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Synthesis and anti-inflammatory study of novel fluorobenzothiazole derivatives

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ABSTRACT

N-{6-fluoro-7-[(substituted)-amino] 1, 3-benzothiazole-2-yl}-2-nitrobenzamides; N-{6-fluoro-7-[(substituted)-amino] 1, 3-benzothiazole-2-yl}-3-nitrobenzamides and N-{6-fluoro-7-[(substituted)-amino] 1, 3-benzothiazole-2-yl}-4-nitrobenzamides derivatives were synthesized. Sythesised compounds were tested for anti-inflammatory activity by carrageenin induced rat hind paw edema method compared to standard Diclofenac.

INTRODUCTION

Inflammation is accompanied by the local liberation of chemical mediators that include histamine, 5-hydroxy tryptamine, bradykinin and eicosanoids. The latter camprises a group of unsaturated fatty acids all with a 20-carbon structure, which are short, lived, extremely potent and formed in almost every tissue in the body [1]. Individual mediators differ in their importance to various types of inflammation [2, 3]. Eicosanoid however, are involved in most types of inflammation and it is on manipulation of their biosynthesis that most of the present anti-inflammatory therapies are based cyclooxygenase, which changes the linear fatty acids into the cyclic structure of the prostaglandins [4, 5]. Evidence that various prostaglandins are components of inflammation includes the following minute quantities of prostaglandin E2 (PGE 2) and prostacyclin (PGI 2) cause erythma and increase local blood flow [6-8]. The PGE 2 cause intense local pain when given I.M. or S.C. to induce absorption, PGE 1, infused subdermally with histamine causes itching; PGE 2 is associated with the production of fever. Non-steroidal anti-inflammatory drugs (NSAIDs) exert their effect by inhibition of cyclooxygenase (prostaglandin synthetase). The same inhibition permits their effects on platelets [9]. Chronic inflammatory conditions lead to the development of diseases including osteoarthritis; rheumatoid arthritis and other inflammatory diseases of the joints [10].

Anti-inflammatory drugs offer symptomatic relief in the inflammatory diseases when the underlying cause of inflammation is unidentified [11]. NSAIDs act by inhibiting the catalytic activity of the enzyme cyclooxygenase (COX). This enzyme is responsible for catalyzing an important intermediate step in the synthesis of prostaglandin and thromboxanes from arachidonic acid. An inflammatory stimulus causes a series of events, which ultimately result in the conversion of arachidonic acid to prostaglandin (PG) and thromboxane (TX) that are mediator of inflammation.

Benzoheterocycles such as benzothiazoles, benzimidazoles and benzoxazoles can serve as unique and versatile scaffolds for experimental drug design. Among the all benzohaterocycles, benzothiazole has considerable place in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities; hence, synthesis of this compound is of considerable interest. 2-substitued benzothiazole has emerged in its usage as a core structure in the diversified therapeutically applications. The studies of structure–activity relationship interestingly reveal that change of the structure of substituent group at C-2 position commonly results the change of its bioactivity. Among those 2-substituted benzothiazole derivatives with fluorine substituted molecules have already received considerable attention due to their potential bioactivities [12]. Since benzothiazoles shows multiple therapeutic values, in 1950s, Since then the medicinal chemists have not taken active interest in this chemical family, although they have been known from ages to be biologically active [13] but as the Riluzole [14] (6-trifluoro-2-benzothiazolamine) was discovered benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity viz antitumor, antitubercular, antimalarial, anticonvulsant anthelmintic, analgesic, anti-inflammatory, antifungal, a topical carbonic anhydrase inhibitor an antihypoxic and an anti-nematode [15-26]. These biological data prompted us to synthesize some new benzothiazole derivatives containing nitro and fluoro group.

EXPERIMENTAL SECTION

Step- I -General synthesis of 2-amino-6-fluoro-7-chloro-benzothiazole (Code- 2AB): To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of 3-chloro-4-fluoro aniline. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while 1.6ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rose beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0c on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85^0c and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to p^H 6 A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow plates of 2-amino-6-fluoro-7-chloro-benzothiazole. After drying in an oven at 80^0C, the dry material (1gm 51.02%) melted at 210-212^0c.

Step-II-General synthesis of N-(7-chloro-6-fluoro-1, 3-benzothiazole-2-yl)-2(3 or 4)-nitrobenzamide (Code – 2-Nb. 3-Nb, 4-Nb)

Solution of 2-(3 or 4)-nitrobenzoylchloride (5.36g, 0.026mol) in dry acetone (50 ml) was add into a solution of 2-amino-6-fluoro-7-chloro-benzothiazole (5.22 g, 0.026 mol) in dry pyridine (50ml), drop wise with continuous stirring at room temperature. After addition was complete, stirring was continued for another 30 minutes. The reaction mixture was poured in ice cold water (200ml) and recrystallized with ethanol.

