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SYNTHESIS AND BIOLOGICAL STUDY OF SOME NOVEL BIS-OXADIAZOLES, BIS-TRIAZOLES AND BIS- THIADIAZOLES.

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ABSTRACT
A series of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) **(2a-c),** 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) **(3a-c)** and 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thiadiazole) derivatives **(5a-c)** were synthesized by employing substituted sydnone as the precursor. The structures of the newly synthesized compounds were confirmed by ^{1}H-NMR, IR, LCMS and elemental analysis. Some of the synthesized compounds exhibited excellent antibacterial and antioxidant activity.

KEYWORDS
Bis-oxadiazoles, Bis-triazoles, Bis-thiadiazoles, Sydnones, Antibacterial, Antioxidant

INTRODUCTION

In recent years, new therapeutic strategies are being used for the synthesis of novel hybrid molecules by combining two different pharmacologically potent heterocyclic moieties. Nitrogen, oxygen and sulfur containing five member heterocyclic compounds have shown broad spectrum of biological activity. 1,3,4-oxadiazoles and 1,2,4-triazoles have been reported to possess remarkable pharmacological activities such as, antimicrobial [I], anti-inflammatory [II], anticonvulsant[III], antinociceptive[IV], antidepressant[V], analgesic[VI], antiviral[VII], antioxidant[VIII], anticancer activity[IX] etc. Whereas 1,3,4-thiadiazoles were reported to be biologically active likely due to the presence of N=C-S[X] pharmacophore and are known for their diverse biological activities such as, anti-inflammatory[XI] , antimicrobial[XII], anticonvulsant[XIII], antitubecular [XIV] etc.
Meanwhile, pyrazole and its derivatives have attracted immense attraction in the field of medicinal chemistry due to their pronounced biological and pharmacological activities such as,

antiviral[XV], antinflammatory[XVI], antimicrobial[XVII], anticancer[XVIII], antidepressant[XIX], anticonvulsant[XX], antipyretic[XXI], analgesic[XXII], antitubercular[XXIII], antioxidant[XXIV] etc.
Encouraged by these observations and in continuation of our work of synthesizing novel hybrid molecules[XXV] [XXVI], we herein report the synthesis, antibacterial and antioxidant study of some novel 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) **(2a-c),** 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) **(3a-c)** and 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thiadiazole) **(5a-c).**

EXPERIMENTAL

MATERIALS AMD METHOD

All the reagents and solvents were purchased from Sigma-Aldrich or Hi-Media and used after distillation/ recrystallization. ^{1}H NMR spectra were recorded on Bruker Avance II NMR spectrometer operating at 400MHz and all the chemical shift values were reported in parts per million (ppm) relative to tetramethylsilane (TMS). Mass spectra were acquired on a SHIMADZU LCMS-8030 mass spectrometer. Melting points of the synthesized compounds were determined in open capillary tubes in Innovative DTC-967A digital melting point apparatus. SHIMADZU FT-IR 157 spectrophotometer was used for recording IR spectra. C H N analysis was performed with Vario-EI Elementar-III model analyzer.

General procedure for the synthesis of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) (2a-c)

1-(Aryl)-1H-pyrazol-3,4-dicarbohydrazide **(3a-c)** (1mmol) was taken in a round bottomed flask, potassium hydroxide (1.68g, 3 mmol) dissolved in water (5mL) was added to it. To this, carbon disulfide (2mL, 3 mmol) was added and refluxed in an oil bath until the evolution of H_2S gas ceased. The reaction mixture was cooled, diluted with water and acidified with hydrochloric acid. The white solid separated was washed thoroughly with water and recystallized from ethanol-acetone mixture.

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) (2a)

IR (KBr cm-1) 3186 (N-H), 1622 (C=N),1246 (C-O-C); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.40 (s, 3H, CH_3), 7.33 (d, 2H, J=8.64 Hz o-protons of p-tolyl), 7.85 (d, 2H, J=8.48 Hz, m-protons of p-tolyl), 9.31 (s, 1H, H of pyrazole ring), 14.78 (s, 2H, SH). LC-MS: m/z: 359.20 [M^++1].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) (2b)

IR (KBr cm-1) 3071 (N-H), 1634 (C=N), 1209 (C-O-C); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.85 (s, 3H, OCH_3), 7.06 (d, 2H, J=9 Hz , o-protons of p-anisyl), 7.88 (d, 2H, J=9.04 Hz, m-protons of p-anisyl), 9.3 (s, 1H, H of pyrazole ring), 13.8 (s, 2H, SH). LC-MS: m/z: 375.05 [M^++1].

