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Synthesis and Anti-Inflammatory Activity of Anthranilic Acid Derivatives

Alka Rani* and Rajkumar

Department of Chemistry, K.G.K College, Moradabad, **INDIA**

Email: rajkumarddc221963@gmail.com

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ABSTRACT

Some new anthranilic acid derivatives were synthesized by reacting Bromine in acetic acid with solution of anthranilic acid. The synthesized compound were identified by special data and screened for anti-inflammatory activity. Some of these compounds showed moderate the considerable anti-inflammatory activity.

Keywords: Synthesis, Anthranilic acid, Anti-inflammatory activity.

INTRODUCTION

Compound with anthranilic acid structure are known the posses antimicrobial, anti-inflammatory, anti-depressant, anti-tubercular activities. In the present study, some new anthranilic acid derivatives have been synthesized by the reaction of Bromine in acetic acid with the solution of anthranilic acid in the presence of glacial acetic acid. The structure of various synthesized compound are assigned on the basis of elemental analysis IR & H'NMR spectral data. These compounds were also screened for their anti-inflammatory activity.

MATERIALS AND METHODS

The melting points were determined in open capillaries point apparatus under are uncorrected. The homogeneity of all newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel-G coated plates.

Elemental analysis of all compound was performed on Carlo Erba-1108 elemental analyzer and result were found within the +0.4% of theoretical values. ^{1}H-NMR spectra were recorded on Bruker DRX-300 FTNMR instrument by using $CDCl_3$as a solvent and tetramethylsilane (TMS) was used as internal reference standard.

General Procedure for the preparation of 5-Bromo-N-anthranilic acid (6b): The solution of 5-Bromo-N-(2'aminoacetyl-1',3',4'-oxadiazole-5'-ylmethyl)anthranilic acid (0.01 mole) and p-methoxybenzaldehyde (0.01) in absolute ethanol in the presence of 2% NaOH (2 mL) was refluxed for 10 h. The excess of solvent was distilled off and residue was cooled, poured into ice water and

filtered and recrystallized from ethanol-water to yield compound m.p. 120°C, yield 68% Molecular formula $C_{20}H_{17}O_5H_4Br$.

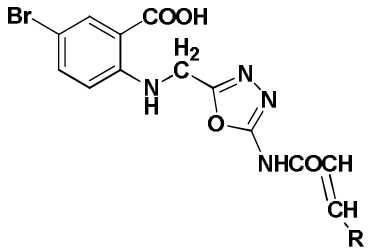
Table 1. Elemental Analysis

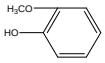
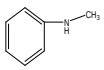
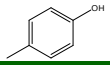
Element percentage	Calculated	Found
C	50.74	50.40
H	3.59	3.88
N	11.84	11.65

Spectral Analysis: IR (KBr) v in cm-[1]: 3485 (O-H), 3155(N-H), 3060 (C-H aromatic), 2920 (C-H aliphatic), 1710 (C=O), 1590 (C-C of aromatic ring), 1600 (C=N), 1200 (C-N), 1124 (C-O-C), 1040 (N-N), 550(C-Br).

^{1}H-NMR ($CDCl_3$) δ in ppm: 7.65-7.20 (m, 3H, Ar-H), 8.80 (bs, 1H, N*H*CO, exchangeable with D_2O), 4.50 (d, 2H, NH-CH2), 5.60 (s, 1H, NH, exchangeable with D_2O), 11.40 (s, 1H, -COOH, exchangeable with D_2O), 2.47 (s, 3H, Ar-$COCH_3$), 8.20 (d, 1H, = CH-Ar). MS: $[M]^+$ at m/z 473.

Table 2. Physical and analytical data of 5-Bromo-N(-2'-aminosubstitutedbenzylideneacetyl-1', 3', 4'-oxadiazole-5-ylmethyl) anthranilic acids



Com. No.	R	M.P. (°C)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental Analysis					
						% C		%H		%N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
6a		152	62	DMF -Water	$C_{19}H_{15}O_4N_4Br$	51.47	51.22	3.39	3.57	12.64	12.90
6b	 4 methoxy benzene	120	68	Ethanol- Water	$C_{20}H_{17}O_5N_4Br$	50.74	50.40	3.59	3.88	11.84	11.65
6c		110	70	Ethanol- Water	$C_{20}H_{17}O_6N_4Br$	49.08	49.40	3.48	3.62	11.45	11.20
6d		98	55	Methanol- Water	$C_{19}H_{20}O_4N_5Br$	51.85	51.60	4.12	4.39	14.40	14.12
6e		138	58	Methanol- Water	$C_{19}H_{15}O_5N_4Br$	49.67	49.92	3.27	3.50	12.20	12.37