Step-III N-{6-fluoro-7-[(substituted)-amino] 1, 3-benzothiazole-2-yl}-4-nitrobenz amides (S-1 to S-45)

The 0.0075 mol (2.7 gm) of N-(7-chloro-6-fluoro-1, 3-benzothiazole-2-yl)-2 (3 or 4)-nitrobenzamides was treated with 0.008 mol of various substituted aniline and refluxed for 2 hrs in presence of DMF (dimethyl formamide) then the mixture was cooled and poured into crushed ice. The solid separated was filter off, dried and recrystallize with super dry alcohol.

General synthesis of N-{6-fluoro-7-[(2-chlorophenyl)-amino] 1, 3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-1).

Mol. Formula- $C_{20}H_{12}O_3SN_4ClF$, M.Wt - 442.85, % Yield – 76, M.P-264-266, Rf value - 0.31, IR Range- 1463cm^{-1}Ar C=C, 1303cm^{-1}C-F, 1641cm^{-1}C=O, 1205cm^{-1}C-S, 1546cm^{-1}C-NO_2, 616cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(3-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-2).

Mol. Formula - $C_{20}H_{12}O_3SN_4ClF$, M.Wt- 442.85, % Yield- 78, M.P.- 269-271, Rf value-0.39, IR Range-1434cm^{-1}Ar C=C, 1304cm^{-1}C-F, 1641cm^{-1}C=O, 1205cm^{-1}C-S, 1547cm^{-1}C-NO_2, 616cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(4-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-3).

Mol. Formula - $C_{20}H_{12}O_3SN_4ClF$, M.Wt- 442.85, % Yield-75, M.P.- 261-263, Rf value-0.34, IR Range-1444cm^{-1}Ar C=C, 1297cm^{-1}C-F, 1630cm^{-1}C=O, 1202cm^{-1}C-S, 1519cm^{-1}C-NO_2, 632cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(2-methylphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-4).

Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-76, M.P.- 268-270, Rf value-0.28, IR Range-1437cm^{-1}Ar C=C, 1346cm^{-1}C-F, 1636cm^{-1}C=O, 1212cm^{-1}C-S, 1517cm^{-1}C-NO_2, 2921cm^{-1}C-CH_3.

General synthesis of N-{6-fluoro-7-[(3-methylphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-5).

Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-78, M.P.- 265-267, Rf value-0.32, IR Range-1444cm^{-1}Ar C=C, 1394cm^{-1}C-F, 1630cm^{-1}C=O, 1202cm^{-1}C-S, 1519cm^{-1}C-NO_2, 2925cm^{-1}C-CH_3.

General synthesis of N-{6-fluoro-7-[(4-methylphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-6).
Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-80, M.P.- 255-257, Rf value-0.26, IR Range-1445cm^{-1}Ar C=C, 1323cm^{-1}C-F, 1605cm^{-1}C=O, 1212cm^{-1}C-S, 1507cm^{-1}C-NO_2, 3002cm^{-1}C-CH_3.

General synthesis of N-{6-fluoro-7-[(2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-7).
Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-82, M.P.- 258-260, Rf value-0.23, IR Range-1486cm^{-1}Ar C=C, 1290cm^{-1}C-F, 1605cm^{-1}C=O, 1202cm^{-1}C-S, 1515cm^{-1}C-NO_2.

General synthesis of N-{6-fluoro-7-[(2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-8).
Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-78, M.P.- 259-261, Rf value-0.29, IR Range-1487cm^{-1}Ar C=C, 1291cm^{-1}C-F, 1604cm^{-1}C=O, 1202cm^{-1}C-S, 1517cm^{-1}C-NO_2..

General synthesis of N-{6-fluoro-7-[(4-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-9).
Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-72, M.P.- 251-253, Rf value-0.26, IR Range-1487cm^{-1}Ar C=C, 1394cm^{-1}C-F,1605cm^{-1}C=O, 1202cm^{-1}C-S, 1517cm^{-1}C-NO_2..

General synthesis of N-{6-fluoro-7-[(2-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-10).
Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-85, M.P.- 272-273, Rf value-0.27, IR Range-1484cm^{-1}Ar C=C, 1311cm^{-1}C-F, 1591cm^{-1}C=O, 1234cm^{-1}C-S, 1508cm^{-1}C-NO_2..

