-naphthol amine, 4-amino benzoic acid, 2-[(4-(Carboxy methyl phenyl) azo]-4,5-diphenyl imidazole and Cryptand C222, this study includes definition hydrochloric acid concentration in aqueous phase and shaking with organic phase necessary for extraction[8]. 2-[4-(Chloro-2-methoxy phenyl) azo]-4,5-diphenyl

imidazole used as a new complexing organic reagent for extraction and determination of Copper(II) in different samples at optimum condition[9]. Determined Cupper at trace level by using 1- nitroso-2- naphthol as complexing agent in presence of anion aqueous micellar solution of 1% sodium dodecyl sulphate. The complex extracted was Cu:$(NNph)_2$[10]. Extracted Mo(VI) from 2M HCl by solvent extraction with 2-n-Octyl amine pyridine in prescience Lithium Chloride as salting agent[11]

II. Instruments

All spectrophotometric measurements and absorbance were registered by using a double beam (UV-Vis) spectrophotometer Shimadzu UV 1700 (Japan) and a Single beam (UV-Vis) spectrophotometer TRIUP international corp. TRUV 74,S (Italy), . Shaker used HY-4 vibrator with adjust about speed multiple(Italy).pH-meter WTW-INOLAB made in Germany.

III. Materials

All chemicals used provided from Fluka and Merck such as Cobalt chloride six hydrate , ammonia, sodium hydroxide, chloroform, hydrochloric acid,1-Nitroso-2-naphthol., But 1-[2-pyridyl azo] -2-naphthol[PAN] was prepared as in [12].

IV. Experimuntal

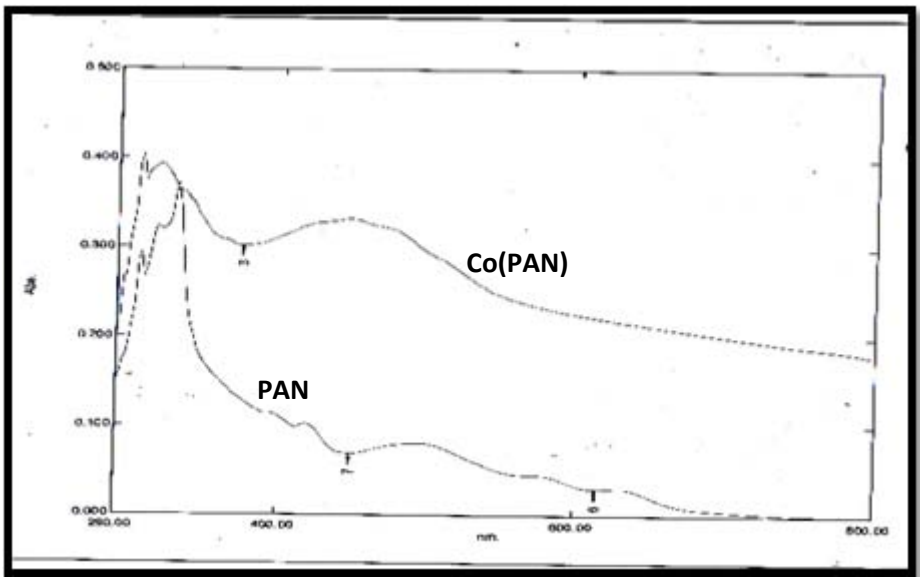
All chemical used were of A.R grads and used as received with out farther more purification, all solution prepared with doubly distilled water, stock solution of Cobalt(II) was prepared by dissolved 0.45 gm of $CoCl_2$ $.6H_2O$ in 100 ml doubly distilled water contain 1ml concentrated HCl also by diluting with doubly distilled water prepared other work solutions .For determination Cobalt(II) in aqueous solutions used 0.5% solution of 1-Nitroso-2-naphthol dissolved in glacial acetic acid according to the procedure detailed in [13].Derivative 1-[2-pyridyl azo] -2-naphthol(PAN) prepared a solution of 1×10^{-4} M by dissolved 0.0249 gm in 100 ml chloroform in volumetric flask.

