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Efficieant Synthesis of 1, 5- Benzothiazepine Derivatives Using Benzyl Tri Ethyl Ammonium Chloride in Ethonol

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Abstract- New Heterocyclic systems namely derivatives **(a-d)** have been synthesized via reaction of - and 4-hydroxy-1-methyl-3-((E)-3-morpholino or piperidin-1-yl or 4-phenylpiperazin-1- yl or 4-(4-methoxyphenyl)piperazin-1-yl)acryloyl)quinolin-2(1*H*)-one **(3a-d)** derivatives and 2-amino thiophenol by using benzyl tri ethyl ammonium chloride in good yields. Some of the compounds have shown good anti inflammation activity.

Index Terms- Heterocycles, 1,5- benzothiazepine, 2-amino thiophenol, benzyl tri ethyl ammonium chloride

I. INTRODUCTION

Oxygen, nitrogen, sulpher containing heterocycles has been under investigation for a long time because of their important medicinal properties. Among these type of molecules, 1,5- benzothiazepines have been shown to have various important biological activities such as coronary vasodialatory[1],tranquiliser[2,3], anti depressant[4], anti spasmodic[5], neuroleptic[6], CNS[7] and anti HIV[8]activity. Synthesis of this group of benzothiazepines have been intensely studied and numerous procedures are described in the literature [9-12] and 2*H*-(1)-quinolin-2-one are also endowed with activity[13] ,modification of these reaction conditions or the development of new procedures are important to get newer insight into the formation of these1,5-benzothiazepines.In continuation of ongoing and previous investigation [14-17] ,The present aim of this study was, therefore to introduce simple and convenient procedures for the synthesis of 3-((E)-2,3-dihydro-2-(morpholino or piperidin-1-yl or 4-phenylpiperazin-1-yl or 4-(4-methoxyphenyl)piperazin-1-yl)benzo[b][1,4]thiazepin-4-yl)-4-hydroxy-1-methylquinolin-2(1*H*)-one **(3a-d)** in very good yield by the reaction of 2-aminothiophened with with 4-hydroxy-1-methyl-3-((E)-3-morpholino or piperidin-1-yl or 4-phenylpiperazin-1- yl or 4-(4-methoxyphenyl)piperazin-1-yl)acryloyl)quinolin-2(1*H*)-one **(2a-d)**, in the presence of benzyl triethyl ammonium chloride in ethnol guided mainly by the observation that many times the combination of two or more hetero cyclic nuclei in singular molecular frame work enhances the biological profile many a fold

II. MATERIALS AND METHOD

The requisite starting material 3-((E)-3-(dimethylamino)acryloyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one **(1)** and 4-hydroxy-1-methyl-3-((E)-3-morpholino or piperidin-1-yl or 4-phenylpiperazin-1- yl or 4-(4-methoxyphenyl)piperazin-1-yl)acryloyl)quinolin-2(1*H*)-one **(2a-d),** have been prepared by the known literature method.[18] Condensation of **(1)** with Varity of alicyclic 2^{o} amines in reflux condition resulted in 4-hydroxy-1-methyl-3-((E)-3-morpholino or piperidin-1-yl or 4-phenylpiperazin-1- yl or 4-(4-methoxyphenyl)piperazin-1-yl)acryloyl)quinolin-2(1*H*)-one **(2a-d)**, these compounds **(2a-d)** are treated with 2-amino thiophenol using catalytic amount of benzyl triethyl ammonium chloride in ethanol afforded 3-((E)-2,3-dihydro-2-(morpholino or piperidin-1-yl or 4-phenylpiperazin-1-yl or 4-(4-methoxyphenyl)piperazin-1-yl)benzo[b][1,4]thiazepin-4-yl)-4-hydroxy-1-methylquinolin-2(1H)-one **(3a-d)** on very good yields. The compounds have been characterized by spectral means such has IR, NMR and mass. In IR spectra characteristic bond at 1600.81 cm^{-1} is attributed to (C=N)bond for the structure**(3a)** was unequivocally proved by the NMR spectra of the protons attached to the carbons C-2 and C-3 which appeared as a typical ABX pattern**(3a):**

δ3.32(1H,dd,J_{AB}=12.5Hz;J_{AX}=15.0Hz;H_A),δ4.85(1H, dd, J_{BA}=12.5 Hz;J_{BX}=15.0 Hz ;H_B)δ5.52(1H, dd, J_{XA}=15.0Hz ;J_{XB}=7.5Hz;H_X] . all physical data of compounds were recored .