General synthesis of N-{6-fluoro-7-[(3-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-11).
Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-77, M.P.- 270-272, Rf value-0.29, IR Range-1483cm^{-1}Ar C=C, 1371cm^{-1}C-F, 1651cm^{-1}C=O, 1263cm^{-1}C-S, 1583cm^{-1}C-NO_2, 3414cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(4-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-12).
Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-86, M.P.- 279-281, Rf value-0.22, IR Range-1456cm^{-1}Ar C=C, 1273cm^{-1}C-F, 1651cm^{-1}C=O, 1224cm^{-1}C-S, 1505cm^{-1}C-NO_2, 3342cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(2-methoxyphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-13).
Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-86, M.P.- 269-271, Rf value-0.24, IR Range-1435cm^{-1}Ar C=C, 1307cm^{-1}C-F, 1594cm^{-1}C=O, 1209cm^{-1}C-S, 1537cm^{-1}C-NO_2 1268cm^{-1}C-OCH_3

General synthesis of N-{6-fluoro-7-[(3-methoxyphenyl)-amino]1,3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-14).
Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-80, M.P.- 296-300, Rf value-0.28, IR Range-1434cm^{-1}Ar C=C, 1311cm^{-1}C-F, 1605cm^{-1}C=O, 1225cm^{-1}C-S, 1515cm^{-1}C-NO_2 1269cm^{-1}C-OCH_3

General synthesis of N-{6-fluoro-7-[(4-methoxyphenyl)-amino] 1, 3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code S-15).
Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-78, M.P.- 295-298, Rf value-0.27, IR Range-1444cm^{-1}Ar C=C, 1391cm^{-1}C-F, 1599cm^{-1}C=O, 1273cm^{-1}C-S, 1519cm^{-1}C-NO_2 1297cm^{-1}C-OCH_3.

General synthesis of N-{6-fluoro-7-[(2-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-16).
Mol. Formula- $C_{20}H_{12}O_3SN_4ClF$, M.Wt - 442.85, % Yield – 72, M.P-282-284, Rf value - 0.25, IR Range- 1485cm^{-1}Ar C=C, 1394cm^{-1}C-F, 1682cm^{-1}C=O, 1231cm^{-1}C-S, 1505cm^{-1}C-NO_2, 695cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(3-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-17).
Mol. Formula- $C_{20}H_{12}O_3SN_4ClF$, M.Wt - 442.85, % Yield –65, M.P-294-296, Rf value - 0.29, IR Range- 14854m^{-1}Ar C=C, 1332cm^{-1}C-F, 1690cm^{-1}C=O, 1295cm^{-1}C-S, 1515cm^{-1}C-NO_2, 696cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(4-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-18).
Mol. Formula- $C_{20}H_{12}O_3SN_4ClF$, M.Wt - 442.85, % Yield – 78, M.P-294-296, Rf value - 0.25, IR Range- 1484m^{-1}Ar C=C, 1331cm^{-1}C-F, 1681cm^{-1}C=O, 1277cm^{-1}C-S, 1509cm^{-1}C-NO_2, 695cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(2-methylphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-19).
Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-74, M.P.- 276-278, Rf value-0.23, IR Range-1448cm^{-1}Ar C=C, 1242cm^{-1}C-F, 1653cm^{-1}C=O, 1204cm^{-1}C-S, 1570cm^{-1}C-NO_2, 2924cm^{-1}C-CH_3.

General synthesis of N-{6-fluoro-7-[(3-methylphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-20).
Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-78, M.P.- 282-285, Rf value-0.30, IR Range-1445cm^{-1}Ar C=C, 1323cm^{-1}C-F, 1636cm^{-1}C=O, 1212cm^{-1}C-S, 1550cm^{-1}C-NO_2, 2925cm^{-1}C-CH_3.

General synthesis of N-{6-fluoro-7-[(4-methylphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-21).
Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-75, M.P.- 289-292, Rf value-0.33, IR Range-1434cm^{-1}Ar C=C, 1324cm^{-1}C-F, 1621cm^{-1}C=O, 1233cm^{-1}C-S, 1554cm^{-1}C-NO_2, 3053cm^{-1}C-CH_3.

General synthesis of N-{6-fluoro-7-[(2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-22).
Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-62, M.P.- 294-296, Rf value-0.31, IR Range-1470cm^{-1}Ar C=C, 1393cm^{-1}C-F, 1651cm^{-1}C=O, 1184cm^{-1}C-S, 1548cm^{-1}C-NO_2,.

General synthesis of N-{6-fluoro-7-[(2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-23).
Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-73, M.P.- 281-284, Rf value-0.25, IR Range-1439cm^{-1}Ar C=C, 1393cm^{-1}C-F, 1644cm^{-1}C=O, 1190 cm^{-1}C-S, 1551cm^{-1}C-NO_2,.

General synthesis of N-{6-fluoro-7-[(4-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-24).
Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-67, M.P.- 128-299, Rf value-0.28, IR Range-1484cm^{-1}Ar C=C, 1402cm^{-1}C-F, 1681cm^{-1}C=O, 1184cm^{-1}C-S, 1590cm^{-1}C-NO_2,.