V. Procedure

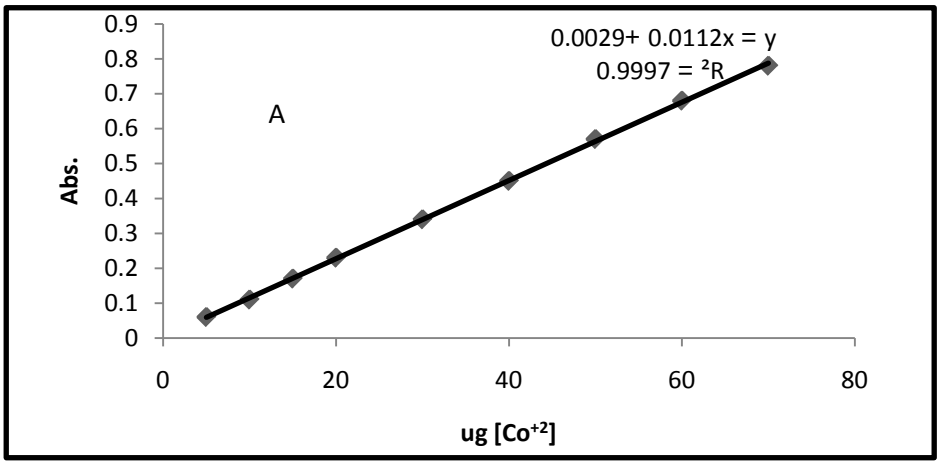
Solvent extraction of Cobalt(II) as complex with (PAN) to apply by taken 5ml aqueous solution contain fixed concentration of Cobalt(II) atpH =7 with 5ml of 1×10^{-4} M of (PAN) dissolved in chloroform ,shake the two immiscible layers for 10 min after that separate the two layers and measure the absorbance of organic phase against PAN solution at λ_{max}=446 nm. And the aqueous phase treated according to 1-Nitroso-2-naphthol method[13] and returning to calibration carve in Fig(2) to determine remainder quantity and the quantity of Cobalt(II) transferred to the organic phase to produce the complex, afterward calculate distribution ratio D of extraction.

VI. Results and Discussion

The spectrum of complex to be formed in organic phase which is in Figure(1)Show λ_{max} =446 nm, and used this wave length to measure the absorbance of complex formed and transferred to the organic phase.



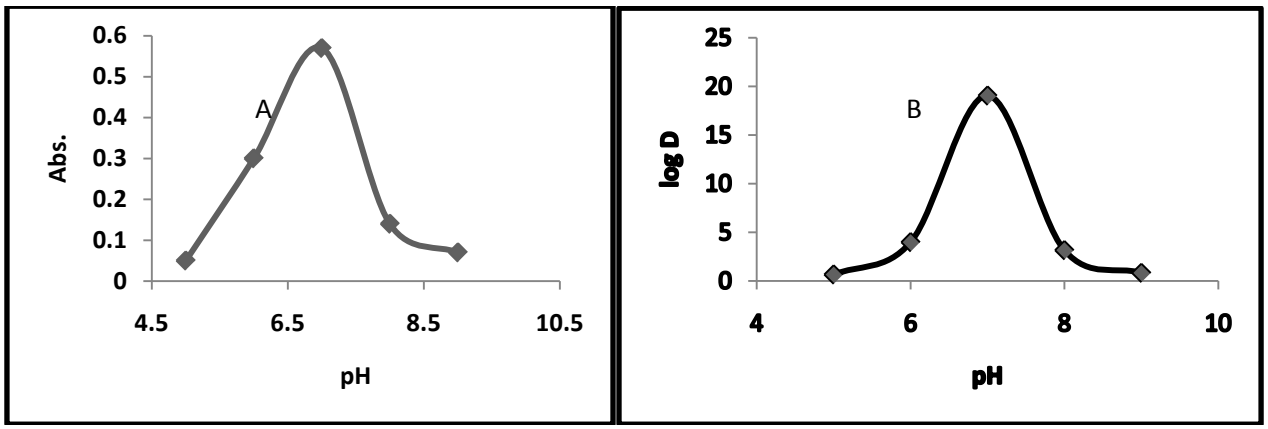
(1) UV VIS spectrum of PAN and Co(PAN)complex



