Research Article

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Synthesis and Biological Activity of Novel 3-phenyl-5-{[(1H-benzo[d]imidazol-2-yl) thio] methyl}-1,2,4-oxadiazoles

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Abstract: A series of novel 5-{[(1H-benzo[d]imidazol-2-yl) thio] methyl}-3-phenyl-1,2,4-oxadiazoles 5(a-i) were synthesized by condensing 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole **3(a-c)** and 2-mercaptobenzimidazoles **4(a-c)** using potassium carbonate in DMF. The chemical structure of the newly synthesized compounds was characterized by spectral methods (IR, ^{1}H, ^{13}C NMR and LC-MS).The title compounds were screened for their antimicrobial, antioxidant and haemolytic activities. All the synthesized compounds showed less than 5% toxicity towards fresh chicken blood. The synthesized compounds **5(a-i)** showed promising against the tested bacterial strain and fungi.

Key words: 1, 2, 4-oxadiazole derivatives, alkylation, antimicrobial, antioxidant, haemolysis.

INTRODUCTION:

The chemistry of heterocyclic compounds is a very complex and interesting part of organic chemistry. Heterocycles have a wide range of physiological and industrial significance and the continual need to have compounds with newer and better activity has prompted researchers to synthesize novel heterocycles or derivatives of heterocycles. Heterocycles find utility as pharmaceuticals, dyestuffs, corrosion inhibitors and in waste decontamination [1].

1, 2, 4-oxadiazole derivatives are well known oxygen and nitrogen containing five membered heterocycles which are used as scaffolds to synthesize many novel therapeutic molecules. They are bioisosteres for amides and esters [2] and possess higher metabolic stability. Since they possess greater hydrolytic and metabolic stabilities, pharmacokinetic and *in vivo* performance is observed to increase which makes this ring very attractive to pharmaceutical industries. These factors have led to many oxadiazole derivatives possessing varied biological activities like, muscaranic agonist[3], anticancer[4], antibacterial [5], anti-inflammatory [6], dopamine transporters [7], antispasmodics [8], immunosuppresants [9], anthelmintic [10], antifungal [11], antirhinoviral [12], growth hormone secretogogues [13], 5-HT agonists[14] and also antiplatelet and antithrombotic agents [15,16].

Another important heterocycle is benzimidazole, which is at times termed as "Master key" as it is present in many biologically active compounds with different activity. The benzimidazole ring may be substituted in any of the seven positions but most of the biologically active compounds bear

substituents in 1-, 2- and/or 5- (or 6-) positions [17]. Thus manipulating the structure of benzimidazole has resulted in many drugs like astemizole an antihistaminic agent, albendazole an anthelmintic agent, cilexitil an antihypertensive, enviradine an antiviral etc. Further research into benzimidazoles has resulted in compounds possessing a wide range of biological activities [18-21].

Thus we decided to synthesize compounds incorporating both benzimidazole and 1,2,4-oxadiazole and evaluated their biological activities.

EXPERIMENTAL:

Materials and Methods: All the solvents and reagents used were of AR grade and used as such without further purification. The proposed structure of the final compounds are confirmed by the ^{1}H-NMR spectra obtained using an AGILENT (400 MHz) NMR spectrometer (Deuterated dimethylsulphoxide as solvent procured from SIGMA ALDRICH, USA and Tetramethyl Silane as internal standard). The following notations denoted the peak types in the spectra: singlet (s), broad singlet (br s), doublet (d), triplet (t), and multiplet (m). The IR, ^{1}H, ^{13}C NMR and LC-MS were used for the confirmation of the molecular structure and the purity of sample. Thin layer chromatography (TLC) was carried out on aluminum sheets coated in Merck Kieselgel silica gel 60, eluting with petroleum ether and ethyl acetate (40%).Antibacterial property and antifungal property of the given compounds was assessed using pure cultures of *Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-2453), *Staphylococcus aureus* (MTCC-3610), *Bacillus subtilis* (MTCC-10619), *Enterococcus faecalis* (MTCC-439), *Aspergillus niger* (MTCC - 3323) and *Candida albicans* (MTCC-227), procured from Microbial Type Culture Collection (MTCC) and Gene Bank, Chandigarh, India. Experiment was performed in well plates and plates were scanned using microplate reader (Thermo scientific, Multiskan^{TM}) at 580-600 nm after the incubation period. Absorbance reading was taken at 517 nm and 541 nm using UV-Vis spectrophotometer (ELICO® SA 165, India) for the assessment of antioxidant activity using DPPH assay and Haemolysis assay respectively.