General synthesis of N-{6-fluoro-7-[(2-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-25).
Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-71, M.P.- 291-293, Rf value-0.32, IR Range-1448cm^{-1}Ar C=C, 1327cm^{-1}C-F, 1623cm^{-1}C=O, 1242cm^{-1}C-S, 1570cm^{-1}C-NO_2, 3364cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(3-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-26).
Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-66, M.P.- 273-275, Rf value-0.29, IR Range-1458cm^{-1}Ar C=C, 1335cm^{-1}C-F, 1621cm^{-1}C=O, 1309cm^{-1}C-S, 1583cm^{-1}C-NO_2, 3414cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(4-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-27).
Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-70, M.P.- 287-289, Rf value-0.35, IR Range-1456cm^{-1}Ar C=C, 1327cm^{-1}C-F, 1614cm^{-1}C=O, 1275cm^{-1}C-S, 1571cm^{-1}C-NO_2, 3494cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(2-methoxyphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-28).
Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-75, M.P.- 285-287, Rf value-0.37, IR Range-1438cm^{-1}Ar C=C, 1311cm^{-1}C-F, 1590cm^{-1}C=O, 1275cm^{-1}C-S, 1484cm^{-1}C-NO_2 1275cm^{-1}C-OCH_3.

General synthesis of N-{6-fluoro-7-[(3-methoxyphenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-29).
Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-68, M.P.- 284-287, Rf value-0.31, IR Range-1438cm^{-1}Ar C=C, 1311cm^{-1}C-F, 1590cm^{-1}C=O, 1114cm^{-1}C-S, 1560cm^{-1}C-NO_2 1182cm^{-1}C-OCH_3.

General synthesis of N-{6-fluoro-7-[(4-methoxyphenyl)-amino] 1, 3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code S-30).
Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-77, M.P.- 291-293, Rf value-0.33, IR Range-1435cm^{-1}Ar C=C, 1311cm^{-1}C-F, 1590cm^{-1}C=O, 1183cm^{-1}C-S, 1538 cm^{-1}C-NO_2 1233 cm^{-1}C-OCH_3.

General synthesis of N-{6-fluoro-7-[(2-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code s-31).
Mol. Formula- $C_{20}H_{12}O_3SN_4ClF$, M.Wt - 442.85, % Yield –65, M.P-295-298, Rf value - 0.34, IR Range- 1438cm^{-1}Ar C=C, 1232cm^{-1}C-F, 1654cm^{-1}C=O,1167cm^{-1}C-S, 1534cm^{-1}C-NO_2, 663cm^{-1}C-Cl.

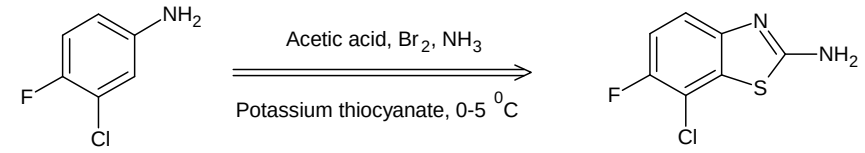
General synthesis of N-{6-fluoro-7-[(3-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-32).
Mol. Formula- $C_{20}H_{12}O_3SN_4ClF$, M.Wt - 442.85, % Yield – 71, M.P-282-285, Rf value - 0.38, IR Range- 1435cm^{-1}Ar C=C, 1263cm^{-1}C-F, 1594cm^{-1}C=O,1209cm^{-1}C-S, 1532cm^{-1}C-NO_2, 632cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(4-chlorophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-33).
Mol. Formula- $C_{20}H_{12}O_3SN_4ClF$, M.Wt - 442.85, % Yield – 68, M.P-288-291, Rf value - 0.35, IR Range- 1453cm^{-1}Ar C=C, 1275cm^{-1}C-F, 1616cm^{-1}C=O, 1147cm^{-1}C-S, 1515cm^{-1}C-NO_2, 721cm^{-1}C-Cl.

General synthesis of N-{6-fluoro-7-[(2-methylphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-34).
Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-70, M.P.- 283-286, Rf value-0.39, IR Range-1435cm^{-1}Ar C=C, 1307cm^{-1}C-F, 1594cm^{-1}C=O, 1209cm^{-1}C-S, 1537cm^{-1}C-NO_2, 2928cm^{-1}C-CH_3.

General synthesis of N-{6-fluoro-7-[(3-methylphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-35).
Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-77, M.P.- 289-291, Rf value-0.36, IR Range-1456cm^{-1}Ar C=C, 1344cm^{-1}C-F, 1651cm^{-1}C=O, 1224cm^{-1}C-S, 1538cm^{-1}C-NO_2, 2925cm^{-1}C-CH_3.

