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Synthesis and biological activity of n-anthranilic acid derivatives

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ABSTRACT

The reaction of 2-[(2, 3-dimethylphenyl) amino] benzocarbohydrazide **(2)** with various aromatic acids in presence of phosphorus oxy chloride to yield N-[2-(5-arylsubstituted-1,3,4-oxadiazole-2-yl) phenyl]-2,3-dimethyl benzene amine **(3a-e)**. Treatment of **(3a-e)** with hydrazine hydrate in presence of anhydrous ethanol were refluxed for 4hrs to get N-[2(1-N-amine-5-arylsubstituted-1,3,4-triazole-2-yl) phenyl]-2,3-dimethyl benzenamine **(4a-e)** respectively. Condensation of **(4a-e)** with substituted aromatic aldehyde in presence of dry benzene to gave N'-(p-chlorobenzylidene)-3-[2-(2, 3-dimethylphenyl amino) phenyl]- 4H-4-amine 5-(aryl substituted)-1, 2, 4-triazole **(5a-e)**. The purity of the compounds was checked by TLC. All newly synthesized compounds were characterized on the basis of IR, ^{1}HNMR, mass spectral data and elemental analysis.

KEYWORDS

Mefanamic acid;
Oxadiazoles;
Triazoles antimicrobial;
Analgesic;
Anti-inflammatory.

INTRODUCTION

In continuation of our research on the synthesis of biologically active heterocycles[1,2] we have now synthesized various heterocyclic derived from N-anthranilic acid derivatives to evaluate their antimicrobial, analgesic, and anti-inflammatory[3] activity Literature survey reveals that various oxadiazole[4-10] and triazole[11-14] have attracted considerable attention as wide range of biological activities. During the course of present investigation a well known anti-inflammatory and analgesic agents, mefenamic acid is used in building several heterocyclic moieties of biological importance like oxadiazole, triazole and Schiff bases derived from triazoles.

In the present investigation 2-[(2, 3-dimethylphenyl) amino] benzocarbohydrazide **(2)** upon reaction with various aromatic acids in presence of phosphorus oxy chloride to yield N-[2-(5-arylsubstituted-1,3,4-oxadiazole-2-yl) phenyl]-2,3-dimethyl benzene amine **(3a-e).** Reaction of **(3a-e)** with hydrazine hydrate in presence of anhydrous ethanol were refluxed for 4hrs to get N-[2(1-N-amine-5-arylsubstituted-1,3,4-triazole-2-yl) phenyl]-2.3-dimethyl benzenamine **(4a-e)** respectively. Condensation of **(4a-e)** with substituted aromatic aldehydes in presence of dry benzene to gave N'-(p-chlorobenzylidene)-3-[2-(2, 3-dimethylphenyl amino) phenyl]- 4H-4-amine 5-(aryl substituted)-1, 2, 4-triazole **(5a-e).** The purity of the compounds was checked by TLC. All newly synthesized compounds were characterized on the basis of IR, ^{1}HNMR, mass spectral data and elemental analysis. The synthesized compounds were studied for antimicrobial, analgesic, anti-inflammatory activity.

EXPERIMENTAL

The reagents and solvents used for the synthesis were obtained commercially and further purified. The melting points were determined by open capillaries and are uncorrected.

Infra red spectra were recorded on an FTIR-8400 Shimadzu Spectrophotometer Department of Pharmaceutical Chemistry, Karnataka College of pharmacy, Bidar. The ^{1}HNMR spectra were recorded ACF 200 Supercon-Switzerland NMR Spectraphotometer. The chemical shifts were expressed in ppm (delta scale). Mass spectra were taken by using LC-MS 2010 (SHIMADZU) and the purity of the compounds was checked by TLC.

2-[(2,3-dimethylphenyl)amino]benzocarbohydrazide (2)

To a solution of 2-[(2,3-dimethylphenyl) amino] ethyl benzoate **(1)** (0.01mol) anhydrous alcohol (50ml), hydrazine hydrate 99% (0.3mol) and Conc. Sulphuric acid (6-8drops) were added. The reaction mixture was refluxed for 24h. The excess of solvent was distilled under reduced pressure and the mixture was poured on crushed ice with constant stirring. The solid separated was filtered, washed, dried and recrystallized from ethanol. Yield 79%, m.p 170^{0}C, (Found C, 70.50, H, 6.67, N, 16.57 $C_{15}H_{17}N_3O$ requires C, 70.56, H, 6.71, N, 16.46 %).