III. RESULTS AND DISCUSION

Among the synthesized compounds, four compounds of 1,5-benzothiazepines derivatives were screened for anti-inflammatory activity by the Carrageenan induced paw edema assay in rats at a Dose of 100 mg/kg Body weight, orally. The data is presented in **Table-1**

In an attempt to carry out structural modifications of the parent molecule and for the optimization of the biological activity, the substituted 1,5-benzothiazepines were substituted with morpholine, piperidne ,phenyl piperazine , (4- methoxy phenyl) piperazine groups and this 1,5-benzothiazepines derivatives were subjected to an anti-inflammatory activity.

In the substituted 1,5-benzothiazepines were substituted by phenyl piperazine and piperidine groups (**sample 3,2**, **Table 1**) at position and they showed less activity than the standard drug. Among these two compounds piperazine derivative have shown greater activity than piperidine derivative

In the phenyl piperazine derivative (**sample 3**, **Table-1**) showed 10.87% inhibition of Rat paw edema indicating mild activity of the pharmacophoric group. Substitution with, (4-methoxy phenyl) piperazine groups (**sample 4**, **Table 1**) causes reduction in the activity and moderate activity when compared with phenyl piperazine substituted derivative. Substitution by morpholine derivative (**sample 1,Table 1**) showed less activity.

Substitution by piperidine derivative (**sample 2, Table 1)** showed negligable activity.

Table 1: Anti-Inflammatory Activity In Carrageenan Induced Rat Paw Edema Model

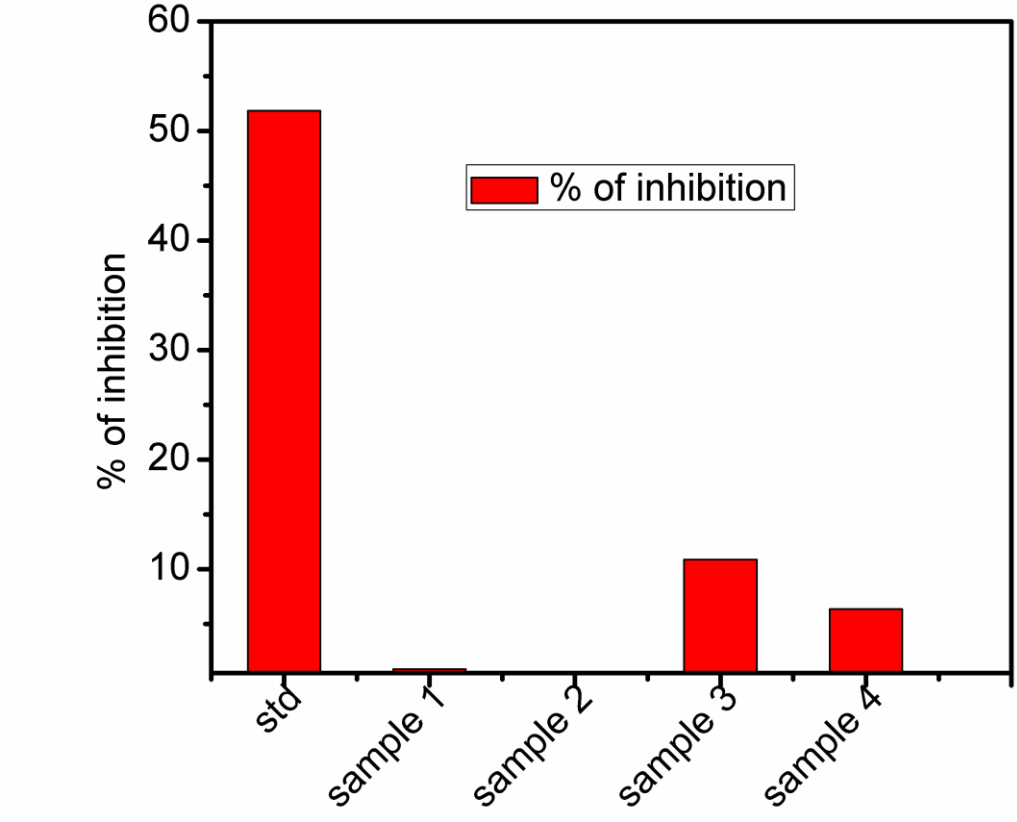
Compound Dose : 100 mg / Kg
Standard [Indomethacin] : 10 mg / Kg