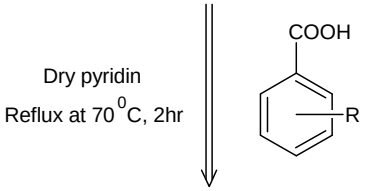
General synthesis of N-{6-fluoro-7-[(4-methylphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-36).
Mol. Formula-$C_{21}H_{15}O_3SN_4F$, M.Wt-422.43, % Yield-74, M.P.- 294-296, Rf value-0.38, IR Range-1450cm^{-1}Ar C=C, 1295cm^{-1}C-F, 1616cm^{-1}C=O, 1207cm^{-1}C-S, 1564cm^{-1}C-NO_2, 2913cm^{-1}C-CH_3.

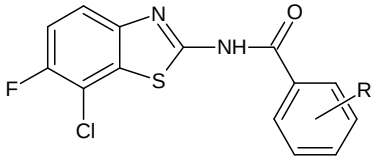


3-chloro-4-fluoroaniline

2-amino-6-fluoro-7-chloro-benzothiazole

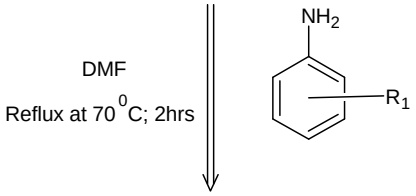
(2-AB)

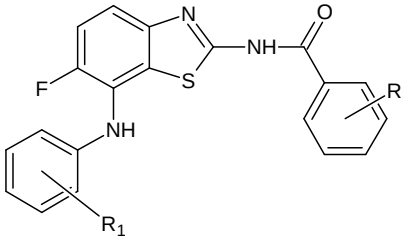




N-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-2 (3 or 4)-nitrobenzamide

(2-Nb, 3-Nb, 4-Nb)





N-(6-fluoro-7-[(substituted)-amino]-1,3-benzothiazole-2-yl)-2 (3 or 4)-nitrobenzamide

(S-1 to S-45)

Comp. Code	R	R_1	Comp. Code	R	R_1	Comp. Code	R	R_1
S-1	2-NO_2	2-Cl	**S-16**	3-NO_2	2-Cl	**S-31**	4-NO_2	2-Cl
S-2	2-NO_2	3-Cl	**S-17**	3-NO_2	3-Cl	**S-32**	4-NO_2	3-Cl
S-3	2-NO_2	4-Cl	**S-18**	3-NO_2	4-Cl	**S-33**	4-NO_2	4-Cl
S-4	2-NO_2	2-CH_3	**S-19**	3-NO_2	2-CH_3	**S-34**	4-NO_2	2-CH_3
S-5	2-NO_2	3-CH_3	**S-20**	3-NO_2	3-CH_3	**S-35**	4-NO_2	3-CH_3
S-6	2-NO_2	4-CH_3	**S-21**	3-NO_2	4-CH_3	**S-36**	4-NO_2	4-CH_3
S-7	2-NO_2	2-NO_2	**S-22**	3-NO_2	2-NO_2	**S-37**	4-NO_2	2-NO_2
S-8	2-NO_2	3-NO_2	**S-23**	3-NO_2	3-NO_2	**S-38**	4-NO_2	3-NO_2
S-9	2-NO_2	4-NO_2	**S-24**	3-NO_2	4-NO_2	**S-39**	4-NO_2	4-NO_2
S-10	2-NO_2	2-OH	**S-25**	3-NO_2	2-OH	**S-40**	4-NO_2	2-OH
S-11	2-NO_2	3-OH	**S-26**	3-NO_2	3-OH	**S-41**	4-NO_2	3-OH

S-12	2-NO_2	4-OH	**S-27**	3-NO_2	4-OH	**S-42**	4-NO_2	4-OH
S-13	2-NO_2	2-OCH_3	**S-28**	3-NO_2	2-OCH_3	**S-43**	4-NO_2	2-OCH_3
S-14	2-NO_2	3-OCH_3	**S-29**	3-NO_2	3-OCH_3	**S-44**	4-NO_2	3-OCH_3
S-15	2-NO_2	4-OCH_3	**S-30**	3-NO_2	4-OCH_3	**S-45**	4-NO_2	4-OCH_3

General synthesis of N-{6-fluoro-7-[(2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-37).

Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-69, M.P.- 275-277, Rf value-0.40, IR Range-1457cm^{-1}Ar C=C, 1362cm^{-1}C-F, 1653cm^{-1}C=O, 1242cm^{-1}C-S, 1540cm^{-1}C-NO_2,

General synthesis of N-{6-fluoro-7-[(2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-38).

Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-73, M.P.- 270-271, Rf value-0.34, IR Range-1434cm^{-1}Ar C=C, 1324cm^{-1}C-F, 1621cm^{-1}C=O, 1263cm^{-1}C-S, 1554cm^{-1}C-NO_2,

General synthesis of N-{6-fluoro-7-[(4-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-39).

