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# Evaluation of Anti-Inflammatory Activity of Some Novel Benzofuropyrimidine Derivatives

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**ABSTRACT**

Benzofuran and its derivatives constitute active compounds possessing biological and pharmacological activities. Several benzofuran analogs reported earlier widely to possess anti-inflammatory activity. Considering the above facts, getting more potential molecules, the derivatives of benzofuropyrimidine were evaluated against the anti-inflammatory activity.

3-amino-5-bromo-1-benzofuran-2-carboxamide (3) were synthesized from 5-bromosalicylonitrile (2) in chloroacetamide, dry acetone and anhydrous $K_2CO_3$. Condensation of compound (3) underwent cyclization with substituted aryl aldehydes in strong acid and ethanol and resulted in the formation of 8-bromo-2(phenylsubstituted) benzofuro [3,2-d]pyrimidin-4(3H)-one (4a-e), in good yields.

The compounds (4a-e) on reaction with phosphorus oxychloride resulted the compounds 8-bromo-4-chlorobenzofuro [3,2-d]pyrimidine(5a-e). Compounds (5a-e) were confirmed by spectral ($^1$H-NMR, IR and Mass) analytical and physical studies.

**KEY WORDS:** Benzofuran, Pyrimidine, Anti-inflammatory.

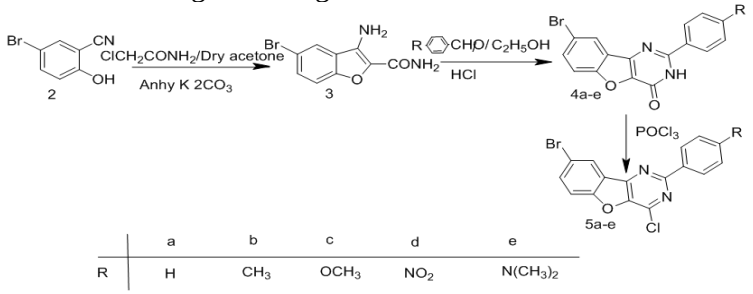
## 1. INTRODUCTION

Benzofuran and its analogs are widely known for their anticonvulsant, antibacterial, antifungal, sedative, hypnotic, anti-inflammatory and CNS stimulant activities (Shisho, 1981; Simpson, 1985; Santana, 1999; Balzarini and Guigane, 2002; Basawaraj, 2008). In view of these biological and pharmacological importance of benzofuran, our work on, some novel benzofuropyrimidine (5a-e) derivatives. Compounds (5a-e) were obtained by reaction with 8-bromo-2(phenylsubstituted) benzofuro [3,2-d]pyrimidin-4(3H)-one(4a-e) and phosphorus oxychloride at reflux temperature.

3-amino-5-bromo-benzofuran-2-carboxamide (3) were synthesized by condensation, of 5-bromo salicylonitrile (2) with chloroacetamide. Compound (3) (3-amino-5-bromo-benzofuran-2-carboxamide) on reaction with aryl aldehyde in presence of HCl in ethanol to give 8-bromo-2 (phenylsubstituted) benzofuro[3,2-d]pyrimidin-4(3H)-ones (4a-e) in good yield.

## 2. MATERIALS AND METHOD

Reagents were obtained commercially, purified and used. Melting points were checked and are uncorrected. Synthesized compounds crystallized, IR spectra studied by FTIR-8400S (SHIMADZU) Perkin-Elmer 1000 Spectrophotometer in KBr. $^1$H-NMR spectra was studied by Bruker 400MHz Spectrophotometer. Chemical shifts reported in ppm (δ). Mass spectra taken from LCMS-2010A Shimadzu Japan. Elemental analysis studied with flash EA1112, CHN conformation thermo finnigan Silica gel 60.




**Scheme: Synthesis of Benzofuropyrimidine derivatives**

**Synthesis of 5-bromosalicylonitrile (2):** 5-bromosalicylaldehyde (0.05mol) was treated with hydroxyl amine hydrochloride (0.055mol) in anhydrous DMF at gentle reflex for 20 minutes. Contents were cooled & transferred into cold water to give solid 5-bromosalicylonitrile (2). Recrystallized from Benzene, m.p. 156$^o$C, yield 82%.

