

Microwave Irradiative Synthesis of Pharmacologically Active N-(6-X benzothiazole-2-yl)-4-(methylsulphonyl) - 2-nitrobenzamide used as Antimicrobial and Anti-Inflammatory Agent

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Abstract

A new series of N-(6-X benzothiazole-2-yl)-4-(methylsulphonyl) - 2-nitrobenzamide have been synthesized and evaluate in vitro as potential antimicrobials. Almost all the compounds are biologically active, showed antifungal and anti-inflammatory potential. Synthesis of substituted 2-aminobenothiazole by the interaction of substituted aniline was treated with a mixture of NH_4CNS and glacial CH_3COOH at room temperature. The thiocynogenation takes place in the presence of thiocynogen, generated in-situ by the reaction of Cu_2Cl_2 and NH_4CNS . This interacts with 4-methylsulphonyl-2-nitrobenzoic acid to form product in the presence of microwave irradiation. This method offers several advantages such as mild reaction condition, high yield, short reaction time, and simple experimental and workup procedure.

Keywords: Synthesis, 2-Aminobenzothiazole, Microwave Irradiation, Antimicrobial Activity, Anti-Inflammatory Activity.

Introduction

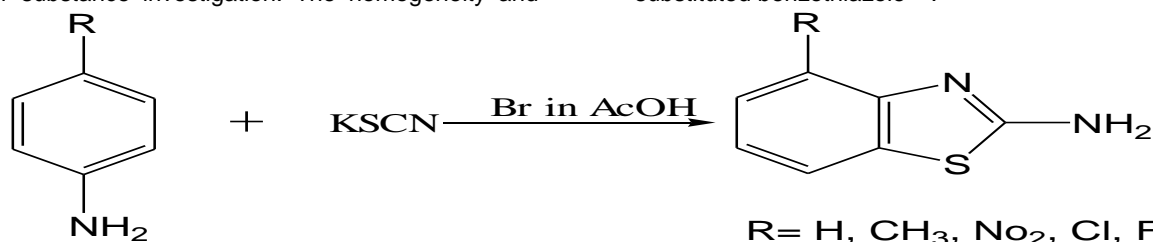
The science of heterocyclic mixes presently shaped a standout amongst the most broad and essential branch of natural science with quick extension of examination in the field of heterocyclic mixes. Heterocyclic mixes are broadly appropriated in nature and are basic to life in different ways. Because of expanded use of countless mixes, for example, pesticides, herbicides, pharmaceuticals and so forth as of late the improvement in heterocyclic science has been exceptionally fast. Serious examination of manufactured mixes, which are commonly analogs of known pharmaceutical specialists, brings about the improvement of new medications. The primary point in every single such examination is dependably to have a more adequate drug with least antagonistic impact.

Review of Literature

Benzothiazole is a heterocyclic compound, feeble base is produced using thiazole ring combined with benzene ring. The little and basic benzothiazole core is available in mixes assessing new items that have fascinating natural exercises like antitumor¹, anticonvulsant², antimicrobial³, anthelmintic⁴, antileishmanial⁵, hostile to tubercular⁶, schistosomicidal⁷, antifungal⁸, against inflammatory⁹ antipsychotic¹⁰ and against diabetic activities¹¹. What's more, benzothiazole ring is available in different marine or earthly regular mixes, which have helpful organic exercises. Because of their significance in pharmaceutical, the combination of various benzothiazole subordinations is an extensive region of current talk. The established technique includes buildup of o-aminothiophenols with substituted aldehydes, acyl chlorides, carboxylic acids or esters, nitriles. Other most usually utilized strategies incorporate Pd/Cu/Mn/chloraniline catalyzed cyclization of o-halothioformanilides. The Benzothiazole are set up by treatment of 2-mercaptoaniline with corrosive chlorides¹². In this present work, the union of substituted 2-aminobenzothiazole utilizing microwave light was researched. Microwave-Instigated Natural Response Improvement (MORE) science has gained fame as a non-regular method

for fast blend and numerous inquires about have portrayed quickened natural responses, and countless have showed up demonstrating the manufactured utility of MORE science in routine natural union¹³⁻²⁵. Microwave-helped natural union could help accomplish exceptional returns and clean response results at short response time. Natural dissolvable free response conditions take out the poisonous quality and combustibility issues related with basic solvents. Together, dissolvable free natural combinations helped by microwave illumination have being viewed as ecologically kindhearted approaches²⁶⁻²⁸. Biodegradation was the major benzothiazole removal route and the biodegradation efficiency obviously improved from 25.7% to 98.3% after adaptation¹⁹.