Fig(2) : Calibration curve for determination Co(II) in aqueous solution by1-Nitroso-2-naphthol

VII. Effect of pH

5ml aqueous solution contain 60ug Co(II) at different pH(5-9), add to each solution 5ml of 1×10^{-4} M of (PAN) dissolved in chloroform, and shaking the two immiscible layers for 10 minute, at latter separate organic phase from aqueous phase and measure the absorbance of organic phase against PAN solution as blanck and the aqueous phase for each solution treated according to 1-Nitroso-2-naphthol method[13],and returning to calibration curve Fig(2) to calculate distribution ratio D for all solutions of different pH. The results obtained was as in Figure (3)



Fig(3) : Effect of pH(A)on complex formation (B) pH effect on D values

VIII. Effect of Metal ion Concentration

Aqueous solution 5ml in volume contain different quantity of Co(II) (5ug-100ug) at pH =7, added 5ml of 1×10^{-4} M of (PAN) dissolved in chloroform, each solution shaking for 10 minutes, and after ending the shaking separate the two layers, and measure the absorbance of each organic phase at 446 nm against PAN solution as blank, and the aqueous solution treated according to 1-Nitroso-2-naphthol method[13], and after returning to calibration curve Fig(4) calculate D values.

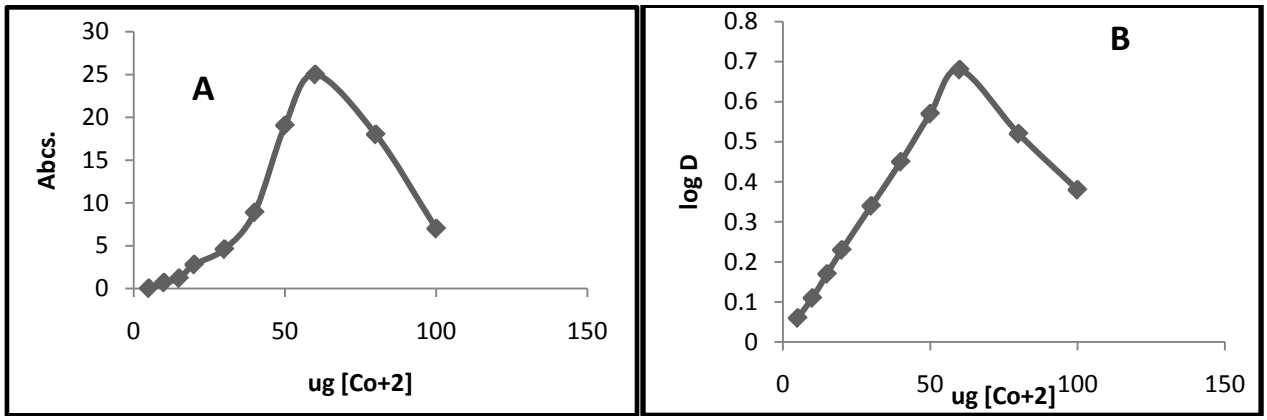


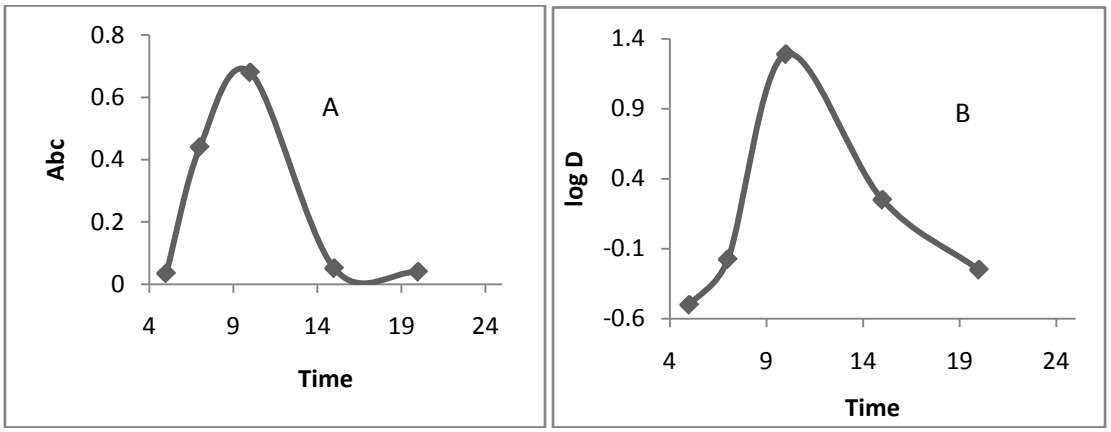
Fig (4) A : Absorbance differ as function of Co(II) concentration in organic phase B: Effect of metal ion concentration in aqueous phase on distribution ratio D

The results demonstrate 60 ug Co(II)/ 5 ml aqueous solution was the optimum concentration value of metal ion giving higher absorbance for complex formed in organic phase as well as higher distribution ratio D.