Synthesis of N-[2-(5-arylsubstituted-1,3,4-oxadiazole-2-yl)phenyl]-2,3-dimethyl ben- zene amine (3a-e)

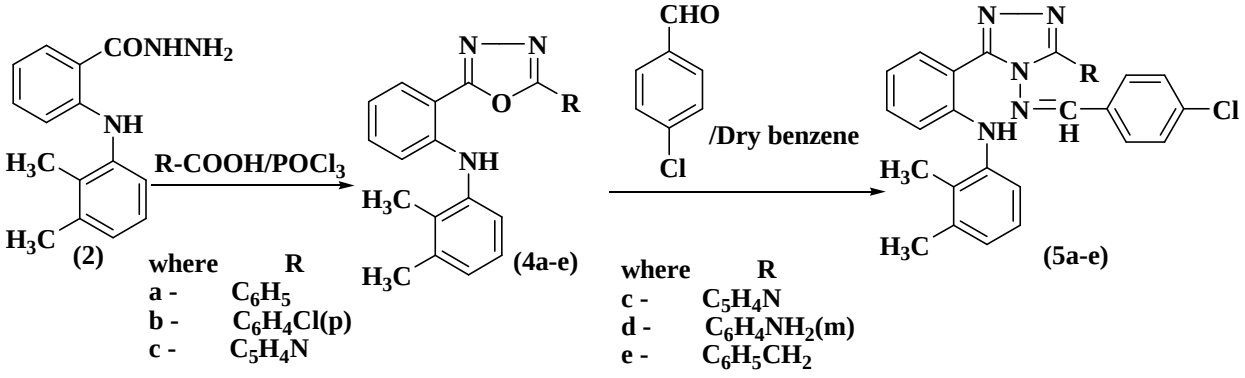
To a mixture of 2-[(2,3-dimethyl phenyl) amino] benzohydrazide **(2)** (0.01 mol) and various substituted aromatic acids (0.01mole) phosphorus oxy chloride (10ml) was added. The mixture was refluxed for 6hrs till the reaction mixture becomes clear solution. The reaction mixture was cooled to room temperature and poured onto crushed ice. The solution was neutralized with liquid ammonia and left overnight. The solid product thus separated was filtered, washed with cold water dried and crystallized from suitable solvent. The characteristic data of synthesized compound are listed in TABLE 1

Synthesis of N-[2(1-N-amine-5-arylsubstituted-1,3,4-triazole-2-yl) phenyl]-2.3-dimet- hyl benzenamine(4a-e)

A mixture of N-[2-(5-arylsubstituted-1,3,4-oxadiazole-2-yl) phenyl]-2,3-dimethyl benzene amine **(3a-e)** (0.001mol) and hydrazine hydrate (99%) (0.002mol) in absolute ethanol were refluxed for 4hrs. It was cooled to room temperature and the content was poured into ice-cold water. On acidification with acetic acid, a solid N-[2(1-N-amine-5-arylsubstituted-1,3,4-triazole-2-yl) phenyl]-2.3-dimethyl benzenamine **(4a-e)** mass separated was collected by filtration and washed with cold water, dried and crystallized from suitable solvents. The characteristic data of synthesized compound are listed in TABLE 1

N'-(4-chlorobenzylidene)-3-[2-(2, 3-dimethylphenyl amino)phenyl]-4H-4-amine 5 (aryl substituted)- 1, 2, 4-triazole (5a-e)

N-[2(1-N-amine-5-arylsubstituted-1,3,4-triazole-2-yl) phenyl]-2.3-dimethyl ben- zenamine **(4a-e)** (0.01mole) and p-chlorobenzaldehyde (0.01mole) dis-



SCHEME 1

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TABLE 1: Physical data of the synthesized compounds

