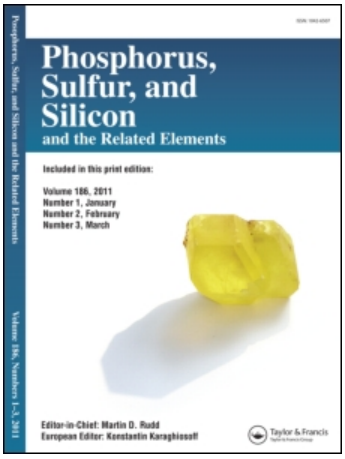

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Some Substituted 10*H*-Phenothiazines, Ribofuranosides, and their Antioxidant Activity

Vibha Gautam[a]; Meenakshi Sharma[a]; R. M. Samarth[b]; Naveen Gautam[c]; Ashok Kumar[b]; I. K. Sharma[a]; D. C. Gautam[a]

[a] Department of Chemistry, University of Rajasthan, Jaipur, India [b] Department of Zoology, University of Rajasthan, Jaipur, India [c] Department of Chemistry, Lal Bahadur Shastri Govt. P. G. College, Jaipur, India

To cite this Article Gautam, Vibha , Sharma, Meenakshi , Samarth, R. M. , Gautam, Naveen , Kumar, Ashok , Sharma, I. K. and Gautam, D. C.(2007) 'Synthesis of Some Substituted 10*H*-Phenothiazines, Ribofuranosides, and their Antioxidant Activity', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 6, 1381 — 1392

To link to this Article: DOI: 10.1080/10426500601161023

URL: http://dx.doi.org/10.1080/10426500601161023

Phosphorus, Sulfur, and Silicon, 182:1381–1392, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500601161023

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Vibha Gautam
Meenakshi Sharma
Department of Chemistry, University of Rajasthan, Jaipur, India

R. M. Samarth
Department of Zoology, University of Rajasthan, Jaipur, India

Naveen Gautam
Department of Chemistry, Lal Bahadur Shastri Govt. P. G. College, Kotputli, Jaipur, India

Ashok Kumar
Department of Zoology, University of Rajasthan, Jaipur, India

I. K. Sharma
D. C. Gautam
Department of Chemistry, University of Rajasthan, Jaipur, India

10H-substituted phenothiazines were prepared by Smiles rearrangement. These prepared phenothiazines were used as base to prepare ribofuranosides by treatment with sugar. Their antioxidant activity was carried out. The structure of both 10H-Phenothiazines and ribofuranosides was established by spectroscopic data and optical rotation data.

Keywords Phenothiazines; ribofuranosides; antioxidant activity

INTRODUCTION

The synthesis of 10H-phenothiazines and their ribofuranosides have attracted tremendous interest evidenced by a large number of

Received July 23, 2006; accepted November 22, 2006

Authors are thankful to the Head, Chemistry Department, University of Rajasthan, Jaipur for laboratory facilities. Thanks are due to CSIR and UGC (Bhopal) for financial support. Thanks are also due to CDRI, Lucknow for providing the IR, proton NMR facilities.

Address correspondence to Vibha Gautam, Department of Chemistry, University of Rajasthan, Jaipur 302 004, India. E-mail: drdcgautam@yahoo.co.in

publications and patents registered worldwide. These compounds are of immense importance and are extensively employed as antibacterial, antifungal, anti-inflammatory, antitumor, and anticancer agents, etc. Some of the recent publications in this area have also demonstrated their significance as antiviral, antifungal, antibacterial, antihypertensive, and anti-AIDS. Research is being persuaded to develop potent anticancer agents. A slight change in the substitution pattern in the phenothiazine nucleus causes a distinguishable difference in their biological activities.[1–12] The synthesized heterocyclic bases and their ribofuranosides have been screened for antioxidant activity.[13–15]

RESULTS AND DISCUSSION

The synthesis of various substituted 10H-phenothiazines (IV) have been carried out by the Smiles rearrangement of substituted 2-formamido-2′-nitrodiphenylsulfides (III). The formyl derivatives have been prepared by diphenylsulfide (II) which in turn was prepared by the condensation of 2-aminobenzenethiols (IA) with o-halonitrobenzene (IB) in ethanolic sodium acetate solution. The IR and NMR studies of these compounds are also included. The substituted 10H-phenothiazines (IV) solution in toluene was then treated with β-D-ribofuranosyl-1-acetate-2,3,5-tribenzoate (V) and stirred in vacuuo on an oil bath, at 155–160°C for 10 hrs, to finally yield ribofuranosides (VI). The structures proposed to the synthesized compounds are well supported by spectroscopic data and elemental analysis (Table III) and optical rotation data. These compounds were screened for their antioxidant activities. The radical scavenging activity of compounds was evaluated using the DPPH and ABTS assays. In the present investigation, the compound displayed strong radical scavenging activity in both the assays. On comparing them to the literature standard, these compounds showed moderate activity.