By the reason of metal ion concentration was a thermodynamic data effect on the thermodynamic equilibrium for complex formation and extraction efficiency, form this truth any concentration of Co(II) less than 60 ug/5 ml not allow to reach thermodynamic equilibrium and giving decrease in absorbance of complex organic phase and D values, as well as any Co(II) concentration more than optimum 60 ug effect to increase back reaction of equilibrium and dissociation complex according to mass action law and Le Chatelier principle.

IX. Shaking Time Effect

Extraction Co(II) from aqueous solutions 5 ml in volume contain 60 ug/5 ml at pH =7 with 5 ml of 1×10^{-4} M of (PAN) dissolved in chloroform after shaking these solution for different time (5-20 min), afterword determine absorbance of organic phase distribution ratio D for the solution at each shaking time, the results obtained was as in Fig(5):

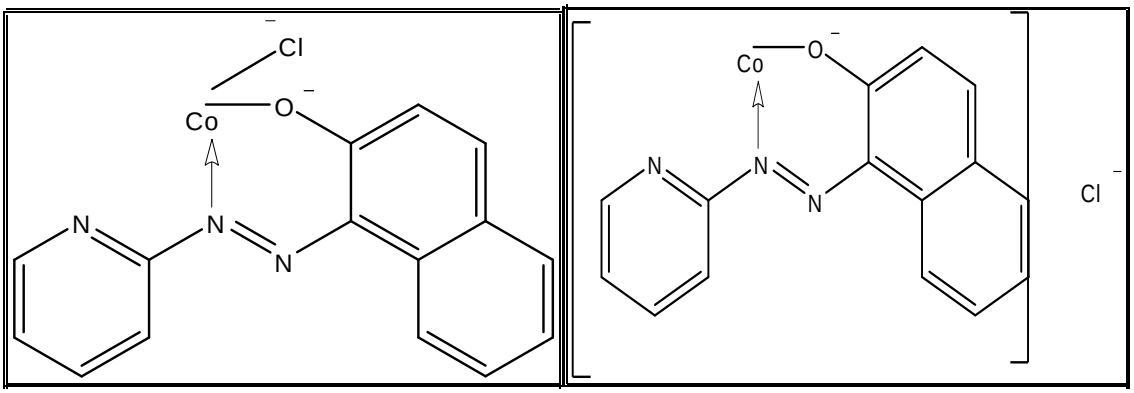


Fig(5) A : Effect on shaking time of complex formation,(B) Effect of shaking time on D values

The results show 10 minutes was the best time for shaking which is giving higher absorbance for organic phase and higher value of distribution ratio D that is mean in this time of shaking time reached to the best thermodynamic equilibrium for complex formation and extraction, but any shaking time less than 10 minutes not enough to reach thermodynamic equilibrium giving decrease in absorbance and D value as well as shaking time more than 10 minutes effected to decline absorbance and D value by increase the rate of dissociation of complex.