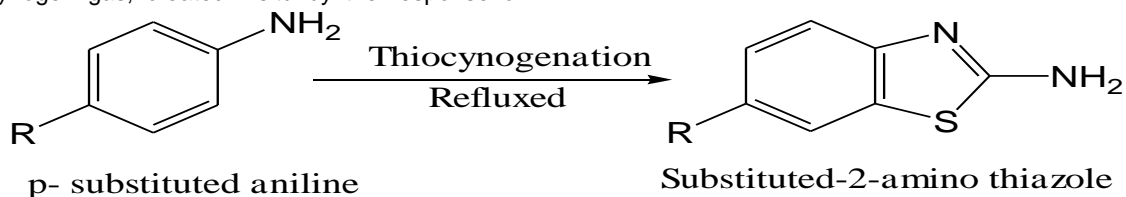
The present examination depicts a straightforward, simple system for the combination of substituted 2-aminobenzothiazole from substituted 2-amino benzothiazole for their pharmacological movement. The recently integrated benzothiazole corrosive subordinations were portrayed by present day physico-compound strategies, for example, IR, NMR spectroscopic examinations and by their substance investigation. The homogeneity and



Scheme-I

Synthesis of Substituted 2-amino benzothiazole by Thiocynogenation

In the Thiocynogenation technique 6-7 substituted aniline (0.1 moles) was treated with a blend of 7.6 gm NH₄CNS and 80 ml frosty CH₃COOH and it refluxes at room temperature for a hour and a half. The thiocynogenation happens within the sight of thiocynogen gas, created insitu by the response of



Scheme-II

Synthesis of N-(6-X benzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide

A blend of 2-Amino-6-X benzothiazoles (3 mol), 4-methylsulphonyl-2-nitrobenzoic corrosive (4 mol), NN'- diisopropylethylamine (9 mol) and HATU (4 mol) in DMF (5 ml) was taken in a container and helped by microwave illumination utilizing a household microwave for 10 min. Finishing of the response was checked by TLC. The abundance of the dissolvable

immaculateness of these mixes were checked by TLC & HPLC.

Experimental Section

Materials

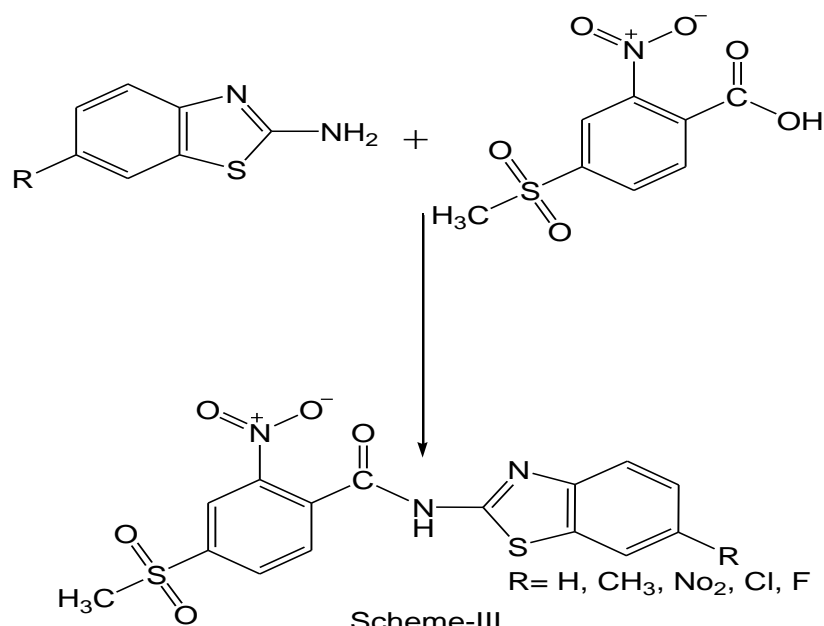
All mixes and synthetic concoctions were obtained from Sigma-Aldrich Synthetics and Merck. Softening focuses were resolved utilizing an open-finished slender tube technique and are uncorrected. TLC was performed on pre-covered plastic sheets of silica gel G/UV of 0.2 mm thickness (Macherey-Nagel, Germany). The homogeneity and virtue of the orchestrated mixes was checked by TLC. A FT-IR range was recorded on a Perkin-Elmer 1605 arrangement FT-IR in a KBr circle. ¹H NMR spectra were recorded at 300 MHz on a Bruker FT-NMR spectrophotometer utilizing TMS as inner standard.