Mol. Formula- $C_{20}H_{12}O_5SN_5F$, M.Wt-453.40, % Yield-60, M.P.- 266-269, Rf value-0.33, IR Range-1434cm^{-1}Ar C=C, 1303cm^{-1}C-F, 1641cm^{-1}C=O, 1277cm^{-1}C-S, 1546cm^{-1}C-NO_2.

General synthesis of N-{6-fluoro-7-[(2-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-40).

Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-61, M.P.- 273-276, Rf value-0.30, IR Range-1436cm^{-1}Ar C=C, 1322cm^{-1}C-F, 1596cm^{-1}C=O, 1222cm^{-1}C-S, 1498cm^{-1}C-NO_2, 3321cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(3-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-41).

Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-64, M.P.- 271-272, Rf value-0.37, IR Range-1436cm^{-1}Ar C=C, 1334cm^{-1}C-F, 1596cm^{-1}C=O, 1126cm^{-1}C-S, 1495cm^{-1}C-NO_2, 3458cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(4-hydroxyphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-42).

Mol. Formula-$C_{20}H_{13}O_4SN_4F$, M.Wt-424.40, % Yield-66, M.P.- 280-283, Rf value-0.32, IR Range-1413cm^{-1}Ar C=C, 1376cm^{-1}C-F, 1635cm^{-1}C=O, 1213cm^{-1}C-S, 1472cm^{-1}C-NO_2, 3523cm^{-1}C-OH.

General synthesis of N-{6-fluoro-7-[(2-methoxyphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-43).

Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-69, M.P.- 279-281, Rf value-0.35, IR Range-1448cm^{-1}Ar C=C, 1327cm^{-1}C-F, 1653cm^{-1}C=O, 1204cm^{-1}C-S, 1570cm^{-1}C-NO_2 1123cm^{-1}C-OCH_3.

Table No.-1 NMR Spectral Data of Compounds

Sl. No.	Comp. Code	Hydrogen	δ (ppm)	Multiplity
1	FCA	-2H	4.6	S
		-2H	7.7	S
2	2-AB	2H-NH	5.8	S
		1H-Ar-H	7.3	S
		1H-Ar-H	7.5	S
3	2-Nb	1H-NH	5.2	S
		2H-Ar-H	7.1	S
		4H-Ar-H	7.7	S
4	3-Nb	1H-NH	5.3	S
		2H-Ar-H	7.2	S
		4H-Ar-H	7.9	S
5	4-Nb	1H-NH	5.7	S
		2H-Ar-H	7.1	S
		4H-Ar-H	7.8	S
6	S-7	1H-NH	5.4	S
		1H-NH	5.8	S
		10H-Ar-H	7.5-7.9	M
7	S-15	1H-NH	5.3	S
		1H-NH	5.9	S
		3H-OCH_3	3.7	S
		10H-Ar-H	7.3-8.0	M
8	S-35	3H- CH_3	1.3	S
		1H-NH	5.6	S
		1H-NH	5.0	S
		10H-Ar-H	7.3-7.8	M

General synthesis of N-{6-fluoro-7-[(3-methoxyphenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-44).

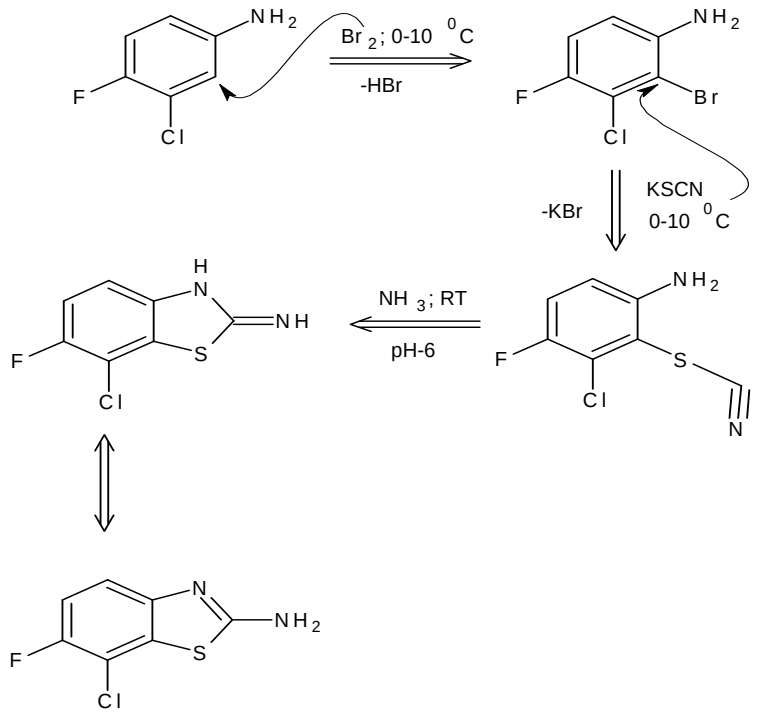
Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-73, M.P.- 265-266, Rf value-0. 13, IR Range-1434cm-1Ar C=C, 1341cm-1C-F, 1605cm-1C=O, 1202cm-1C-S, 1515cm-1C-NO2 1128cm-1C-OCH3.