X. Stoichiometry

To knowledge the structure of complex formed between Co(II) and PAN follow two spectrophotometric methods (mole ratio method, continuous variation method) , the two methods show the structure of complex was 1:1, metal: ligand that is mean the complex is ion pair association complex $[Co(PAN)]^{+}Cl^{-}$ or chelate complex $[Co^{+2}(PAN)^{-}(Cl)^{-}]$:



XI. Organic Solvent Effect

Extraction Co(II) from aqueous solution 5 ml in volume contain 60 ug dissolved in different organic solvent differ in dielectric constant, after shaking and separating and determine absorbance and D values the results was as the Table(1):

Table(1) : effect organic solvent on solvent extraction of Co(II)

Organic solvent	dielectric constantε	-ΔGTKJ mol^{-}	K_A10^{+4}	D	$K_{ex}10^{+8}$	$-\Delta G_{ex}$ KJmol^{-}
Nitro benzene	35.74	0.0424	18.05	4.81	15.94	51.36
Amyl alcohol	15.80	0.1412	48.43	8.66	43.3	53.76
1,2-D chlorɔ ethane	10.650	0.2263	27.69	6.39	23.94	53.32
Ch orobehzen	5.708	0.4523	387.59	25	372.08	58.47
Chloroform	4.808	0.5433	59.35	9.55	53.63	64.96
Benzene	2.804	0.9566	34.47	7.15	30.51	52.88
Toluene	2.438	1.1056	34.59	7.16	30.32	52.89

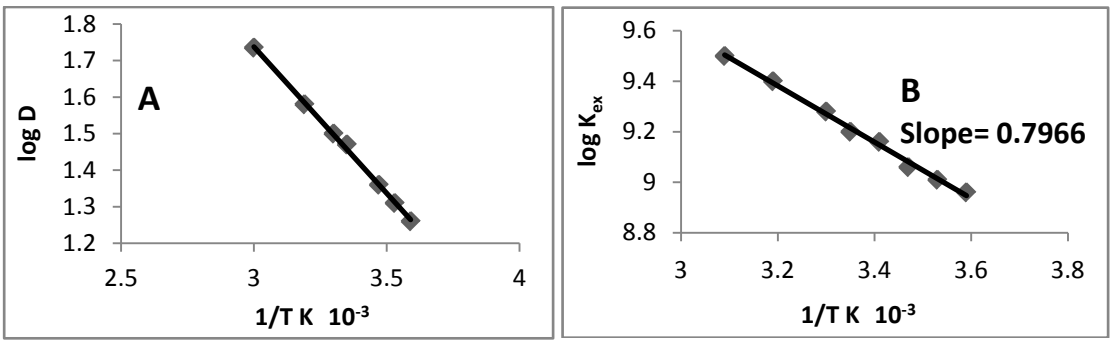
The results in Table (1) demonstrate there is not any relation between dielectric constant of organic solvent and distribution ratio values of extraction but there is unaffected for organic solvent structure as well as this results reflect participation of organic solvent in the formation of ion pair complex extracted, and chloroform organic solvent giving higher distribution ratio.

XII. Effect of Temperature and the Thermodynamic Study

Aqueous solution in 5 ml volume contains 60 ug Co(II) at pH =7 axtracted with 5 ml of 1×10^{-4} M (PAN) dissolved in chloroform at different temperature (5-60)C° after separated the two layers determine, distribution ratio D at each temperature, and calculate extraction constant K_{ex} at each temperature by application the relation below:

$$K_{ex} = \frac{D}{[Co(II)]_{aq}\,[PAN]_{org}}$$

The result shown in the Fig(6):



Fig(6) : (A) Effect temperature on distribution ratio D,(B) Effect temperature on extraction constant K_{ex}.