General Procedure for Synthesis of Substituted 2-Amino Benzothiazole

One stage process for blend of substituted-2-aminobenzothiazole have been accounted for utilizing substituted aniline, potassium thiocyanate and bromine in acidic condition at low temperature (0-5°C). For the acidic media acidic corrosive as dissolvable is utilized for the amalgamation of 2-amino substituted benzothiazole¹².

Cu₂Cl₂ and NH₄CNS. Subsequent to cooling, 100 ml of concentrated HCl (6N) is added to the blend and warmth again for 30 minutes, cool and immersed arrangement of (Na₂CO₃) is added to kill it, till the strong was framed. Channel the strong isolated out, wash with cool water, dried and recrystallized with ethanol.

was expelled by rotavapour. The response blend was weakened with water and item was solidified in watery arrangement, separated under vacuum and solidified with ethanol. The item was sanitized by section chromatography on silica gel. The mixes got by his technique were looked at based on basic examination, IR, ¹H NMR, ¹³C NMR and mass mass spectra.



Synthesis of N-(benzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide

A light yellow solid, m.p. 155-259°C, Yield 60.12%, molecular formula $C_{14}H_{11}O_5N_3S_2$, anal. Calcd for $C_{14}H_{11}O_5N_3S_2$ (365.36): C, 46.02; H, 3.03; O, 21.36; N, 11.50; S, 17.55. Found: C, 46.40; H, 3.12; O, 21.34; N, 11.48; S, 17.64., 1H NMR ($CDCl_3$) δ in ppm, 2.34 (s, 3H, CH_3), 9.30 (s, 1H, —NH), 7.65-6.85 (m, 6H, Ar—H), IR (KBr) in cm^{-1} 1440 (C-C), 685 (C-S-C), 1040 (NO_2), 1680 (C=O), 1560 (C=N), 1560 (C=C of aromatic ring), 1309 (C-N), GCMS (H^+) m/e 398.88,

Synthesis of N-(6-methylbenzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide

A light yellow solid, m.p. 157- 261°C, Yield 70.12%, molecular formula $C_{15}H_{13}O_5N_3S_2$, anal. Calcd for $C_{15}H_{13}O_5N_3S_2$ (379.30): C, 46.02; H, 3.03; O, 21.36; N, 11.50; S, 17.55. Found: C, 46.40; H, 3.12; O, 21.34; N, 11.48; S, 17.64., 1H NMR ($CDCl_3$) δ in ppm, 2.34 (s, 6H, CH_3), 9.30 (s, 1H, —NH), 7.65-6.85 (m, 6H, Ar—H), IR (KBr) in cm^{-1} 1440 (C-C), 685 (C-S-C), 1040 (NO_2), 1680 (C=O), 1560 (C=N), 1560 (C=C of aromatic ring), 1309 (C-N), GCMS (H^+) m/e 378.30

Synthesis of N-(6-fluorobenzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide

A yellow solid, m.p. 161-163 °C, Yield 60.25%, molecular formula $C_{14}H_{10}O_5N_3S_2F$, anal. Calcd for $C_{14}H_{10}O_5N_3S_2F$ (383.35): C, 43.86; H, 2.63; O, 20.87; N, 10.96; S, 16.73; F, 4.95;. Found: C, 42.96; H, 2.53; O, 21.13; N, 11.18; S, 16.74; F, 5.36., 1H NMR ($CDCl_3$) δ in ppm, 2.34 (s, 3H, CH_3), 9.30 (s, 1H, —NH), 7.65-6.85 (m, 6H, Ar—H), IR (KBr) in cm^{-1} 1440 (C-C), 685 (C-S-C), 1040 (NO_2), 1680 (C=O), 1560 (C=N), 1560 (C=C of aromatic ring), 1309 (C-N), GCMS (H^+) m/e 382.35,

Synthesis of N-(6-chlorobenzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide

A yellow solid, m.p. 160-164 °C, Yield 65.32%, molecular formula $C_{14}H_{10}O_5N_3S_2Cl$, anal.