General Procedure for the synthesis of 5-{[(1H-benzo[d]imidazol-2-yl) thio] methyl}-3-phenyl-1,2,4-oxadiazoles 5(a-i): To a solution of 3-aryl-5-chloromethyl-1,2,4-oxadiazole and 2-mercaptobenzimidaole derivative in DMF, K_2CO_3 was added. The reaction mixture was stirred at 90-100^{o}C for 1.5 h and the completion of the reaction mixture was monitored through thin layer chromatography. To the reaction mixture water was added and it was extracted with ethylacetate, the organic layer then washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to get the crude product. The product was crystallized from methanol to obtain pure 5-{[(1H-benzo[d]imidazol-2-yl) thio] methyl}-3-phenyl-1,2,4-oxadiazoles.

Typical Procedure for the synthesis of 5-{[(6'-chloro-1'*H*-benzo[*d*]imidazol-2'-yl)thio]methyl}-3-phenyl-1,2,4-oxadiazole (5a): To a solution of (4a) 5-chloro-2-mercaptobenzimidazole (184mg, 1mmol) and (3a) 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (195mg, 1mmol) in 5 mL of DMF ,K_2CO_3 was added and stirred at 90^{o}C for 1.5 hrs. The completion of the reaction was monitored by thin layer chromatography. To the reaction mixture water was added and extracted with 15 mL of ethylacetate. The combined organic layers was washed with 15mL of brine, dried over Na2SO4 and concentrated under reduced pressure to obtain the crude product. The crude product was then crystallized using methanol as the solvent to afford 5-{[(6'-chloro-1'*H*-benzo[*d*]imidazol-2'-yl) thio] methyl}-3-phenyl-1,2,4-oxadiazole as white solid in 84-86% yield. M.P- 156-158 ^{o}C; IR (cm^{-1}): 1448, 1590, 2968, 3272;

^{1}H NMR (DMSO-d_6, 400MHz) δ 4.10 (s, 2H), 7.10 (d, J=7.4 Hz, 1H) , 7.39(t, J= 8.0Hz,1H), 7.50 (m, 3H), 7.90 (d, J= 8.4 Hz, 2H), 8.42 (d, J=9.0 Hz, 1H), 12.10 (br s, N-H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 35.0, 115.5, 116.5, 123.9, 126.3, 127.9, 129.2, 129.5, 131.2, 136.3, 141.2, 149.1, 163.3, 168.9. LC-MS (m/z) 343.02 (M+1), 345.03(M+3). Anal. Calcd for $C_{16}H_{11}ClN_4OS$: C, 56.06; H, 3.23; N, 16.34%; Found: C, 56.02; H, 3.28; N, 16.35%.

5-({[6'-(difluoromethoxy)-1'*H*-benzo[*d*]imidazol-2'-yl]thio}methyl)-3-phenyl-1,2,4-oxadiazole (5b): M. P- 134-136 ^{o}C; IR (cm^{-1}): 1456, 1596, 2960, 3270; ^{1}H NMR (DMSO-d_6, 400MHz) δ 4.07 (s, 2H),6.75(d, J=7.4 Hz, 1H), 7.10 (s, 1H) ,7.35 (t, J= 8.0Hz,1H),7.42 (s, 1H), 7.52 (m, 3H), 7.82 (d, J=7.9 Hz, 2H), 12.01(br s, N-H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 35.9, 100.1, 112.3, 115.9, 125.9, 127.8, 128.8, 130.9, 131.8, 138.7, 148.7, 155.6, 162.8, 168.1, 169.2. LC-MS (m/z) 375.05 (M+1). Anal. Calcd for $C_{17}H_{12}F_2N_4O_2S$: C, 54.54; H, 3.23; N, 14.97%; Found: C, 54.57; H, 3.28; N, 14.95%.