Comp. no	R	M P (^{0}C)	Yield (%)	Molecular formula	Solvent for cryst…	Rf value	Found (%) (calc)		
							C	H	N
(3a)	C_6H_5	230-231	75.45	$C_{22}H_{19}ON_3$	Ethanol	0.38	77.40(77.50)	5.61(5.64)	12.31(12.64)
(3b)	C_6H_4Cl(p)	110-112	83.63	$C_{22}H_{18}ON_3Cl$	Ethanol	0.45	70.30(71.01)	4.83(4.89)	11.18(11.31)
(3c)	C_5H_4N	138-140	72.15	$C_{21}H_{18}ON_4$	Ethanol	0.49	73.67(73.91)	5.30(5.00)	16.36(16.91)
(3d)	$C_6H_4NH_2$(m)	180-181	78.00	$C_{22}H_{20}ON_4$	Ethanol	0.54	74.14(74.88)	5.66(5.82)	15.72(15.77)
(3e)	$C_6H_4CH_2$	105-107	80.21	$C_{23}H_{20}ON_3$	Ethanol	0.39	77.72(77.97)	5.96(6.00)	11.82(11.99)
(4a)	C_6H_5	260-263	75.16	$C_{22}H_{21}N_5$	Benzene	0.46	74.34(74.36)	5.96(6.01)	19.70(19.90)
(4b)	C_6H_4Cl(p)	210-212	70.34	$C_{22}H_{20}N_5Cl$	Ethanol	0.37	67.77(67.81)	5.17(5.27)	17.96(18.05)
(4c)	C_5H_4N	154-157	78.24	$C_{21}H_{20}N_6$	Benzene	0.33	70.77(70.78)	5.66(5.87)	23.58(23.61)
(4d)	$C_6H_4NH_2$(m)	160-162	69.12	$C_{22}H_{22}N_6$	Ethanol	0.31	71.33(71.35)	5.99(6.01)	22.69(22.83)
(4e)	$C_6H_4CH_2$	189-191	80.16	$C_{23}H_{23}N_5$	Benzene	0.51	74.77(74.79)	6.27(6.30)	18.96(18.99)
(5a)	C_6H_5	202-205	70.13	$C_{29}H_{24}N_5Cl$	Dioxin	0.55	72.87(72.66)	5.06(5.11)	14.65(14.70)
(5b)	C_6H_4Cl(p)	192-194	86.23	$C_{29}H_{23}N_5Cl_2$	Ethanol	0.31	67.97(67.81)	4.52(4.57)	13.67(13.075)
(5c)	C_5H_4N	198-201	65.55	$C_{28}H_{23}N_6Cl$	Dioxin	0.39	70.21(70.28)	4.84(4.87)	17.55(17.61)
(5d)	$C_6H_4NH_2$(m)	225-227	75.65	$C_{29}H_{25}N_6Cl$	Benzene	0.41	70.65(70.85)	5.11(5.21)	17.05(17.11)
(5e)	$C_6H_4CH_2$	189-191	80.28	$C_{30}H_{26}N_5Cl$	Dioxin	0.54	73.23(73.29)	5.33(5.30)	14.23(14.39)

solved in dry benzene (30ml) were refluxed in a round bottom flask for 6hrs. The excess of solvent was distilled under reduced pressure. The product obtained is filtered N'-(p-chlorobenzyli- dene)-3-[2-(2, 3-dimethyl phenyl amino) phenyl]- 4H-4-amine 5-(aryl substituted)-1, 2, 4-triazole (Schiff's base) **(5a-e)** washed with little sodium bisulphite solution to remove the unreacted aldehyde and then wash with diluted hydrochloric acid and water, the product is dried and crystallized with suitable solvent. The characteristic data of synthesized compounds are listed in TABLE 1.

RESULT AND DISCUSSION

Compounds synthesized during the present investigation were established on the basis of analytical, physical and spectral data as IR, ^{1}HNMR and mass spectra. 2-[(2,3-dimethylphenyl) amino] benzocarbohydrazide **(2)** was confirmed on the basis of spectral data. The IR spectrum of **(2)** showed strong absorption band at 3326 cm^{-1} due to NH stretching, 1650 cm^{-1} due to C=O respectively. The ^{1}HNMR spectrum of **(2)** exhibited a two singlet at δ 2.0 and 2.2 corresponding six protons of two methyl groups and singlet at δ 4.1 two protons of NH_2 and multiplet at δ 6.5-7.0 corresponds to seven protons of aromatic ring and singlet at δ 7.3 and 8.0 corresponds to each proton of –NH and CO-NH. Further the structure of compound **(2)** is supported by mass spectrum show a molecular ion peak at m/z 256, which corresponds to its molecular formula. The elemental analysis of **(2)** shows (Found C, 70.50, H, 6.67, N, 16.57 $C_{15}H_{17}N_3O$ requires C, 70.56, H, 6.71, N, 16.46 %).