Calcd for $C_{14}H_{10}O_5N_3S_2Cl$ (399.88): C, 42.05; H, 2.52; O, 20.00; N, 10.51; S, 16.04; Cl, 8.87;. Found: C, 42.96; H, 2.53; O, 21.13; N, 11.18; S, 16.74; F, 5.36., 1H NMR ($CDCl_3$) δ in ppm, 2.34 (s, 3H, CH_3), 9.30 (s, 1H, —NH), 7.65-6.85 (m, 6H, Ar—H), IR (KBr) in cm^{-1} 1440 (C-C), 1680 (C=O), 1560 (C=N), 1560 (C=C of aromatic ring), 1309 (C-N), GCMS (H^+) m/e 398.88,

Synthesis of N-(6-Nitrobenzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide

A dark yellow solid, m.p. 163-167 °C, Yield 58.69%, molecular formula $C_{14}H_{10}O_7N_4S_2$, anal. Calcd for $C_{14}H_{10}O_7N_4S_2$ (410.36): C, 40.97; H, 2.45; O, 27.29; N, 13.65; S, 15.63. Found: C, 40.11; H, 2.33; O, 28.87; N, 13.33; S, 15.39., 1H NMR ($CDCl_3$) δ in ppm, 2.34 (s, 3H, CH_3), 9.30 (s, 1H, —NH), 7.65-6.85 (m, 6H, Ar—H), IR (KBr) in cm^{-1} 1440 (C-C), 680 (C-S-C), 1045 (NO_2), 1682 (C=O), 1560 (C=N), 1560 (C=C of aromatic ring), 1309 (C-N), GCMS (H^+) m/e 409.36

Results and Discussion

The objective mixes were set up by standard engineered systems. At first, Substituted-2-aminobenzothiazole incorporated by thiocyanogen procedure of 6-7 substituted aniline was treated with a blend of NH_4CNS and 80 ml frosty CH_3COOH and it refluxes at room temperature for a hour and a half. The thiocyanogen happens within the sight of thiocyanogen gas, produced insitu by the response of Cu_2Cl_2 and NH_4CNS . The acquired substituted - 2-aminobenzothiazole mixes additionally treated with 4-methylsulphonyl-2-nitrobenzoic corrosive in a brief timeframe with microwave illumination. The last mixes were portrayed by IR, 1H NMR, ^{13}C NMR, Mass spectroscopic information and basic investigations comes about. Orchestrated N-(6-X benzothiazole-2-yl)- 4-(methylsulphonyl) - 2-nitrobenzamide were utilized as antimicrobial and mitigating drugs.

Antimicrobial Studies

As indicated by the Clinical Research facility Guidelines Establishment (CLSI) guidelines [29] mixes appeared in Fig. A-Z was screened against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *E. faecalis*, *Escherichia coli* and *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Aspergillus niger* for using Norfloxacin (NRF) and Fluconazole as reference medication to decide the antibacterial movement and antifungal action separately. The trial after effects of antibacterial action [30] and antifungal movement communicated as MIC (mg/mL) are recorded in Table 1. The antibacterial action demonstrated a variable level of viability of the mixes against various stain of bacterial. As per table 1, mixes N-(benzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, N-(6-methylbenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide and N-(6-chlorobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide are more successful against *Staphylococcus aureus*, *E. faecalis*, *E. Coli* and *Pseudomonas* as reference sedate Norfloxacin. The rest compound N-(6-flourobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide and N-(6-chlorobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide are equivalent successful against

Staphylococcus aureus like as reference medication and *E. faecalis*, *E. Coli* and *Pseudomonas aeruginosa* indicated direct action contrasted with Norfloxacin. As it found in Table 1 mixes N-(benzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, N-(6-methylbenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, N-(6-flourobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, N-(6-chlorobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide and N-(6-Nitrobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide have articulated antifungal movement and surpass that of fluconazole utilizing as a source of perspective medication for antifungal action. All orchestrated mixes are less successful against the *Candida albicans* and *Candida parapsilosis* as reference medicate. The N-(benzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, and N-(6-methylbenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, are level with compelling against *Candida tropicalis* and Compound N-(benzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, indicated direct action against the *Aspergillus niger* contrasted with Fluconazole. The outcomes recommend that all orchestrated mixes might be worth concentrate promote as far as their antimicrobial movement.