5-{[(1H-benzo[d]imidazol-2-yl) thio] methyl}-3-phenyl-1,2,4-oxadiazole (5c): . M.P- 108-110 ^{o}C; IR (cm^{-1}): 1477, 1596, 2970, 3284; ^{1}H NMR (DMSO-d_6, 400MHz) δ 4.12 (s, 2H), 7.20 (d, J= 8Hz, 2H), 7.40(t, J= 8.2Hz,1H), 7.55(m, 4H), 7.85 (d, J=7.6Hz, 2H), 12.05 (br s, N-H); ^{13}C NMR (DMSO-d_6,100MHz) δ 35.1, 116.0, 123.5, 125.8, 128.1, 130.2, 132.0, 138.8, 150.2, 164.1, 169.2. LC-MS (m/z) 309.09 (M+1). Anal. Calcd for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17 %; Found: C, 62.30; H, 3.96; N, 18.12%.

5-{[(6'-chloro-1'*H*-benzo[*d*]imidazol-2'-yl)thio]methyl}-3-(4''-chlorophenyl)-1,2,4-oxadiazole (5d): M. P- 174-176 ^{o}C; IR (cm^{-1}): 1450, 1600, 2942, 3265; ^{1}H NMR (DMSO-d_6, 400MHz) δ 4.17 (s, 2H), 7.11 (d, J=7.6 Hz, 1H), 7.56 (m, 3H), 8.09 (d, J= 8.1 Hz, 2H), 8.40 (s, 1H), 12.21 (br s , N-H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 34.1, 115.1, 116.3, 123.5, 124.3, 127.9, 129.4, 129.6, 134.0, 137.2, 141.1, 150.0, 162.2, 169.3. LC-MS (m/z) 377.05 (M+1), 378.98 (M+3), 380.91(M+5). Anal. Calcd for $C_{16}H_{10}Cl_2N_4OS$: C, 50.94; H, 2.67; N, 14.85%; Found: C, 50.91; H, 3.01; N, 2.66%.

3-(4''-chlorophenyl)-5-({[6'-(difluoromethoxy)-1'*H*-benzo[*d*]imidazol-2'-yl]thio}methyl)-1,2,4-oxadiazole (5e): M. P- 150-152 ^{o}C; IR (cm^{-1}): 1432, 1604, 2948, 3280; ^{1}H NMR (DMSO-d_6, 400MHz) δ 4 .07 (s, 2H),6.79(d, J=7.4 Hz, 1H), 7.14 (s, 1H), 7.45 (d, J=7.4 Hz, 1H), 7.60 (d, J=8.0 Hz, 2H), 8. 14 (d, J=8.0 Hz, 2H), 12.06 (br s, N-H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 35.1, 100.5, 111.0, 116.9, 124.1, 128.2, 129.5, 130.2, 134.6, 138.5, 149.0, 155.5, 163.8, 167.2, 169.1. LC-MS (m/z) 409.01 (M+1), 411.00 (M+3). Anal. Calcd for $C_{17}H_{11}ClF_2N_4O_2S$: C, 49.95; H, 2.71; N, 13.70%; Found: C, 50.00; H, 2.76; N, 13.66%.

5-{[(1'*H*-benzo[*d*]imidazol-2'-yl)thio]methyl}-3-(4''-chlorophenyl)-1,2,4-oxadiazole (5f): M. P- 118-120 ^{o}C; IR (cm^{-1}): 1478, 1582, 2959, 3290; ^{1}H NMR (DMSO-d_6, 400MHz) δ 4.15 (s, 2H), 7.24 (d, J= 8.1Hz, 2H), 7.50 (d, J=9.0 Hz, 2H), 7.62 (d, J=8.1 Hz, 2H), 8.21(d, J=9.0 Hz, 2H), 12.16 (br s, N-H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 34.6, 114.9, 122.0, 123.3, 128.2, 129.6, 133.3, 139.2, 148.8, 162.8, 169.1. LC-MS (m/z) 343.04 (M+1), 345.02(M+3). Anal. Calcd for $C_{16}H_{11}ClN_4OS$: C, 56.06; H, 3.23; N, 16.34%; Found: C, 56.07; H, 3.24; N, 16.38%.