The results show the extraction method was endothermic as well as thermodynamic parameters after calculated was:

ΔH_{ex}= 0.0149 KJmol^{-}

ΔG_{ex}= -58.81 KJ mol^{-}

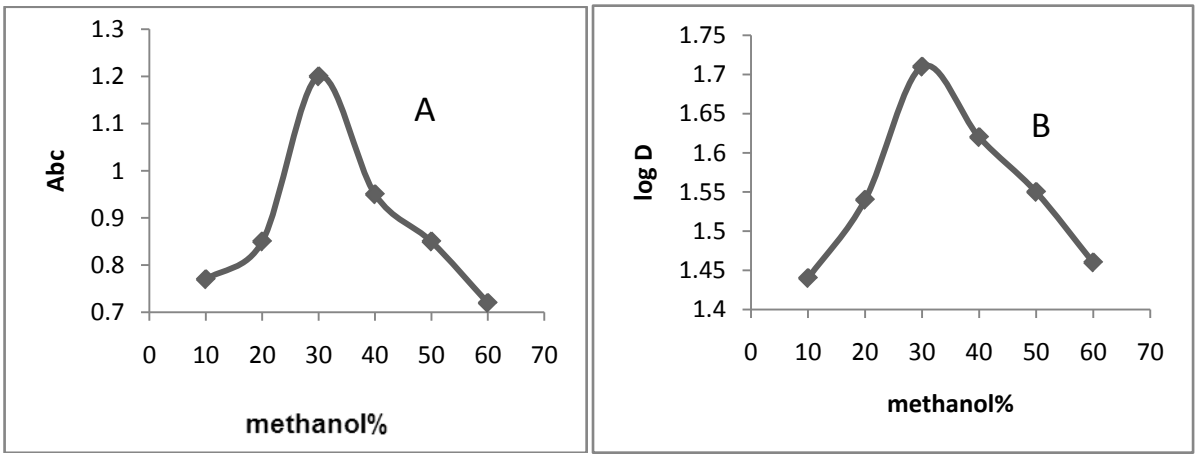
ΔS_{ex}= 176.55 J mol^{-}

The high value of entropy reflect the combination metal ion Co(II) with negative charged PAN

molecule at pH= 7 to approach one another with temperature rising which is help to increase in destroyed hydration shell and giving more stable complex extracted to organic phase as well as this reflect the extraction method is entropic in region.

XIII. Methanol Effect

Extraction Co(II) from aqueous solution 5 ml in volume contain 60 ug metal ion at pH =7 with different percentage of methanol 10% - 60%, with 5 ml of 1×10^{-4} M (PAN) dissolved in chloroform after shaking these two layers for 10 minutes, after finishing shaking separate the two layers and measure the absorbance of organic phase and calculate D values at each percentage of methanol . The results was as in Fig (7):