IR Spectra

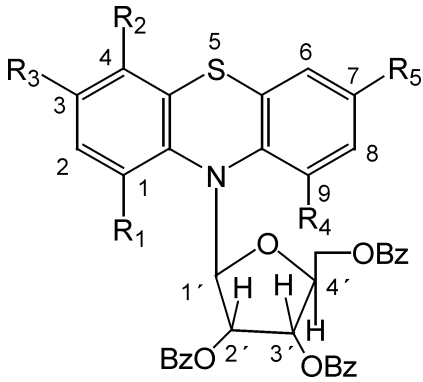
The characteristic IR bands of synthesized compounds are presented in Table I. Compounds $II_{(a-e)}$ showed two peaks in the regions 3480–3420 cm^{-1} and 3420–3300 cm^{-1} due to asymmetric and symmetric vibration of the primary amino group. Two peaks were observed in the region 1550–1500 cm^{-1} and 1390–1350 cm^{-1} due to asymmetric and symmetric vibrations of the nitro group. Compounds $III_{(a-e)}$ showed a single peak in the region 3050–3310 cm^{-1} due to N—H stretching vibration and an additional peak in the region 1690-1650 cm^{-1} was obtained due to C=O stretching vibration. Compounds $IV_{(a-e)}$ exhibit a single sharp

peak in the region 3450–3300 cm^{-1} due to N—H stretching band, which was found absent in compounds $VI_{(a-e)}$ clearly indicating it to be the site of ribosylation. Further, in compounds $VI_{(a-e)}$, bands due to C–O–C linkage of the sugar appeared in the region 1165–1040 cm^{-1}.

^{1}H NMR Spectra

The ^{1}H NMR data of compounds $IV_{(a-e)}$ and $VI_{(a-e)}$ are presented in Table (I). Compounds $IV_{(a-e)}$ showed a multiplet due to aromatic protons, which appeared in the region δ 6.74–8.13 ppm. The >NH proton appeared as a singlet between δ 9.10–8.53 ppm. The ^{1}H NMR spectra of ribofuranosides $VI_{(a-e)}$ did not show any peak due to >NH, indicating, the formation of ribofuranosides.

^{13}C NMR for the Synthesized Compounds



SCHEME 1

Optical Rotation Data of Compounds VI_{a-e}

Compound VI_a: $[\alpha]_D^{23} = -16.66^\circ$
Compound VI_b: $[\alpha]_D^{23} = +23.5^\circ$
Compound VI_c: $[\alpha]_D^{24} = -25.58^\circ$
Compound VI_d: $[\alpha]_D^{24} = -25.58^\circ$
Compound VI_e: $[\alpha]_D^{23} = -23.78^\circ$

EXPERIMENTAL

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on NICOLET-MEGNA FT-IR 550 spectrometer, and ^{1}H NMR spectra were recorded on a JEOL AL-300 spectrometer (300 MHz) in $CDCl_3$/DMSO-d_6 using TMS as an