General synthesis of N-{6-fluoro-7-[(4-methoxyphenyl)-amino] 1, 3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code S-45).

Mol. Formula- $C_{21}H_{15}O_4SN_4F$, M.Wt-438.43, % Yield-68, M.P.- 263-265, Rf value-0.30, IR Range-1444cm^{-1}Ar C=C, 1297cm^{-1}C-F, 1630cm^{-1}C=O, 1202cm^{-1}C-S, 1519cm^{-1}C-NO_2 1134cm^{-1}C-OCH_3.

Cyclisation Mechanism of Benzothiazole

Since, in 3-chloro -4fluoro aniline, the 2nd and 6th position is the most positive center but 2nd position behave as a more electrophilic centre. As the attack however was on the 2nd position, which is the electrophilic center and it is probable that bromine being as pseudo halogen, behaves as an electrophile by attacking this electrophilic center followed by replacement of hydrogen of 2nd position as one hydrogen bromide while one bromine atom remain attached. Replacement of bromine takes place by attack of thiocyanogen, behaves as a pseudo halogen (electrophile) followed by elimination of potassium bromide. Finally ring closure occur when pH adjusted at pH6 with ammonia and further rearrangement produce 2-amino-6-fluoro-7-chloro-(1, 3)-benzothiazole. Thus the reaction sequence can be as follows.



Antiinflammatory activity

Anti-inflammatory activity by carrageenin induced rat hind paw edema method: Healthy wistar albino rats of either sex weighing between 100-200gm were used for the evaluation of anti-inflammatory activity. The rats were housed comfortably in a group of five in a single clean plastic cage with metal frame lid on its top. They were housed under standard environmental conditions of temperature ($24+2^0$C) and relative humidity of 30-70%. All animals had free access to water and standard palletized laboratory animal diet *ad libitum.* In the present study, animals were provided with clean paddy husk bedding. Bedding was changed every alternate day to maintain proper hygienic conditions. Diclofenac (20mg/kg) aq. Suspension was prepared using 1% w/v solution of acacia as suspending agent. Suspension of compounds were prepared and administered orally similar to that of standard drug in dose 20 mg/kg body weight (b.w.) .Carragenan solution (1%w/v) in distilled water was prepared and injected (0.05ml) in sub-planter region to induce paw edema.

Male or female wistar albino rats with body weight 100-200 gm were taken. The animals were stared overnight before start of the study. Animals were divided into control, standard, different test groups comprising of five animals in each group. The animals were dosed orally with 20 mg/kg b.w. of the test drugs (suspended in 1% w/v solution of acacia), standard Diclofenac and control received the same volume of water. After 30 minutes freshly prepared 0.05ml of 1% solution of carrageenan was injected into the Sub-plantar side of the left hind paw. The paw was marked with ink at the level of lateral malleolus and immersed in mercury up to the mark to determine the paw volume. The paw volume was measured plethysmometrically at 0 hr and 3 hrs after carrageenin injection. Mean difference in paw volume was measured and percentage inhibition was calculated.

RESULTS AND DISCUSSION

In the present work, fluorochloroaniline was treated with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino-6-fluro-7-chloro (1, 3)-benzothiazole with yield around 51%, which was condensed with 2 (3 or 4)- nitrobenzoyl chloride in presence of dry pyridine and acetone to get N-(7-chloro-6-fluoro-1, 3-benzothiazole-2-yl)-2 (3 or 4)-nitrobenzamides with yield around 45-55% . To the above product 2-chloroaniline, 3-chloroaniline, 4-chloroaniline, o-toludine, m-toludine, p-toludine, 2-nitroaniline, 3-nitroaniline, 4-nitroaniline, 2-aminophenol, 3-aminophenol, 4-aminophenol, 2-anisidine, 3-anisidine and 4-anisidine in presence of DMF were treated to get newly synthesized N-{6-fluoro-7-[(substituted)-amino] 1, 3-benzothiazole-2-yl}-4-nitrobenzamides derivatives through replacing at 7^{th} position chlorine with yield around 58-78%. Reaction progress was monitored by thin layer chromatography. All the synthesized compounds of were characterized by melting point, solubility, TLC, IR, ^{1}HNMR spectra studies.