**Synthesis of 3-amino-5-bromo-benzofuran-2-carboxamide (3):** To a solution of 5-bromosalicylonitrile (2) (0.01mol) in anhydrous acetone (15ml), chloroacetamide (0.01 mol) and anhydrous $K_2CO_3$. Reaction contents were heated for 8-10 hours, the potassium salt were filtered off. The solvent is eliminated under reduced pressure to produce 3-amino-5-bromo-benzofuran-2-carboxamide (3) as yellow coloured compound and crystallized. Yield 78% and m.p. 185$^o$C.

**Synthesis of 8-bromo-2(phenyl substituted)benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one (4a-e):**

**General procedure** (Sangapure, 2000; Basawaraj, 2009)**:** A mixture of 3-amino-5-bromo-benzofuran-2-carboxamide (3) (0.002mol) in Ethanol (10ml), aromatic aldehyde (0.002 mol) and catalyst HCl (0.05ml). The Reaction contents were heated for 4 hrs. On cooling the compound collected and crystallized with Ethanol.

**Synthesis of 8-bromo-4-chlorobenzofuro [3,2-d]pyrimidine (5a-e):**

**General procedure** (Sangapure, 2000; Basawaraj, 2009)**:** A mixture of 8-bromo-2(phenyl substituted)benzofuro[3,2-d]pyrimidin-4(3H)-one (4a-e) (0.00032mol) and phosphorus oxychloride (2 ml) were added, reaction contents heated for 1 hr, then cooled & transferred to ice. The solid separated were filtered, washed and crystallized with benzene and petroleum ether. Physical characterization reports and spectral data's of compounds (5a-e) were summarised in Table.1 and Table.2 respectively.

**Table.1. Physical Characterization Data of Compounds (5a-e)**

| Comp. code | R | S | m.p. °C | Yield % | Elemental Analysis Found (calculated)% | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **5a** | **H** | **B** | **180** | **75** | 53.44 (53.41) | 2.24 (2.27) | 7.79 (7.81) |
| **5b** | $-CH_3$ | **B** | **141** | **70** | 54.65 (54.68) | 2.70 (2.71) | 7.50(7.49) |
| **5c** | $-OCH_3$ | **B** | **175** | **68** | 52.40 (52.38) | 2.59 (2.61) | 7.19(7.20) |
| **5d** | $-NO_2$ | **B** | **194** | **69** | 47.50 (47.49) | 1.74 (1.72) | 10.39(10.41) |
| **5e** | $-N(CH_3)_2$ | **B** | **254** | **60** | 53.69 (53.71) | 3.25 (3.22) | 10.44 (10.46) |

S= Solvent for crystallization, B=Benzene and petroleum ether.

**Table.2. Spectral Data of Compounds (5a-e)**

| Comp. code | IR (KBr) $cm^{-1}$ | $^1$H-NMR (ppm)δ | Mass (m/z) |
|---|---|---|---|
| **5a** | 3040 (C-H, Ar), 1580-1620 (C=N), 1565, 1530 (C=C), at 1250 (C-N), at 1180, 1062 (C-O-C), at 850 (C-Br) and at 659 (C-Cl) | 7.20-8.60 (m, Ar-H) | 360 (M+) |
| **5b** | 3020 (C-H, Ar), 2960 (CH, $CH_3$), 1618 (C=N), 1565, 1530 (C=C), 1250 (C-N), 850 (C-Br) and 659 (C-Cl) | 7.20-8.40 (m, Ar-H), 1.28 (s, 3H, $CH_3$) | 376(M+) |
| **5d** | 3000 (C-H, Ar) 1520, 1350(C-$NO_2$), 1620 (C=N), 1452 (C=C), 1280 (C-N), 850 (C-Br) and 659 (C-Cl) | 7.20-8.60 (m, Ar-H) | 405 (M+100%), 407(M+ 24%) 373, 169 and 116 or 117 |
| **5e** | 3040 (C-H, Ar), 2960, 2840 [CH, $(CH_3)_2$], 1614 (C=N), 1565, 1530 (C=C), 1250 (C-N), 1180, 1062 (C-O-C), 850 (C-Br) and 659 (C-Cl) | 6.8-8.4 (m, Ar-H), 2.62 [s,6H, $(CH_3)_2$ | 402 (M+100%) 93 and 77 |

**Anti-Inflammatory Activity:**

**Carrageenan induced rat paw oedema method** (Winter, 1962; Cotran, 2001)**:** Wistar albino rats, any sex weighing between 150-200 gms were selected. They were maintained on diet and free access to water.