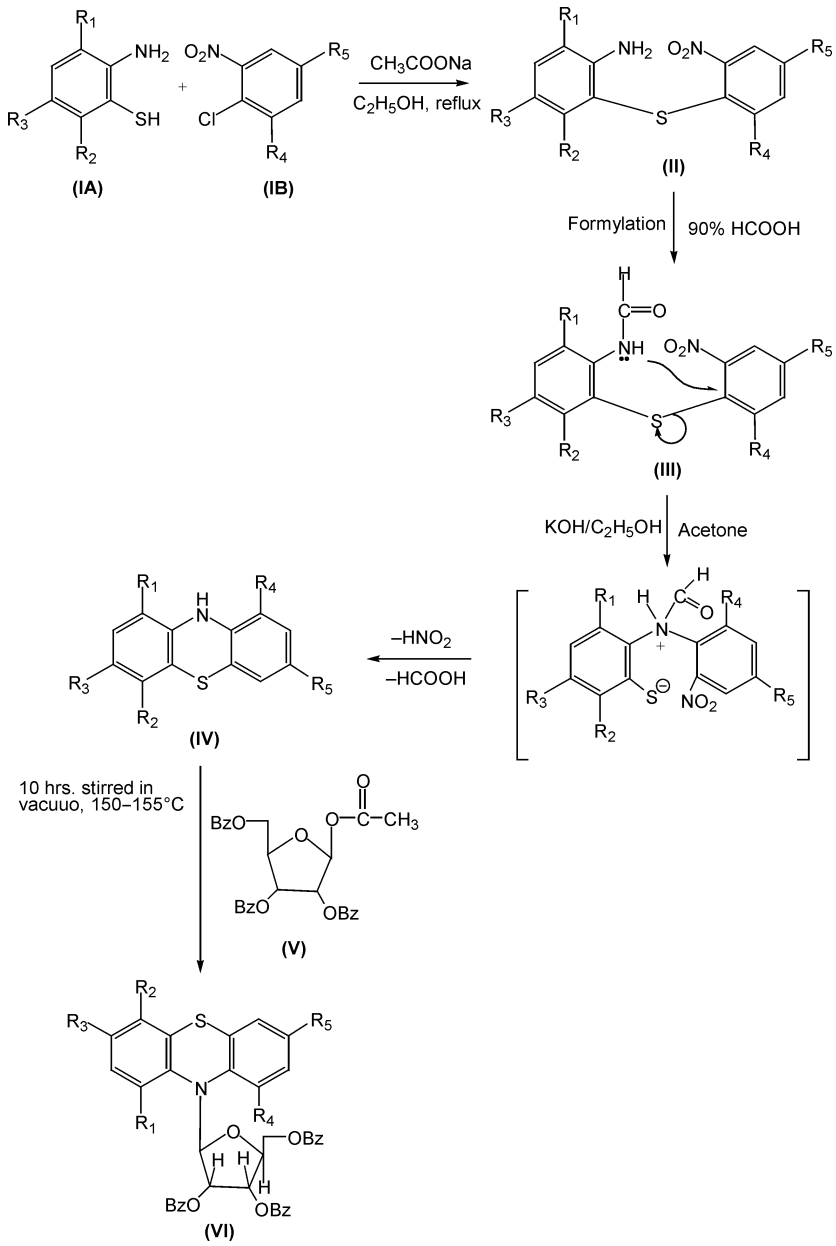
TABLE I The ^{1}H NMR and IR Spectral Data of Synthesized Compounds

Compound[a] No.	^{1}H NMR (δ ppm from TMS) >NH	Ar—H multiplet	IR (KBr : ν_{max} cm^{-1}) >NH	O ‖ N→O	C—Cl	CF_3	—C—Br	C—O—C
IV_a	8.69	6.83–7.82	3300	—	810	1320, 1140	—	—
IV_b	9.10	6.79–8.05	3050	1520, 1390	—	—	640	—
IV_c	8.53	6.92–7.97	3340	—	760	—	600	—
IV_d	9.00	6.98–8.13	3020	1500, 1360	—	1320, 1100	630	—
IV_e	8.90	6.82–7.85	3320	—	790	—	660	—
VI_a	—	6.87–8.09	—	—	820	1340, 1130	—	1040
VI_b	—	6.90–7.95	—	1550, 1350	—	—	630	1100
VI_c	—	7.10–8.08	—	—	770	—	660	1090
VI_d	—	6.82–7.89	—	1535, 1350	—	1330, 1120	620	1165
VI_e	—	6.74–8.10	—	—	795	—	650	1140

[a]The elemental analysis (C, H and N) of these compounds were obtained in good agreement with the calculated value.