5-{[(6'-chloro-1'*H*-benzo[*d*]imidazol-2'-yl)thio]methyl}-3-(3'',4''-dimethoxyphenyl)-1,2,4-oxadiazole (5g): M. P- 124-126 ^{o}C; IR (cm^{-1}): 1445, 1601, 2975, 3284; ^{1}H NMR (DMSO-d_6, 400MHz) δ 3.85 (s, 6H), 4 .17 (s, 2H), 6.93 (d, J=7.4Hz, 1H), 7.10 (d, J=8.1 Hz, 1H), 7.3 (s, 1H), 7.57 (m, 2H), 8.40 (s, 1H), 12.16 (br s, N-H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 34.1, 56.1, 111.1, 112.9, 115.2, 116.1, 122.4, 124.2, 125.1, 129.5, 137.1, 140.0, 147.1, 149.9, 150.1, 163.1, 167.7. LC-MS (m/z) 403.03 (M+1),

404.99 (M+3). Anal. Calcd for $C_{18}H_{15}ClN_4O_3S$: C, 53.67; H, 3.75; N, 13.91%; Found: C, 53.72; H, 3.79; N, 13.93%.

5-({[6'-(difluoromethoxy)-1'*H*-benzo[*d*]imidazol-2'-yl]thio}methyl)-3-(3'',4''dimethoxyphenyl)-1,2,4-oxadiazole (5h): M. P- 170-172 ^oC; IR (cm^{-1}): 1466, 1598, 2943, 3256; ^1H NMR (DMSO-d_6, 400MHz) δ 3.84 (s, 6H), 4 .12 (s, 2H), 6.99 (m,2H), 7.10 (s, 1H), 7.21 (s, 1H), 7.30 (s, 1H), 7.51 (m, 2H), 12.10 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 35.0, 56.1, 100.4, 111.6, 112.0, 112.2, 116.0, 122.0, 124.0, 130.8, 138.7, 149.5, 149.8. 150.2, 155.8, 163.0, 167.6, 168.2. LC-MS (m/z) 435.03 (M+1). Anal. Calcd for $C_{19}H_{16}F_2N_4O_4S$: C, 52.53; H, 3.71; N, 12.90%; Found: C, 52.54; H, 3.76; N, 12.85%.

5-{[(1'*H*-benzo[*d*]imidazol-2'-yl)thio]methyl}-3-(3'',4''-dimethoxyphenyl)-1,2,4-oxadiazole (5i): M. P- 130-132 ^oC; IR (cm^{-1}): 1470, 1596, 2944, 3256; ^1H NMR (DMSO-d_6, 400MHz) δ 3.83 (s, 6H), 4 .12 (s, 2H), 7.00 Hz (d, J= 7.5 Hz, 1H), 7.26 (m, 3H), 7.51 (m, 3H), 12.10 (br s, N-H). ^{13}C NMR (DMSO-d_6, 100MHz) δ 34.9, 56.3, 110.2, 112.4, 115.6, 122.4, 123.1, 124.3, 138.6, 149.6, 149.8, 150.6, 163.4, 168.2. LC-MS (m/z) 369.06 (M+1). Anal. Calcd for $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.38; N, 15.21%; Found: C, 59.92; H, 4.36; N, 15.24%.

RESULTS AND DISCUSSION:

The desired compounds 5-{[(1H-benzo[d]imidazol-2-yl)thio]methyl}-3-phenyl-1,2,4-oxadiazoles **5(a-i)** were synthesized as outlined in scheme 2. Compounds **5(a-i)** were synthesized by condensing compounds 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole **3(a-c)** and 2-mercaptobenzimidazoles **4(a-c)** in the presence of potassium carbonate as a base and dimethylformamide as the solvent. The synthetic route for 3(a-c) is depicted in scheme 1.