The Twenty-eight rats, in seven groups, each group having four rats. Control group rats treated with 2% gum acacia (0.2 ml). Standard group rats received Diclofenac sodium at 4.5 mg/kg body weight, p.o. (Ghosh, 2005). Similarly the remaining five groups were treated with test compounds at 50 mg/kg body weight, p.o. (Sanmugapriya and Venkataraman, 2006).

The test compounds, standard drug and control was given to rats thirty minutes before carrageenan suspension injection of 1% in normal saline (0.1 ml), into sub planar region of left hind paw. Right hind paw serves reference immediately oedema volume of injected paws were reported plethysmographically by mercury displacement process. For comparison, volume of oedema at prefixed time interval were taken. Difference between paw volumes of treated animals were reported and mean oedema volume determined.

Percentage reduction in oedema volume were determined by following formula,

$$\text{Percentage reduction} = \frac{V_0 - V_t}{V_0} \times 100$$

Where, Vo = Volume of the paw of control at time 't', Vt = Volume of the paw of drug treated at time 't'.

From data's, mean oedema volume with standard deviation (SD), standard error of mean (SEM) and percentage (%) decrease in oedema were determined. Results were given in Table.3.

**Statistical Analysis**: The results obtained from the study were given as Mean ± SEM (standard error mean). The results were analysed with variance (ANOVA), followed by Dunnet's test, were test compound groups were compared with control group.

**Table.3. Anti-inflammatory activity data of compounds (5a-e)**

| Comp. Code | Dose (mg/kg) | Mean difference in paw volume (±S.E) at 3hrs (ml) | % inhibition of inflammation |
|---|---|---|---|
| Control | - | 0.80 (±0.009) | - |
| Standard | 4.5 | 0.16 (± 0.001) | 82.00 |
| 5a | 50 | 0.51 (± 0.005) | 36.75 |
| 5b | 50 | 0.54 (± 0.004) | 32.95 |
| 5c | 50 | 0.32 (± 0.001)*** | 60.85 |
| 5d | 50 | 0.33 (± 0.001)*** | 59.00 |
| 5e | 50 | 0.45 (± 0.002) | 43.75 |

Significance at *P<0.05, **P<0.01 and ***P<0.001.

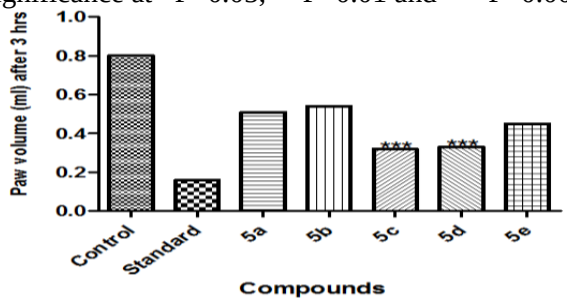



**Figure.1. Graphical representation of Anti-inflammatory activity compounds (5a-e)**

## 3. RESULT AND DISCUSSION

Compounds (5a-e) was screened for anti-inflammatory activity. The reported values clearly shown that the compound (5c) and (5d) exhibited moderate activity. Other representative compounds of the series (5a), (5b) and (5e) possess weak activity in comparison to Diclofenac sodium.

## 4. CONCLUSION

The conclusion of the present work may be;

- The synthesized compounds confirmed by spectral data's such as IR, $^1$H-NMR and mass spectroscopy, and the spectral data's of compounds were in agreement with their structure.
- Our study investigated that certain benzofuropyrimidine derivatives were displayed moderate anti-inflammatory activity when compared with the reference standard.
- Thus the present work provides a new outline of the study of anti-inflammatory activity of benzofuran moiety coupled with pyrimidine.

The outcome of this work suggested that biheterocyclic compounds containing benzofuran moiety coupled with pyrimidine are of interesting molecules. The study has proved that the efficacy of benzofuran derivatives when incorporated with other heterocyclic moieties produced useful therapeutic agents. Thus intended to study active molecules at different concentrations.

## 5. ACKNOWLEDGEMENT

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