The reaction of 2-(2,3-dimethyl phenylamino)-N-benzohydrazide **(2)** which is key intermediate for the synthesis of oxadiazole **(3e)** was prepared according to reported method Cyclisation of hydrazide **(2)** with phenyl acetic acid was carried out using phosphorous oxychloride to yield oxadiazole **(3e)** in good yield.

The compound **(3e)** displayed characteristic absorption bands in its IR spectrum 3456 cm^{-1} due to NHstr, 3083 cm^{-1} due to aromatic CHstr, 1612 cm^{-1} due to C=N, 1525 cm^{-1} due to aromatic C=C and 1172 cm^{-1} due to C-O-C functional groups respectively. The ^{1}HNMR spectrum of compound **(3e)** exhibited a two singlet peaks at δ 2.2 and δ 2.4 corresponds to six protons of two methyl groups, another two singlet peaks at δ 3.6 due to two protons of $–CH_2$ of benzyl group. Multiplet peaks observed in the region at δ 7.2-7.9 corresponds to 12 protons of aromatic ring and 1 proton of NH. Further the structure of compound **(3e)** is supported by mass spectrum. Compound **(3e)** in its mass spectrum exhibited a molecular ion peak at 354(M^+) which is equivalent to its molecular weight. The remaining structures of **(3a, 3b, 3c** and **3d)** compounds are agreed with the spectral data.

The reaction of N-[2-(5-phenyl-1,3,4-oxadiazole-2yl) phenyl]-2,3 dimethyl benzenamine **(3a)** reaction with hydrazine hydrate in anhydrous ethanol to afford compound **(4a)** as our targeted compound.

The compound **(4a)** displayed characteristic absorption bands in its IR spectrum 3450 cm^{-1} due to

TABLE 2 : Antimicrobial activity of synthesized compounds

Comp No.	R	Zone of inhibition in mm			
		Antibacterial activity		Antifungal activity	
		E.coli	*B.subtilis*	*A.niger*	C.albicans
(3a)	C_6H_5	14	12	11	10
(3b)	$C_6H_4Cl(p)$	20	19	21	18
(3c)	C_6H_4N	16	17	19	18
(3d)	$C_6H_4NH_2(m)$	14	15	14	15
(3e)	$C_6H_4CH_2$	18	20	15	16
(4a)	C_6H_5	12	10	12	10
(4b)	$C_6H_4Cl(p)$	19	21	22	19
(4c)	C_6H_4N	11	10	15	16
(4d)	$C_6H_4NH_2(m)$	13	14	13	14
(4e)	$C_6H_4CH_2$	18	19	11	13
(5a)	C_6H_5	15	13	12	10
(5b)	$C_6H_4Cl(p)$	18	19	19	21
(5c)	C_6H_4N	13	15	14	16
(5d)	$C_6H_4NH_2(m)$	13	14	13	14
(5e)	$C_6H_4CH_2$	14	15	11	13

NH_2, 3244 cm^{-1} due to NH, 3053 cm^{-1} due to CHstr, of aromatic, 2923 cm^{-1}due to CHstr of methyl (asymmetric and symmetric), 1612 cm^{-1} due to C=N and 1525 cm^{-1} due to C=C. The ^{1}HNMR spectrum revealed singnal due to six protons of two methyl groups at 2.2 and δ 2.4 as singlet, a singlet observed at δ 4.2 may be due to a proton of NH, 12 aromatic and 2 protons of NH_2 have appeared in the region δ 6.6-8.0 as multiplet. In the mass spectrum of the compound **(4a)** gave a molecular ion peak at 355 (M^+). The remaining structures of **(4b, 4c, 4d** and **4e)** compounds are agreed with the spectral data.

The compound **(5a)** obtained by reaction of N-[2(1-N-amine-5-substituted-1,3,4-triazole-2-yl) phenyl]-2.3-dimethyl benzenamine **(4a)** and benzaldehyde in presence of dry benzene solvent afford the target compound **(5a)** in good yield. The IR spectrum of compound **(5a)** exhibited absorption band at 3311 cm^{-1} due to NH, other absorption band at 2923, 2856,cm^{-1} due to CH sterching of methyl groups (asymmetric and symmetric), 1595 cm^{-1}due to C=N and C=C ring stretching, 1460 cm^{-1} due to C-N stretching of Schiff bases functions respectively. The disappearance of absorption band at 3311 cm^{-1} due to NH_2 confirms the formation of Schiff's base.