Rat No.	**Group**	**Initial Paw Volume(mL)**	**Final paw Volume(mL)**	**Difference in Paw Volume(mL)**	**% of inhibition**
1	**CONTROL**	1.12	2.26	1.14	
2		1.20	2.39	1.19	
3		1.33	2.44	1.11	
4		1.44	2.56	1.12	
Mean ± SE				**1.14±0.03**	
5	**STD**	1.29	1.77	0.48	57.80
6		1.32	1.87	0.55	51.40
7		1.39	2.00	0.61	46.40
Mean ± SE					**51.87±3.30**
8	**1**	1.35	2.46	1.11	2.60
9		1.25	2.47	1.22	0.00
10		1.36	2.55	1.19	0.00
Mean ± SE					**0.87±0.87**
11	**2**	1.22	2.55	1.33	0.00
12		1.21	2.41	1.20	0.00
13		1.23	2.68	1.45	0.00
Mean ± SE					**0.00±0.00**
14	**3**	1.23	2.27	1.04	10.30
15		1.28	2.27	0.99	14.60
16		1.19	2.26	1.07	7.70
Mean ± SE					**10.87±2.01**
	4	1.35	2.42	1.07	6.07
		1.24	2.23	0.99	13.00
		1.27	2.56	1.19	0.00
Mean ± SE					**6.36±3.76**

ANTI-INFLAMMATORY ACTIVITY IN CARRAGEENAN INDUCED RAT PAW EDEMA MODEL

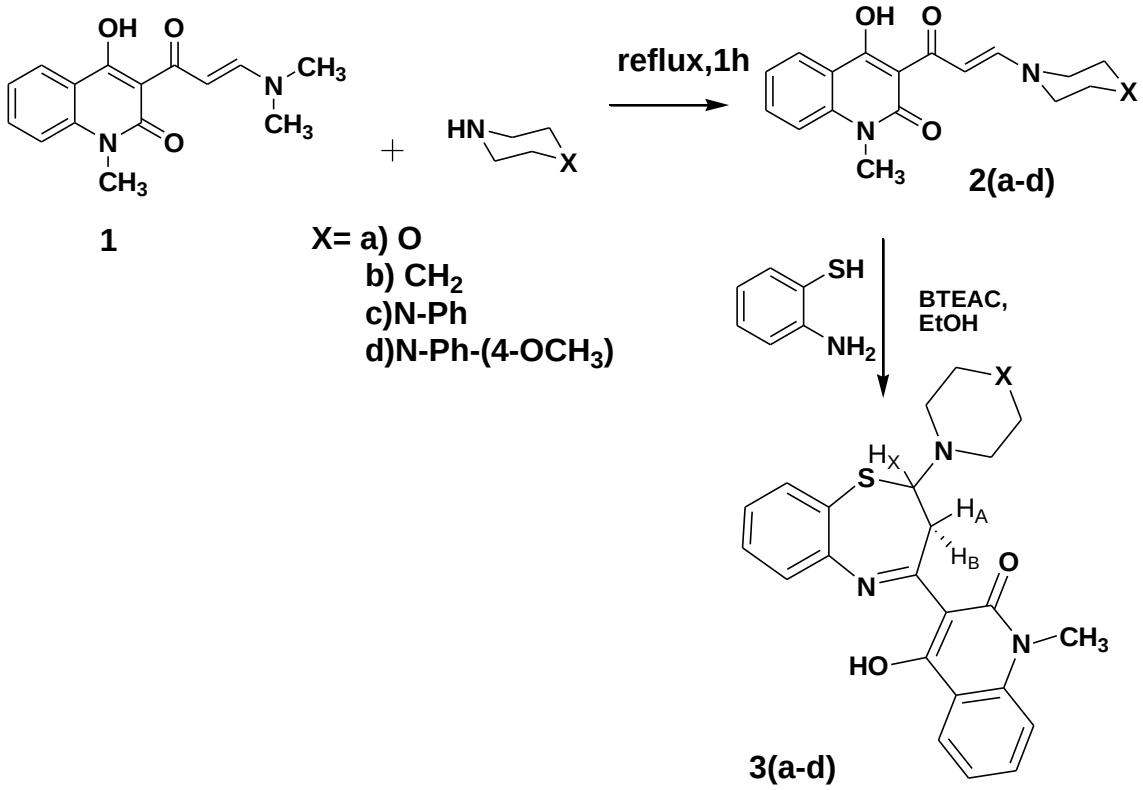
Compound Dose : 100 mg / Kg

Standard [Indomethacin] : 10 mg / Kg



.