General Procedure for the Preparation of 5-Bromo-N-(2`amino(1``acetyl-5``-(p-methoxyphenyl)-2``pyrazolin-3``-yl] 1`,3`,4`-oxadiazol-5`-ylmethyl)anthranilic acid(7b): To the solution of compound **6b** (0.02 mole) in absolute ethanol (50 mL), hydrazine hydrate (99%, 0.04 mole) was added drop by drop with constant stirring in the presence of few drops of glacial acetic acid. The reaction mixture was refluxed for 12 h, distilled off and cooled. The separated solid was filtered, washed with petroleum, ether and recrystallized form methanol-water to give compound **7b** m.p. 192°C, yield 65% molecular formula $C_{22}H_{21}O_5N_6Br$(529)

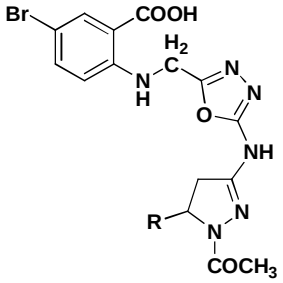
Table 3. Elemental Analysis

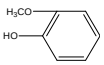
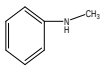
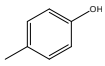
Element percentage	Calculated	Found
C	49.91	49.58
H	3.97	4.21
N	15.88	16.15

Spectral Analysis: IR(KBr) v in cm-^{1}: 3480 (O-H), 3160(N-H), 3065(C-H aromatic), 2923 (C-H aliphatic), 2850(C-H of $COCH_3$) 1690(C=O), 1550 (C-C of aromatic ring), 1580 (C=N), 1220 (C-N), 1115 (C-O-C), 1030 (N-N), 555 (C-Br).

^{1}H-*NMR* ($CDCl_3$) δ in ppm: 7.90-7.25 (m,7H, Ar-*H*), 6.15 (bs, 1H, N*H*, exchangeable with D_2O), 4.75 (d, 2H, NH-NH-CH_2), 5.65 (s, 1H, N*H*, exchangeable with D_2O), 11.15 (s, 1H, -COOH, exchangeable with D_2O), 3.45 (s, 3H, Ar-OCH_3), 5.25 (d, 2H, CH_2 of pyrazoline ring) 6.95 (t,1H, CH-Ar of pyrazoline ring) 2.35 (s, 3H, $COCH_3$). MS:$[M]^+$ at m/z 529.

Table 4. Physical and analytical data of 5-Bromo-N-(2'-amino-(1``-acetyl-5``subsitutedaryl-2``. pyrazoline-3``-1`,3`,4`-oxadiazole-5-ylmethyl) anthranilic acids(7a-7e)



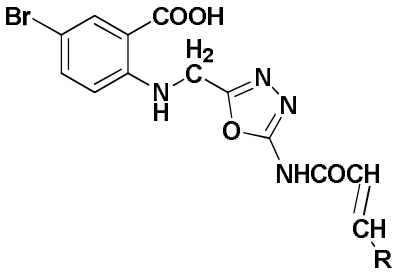
Com No.	R	M.P. (°C)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental Analysis					
						% C		%H		%N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
7a		170	70	Acetone	$C_{21}H_{19}O_4N_6Br$	50.50	50.80	3.81	3.60	16.83	16.64
7b	 4 methoxy benzene	192	65	Methanol-Water	$C_{22}H_{21}O_5N_6Br$	49.91	49.58	3.97	4.21	15.88	16.15
7c		183	62	Ethanol- Water	$C_{22}H_{21}O_6N_6Br$	48.44	48.17	3.85	3.99	15.41	15.18
7d		167	55	Ethanol- Water	$C_{23}H_{24}O_4N_7Br$	50.92	51.25	4.43	4.18	18.08	18.32
7e		175	44	Acetone	$C_{21}H_{19}O_5N_6Br$	48.93	48.70	3.680	16.31	16.31	16.01

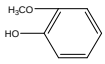
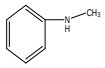
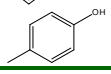
RESULTS AND DISCUSSION