In its ^{1}HNMR spectrum two singlet peaks at δ 2.1 and δ 2.3 were due to two methyl groups, another singlet peak at δ 4.1 accounting each one proton of ph-NH-ph , multiplet peak at δ 6.6-7.6 accounts for 16 protons of aromatic ring and δ 9.0 singlet due to N=CH proton. Further the structure of compound **(5a)** is supported by mass spectrum exhibited a molecular ion peak at m/z 478, 479(M^+) which aggress with its molecular weight. The other prominent peaks are obtained at m/z 424, 405, 286, 241, 208, 152, 103, 96 and 77. The remaining structures of **(5b, 5c, 5d** and **5e)** compounds are agreed with the spectral data.

Evaluation of antimicrobial, analgesic and anti-inflammatory activity.

Antibacterial and antifungal activity

The newly synthesized compounds were subjected to *invitro* antimicrobial activity against by Cup-Plate diffusion method[15] using organisms *E.coli, B.subtilis* for antibacterial activity where as *A.niger* and *C.albican* for antifungal activity. All the test compounds were prepared at the concentration of 100μg/ml in distilled DMF. The solution of ciprofloxacine and flucanazole were prepared at the concentration of 100μg/ml in sterile water as standard solution for compression of antibacterial and antifungal activities and DMF was used as control for both activity, the results were presented in TABLE 2.

The compounds **(3b**, **3e, 4b, 4e** and **5b)** shown good antibacterial activity against *E.coli, B.subtilis* and remaining compounds are exhibited moderate activity against the *E.coli, B.subtilis.* In fungicidal activity the compounds **(3b, 3c, 4b** and **5b)** exhibited significant antifungal activity against *A.niger* and *C.albican* where as remaining compounds are exhibited moderate to weak activity against the *A.niger* and *C.albican,* The results were presented in TABLE 2.

Analgesic activity for (3a-e) and (4a-e)

Analgesic activity of the compounds was determined by thermal stimulus method. In this method, the test animal is placed on a hot surface or the tail of the animal is immersed in hot water and the response of the animal to a thermal stimulus is assessed.

Fourty-eight mice of either sex weighing between 20-25g which shows positive response were selected and divided into12 groups with four rats in each group. The first group served as control which received 2% gum acacia. Second group served as standard which received analgin at a dose of 100mg/kg body weight

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TABLE 3 :Algesic activity results of compounds (3a-e) and (4a-e)

Compound	R	Dose(mg/kg) per oral	Average (±SE) reaction time (sec)Time after drug treatment (min)			
			0	30	60	90
Control	-	100	3.00(±0.00)	3.00(±0.00)	3.00(±0.05)	3.00(±0.05)
Standard(analgin)	-	100	3.00(±0.25)	6.00(±0.40)	9.25(±0.25)	10.25(±0.40)
3a	C_6H_5	100	2.75(±0.25)	3.00(±0.40)	3.00(±0.00)	2.75(±0.25)
3b	$C_6H_4Cl(p)$	100	3.00(±0.42)	3.25(±0.25)	3.00(±0.00)	3.00(±0.25)
3c	C_6H_4N	100	3.00(±0.40)	3.50(±0.25)	3.75(±0.25)	3.75(±0.00)
3d	$C_6H_4NH_2(m)$	100	3.00(±0.25)	3.50(±0.25)	3.50(±0.40)	3.00(±0.42)
3e	$C_6H_5CH_2$	100	3.00(±0.70)	3.25(±0.62)	3.00(±0.70)	4.000±0.25)
4a	C_6H_5	100	2.75(±0.25)	3.25(±0.25)	7.25(±0.25)	7425(±0.25)
4b	$C_6H_4Cl(p)$	100	3.00(±0.00)	3.25(±0.25)	8.00(±0.40)	8.25(±0.52)
4c	C_6H_4N	100	3.25(±0.25)	2.25(±0.40)	3.00(±0.42)	4.25(±0.25)
4d	$C_6H_4NH_2(m)$	100	3.25(±0.25)	2.75(±0.47)	3.00(±0.00)	3.25(±0.40)
4e	$C_6H_5CH_2$	100	2.75(±0.25)	2.75(±0.25)	2.25(±0.40)	2.25(±0.40)