EXPERIMENTAL DATA



All the reaction mixtures were stirred magnetically and were monitored by TLC using 0.25mm. which were visualized with UV light. Melting points were recorded on a Buchie R-535 apparatus. IR spectra were recorded on a perkin-Elmer FT-IR 240-c spectrophotometer. Mass spectro were on a finnigan MAT 1020 mass spectrometer. Proton NMR were recorded on 200 MHz spectrometer in $CDCl_3$. and the chemical shift values were reported in δ (ppm) and J values are expressed in hertz.

3-((*E*)-3-(dimethylamino)acryloyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one : **(1)**
Synthesized according to the reported procedure"[18].

4-hydroxy-1-methyl-3-((*E*)-3-morpholino or piperidin-1-yl or 4-phenylpiperazin-1- yl or 4-(4-methoxyphenyl)piperazin-1-yl)acryloyl)quinolin-2(1*H*)-one : 2(a-d)
Synthesized according to the reported procedure"[18].

3-((*E*)-2,3-dihydro-2-(morpholino or piperidin-1-yl or 4-phenylpiperazin-1-yl or 4-(4-methoxyphenyl)piperazin-1-yl)benzo[b][1,4]thiazepin-4-yl)-4-hydroxy-1-methylquinolin-2(1*H*)-one: 3(a-d)[19]
4-hydroxy-1-methyl-3-((*E*)-3-morpholino or piperidin-1-yl or 4-phenylpiperazin-1- yl or 4-(4-methoxyphenyl)piperazin-1-yl)acryloyl)quinolin-2(1*H*)-one **2(a-d)** (0.0lmmole)was dissolved in ethanol (20ml),to this 2-amino thiophenol (0.0lmmole) and catalytic amount of BTEAC(0.06mmole) was added and the reaction mixture was refluxed on water bath .after1hr a yellow fluffy solid starts separating out . the reaction mixture was further refluxed for one more hour, cooled and the separated solid was filtered and washed several times with hot ethanol. The compound was dried and recrystallised using acetone to get pure 1,5-benzothiazepines.all other derivatives were prepared accordingly. The results are shown below.

3-((E)-2,3-dihydro-2-morpholinobenzo[b][1,4]thiazepin-4-yl)-4-hydroxy-1-methylquinolin-2(1H)-one:3a
MP:251°C , Yield :79%, IR(KBr, $v_{max}cm^{-1}$) : 1601.83 (C=N), ^{1}H NMR (400 MHz, $CDCl_3$)
: δ 2.21-2.40 (m, 4H, $N(CH_2)_2$), δ2.72-2.79(m,4H,),δ3.32(1H,dd,J_{AB}=12.5Hz;J_{AX}=15.0Hz;H_A

δ3.82(s,3H,N-CH_3),δ4.38(dd,J_1=12.5 Hz,J_2=7 Hz,IH), δ4.85(1H, dd, J_{BA}=12.5 Hz; J_{BX}=15.0 Hz ;H_B)δ5.52(1H, dd, J_{XA}=15.0Hz ; J_{XB}=7.5Hz;H_X) δ 7.02-7.15(M,4H) δ 7.22-7.34(m,3H) δ

7.49-7.55(m,2H) δ7.59-7.62(m,1H),δ7.70-7.79(m,1H), δ 8.30(d,J=6.6,1H) ESI-MS (m/z) : 421$[M+1]^+$ Anal Calcd for $C_{23}H_{23}N_3O_3S$: C 65.54; H, 5.50; N, 9.97; O 11.39; S, 7.61 Found; C 65.44; H, 5.45; N, 9.90; O 11.31; S, 7.59.