TABLE II ^{13}C NMR for the compounds in $CDCl_3$

Compd. IV_a	δ 131.7 (C-1), δ 117, δ 115.5 (C–2, C–3); δ 130.2 (C–4); δ 110.1, 116.4, 112.1 (C–6, C–7, C–8) δ 135.5 (C–9)
Compd. IV_b	δ 145.8 (C–1); δ 112 (C–2); δ 139.5, 114.5 (C–3, C–4) δ 117.6, 136.4, 113.5, 112.4 (C–6, C–7, C–8, C–9)
Compd. IV_c	δ 146.7 (C–1); δ 113.4, 140.1, 116.4, 112.3 (C–2, C–3, C–4, C-6), δ 142.7 (C–7); δ 110.1, δ 144.6 (C–8, C–9)
Compd. IV_d	δ 136.4, 114.5, 109.6 (C–1, C–2, C–3); δ 138.5 (C–4) δ 116.5, 132.3 (C–6, C–7); δ 111.3, 141.2 (C–8, C–9)
Compd. IV_e	δ139.5, 116.3, 118.8(C–1, C–2, C–3); δ 123.1 (C–4); δ 118.4, 116.6, 114.7 (C–6, C–7, C–8); δ 144.9 (C–9)
Compd. VI_a	δ130.3(C–1); δ 118, 117.5 (C–2, C–3); δ 130.4 (C–4); δ 110.7, 116.8, 113.4 (C–6, C–7, C–8); δ 136.7 (C–9); δ 95.4 (C–1′); δ 1.49, 80.88 (C–2′, C–3′), δ 93.8 (C–4′)
Compd. VI_b	δ146.(C–1); δ 112.5 (C–2); δ 140.5, 114.5 (C–3, C–4) δ 118.3, 137.4, 113.9, 113.5 (C–6, C–7, C–8, C–9); δ 96.7 (C–1′); δ 82.91, 80.18 (C–2′, C–3′), δ 94.2 (C–4′)
Compd. VI_c	δ148.3(C–1); δ 114.5, 141.3, 115.9, 112.6 (C–2, C–3, C–4, C–6); δ 144.1 (C–7); δ 112.1, 144.5 (C–8, C–9); δ 94.9 (C–1′); δ 83.51, δ 82.41 (C–2', C–3'); δ 95.1 (C–4')
Compd. VI_d	δ135.9, 115.1, 109.7(C–1, C–2, C–3); δ 139.2 (C–4); δ 116.9, 132.4 (C–6, C–7); 112.3, 141.1 (C–8, C–9); δ 96.1 (C–1'); δ 81.91, 81.25 (C–2′, C–3′); δ 98.2 (C–4′)
Compd. VI_e	δ141.2, 117.2, 118.4(C–1, C–2, C–3); δ 123.6 (C–4) δ 119.3, 117.3, 115.1 (C–6, C–7, C–8); δ 144.5 (C–9); δ 96.5 (C–1′); δ 83.12, 81.34 (C–2′, C–3′); δ 96.9 (C–4′)



SCHEME 2

TABLE III Elemental Analysis of Phenothiazines and Their Ribofuranosides

Compound No.	R_1	R_2	R_3	R_4	R_5	Mol. Formula	Mol. Weight	Elemental analysis Found (calcd.) C	H	N
IV_a	Cl	CF_3	H	Cl	H	$C_{13}H_6Cl_2F_3NS$	336	46.35 (46.42)	1.81 (1.79)	4.18 (4.16)
IV_b	F	H	Br	NO_2	NO_2	$C_{12}H_5BrFN_3O_4S$	385	37.68 (37.40)	1.30 (1.29)	10.92 (10.90)
IV_c	F	H	Br	H	Cl	$C_{12}H_6BrClFNS$	329.5	43.58 (43.70)	1.83 (1.82)	4.27 (4.25)
IV_d	Br	Br	H	NO_2	CF_3	$C_{13}H_5Br_2F_3N_2O_2S$	468	47.30 (47.19)	1.99 (1.97)	7.89 (7.87)
IV_e	Br	Br	H	Cl	H	$C_{12}H_6Br_2ClNS$	389.5	36.89 (36.97)	1.52 (1.50)	3.62 (3.59)
VI_a	Cl	CF_3	H	Cl	H	$C_{39}H_{26}Cl_2F_3NO_7S$	780	60.21 (60.00)	3.35 (3.33)	1.81 (1.79)
VI_b	F	H	Br	NO_2	NO_2	$C_{38}H_{25}BrFN_3O_{11}S$	830	54.99 (54.94)	3.04 (3.01)	5.08 (5.06)
VI_c	F	H	Br	H	Cl	$C_{38}H_{26}BrClFNO_7S$	773.5	58.88 (58.95)	3.40 (3.36)	1.84 (1.81)
VI_d	Br	Br	H	NO_2	CF_3	$C_{39}H_{25}Br_2F_3N_2O_9S$	912	51.55 (51.32)	2.78 (2.74)	1.59 (1.54)
VI_e	Br	Br	H	Cl	H	$C_{38}H_{26}Br_2ClNO_7S$	833.5	54.92 (54.71)	3.32 (3.12)	1.71 (1.68)