Anti-inflammatory activity against carrageen an induced rat's paw oedema: Acute toxicity study (ALD_{50} mg kg^{-1} p.o.). All the compounds of this series showed ALD_{50}>800 mg kg^{-1} p.o. (Table 5 and 6) with the maximum in compound **7b**. Random Screening of compounds **6a-6e, 7a-7e** was performed at 50 mg kg^{-1} p.o. Compound **7b** was found to possess the most potent anti-inflammatory

activity (50.66% at 50 mg kg^{-1} p.o. in comparison to the reference drug, which showed 45.52% inhibition of oedema at same dose).

Table (5). Biological data of 5-Bromo-N(-2'-aminosubstitutedbenzylideneacetyl-1',3',4'-oxadiazole-5-ylmethyl) anthranilic acids (6a-6e)



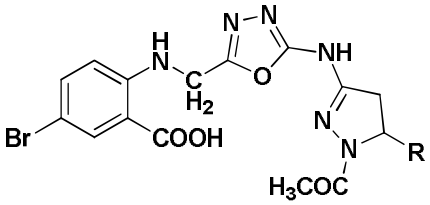
Com. No.	R	Dose (mg kg^{-1} p.o)	Anti-inflammatory (%)	Acute Toxicity (ALD 50 mg kg^{-1} p.o)
6a		50	32.57*	>800
6b		50	40.39**	>800
6c		50	38.7	>800
6d		50	24.78**	>800
6e		50	28.23*	>800

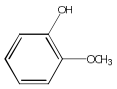
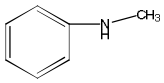
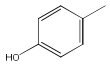
All these new compound 6a-6e, 7a-7e were tested in order to evaluate their pharmacological activity. These compounds were screened for anti-inflammatory profile as a dose of 50mg kg^{-1} p.o. exhibiting substantive anti-inflammatory property. It was observed that compound, 6a, having phenyl group as a substituent, showed the least % inhibition of oedema i.e. 32.57%, while the compound, 6b substituted with p-methoxyphenyl group exhibited maximum anti-inflammatory activity, 40.39%. Compound 6c having m-methoxy-p-hyroxyphenyl group as a substituent also showed good anti-inflammatory activity i.e. 38.7%.

It is clear that from the result obtained that Cyclization of substituted benzylidene derivatives 6a-6e in their corresponding derivative compound 7a-7e enhanced the anti-inflammatory activity, having oxadiazolyl moiety showed better inflammatory activity.

The anti-inflammatory activity of compound 7b (50.66%) was more than that of phenylbutaone (45.52%) at all doses tested as shown in figure-5. However, 5-bromo-N-{2'-amino-[1''-acetyl-5''-{;7-niethoxyphenyl)-2''-pyrazolin-3''-yl]-r, 3`, 4`-oxadiazol-5`-ylmethyl} anthranilic acid (7b) was found to be the most active compound of the present series which has oxadiazolyl moiety. Furthermore, this compound and reference drug have been tested for ulcerogenic liability and this compound exhibited less ulcerogenic potentiality as compared to phenylbutazone (UDso of 7b=170.52 mg kg^{-1} i.p.). ALDso of compound 7b was found to be more than 1600 mg kg^{-1} p.o.

Table 6. Biological data of 5-bromo-N[2`amino-(1``-acetyl-5``-subsitutedaryl-2``-pyrazolin-3``-yl)-1`, 3`, 4`-oxadiazol-5`ylmethyl] anthranilic acids (7a-7e)



Com. No.	R	Dose (mg kg^{-1} p.o)	Anti-inflammatory (%)	Ulecerogenic Activity (UD50 mg kg^{-1}i.p.)	Acute Toxicity (ALD 50mg kg^{-1} p.o)
7a		50	40.2	-	>800
7b		25 50 100	29.75** 50.66*** 70.18**	170.52	>800
7c		50	44.7*	-	>800
7d		50	32.92**	-	>800
7e		50	36.3*	-	>800

CONCLUSION

a. Substituted benzylidene derivatives exhibit mild to moderate anti-inflammatory profile.
b. Cyclization of these substituted benzylidene derivatives info pyrazoline congeners enhances the inflammation inhibiting property.
c. Presence of electronegative atom, Br, may play a pivotal role in the modulation of anti-inflammatory activity.

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