The desired oxadiazoles **3(a-c)** were synthesized by the cycloaddition of nitrile oxides to 2-chloroacetonitriles. Nitrile oxides are unstable species and thus they are generated *in situ* in the presence of a dipolarophile. One of the attractive sources for nitrile oxides are amidoximes **2(a-c)** which can be prepared from the corresponding aromatic nitriles and hydroxylamine hydrochloride. The amidoximes **2(a-c)** thus synthesized is converted into nitrile oxides [22] by employing $ZnCl_2$/PTSA catalyst in DMF at 80^oC, which reacts with dipolarophile present to give the required oxadiazoles **5(a-i)**.

Antimicrobial activity: Antimicrobial activity of the given compounds was tested against five bacterial strains and two fungi. Percentage antibacterial activity was calculated from the absorbance reading, using the following formula Eqs. (1) and (2) and tabulated.

$$P_g = \frac{S - S_b}{C_p - C_n} \times 100 \quad (1)$$

Where, P_g – percentage growth, S – absorbance of the sample with inoculum, S_b – absorbance of the sample blank, C_p – absorbance of the positive control (pen-strep antibiotic) and C_n – absorbance of the negative control.

Percentage inhibition (P_i) can be calculated from Eqs. (2):

$$P_i = 100 - P_g \quad (2)$$

It is evident from the results tabulated in Table1, on keeping the substituent at the third position of the oxadiazole constant that, against the tested strains of Gram negative bacteria the compounds which

contain the -5or-6 unsubstituted benzimidazole unit in them **(5c, 5f, 5i)** show lower activity while compared to that of compounds containing either electron withdrawing or electron donating substituents at -5 or -6 position in the benzimidazole ring. Similarly, in the case of Gram positive bacteria the compounds containing the unsubstituted benzimidazole moiety **(5c, 5f, 5i)** mostly show higher activity than the compounds containing substituted benzimidazole unit. Almost all the synthesized compounds show comparable antifungal activity against the tested fungi. Compound **5a, 5g** shows the least antifungal activity against *C.albicans* while compound 5i shows the least activity against *A.niger*.

Antioxidant Activity: Standard protocol was followed to determine antioxidant property of the compounds 5(a-f) using 1, 1-diphenyl 2-picrylhydrazyl (DPPH).

Methanol was used as reference and DPPH stock solution (0.004%) was used as control. Percentage of DPPH-free radical scavenging activity was calculated using Eq (3):

$$\% \text{ Free radical scavenging} = \frac{(A_c - A_s)}{A_c} \times 100 \quad (3)$$

Where, (A_s) is the absorbance of the sample and (A_c) is the absorbance of the control. The results obtained were plotted in the graph shown in Fig. 1

It is evident from the results obtained, on keeping the substituent at the third position of the oxadiazole the same that, Compounds containing chloro substituted benzimidazole moeity **5d**, **5g** showed better activity than the other compounds when the third position of the oxadiazole ring is occupied either by electron withdrawing 4-chloro or electron donating 3,4-dimethoxyphenyl groups. In case of unsubstituted phenyl group being present at the third position, compound **5c** which contains the unsubstituted benzimidazole group shows higher activity.

Haemolysis assay: Haemolysis assay of the given compounds were performed using fresh chicken blood. At an exposure period of 3 hr, the synthesized compounds **5(a-i)** showed less than 5% toxicity towards blood with compounds **5d** and **5g** showing maximum haemolysis activity. The results obtained were plotted in the graphs shown in Fig. 2.

CONCLUSION:

In conclusion, we have reported a facile route for the synthesis of novel 5-{[(1H-benzo[d]imidazol-2-yl)thio]methyl}-3-phenyl-1,2,4-oxadiazoles **5(a-i),** from 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole 3(a-c) and 2-mercaptobenzimidazoles **4(a-c)** using potassium carbonate in DMF. All of the synthesized compounds also showed less than 5% toxicity to fresh chicken blood. The synthesized compounds show promising antimicrobial activity against the tested bacterial strains and fungi. Compounds 5d, 5g and 5c show superior antioxidant activity compared to the other synthesized compounds.