internal standard (chemical shifts are measured in δ ppm) and ^{13}C NMR spectra (Table II) in $CDCl_3$ were measured. The purity of the compounds were checked by TLC using silica gel "G" as an adsorbent, visualizating these by UV light or an iodine chamber. The optical rotation data were measured by Laurent's half shade device.

Synthesis of 2-amino-2′-nitro diphenylsulfides (II)

2-aminobenzenethiol (IA) (0.1 mole) was dissolved in ethanol (20 ml) containing 0.1 mole of anhydrous sodium acetate in a 50-mL round bottom flask, and halonitrobenzne (IB) (0.1 mole) in 10 mL ethanol was added. The reaction mixture was refluxed for 4–5 h and concentrated in an ice bath overnight. The solid that separated out was filtered, washed with 30% ethanol, and recrystallized from methanol.

Synthesis of 2-formamido-2′-nitrodiphenylsulfides (III)

The diphenylsulphides (II) (0.1 mole) obtained was refluxed for 4 h. in 90% formic acid (20 mL). The contents were then poured into a

TABLE IV Antioxidant Activity of Synthesized Compounds

Compound No.	DPPH % Inhibition of 1 mg/mL of the Compound
IV_a	26.84 ± .06
IV_b	1.76 ± .02
IV_c	52.09 ± .03
IV_d	31.33 ± .08
IV_e	40.00 ± 1.2
VI_a	19.00 ± .09
VI_b	28.90 ± 1.2
VI_c	38.90 ± .09
VI_d	55.09 ± 1.5
VI_e	20.00 ± .07

Inhibition (%) of DPPH radical scavenging activity of various compounds at a particular concentration. Stock solution of crude compound was prepared as 1 mg/mL in methanol. Fifty microlitres of samples of particular concentration were added to 5 ml of 0.004% methanol solution of $DPPH^{\cdot}$. After 30 min. of incubation in the dark at room temperature, the absorbance was read against a blank at 517 nm.

beaker containing crushed ice; a solid that separated out was filtered, washed with water until the filtrate was neutralized, and crystallized from benzene.

Synthesis of Phenothiazine (IV)

Formyl derivatives (III) (0.1 mole) in acetone (15 mL) was refluxed and an alcoholic solution of potassium hydroxide (0.2 gm in

TABLE V Antioxidant Activity of Synthesized Compounds

	ABTS Activity at Different Time Intervals Minutes				
Compound No.	0 min	1 min	2 min	4 min	6 min
IV_a	0.723	0.280	0.280	0.280	0.280
IV_b	0.732	0.692	0.691	0.690	0.690
IV_c	0.731	0.150	0.150	0.150	0.150
IV_d	0.722	0.205	0.205	0.205	0.205
IV_e	0.721	0.230	0.228	0.228	0.228
VI_a	0.722	0.659	0.640	0.640	0.640
VI_b	0.738	0.649	0.645	0.645	0.645
VI_c	0.727	0.617	0.613	0.613	0.613
VI_d	0.730	0.059	0.042	0.038	0.022
VI_e	0.722	0.107	0.106	0.102	0.100

(ABTS activity at different time intervals) of Phenothiazines(IV)