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) (2c)

IR (KBr cm-1) 3190 (N-H), 1641 (C=N), 1246 (C-O-C); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.44 (t, 1H, J=7.44 Hz , p-protons of phenyl), 7.55 (dd, 2H, J=7.56 Hz, o-protons of phenyl), 8.01 (dd, 2H, J=7.68 Hz, m-protons of phenyl), 9.45 (s, 1H, H of pyrazole ring), 14.75 (s, 2H, SH). LC-MS: m/z: 345.20 [M^++1].

General procedure for the synthesis of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) (3a-c)

1-(Aryl)-1H-pyrazol-3,4-dicarbohydrazide **(1a-c)** (1 mmol), was added to ethanolic potassium hydroxide (1.68g, 3 mmol, 10mL) solution. To this mixture, carbon disulfide (1.81mL, 3 mmol) was added slowly with continuous stirring by maintaining the temperature below 25^0C. Yellow solid mass gets separated after the completion of addition. The reaction mixture was further stirred for 24 hours. The solid mass obtained was diluted with anhydrous ether (100 mL) and filtered. Yellow colored potassium dithiocarbazinate obtained was washed with ether and dried.
To potassium dithiocarbazinate (1 mmol), hydrazine hydrate (2.5 mL, 5 mmol) in water (5mL) was added and refluxed in an oil bath until the evolution of H_2S gas ceased. The reaction mixture was cooled to room temperature, diluted with water and acidified with hydrochloric acid. The solid separated was washed with water, dried and recystallized from acetone-dimethyl formamide mixture.

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) (3a)

IR (KBr cm-1) 3088 (N-H), 1634 (C=N); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.77 (s, 3H, CH_3), 5.51-5.69 (m, 4H, NH_2), 7.57 (d, 2H, J=8.28 Hz o-protons of p-tolyl), 8.07 (d, 2H, J=7.84 Hz, m-protons of p-tolyl), 9.39 (s, 1H, H of pyrazole ring), 14.30 (s, 2H, SH). LC-MS: m/z: 387.10 [M^++1].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) (3b)

IR (KBr cm-1) 3190 (N-H), 1643 (C=N); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.83(s, 3H, OCH_3), 5.51-5.67 (m, 4H, NH_2), 7.07 (d, 2H, J=8.8 Hz o-protons of p-anisyl), 7.85 (d, 2H, J= 9 Hz, m-protons of p-anisyl), 9.45 (s, 1H, H of pyrazole ring), 13.93 (s, 2H, SH). LC-MS: m/z: 403.05 [M^++1].

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) (3c)

IR (KBr cm-1) 3210 (N-H), 1640 (C=N); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.53-5.71 (m, 4H, NH_2), 7.45-8.10 (m, 5H, Ar-H), 9.45 (s, 1H, H of pyrazole ring), 14.16 (s, 2H, SH). LC-MS: m/z: 373.57 [M^++1].

General procedure for the synthesis of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thiadiazole) (5a-c)

1-(Aryl)-1H-pyrazol-3,4-dicarboxylic acid **(4a-c)** (1 mmol), 2-phenyl thiosemicarbazide (2 mmol) was taken in a round bottomed flask, to this phosphorus oxychloride (15 mL) was added. The contents were heated for 6 hours at 90^0C. After the completion of the reaction, the contents were cooled to room temperature and then carefully poured into a beaker containing ice flakes. The solid separated was filtered and washed with sodium bicarbonate followed by water. Recrystallization was done using ethanol-dichloromethane mixture.

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thiadiazole) derivatives (5a)

IR (KBr cm-1)3100 (N-H), 1601 (C=N), 744 (C-S-C); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.47(s, 3H, CH_3), 6.98-7.06 (m, 2H, protons of phenyl ring), 7.29-7.31 (m, 4H, protons of phenyl ring), 7.43 (d, 2H, J=8.48 Hz o-protons of p-tolyl), 7.69-7.70 (m, 4H, protons of phenyl ring), 7.87 (d, 2H, J= 8.8 Hz, m-protons of p-tolyl), 9.15 (s, 1H, H of pyrazole ring), 10.40 (s, 1H, NH), 10.58 (s, 1H, NH). LC-MS: m/z: 510.34 [M^++1].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thiadiazole) derivatives (5b)

IR (KBr cm-1) 3202 (N-H), 1599 (C=N), 745 (C-S-C); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.84 (s, 3H, OCH_3), 6.99-7.07 (m, 2H, protons of phenyl ring), 7.12 (d, 2H, J= 9.08 Hz, o-protons of p-anisyl), 7.34-7.42 (m, 4H, protons of phenyl ring), 7.67-7.72 (dd, 4H, J= 7.88 Hz, protons of phenyl ring), 7.91 (d, 2H, J= 9.04 Hz, m-protons of p-anisyl), 9.19 (s, 1H, H of pyrazole ring), 10.44 (s, 1H, NH), 10.68 (s, 1H, NH). LC-MS: m/z: 525.05 [M^++1].

