Synthesis and evaluation of acetamide derivatives – synthesis intermediate approach

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INTRODUCTION

A new series of acetamide derivatives containing saccharin moiety has been synthesized based on the principle of drug discovery from synthesis intermediates. Synthesis intermediates (Wermuth C.G., 2004) are chemically connected to final products therefore it can be conceived that they might share some pharmacological properties. The fact that saccharin is used as an intermediate in the synthesis of Piroxicam – a NSAID (Vardanyan R.,2006), was taken into account.

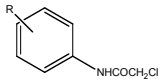
MATERIALS AND METHOD

Melting points were determined in open glass capillary and are uncorrected. IR spectra were recorded on Shimadzu 470 infrared spectrophotometers using KBr pellets. ^{1}HNMR spectra were recorded on a Varian A 60-D instrument using TMS as an internal reference (chemical shift in δ).

These compounds were prepared by the reaction of chloro-N-[(substituted) phenyl] acetamides with sodium salt of saccharin in dimethylformamide.

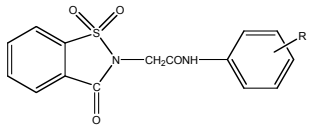
General Procedure for Preparation of 2-chloro-n-[(substituted)phenyl]acetamides : Substituted aniline (Wermuth C.G., 2004), (0.1 mol) was dissolved in ethyl methyl ketone (25 ml) in a three – necked round bottom flask fitted with two dropping funnels. In one dropping funnel a solution of chloroacetyl chloride (Vardanyan R., 2006), (0.1 mol) in ethyl methyl ketone (25 ml) was taken and a solution of sodium carbonate in another. The temperature of reaction mixture was maintained at 7 – 10 ^{0}C throughout the addition. After 30 mins, the reaction mixture was transferred to a separating funnel. The aqueous layer was washed twice with water and transferred to a conical flask. A small amount of sodium sulphate was added to the reaction mixture and kept overnight. The organic layer was decanted and solvent removed under reduced pressure. The solids so obtained were recrystallised with ethanol (Table 1).

General Procedure for Preparation of 2–(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-(substituted phenyl) acetamides : Equimolar quantities of sodium saccharin (Robert M. S., 1998) and 2-chloro-N-[(substituted) phenyl] acetamides (William K., 2003) were dissolved in dimethyl formamide (10 ml). The reaction mixture was heated on an oil bath at 125-130^{0}C with continuous stirring for 2 hrs. Separation of sodium chloride crystals after about 30 mins marked the completion of the reaction. The reaction mixture was left overnight, and then poured in water (150 ml). The white precipitate obtained was collected by filtration and washed with water. The crude product was recrsytallized with a mixture of ethanol and acetone (1:1) to give 2–(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-(substituted phenyl) acetamides (Winter C.A., 1952).



S. No.	R	m.p.(^{0}C)	% YIELD
1.	H	113-114	80
2.	2-CH3	86-88	81
3.	4-CH3	161-162	75
4.	2,3(CH3)2	127-129	90
5.	4-Cl	162-164	89

Table 1 : 2-chloro-N-[(substituted) phenyl] acetamides



S. No.	R	m.p.(^{0}C)	% YIELD
1.	H	185-186	41
2.	2-CH3	179-180	62
3.	4-CH3	190	60
4.	2,3(CH3)2	216-217	52
5.	4-Cl	186-187	64

Table 2 : 2–(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-(substituted phenyl) acetamides

Spectral data (William K. (2003), Robert M. S. (1998)):

1. 2- (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-phenyl acetamide:
IR (KBr):3237 (NH), 1695 (CO), 1678 (CO), 1393,1168 (SO_2) cm^{-1};
^{1}HNMR (CD_3OD): (δ ppm) : 4.10 (s, 2H, N-CH_2), 7.00-8.23 (m, 8H, ArH), 8.52 (s,1H,NH)

2. 2- (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-(2-methylphenyl)acetamide:
IR (KBr):3254 (NH), 1738 (CO), 1669 (CO), 1332,1180 (SO_2) cm^{-1};
^{1}HNMR (CD_3OD): (δ ppm) : 2.2 (s, 3H, CH_3), 4.61 (s, 2H, N-CH_2), 7.08-8.36 (m, 8H, ArH), 9.71 (s,1H,NH)