3-((E)-2,3-dihydro-2-(piperidin-1-yl)benzo[b][1,4]thiazepin-4-yl)-4-hydroxy-1-methylquinolin-2(1H)-one:3b

MP:237°C ,Yield:71% ,IR(KBr, $v_{max}cm^{-1}$) : 1601.53 (C=N`), ^{1}H NMR (200 MHz, $CDCl_3$) :δ1.52-1.65(m,6H,$(CH_2)_3$),δ2.42-2.50(m,4H,N$(CH_2)_2$),δ2.72- 2.82(1H,dd,J_{AB}=12.5Hz;J_{AX}=15.0Hz;H_A),δ3.45(S,3H,N-CH_3)δ 4.16(1H, dd J_{BA}=15 Hz;,J_{BX}=7.0 Hz ;H_B) δ 5.41(1H, dd, J_{XA}=15.0Hz ; J_{XB}=7.0Hz;H_X), δ 7.08- 7.16(m,4H) δ 7.13-7.31(m,3H), 7.35-7.46(m,2H) δ 7.50-7.70(m,2H) , δ 8.29(d,*J*=6.8 Hz,1H) ESI-MS (m/z) : 422$[M+1]^+$

Anal Calcd for$C_{24}H_{25}N_3O_2S$: C 68.71; H, 6.01; N, 10.02; O, 7.63; S, 7.64; Found; C 68.69; H, 5.97; N, 9.53;O 7.60 ; S, 7.63

3-((E)-2,3-dihydro-2-(4-phenylpiperazin-1-yl)benzo[b][1,4]thiazepin-4-yl)-4-hydroxy-1-methylquinolin-2(1H)-one:3c

MP 232°C Yield:73% ,IR(KBr, $v_{max}cm^{-1}$) : 1644.7(C=N), ^{1}H NMR (400 MHz, $CDCl_3$) :δ1.8-1.92(m,4H), δ 2.2- 2.36(m,4H) δ2.96(1H,dd,J_{AB}=12.5Hz;J_{AX}=13.0Hz;H_A)δ3.63(S,3H,N-CH3) δ4.47(1H, dd, J_{BA}=12.5 Hz;J_{BX}=7.0 Hz ;H_B) δ5.80(1H, dd, J_{XA}=15.0Hz ;J_{XB}=7.5Hz;H_X) δ7.25-7.34(m,5H),δ7.41-7.50(m.4H) δ 7.53-7.61(m,3H) ,δ 7.63-7.78(m,2H), δ 7.81-7.89(m,1H), δ 7.92-7.99(m,1H), δ 8.29(d,*J*=6.6 Hz,1H), ESI-MS (m/z) : 497$[M+1]^+$
Anal Calcd for $C_{29}H_{28}N_4O_2S$: C 70.14; H, 5.68; N, 11.28; O 6.44; S, 6.46
Found C 70.12; H, 5.60; N, 11.24; O 6.41; S, 6.43.

3-((E)-2,3-dihydro-2-(4-(4-methoxyphenyl)piperazin-1-yl)benzo[b][1,4]thiazepin-4-yl)-4-hydroxy-1-methylquinolin-2(1H)-one: 3d

MP :267°C, Yield :76%, IR(KBr) : 1644.7(C=N) HNMR(400MHz,$CDCl_3$) : δ 1.81-1.91(m,4H) δ 2.21-2.38(m,4H), 2.96(1H,dd,J_{AB}=12.5Hz;J_{AX}=13.0Hz;H_A), δ 3.65(S,3H,N- CH3),δ 3.90(S,3H,O-CH3) , δ 4.80(1H, dd, J_{BA}=12.5 Hz;J_{BX}=7.0 Hz ;H_B) δ 5.52(1H, dd, J_{XA}=15.0Hz ;J_{XB}=7.5Hz;H_X) δ 7.1-7.3(m,4H,) δ 7.3-7.41(m,3H), δ 7.44-7.52(m,2H) δ 7.58-7.65(m,1H), δ 7.71-7.82(m,1H) δ 8.21(d,*J*=6.8,1H), ESI- MS (m/z) : 497 $[M+1]^+$ Anal Calcd for $C_{29}H_{28}N_4O_2S$: C 70.14; H, 5.68; N, 11.28; O 6.44; S, 6.46 Found C 70.12; H, 5.60; N, 11.24; O 6.41; S, 6.4

IV. CONCLUSION

- The proposed compounds were synthesized successfully and characterized.
- They were evaluated for Anti-inflammatory activity by Carrageenan induced Rat Paw Edema model. All the compounds screened were found to be less active than standard in case of Anti-inflammatory activity .
- Hence, it is concluded that there is ample scope for further developing this field.

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