All the newly synthesized compounds were evaluated for anti-inflammatory activity. Anti-inflammatory activity of synthesized compounds were perform by carrageenin induced rat hind paw edema method on healthy wistar albino rats of either sex weighing between 100-200gm using dose 20 mg/kg body weight (b.w.) for all the synthesized compounds as well as for diclofenac as standard.

The response to injected carrageenin provides a convenient experimental model of inflammation which has been widely used for evaluating anti-inflammatory drugs. However, from the obtained results by anti-inflammatory activity it found that compound S-7, S-8, S-9, S-202, S-21, S-22 and S-35 exhibited excellent percentage of inhibition as compared to diclofenac.

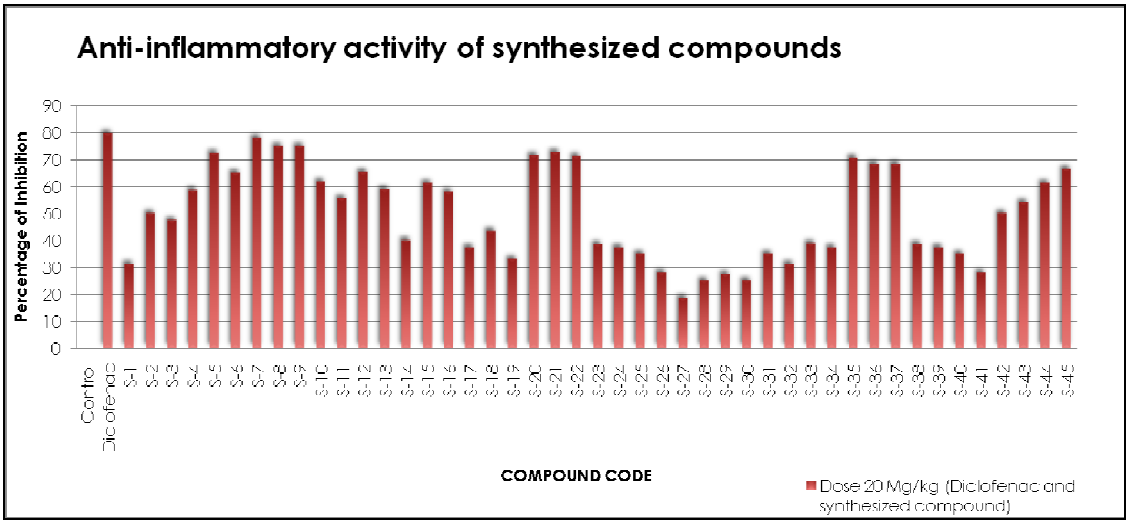


Fig. No. 1 Anti-inflammatory activity of synthesized compounds

Table No.-2Antiinflammatory activity (*in-vivo* model) Compound Code

S. No.	Name Compound/ Compound Code	Dose Mg/kg	Percentage of Inhibition
01	Control	--	--
02	Diclofenac	20	80.00
03	S-1	20	31.25
04	S-2	20	50.00
05	S-3	20	47.50
06	S-4	20	58.75
07	S-5	20	72.50
08	S-6	20	65.25
09	S-7	20	78.00
10	S-8	20	75.05
11	S-9	20	75.25
12	S-10	20	62.00
13	S-11	20	55.75
14	S-12	20	65.50
15	S-13	20	59.00
16	S-14	20	40.00
17	S-15	20	61.25
18	S-16	20	58.00
19	S-17	20	37.50
20	S-18	20	43.75
21	S-19	20	33.00
22	S-20	20	71.50
23	S-21	20	72.75
24	S-22	20	71.25
25	S-23	20	38.75
26	S-24	20	37.50
27	S-25	20	35.00
28	S-26	20	28.00
29	S-27	20	18.75
30	S-28	20	25.00
31	S-29	20	27.50
32	S-30	20	25.00
33	S-31	20	35.00
34	S-32	20	31.25
35	S-33	20	39.00
36	S-34	20	37.50
37	S-35	20	70.75
38	S-36	20	68.25
39	S-37	20	68.50
40	S-38	20	38.75
41	S-39	20	37.50
42	S-40	20	35.00
43	S-41	20	28.00
44	S-42	20	50.00
45	S-43	20	54.25
46	S-44	20	61.25
47	S-45	20	66.75

P<0.001 when compared to control group

CONCLUSION

Benzothiazole belongs to an important class of heterocyclic compounds and exhibits a wide range of biological properties and due to its potent activities, thus the synthesis of benzothiazole is an area of current interest. From the obtained results by anti-inflammatory activity it found that compound S-7 exhibited excellent percentage of inhibition as compared to diclofenac.

In summary, fluorobenzothiazole derivatives have been synthesized with a systematically substituted series of chloro, methyl, nitro, hydroxyl and methoxy for structure-activity relationship studies. These substituted fluorobenzothiazoles are very stable compounds, which renders them beneficial substances for biological or pharmacological trials.

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