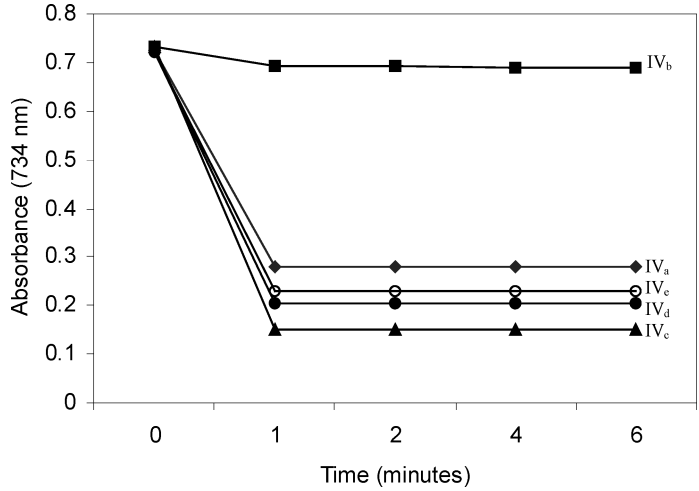


FIGURE 1 The effect of time on the suppression of absorbance of ABTSby phenothiazines(IV). After the addition of 1 mL of diluted ABTS solution (A 734 nm = 0.700±0.020) to 10 μL of the compound, the absorbance reading was taken at 30°C exactly 1 min, after initial mixing and up to 6 min. All determinations were carried out in triplicates.

5 mL ethanol) was added. The contents were heated for 30 min. A second lot of potassium hydroxide (0.2 gm in 5 mL ethanol) was added to the reaction mixture and refluxed for 4 h. The contents were poured into beaker containing crushed ice and were filtered. The residue obtained was repeatedly washed with cold water and finally with 30% ethanol and then crystallized from benzene.

Yield and M. P. of Compounds IVa–e

Compound IV_a: $R_1 = Cl$; $R_2 = CF_3$; $R_3 = H$; $R_4 = Cl$; $R_5 = H$; yield = 48%; m.p. = 230°C

Compound IV_b: $R_1 = F$; $R_2 = H$; $R_3 = Br$; $R_4 = NO_2$; $R_5 = NO_2$; yield = 40%; m.p. =150°C

Compound IV_c: $R_1 = F$; $R_2 = H$; $R_3 = Br$; $R_4 = H$; $R_5 = Cl$; yield = 42%; m.p. = 85°C

Compound IV_d: $R_1 = Br$; $R_2 = Br$; $R_3 = H$; $R_4 = NO_2$; $R_5 = CF_3$; yield = 33%; m.p. =315°C

Compound IV_e: $R_1 = Br$; $R_2 = Br$; $R_3 = H$; $R_4 = Cl$; $R_5 = H$; yield = 28%; m.p. = 280°C

Synthesis of Substituted N-(2′,3′,5′-tri-o-benzoyl-β-D-ribofuranosyl) Phenothiazine (VI)

To a concentrated solution of $IV_{(a-e)}$ (0.002 mole) in toluene, β-D-ribofuranose-1-acetate-2,3,5-tribenzoate (0.002 mole) was added and stirred, in vacuuo, on an oil bath, at 155–160°C, for 15 minutes. The vacuuo was broken and the reaction was protected from moisture, by using a guard tube. Stirring was further continued for 10 h. with application of a vacuum for 15 minutes after every hour. The melt was dissolved in methanol, boiled for 10 minutes, and cooled to room temperature. The precipitate was filtered, and the filtrate was evaporated to dryness. The viscous residue thus obtained was dissolved in ether, filtered, concentrated, and kept in a refrigerator overnight to get crystalline ribofuranoside.

Yield and M. P. of Compounds VIa–e

Compound VI_a: $R_1 = Cl$; $R_2 = CF_3$; $R_3 = H$; $R_4 = Cl$; $R_5 = H$; yield = 30%; m.p. =85°C

Compound VI_b: $R_1 = F$; $R_2 = H$; $R_3 = Br$; $R_4 = NO_2$; $R_5 = NO_2$; yield = 24%; m.p. = 110°C

Compound VI_c: $R_1 = F$; $R_2 = H$; $R_3 = Br$; $R_4 = H$; $R_5 = Cl$; yield = 29%; m.p. =100°C

Compound VI_d: $R_1 = Br$; $R_2 = Br$; $R_3 = H$; $R_4 = NO_2$; $R_5 = CF_3$; yield = 19%; m.p. = 70°C

Compound VI_e: $R_1 = Br$; $R_2 = Br$; $R_3 = H$; $R_4 = Cl$; $R_5 = H$; yield = 21%; m.p. = 120°C

ANTIOXIDANT ACTIVITY

All the synthesized compounds $IV_{(a-e)}$ and their ribofuranosides $VI_{(a-e)}$ were screened for their antioxidant activity by 1,1-diphenyl-2-picryl hydrazyl (DPPH) radial scavenging assay and 2,2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS.^+$) radial cation decolorization assay.