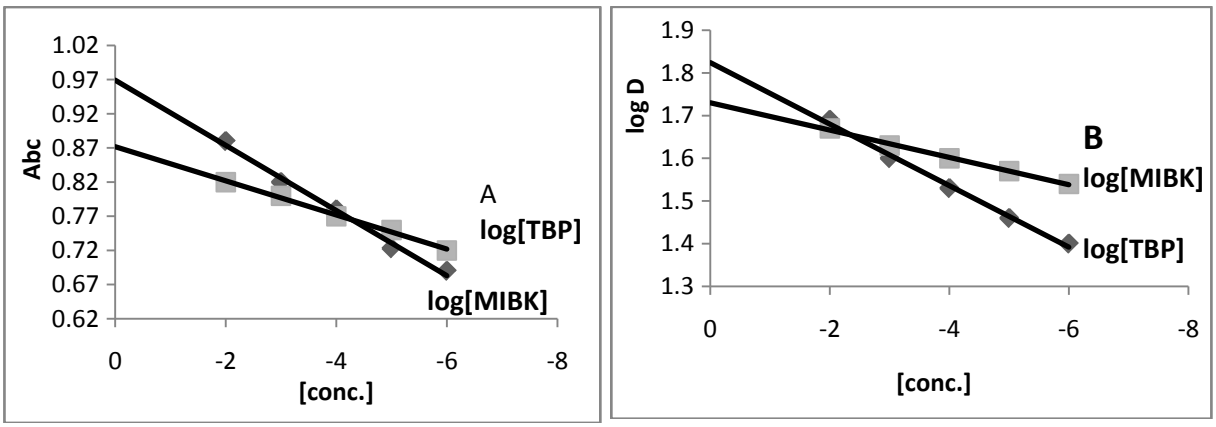
Fig(7) A : Methanol effect on complex formation, B: Methanol effect on D values

The results demonstrate presence methanol in aqueous solution effect to increase extraction efficiency until reached to the optimum quantity of methanol in aqueous phase, more than this value effect to decline efficiency of extraction as well as at very high percentage of methanol effect to decrease absorbance of organic phase and D values less than values in the case of without methanol, and the optimum value of methanol in procedure is 30%.

These results demonstrate methanol help in aqueous solution to destroyed the hydration shell of metal ion Co(II) so lone pair electron in function position of PAN molecule this destroyed increase as a function to percentage of methanol in aqueous solution to reacted maximum effect in 30% methanol more than 30% effect to decrease polarity of water this behavior effect to partition PAN molecular to the aqueous phase and decrease extraction efficiency to organic phase .

XIV. Synergism Effect

Extraction Co(II) from 5 ml aqueous solution contain 60ug Co(II) at pH =7 by 5 ml of 1×10^{-4} M (PAN) dissolved in chloroform contain different concentration(1×10^{-3} M - 1×10^{-6} M) from tributyl phosphate (TBP) or methyl isobutyl ketone, after shaking and separating the two layers determine absorbance of complex to the organic phase and D-values. The results was as in Figs (8).



Fig(8) A : Effect [TPT]&[IMBK] on complex formation, B: Effect of [TPT]&[IMBK] on D- values

The results shows the absorbance and D. values in presence of TBP or MIBK was higher than in the case of absents TBP or MIBK and for all concentrations because TBP or MIBK participate in the complex formation by displacement TBP or MIBK molecules instead of water in the coordination shell of the metal ion Co(II) this giving more stable and more hydrophobicity for the complex and increase in the efficiency of extraction with higher absorbance and D. values .

As well as from the slope of straight lines Fig(8) is appear there is one molecule of TBP or MIBK participated in the structure of complex extracted to the organic phase.

$[Co(PAN)^{-}(TBP)]^{+}; Cl^{-}$, $[Co\ (PAN)^{-}(MIBK)]^{+}; Cl^{-}$

$[Co^{+2}(PAN)^{-}\ (Cl^{-})(TBP)]$, $[Co^{+2}\ (PAN)^{-}(Cl^{-})(MIBK)]$

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Search engines for most searches, use Boolean searching, which is somewhat different from Internet searches. The Boolean search uses "operators," words (and, or, not, and near) that enable you to expand or narrow your affords. Tips for research paper while preparing research paper are very helpful guideline of research paper.

Choice of key words is first tool of tips to write research paper. Research paper writing is an art.A few tips for deciding as strategically as possible about keyword search:

- One should start brainstorming lists of possible keywords before even begin searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in research paper?" Then consider synonyms for the important words.
- It may take the discovery of only one relevant paper to let steer in the right keyword direction because in most databases, the keywords under which a research paper is abstracted are listed with the paper.
- One should avoid outdated words.