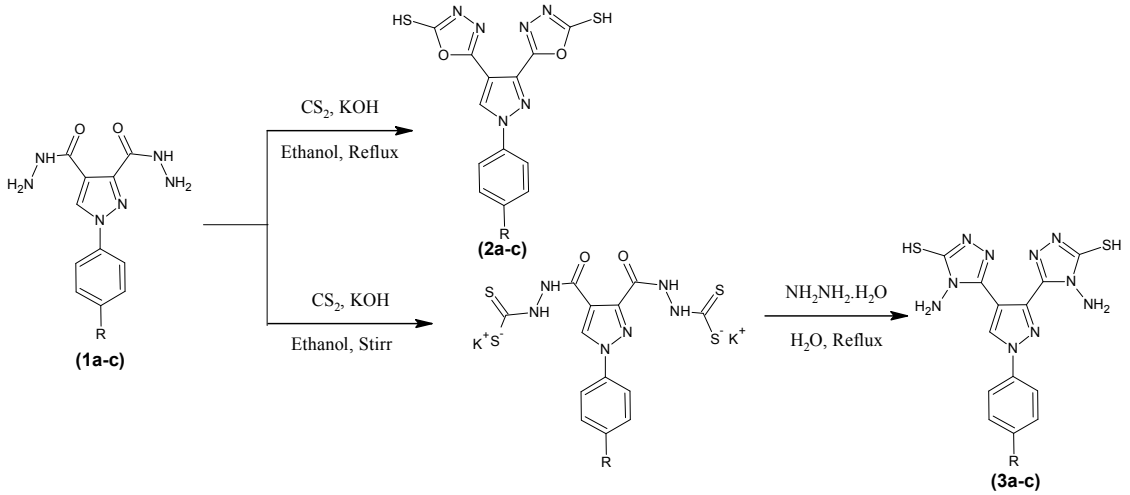
5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thiadiazole) derivatives (5c)

IR (KBr cm-1) 2980 (N-H), 1599 (C=N), 701 (C-S-C); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.96-7.04 (m, 2H, protons of phenyl ring), 7.30-7.37 (m, 5H, protons of phenyl ring), 7.39 (t, 2H, J= 7.36 Hz, protons of phenyl ring), 7.54 (t, 2H, J= 7.64 Hz, protons of phenyl ring), 7.68 (t, 4H, J= 8.48 Hz, protons of phenyl ring), 7.97 (d, 2H, J= 7.76 Hz, protons of phenyl ring), 9.14 (s, 1H, H of pyrazole ring), 10.28 (s, 1H, NH), 10.50 (s, 1H, NH). LC-MS: m/z: 495.45 [M^++1].

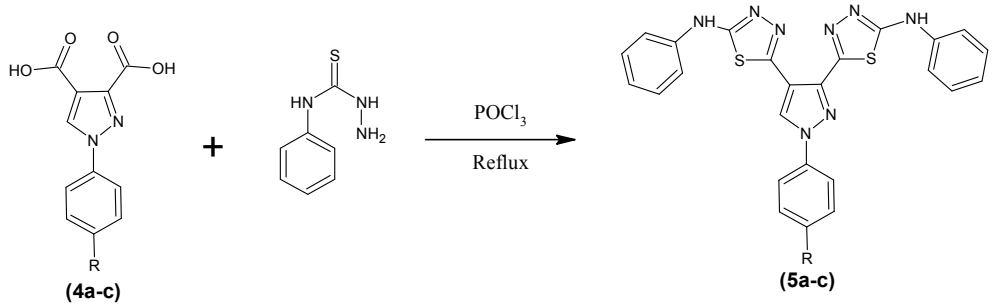
RESULTS AND DISCUSSION

3-Aryl substituted sydnones were obtained by the reaction of appropriately substituted aniline with ethyl chloroacetate followed by hydrolysis, nitrosation and cyclization with acetic anhydride as per the procedure reported in the literature [XXVII]. 1-(Aryl)-1H-pyrazol-3,4-dicarbohydrazide **(1a-c)** [XXVIII] were synthesized by the hydrazinolysis 1-(aryl)-1H-pyrazole-3, 4-dimethylcarboxylate with hydrazine hydrate. Whereas, 1-(aryl)-1H-pyrazole-3,4-dicarboxylic acid[XXIX] **(4a-c)** were prepared by the hydrolysis of 1-(aryl)-1H-pyrazole-3, 4-dimethylcarboxylate with aqueous alcoholic sodium hydroxide.