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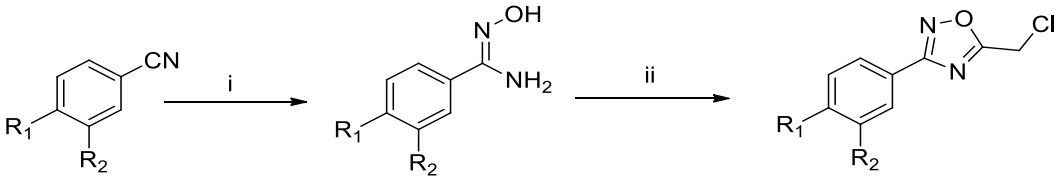
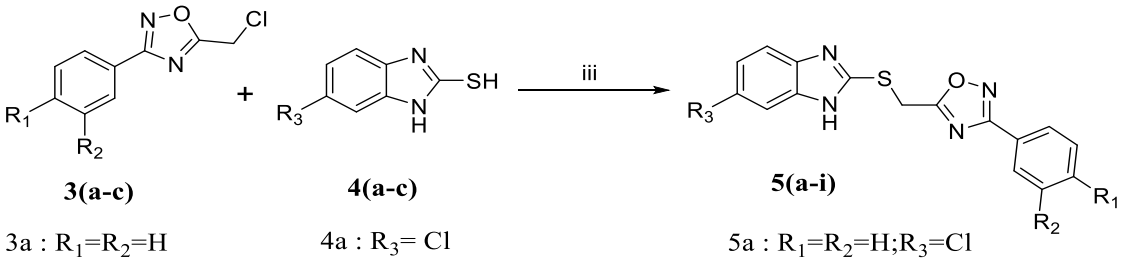
SCHEMES



1(a-c) **2(a-c)** **3(a-c)**

Scheme 1: Reagent and conditions (i) hydroxylamine hydrochloride, NaOH, EtOH & H_2O, rt, 4 h; (ii) Chloroacetonitrile $ZnCl_2$, PTSA, DMF, 80°C.



3(a-c) **4(a-c)** **5(a-i)**

3a : R_1=R_2=H
3b : R_1=Cl; R_2=H
3c : R_1=R_2= OCH_3

4a : R_3= Cl
4b : R_3= OCF_2H
4c : R_3= H

5a : R_1=R_2=H;R_3=Cl
5b : R_1=R_2=H; R_3= OCF_2H
5c : R_1=R_2=H; R_3= H
5d : R_1=Cl; R_2=H; R_3= Cl
5e : R_1=Cl; R_2=H; R_3= OCF_2H
5f : R_1=Cl; R_2=H; R_3= H
5g : R_1=R_2= OCH_3; R_3= Cl
5h : R_1=R_2= OCH_3; R_3= OCF_2H
5i : R_1=R_2= OCH_3; R_3= H

Scheme 2: Reagent and conditions (iii) K_2CO_3, DMF, 90-100°C.

Table1: Percentage antimicrobial activity of synthesized compounds 5(a-i).

	Percentage antimicrobial activity (%)						
	Bacteria					**Fungi**	
	Gram negative			**Gram positive**			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*E. faecalis*	*A. niger*	*C. albicans*
5a	75	65	83	67	63	65	43
5b	43	55	76	69	65	66	75
5c	56	65	73	65	76	84	76
5d	77	65	54	73	65	77	65
5e	76	67	76	78	56	67	87
5f	45	80	46	84	67	75	64
5g	66	56	76	55	29	56	47
5h	85	71	65	65	56	65	75
5i	45	54	34	77	65	47	89