Table 1 Minimum Inhibitory Concentration (MIC) Values for 6- N-(6-X benzothiazole-2-yl)- 4-(methylsulphonyl) -2-nitrobenzamide and Reference Drug for Antibacterial Activity

| Compound | MIC (µg/ml) | | | | | | | |
|---|-----------------------|----------------------|------------------|------------------------|------------------|----------------------|--------------------|-------------------|
| | Staphylococcus aureus | Escherichia faecalis | Escherichia Coli | Pseudomonas aeruginosa | Candida albicans | Candida parapsilosis | Candida tropicalis | Aspergillus niger |
| C ₁₄ H ₁₁ O ₅ N ₃ S ₂ | 125 | 125 | 250 | 250 | 125 | 125 | 125 | 250 |
| C ₁₅ H ₁₃ O ₅ N ₃ S ₂ | 125 | 125 | 250 | 250 | 125 | 125 | 125 | 125 |
| C ₁₄ H ₁₀ O ₅ N ₃ S ₂ F | 62.5 | 62.5 | 125 | 125 | 62.5 | 62.5 | 62.5 | 125 |
| C ₁₄ H ₁₀ O ₅ N ₃ S ₂ Cl | 62.5 | 62.5 | 125 | 125 | 62.5 | 62.5 | 62.5 | 125 |
| C ₁₄ H ₁₀ O ₇ N ₄ S ₂ | 125 | 125 | 250 | 250 | 62.5 | 62.5 | 62.5 | 62.5 |
| Norfloxacin | 62.5 | 2.95 | 4.9 | 62.5 | -- | -- | -- | -- |
| Fluconazole | -- | -- | -- | -- | 250 | 250 | 125 | 125 |

Anti-Inflammatory Activity

In the ongoing years various benzothiazole subsidiaries have been blended and found to have mitigating movement. The action of recently orchestrated mixes contrasted with indomethacin as a kind of perspective compound was estimated previously and 4 hours after carrageenan infusion. Percent of the oedema restraint was ascertained as respects saline control gathering and power was figured as respects the level of the difference in Indomethacin as a kind of perspective medication and tried mixes, as appeared in Table 2. All the tried mixes demonstrated a sensible hindrance of oedema measure running between 51.17% for compound N-(benzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, 70.85 % for compound N-(6-flourobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-

nitrobenzamide, 73.10 % for compound N-(benzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide, 76% for mixes N-(6-methylbenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide and N-(6-chlorobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide and 79.92% for Indomethacin utilizing as reference sedate. In action relationship perspective, the mitigating movement of the N-(6-methylbenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide and N-(6-chlorobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide was observed to guarantee one. Be that as it may, N-(benzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide and N-(6-flourobenzothiazole-2-yl)- 4-(methylsulphonyl)- 2-nitrobenzamide likewise demonstrated great calming action 73.10% and 70.85% individually.

Table 2: Anti-Inflammatory Activity of 6- N-(6-X Benzothiazole-2-yl)-4-(Methylsulphonyl)-2-nitrobenzamide on Carrageenan Induced Oedema of Laboratory Mice

| Compound | Oedema Volume (ml) | | | |
|---|--------------------|------------|-------------|----------------------------|
| | Dose (mg/kg) | Zero Min. | 4 hour | % Inhibition after 4 hours |
| Control | Normal saline | 29.83±1.23 | 148.34±2.35 | -- |
| C ₁₄ H ₁₁ O ₅ N ₃ S ₂ | 250 mg/kg | 27.23±1.44 | 72.42±1.21 | 51.17 |
| C ₁₅ H ₁₃ O ₅ N ₃ S ₂ | 250 mg/kg | 23.83±1.41 | 34.34±1.42 | 76.85 |
| C ₁₄ H ₁₀ O ₅ N ₃ S ₂ F | 250 mg/kg | 28.83±1.87 | 43.67±1.28 | 70.85 |
| C ₁₄ H ₁₀ O ₅ N ₃ S ₂ Cl | 250 mg/kg | 26.73±1.63 | 35.27±1.62 | 76.22 |
| C ₁₄ H ₁₀ O ₇ N ₄ S ₂ | 250 mg/kg | 27.23±1.44 | 39.89±1.34 | 73.10 |
| Indomethacin | 10 mg/kg | 27.83±1.72 | 30.22±1.57 | 79.62 |

Conclusion

All in all, we have created basic and green convention for blend of novel 6-N-(6-X benzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide with the response of 2-amino-6-X benzothiazole and 4-methylsulphonyl-2-nitrobenzoic corrosive. Amide combination response is within the sight of HATU response went before in worthy yields. This strategy offers a few favorable circumstances, for example, mellow response condition high return, short response time, and straightforward exploratory and workup technique. The vast majority of the mixes showed great antimicrobial movement and calming action.

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