5,5'-(1-(Aryl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) **(2a-c)** was synthesized by refluxing the mixture of 1-(aryl)-1H-pyrazol-3,4-dicarbohydrazide **(1a-c)** and carbon disulphide in aqueous potassium hydroxide solution, whereas 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) **(3a-c)** was obtained by the treatment of potassium dithiocarbazinate with hydrazine hydrate. **(Scheme 1).** 5,5'-(1-(Aryl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thiadiazole) derivatives **(5a-c)** were prepared by the cyclocondensation of 1-(aryl)-1H-pyrazol-3,4-dicarboxylic acids **(4a-c)** with phenyl thiosemicarbazide **(Scheme 2)** which in turn synthesized by the reaction of phenyl isothiocyanate with hydrazine hydrate[XXX].



Scheme 1: Synthesis of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(5-mercapto-1,3,4-oxadiazole) **(2a-c)** and 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(4-amino-3-mercapto-1,2,4-triazole) **(3a-c)**.



Scheme 2: Synthesis of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-phenylamino-1,3,4-thia diazole) **(5a-c).**

Table 1: Characterization data of bis-(1,3,4-oxadiazoles) **(2a-c),** bis-(1,2,4-triazoles) **(3a-c)** and bis-(2-phenylamino-1,3,4-thiadiazole) **(5a-c).**

Comp No.	R	M.P (^oC) (Yield %)	Molecular Formula (Mol. Wt)	Colour and crystal nature	Halochromism with sulfuric acid	**% Analysis Found (Calculated)**		
						C	H	N
2a	CH_3	289 (77)	$C_{14}H_{10}N_6O_2S_2$ (358)	White amorphous solid	Orange	46.87 (46.92)	2.86 (2.81)	23.51 (23.45)

2b	OCH_3	270 (79)	$C_{14}H_{10}N_6O_3S_2$ (374)	White amorphous solid	Yellow	44.90 (44.91)	2.75 (2.69)	22.41 (22.45)
2c	H	303 (81)	$C_{13}H_8N_6O_2S_2$ (344)	White amorphous solid	White	45.30 (45.34)	2.29 (2.34)	24.46 (24.40)
3a	CH_3	268 (78)	$C_{14}H_{14}N_{10}S_2$ (386)	White amorphous solid	Yellow	43.55 (43.51)	3.68 (3.65)	36.19 (36.24)
3b	OCH_3	247 (95)	$C_{14}H_{14}N_{10}OS_2$ (402)	Yellow amorphous solid	Pale yellow	41.72 (41.78)	3.53 (3.51)	34.81 (34.80)
3c	H	301 (79)	$C_{13}H_{12}N_{10}S_2$ (372)	Yellow crystalline solid	Yellow	41.99 (41.92)	3.20 (3.25)	37.56 (37.61)
5a	CH_3	279 (70)	$C_{26}H_{20}N_8S_2$ (508)	White amorphous solid	Orange	61.38 (61.40)	3.91 (3.96)	22.08 (22.03)
5b	OCH_3	282 (83)	$C_{26}H_{20}N_8OS_2$ (524)	Yellow amorphous solid	Orange	59.46 (59.52)	3.81 (3.84)	21.39 (21.36)
5c	H	>303 (76)	$C_{25}H_{18}N_8S_2$ (494)	Pale yellow amorphous solid	Green	60.68 (60.71)	3.61 (3.67)	22.63 (22.66)

ANTIBACTERIAL STUDIES

Bacterial strains were purchased from National collection of industrial microorganisms, Pune, India. Newly synthesized compounds were tested for their antibacterial activity against Gram-positive bacteria *Staphylococcus aureus* (NCIM - 5021), *Bacillus subtilis* (NCIM 2197) and

Gram-negative bacteria *Escherichia coli* (NCIM-2931)*, Pseudomonas aeruginosa* (NCIM-2036) using cup plate method.[XXXI, XXXII] Ciprofloxacin was used as the reference drug. Compound **5a** showed good activity against *Staphylococcus aureus,* whereas compounds **3a** and **3c** exhibited significantly good activity against *Bacillus subtilis* and *Escherichia coli.* Rest of the compounds displayed comparatively moderate activity (**Table 2).**