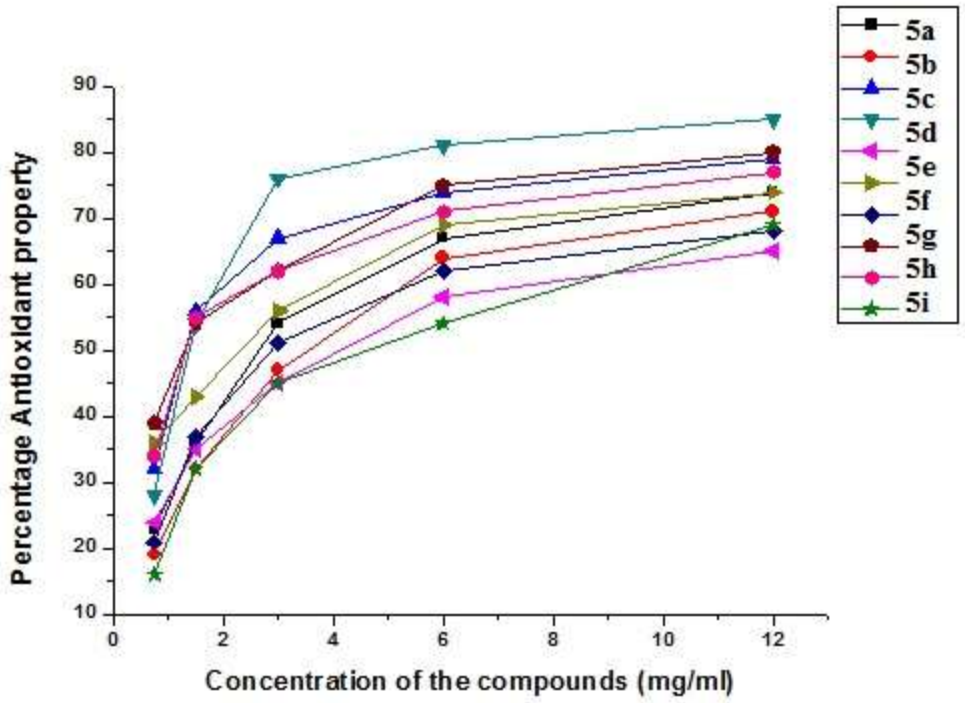


Fig. 1: Percentage antioxidant activity of 5(a-i)

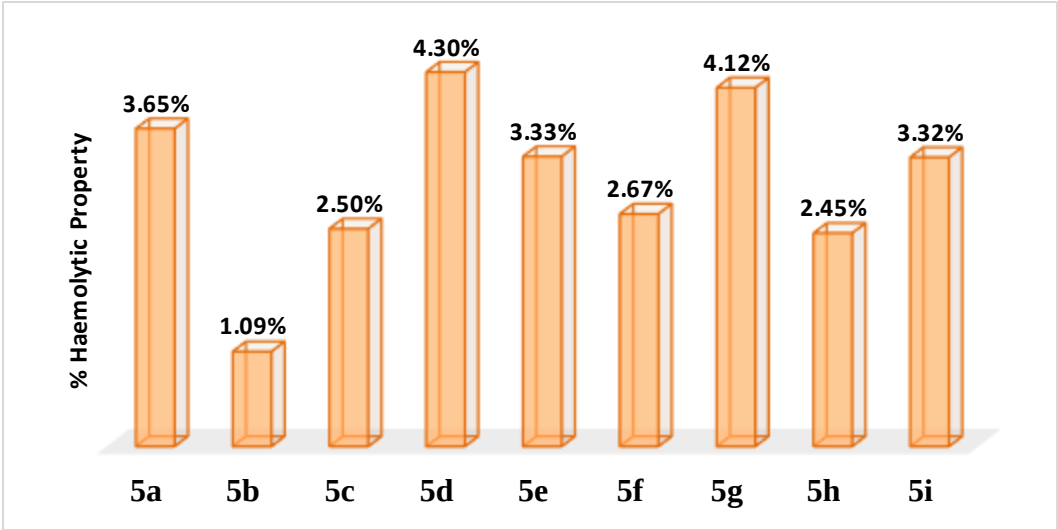


Fig. 2: Percentage haemolysis assay of 5(a-i)

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