3. 2- (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-(4-methylphenyl) acetamide:
IR (KBr):3317 (NH), 1739 (CO), 1688 (CO), 1338, 1190 (SO2) cm^{-1};
^{1}HNMR (CD_3OD): (δ ppm): 2.2 (s, 3H, CH_3), 4.55 (s, 2H, N-CH_2), 7.11-8.28 (m, 8H, ArH), 10(s, 1H, NH)

4. 2- (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-(2,3,dimethyl phenyl) acetamide:
IR (KBr):3254 (NH), 1740 (CO), 1664 (CO), 1331, 1183 (SO_2) cm^{-1};
^{1}HNMR (CD_3OD): (δ ppm): 2.35 (s, 6H, $(CH_3)_2$), 4.36 (s, 2H, N-CH_2), 6.68-8.11 (m, 8H, ArH), 9.54(s, 1H, NH)

5. 2- (1, 1-dioxido-3-oxo-1, 2-benzisothiazol-2(3H)-yl)-N-(4-chloro phenyl)acetamide:
IR (KBr):3317 (NH), 1733 (CO), 1672 (CO), 1344, 1186 (SO_2) cm^{-1};
^{1}HNMR (CD_3OD): (δ ppm): 4.43-4.57 (s, 2H, N-CH_2), 7.19-8.30 (m, 8H, ArH), 10.2(s, 1H, NH)

RESULTS AND DISCUSSION

Statistical analysis: Results were expressed as Mean ± SEM and evaluated by Dunnett test. Values of $P < 0.001$ were considered statistically significant.

Anti-inflammatory activity: The synthesized compounds were tested plethysmographically for anti-inflammatory activity by carrageenan induced paw edema in rats. For this method albino rats (weighing 180-200 gm of either sex) were divided into 10 groups each consisting of 6 animals. One group served as positive control (received diclofenac 20 mg/kg), one group as negative control (received 10 % v/v gum acacia 1ml/kg) and rest of the groups received 2–(1,-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-N-(substituted phenyl) acetamides (80 mg /kg), orally, 30 mins prior to the injection of inflammatory agent . Suspension of carrageenan (0.1ml of 1% w/v) was injected subcutaneously at the subplantar region of the left hind paw of all groups. The paw volume was measured by mercury displacement at 1,2 and 3 hrs after carrageenan injection.

The edema volume of control group (Vc) and that of groups treated with test compound (Vt) was measured and the percentage inhibition of edema was calculated using the formula:

$$\% \text{ inhibition} = \frac{(Vc-Vt)}{Vc} \times 100$$

Treatment	Dose	Mean increase in paw volume				% inhibition in paw volume
		Time in minutes				
		0.00	60.0	120.0	180.0	
Control	5ml/kg	2.05± 0.2527	2.2 ± 1.291	2.233 ± 0.133	3.2 ± 0.1249	-------
Diclofenac sodium	20 mg/kg	1.26 ± 0.0326*	1.28 ± 0.05**	1.26 ± 0.536**	1.1 ± 0.034**	65.62
1 (a)	80 mg/kg	1.1 ± 1.461**	1.3 ± 0.11 **	1.69 ± 0.9875**	1.69 ± 0.9875**	47.18
1(b)	80 mg/kg	2.1 ± 0.6132	2.16 ± 0.2179	2.16 ±0.2179	2.17 ± 0.22**	32.18
1(c)	80 mg/khg	2.21 ± 0.2116	2.13 ± 0.2348	2.21 ± 0.2179	2.1 ± 0.2503**	34.37
1(d)	80 mg/kg	1.23 ± 0.0703*	1.32 ± 0.092**	1.68 ± 0.102**	1.65 ± 0.063**	48.43
1(e)	80 mg/kg	2.0 ± 0.22	2.14 ± 0.249	2.24 ± 0.245	2.12 ± 0.223**	33.75

Table 3: Anti inflammatory activity of 2 – (1, 1-dioxido-3-oxo-1, 2-benzisothiazol-2(3H)-yl)-N-(substituted phenyl) acetamides

CONCLUSION

Synthesis intermediates can find wide applications in the discovery and designing of receptor specific drugs. The synthesized saccharin derivatives have exhibited moderate anti-inflammatory activity in carrageenan induced rat paw edema. Moreover, such derivatives have immense opportunity to be further synthesized and explored for receptor specificity. Further investigations are still underway to synthesize derivatives, perform QSAR studies and study their biological properties alongwith receptor specificity.

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