Table 2: Antibacterial activity bis-(1,3,4-oxadiazoles) **(2a-c),** bis-(1,2,4-triazoles) **(3a-c)** and bis-(2-phenylamino-1,3,4-thiadiazole) **(5a-c).**

Compounds	Diameter of zone of inhibition (in mm) at 100µg/mL			
	Antibacterial activities			
	Gram positive bacteria		Gram negative bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*P.aeruginosa*
2a	10.5±0.5	12.5±0.5	10.5±0.5	12.5±0.5
2b	10±1	12±1	14±1	12±1
2c	10.5±0.5	11.5±0.5	11±0	11.5±0.5
3a	11±1	**21±1**	12±1	12±0
3b	11.5±0.5	13.5±0.5	11±1	12.5±0.5
3c	14±1	10.5±0.5	**20±0**	14±1
5a	11±1	13±0	11.5±0.5	12±0
5b	12±0	15±0	10±1	10±0
5c	**21±1**	15.5±0.5	10.5±0.5	12±0
Ciprofloxacin	24.5± 0.50	22.5± 0.50	23.5± 0.50	23.5± 0.50

ANTIOXIDANT STUDIES

Free radical scavenging activity of the synthesized compounds was carried out as per the reported procedure [XXXIII]. The absorbance of stable DPPH radical was measured at 517 nm. Radical scavenging activity was expressed as the inhibition percentage and was calculated using the equation of DPPH radical scavenging activity and the result are presented in **Table 3.**

$$\text{DPPH radical scavenging activiy (\%)} = \frac{(\text{Abc - Abs})}{(\text{Abc})} \times 100$$

Where Abc is the absorbance of DPPH radical + methanol; Abs is the absorbance of DPPH radical + test sample/standard BHA.

Bis-(1,3,4-oxadiazoles) **(2a-c),** bis-(1,2,4-triazoles) **(3a-c)** and bis-(2-phenylamino-1,3,4-thiadiazole) **(5a-c)** showed DPPH scavenging activity varying from 94.8% to 9%, whereas standard drug BHA showed 90% inhibition. Compound **2a, 3a** and **3c** displayed highest radical scavenging activity i.e. 92.8%, 85.7% and 89.8% respectively. The percentage radical scavenging activity of bis-(1,3,4-oxadiazoles) **(2a-c),** bis-(1,2,4-triazoles) **(3a-c)** and bis-(2-phenylamino-1,3,4-thiadiazole) **(5a-c)** has been described in **Figure 1.**

Table 3: DPPH scavenging activity of bis-(1,3,4-oxadiazoles) **(2a-c),** bis-(1,2,4-triazoles) **(3a-c)** and bis-(2-phenylamino-1,3,4-thiadiazole) **(5a-c).**

Compound	DPPH Assay in %
2a	94.8
2b	79.1
2c	84.8
3a	85.7
3b	64.2
3c	89.8
5a	23.8
5b	9
5c	13.96
Standard BHA	90

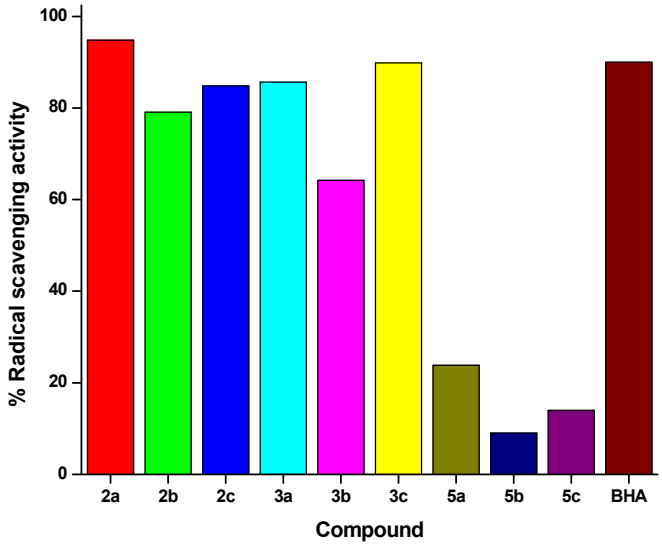


Figure 1: Bar diagram representing DPPH scavenging activity of bis-(1,3,4-oxadiazoles) **(2a-c),** bis-(1,2,4-triazoles) **(3a-c)** and bis-(2-phenylamino-1,3,4-thiadiazole) **(5a-c).**

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