The present study demonstrated that the synthesized compounds showed mixed radical scavenging activity in both DPPH and $ABTS.^+$ assays (Figures 1 and 2).

(1) Compounds (IV_c) and (VI_d) showed strong radical scavenging activity in DPPH assay that have DPPH% inhibition ≥50.
(2) Compounds (IV_d) (IV_e) and (VI_c) showed moderate radical scavenging activity in DPPH assay that have a DPPH% inhibition ≥30.

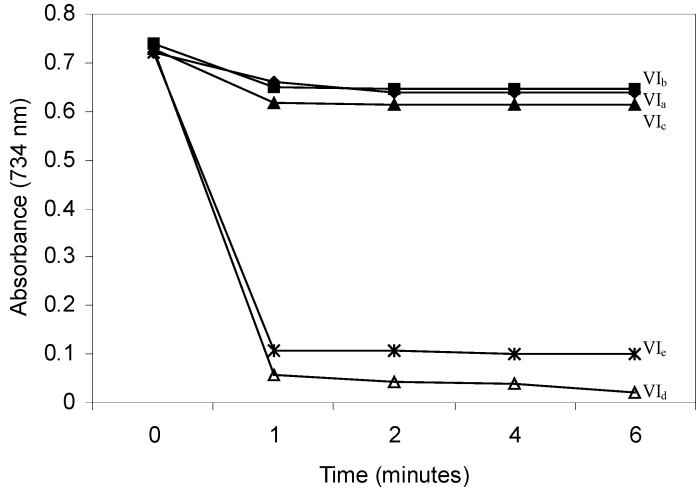


FIGURE 2 The effect of time on the suppression of absorbance of ABTS by ribofuranosides(VI). After the addition of 1 mL of diluted ABTS solution (A 734 nm = 0.700 ± 0.020) to 10 μl of the compound, the absorbance reading was taken at 30°C exactly 1 min., after initial mixing and up to 6 min. All determinations were carried out in triplicate.

(3) Compounds (IV_a) (IV_b) (VI_a) (VI_b) and (VI_e) showed mild radical scavenging activity in DPPH assay that have a DPPH% inhibition <30.
(4) Compounds (IV_a) (IV_c) (IV_d) (IV_e) (VI_d) (VI_e) were found to be more active in ABTS $^+$ assay which showed much decline in graph.

The study reveals that ribofuranosides (VI_b) and (VI_d) showed better chemopreventive action and antigenotoxic effect than their respective bases in DPPH assay. Ribofuranosides (VI_b), (VI_d), and (VI_e) showed better antioxidative (IV) effect than their respective base in $ABTS^{\cdot+}$ assay (Tables IV and V).

DPPH RADICAL SCAVENGING ASSAY

Radical scavenging activity of compound $IV_{(a–e)}$ and $VI_{(a–e)}$ against stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical was determined spectrophotometrically as described by Cuendet et al.,[13] A stock solution of 1 mg/mL of the compound was prepared in methanol. Fifty microliter of compounds were added to 5 ml of a 0.004% methanol solution of DPPH. After 30 min of incubation in the dark at room temperature, the absorbance was read against a blank at 517 nm.

The assay was carried out in triplicate, and the percentage of inhibition was calculated using the following formula.

$$\% \text{ Inhibition} = \frac{(AB - AA)}{AB} \times 100 \quad (1)$$

where
AB = Absorption of blank and
AA = Absorption of test

ABTS RADICAL CATION DECOLORIZATION ASSAY

The 2,2-azinobis(3-ethybenzothiazoline-6-sulphonic acid) radical cation (ABTS) decolorization test was also used to assess the antioxidant activity of compounds IV and VI. The ABTS assay was carried out using the improved assay of Re et al.[14] In brief, $ABTS^{\cdot+}$ was generated by oxidation of ABTS with potassium persulphate. For this purpose, ABTS was dissolved in deinoized water at a concentration of 7 mM, and potassium persulphate was added to a concentration of 2.45 mM. The reaction mixture was left at room temperature overnight (12–16 h) in the dark before use; the $ABTS^{\cdot+}$ solution then was diluted with ethanol to an absorbance of 0.700 ± 0.020 at 734 nm. After the addition of 1 mL of the diluted ABTS solution to 10 μL of compound and mixing, absorbance readings were taken at 30°C at intervals of exactly 1-6 min. later. All determinations were carried out in triplicate.

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