TABLE 4 : Anti-inflammatory activity of compounds (3a-e) and (4a-e)

Comp no.	R	Dose(mg/ kg body weight)	Mean value (± SE) of oedema volume at different intervals		Percentage of anti inflammation at different intervals	
			2h	4h	2h	4h
Control(2% gumacacia)		100	0.252(±0.009)	0.205(±0.007)		
Standard(Phenyl butazone)		100	0.126(±0.018)	0.036(±0.003)	50.00	82.43
(3a)	C_6H_5	100	0.185(±0.005)	0.142(±0.002)	26.58	30.73
(3b)	$C_6H_4Cl(p)$	100	0.145(±0.007)	0.121(±0.002)	42.46	40.97
(3c)	C_5H_4N	100	0.139(±0.009)	0.101(±0.003)	44.84	50.73
(3d)	$C_6H_4NH_2(m)$	100	0.180(±0.009)	0.139(±0.004)	28.57	32.19
(3e)	$C_6H_5CH_2$	100	0.162(±0.006)	0.122(±0.003)	35.71	40.48
(4a)	C_6H_5	100	0.190(±0.005)	0.136(±0.002)	24.60	33.65
(4b)	$C_6H_4Cl(p)$	100	0.147(±0.003)	0.123(±0.007)	41.66	40.00
(4c)	C_5H_4N	100	0.171(±0.008)	0.131(±0.001)	32.14	36.09
(4d)	$C_6H_4NH_2(m)$	100	0.147(±0.004)	0.111(±0.002)	41.66	45.85
(4e)	$C_6H_5CH_2$	100	0.186(±0.007)	0.136(±0.001)	26.19	33.65

orally. Group 3-47 received 10 test compounds at a dose of 100mg/kg body weight of mouse, orally.

The tail of the mouse was dipped (up to 5 cm) in a water bath at 55±0.7^{0}C. The time taken to withdraw the tail clearly out of water was considered as the reaction time with the cut-off time being 60 seconds. The first reading was taken immediately after administration of the standard drug and test compounds and afterwards at the intervals of 30 minutes. The response time was recorded. The test compounds **(4a** and **4b)** displayed good analgesic activity. The remaining compounds moderate to weakly active when compared to standard drug analgin. The result are described in TABLE 3

Anti-inflammatory activity (3a-e) and (4a-e)

The inflammatory reaction is readily produced in rats in the form of paw edema with help of irritants are inflammagens carageenan. Carageenan-induced paw edema is the most commonly used method in experimental pharmacology. 48 Albino rats of either sex weighing between 160-180g were divided into 12 groups of four animals each and they were numbered individually.

The animals were fasted for 24h with water Adlibitum. Animals were marked on their hind paws (right and left) just beyond tibio- tarsal junction to ensure the constant dipping every time in the mercury column up to the fixed mark. Group-I injected with 0.5 ml of Tween-80 suspension, which served as control. Group-II injected with 30mg/kg body weight of phenylbutazone and served as standard. Group 3to 12 received drug samples of 1, 2, and 3 respectively, the dose being 30 mg/kg selected on the basis of the standard drug dose used.

All the drugs were administered intraperitoneally as suspension in 1% Tween-80. After 30 minutes, 0.1 ml of 1% w/v carrageenan solution was injected into the plantar region of the left paw of the control, stan-

dard and group-1, 2, 3 etc…, animals. Immediately after injecting carrageenan, paw volume was measured by using plethysmograph (mercury displacement method) to note initial volume of the paw. The right paw served as reference, non-inflammed paw for comparison. The rat paw oedema of both legs of control, standard and group 1to12 were measured similarly at 3h and 5h after carrgeenan injection, with the help of plethysmograph. The difference between the initial and subsequent reading gave oedema volume.

In the same way 4 rats of different groups were used for evaluating the anti-inflammatory activities. Thus oedema in control (V_c) and in groups 1-12 (V_t) were calculated. Then the percentage inhibition of the inflammation in the drug treated animals was recorded using the formula:

Percentage inhibition (%) =100(1-Vt /Vc)

Where V_t and V_c are mean volumes of oedema of drugs treated and control respectively.

Compounds **(3c)** and **(4d)** have exhibited significant anti-inflammatory activity after 4hrs of treatment. Remaining compounds have shown moderate to weak activity. The result are described in TABLE 4.

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