Keywords are the key that opens a door to research work sources. Keyword searching is an art in which researcher's skills are bound to improve with experience and time.

Numerical Methods: Numerical methods used should be clear and, where appropriate, supported by references.

Acknowledgements: Please make these as concise as possible.

References

References follow the Harvard scheme of referencing. References in the text should cite the authors' names followed by the time of their publication, unless there are three or more authors when simply the first author's name is quoted followed by et al. unpublished work has to only be cited where necessary, and only in the text. Copies of references in press in other journals have to be supplied with submitted typescripts. It is necessary that all citations and references be carefully checked before submission, as mistakes or omissions will cause delays.

References to information on the World Wide Web can be given, but only if the information is available without charge to readers on an official site. Wikipedia and Similar websites are not allowed where anyone can change the information. Authors will be asked to make available electronic copies of the cited information for inclusion on the Global Journals Inc. (US) homepage at the judgment of the Editorial Board.

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Tables: Tables should be few in number, cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g. Table 4, a self-explanatory caption and be on a separate sheet. Vertical lines should not be used.

Figures: Figures are supposed to be submitted as separate files. Always take in a citation in the text for each figure using Arabic numbers, e.g. Fig. 4. Artwork must be submitted online in electronic form by e-mailing them.

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For scanned images, the scanning resolution (at final image size) ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs) : >350 dpi; figures containing both halftone and line images: >650 dpi.

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Before start writing a good quality Computer Science Research Paper, let us first understand what is Computer Science Research Paper? So, Computer Science Research Paper is the paper which is written by professionals or scientists who are associated to Computer Science and Information Technology, or doing research study in these areas. If you are novel to this field then you can consult about this field from your supervisor or guide.

TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:

1. Choosing the topic: In most cases, the topic is searched by the interest of author but it can be also suggested by the guides. You can have several topics and then you can judge that in which topic or subject you are finding yourself most comfortable. This can be done by asking several questions to yourself, like Will I be able to carry our search in this area? Will I find all necessary recourses to accomplish the search? Will I be able to find all information in this field area? If the answer of these types of questions will be "Yes" then you can choose that topic. In most of the cases, you may have to conduct the surveys and have to visit several places because this field is related to Computer Science and Information Technology. Also, you may have to do a lot of work to find all rise and falls regarding the various data of that subject. Sometimes, detailed information plays a vital role, instead of short information.

2. Evaluators are human: First thing to remember that evaluators are also human being. They are not only meant for rejecting a paper. They are here to evaluate your paper. So, present your Best.

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6. Use of computer is recommended: As you are doing research in the field of Computer Science, then this point is quite obvious.

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9. Use and get big pictures: Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

10. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right! It is a good habit, which helps to not to lose your continuity. You should always use bookmarks while searching on Internet also, which will make your search easier.

11. Revise what you wrote: When you write anything, always read it, summarize it and then finalize it.

12. Make all efforts: Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

13. Have backups: When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

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15. Use of direct quotes: When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

16. Use proper verb tense: Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

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18. Pick a good study spot: To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

19. Know what you know: Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

20. Use good quality grammar: Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

21. Arrangement of information: Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

22. Never start in last minute: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

23. Multitasking in research is not good: Doing several things at the same time proves bad habit in case of research activity. Research is an area, where everything has a particular time slot. Divide your research work in parts and do particular part in particular time slot.

24. Never copy others' work: Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. Take proper rest and food: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. Go for seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

27. Refresh your mind after intervals: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. Make colleagues: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. Think technically: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. Think and then print: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

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33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.

Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

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· Shun use of extra pictures - include only those figures essential to presenting results

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Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.

Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

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- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

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The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

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- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
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- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

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- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
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- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

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- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

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- Resources and methods are not a set of information.
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- Leave out information that is immaterial to a third party.

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The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
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- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

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- If you desire, you may place your figures and tables properly within the text of your results part.

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- In spite of position, each table must be titled, numbered one after the other and complete with heading
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- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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