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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-aminobenothaizole 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-nitrobezoic 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-Aminobezothiazole, 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 antitumor[1], anticonvulsant[2], antimicrobial[3], anthelmintic[4], antileishmanial[5], hostile to tubercular[6], schictosomicidal[7], antifungal[8], against inflammatory[9] antipsychotic[10] and against diabetic activities[11]. 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 variousbenzothiazole subordinates 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/chloranilne catalyzed cyclization of o-halothioformanilides. TheBenzothiazole are set up by treatment of 2-mercaptoaniline with corrosive chlorides [12]. In this present work, the union of substituted 2-aminobenzothiazole utilizing microwave light was researched. Microwave-Instigated Natural Response Improvement (MORE) science hasgained 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 union[13-25]. 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 approachs[26-28]. Biodegradation was the major benzothiazole removal route and the biodegradation efficiency obviously improved from 25.7% to 98.3% after adaptation [19].

The present examination depicts a straightforward, simple system for the combination of substituted2-amonibenothaizoleacid subordinates from substituted 2-amino benzothiazolefor their pharmacological movement. The recently integrated benzothaizole corrosive subordinates were portrayed by present day physico-compound strategies, for example, IR, NMR spectroscopic examinations and by their substance investigation. The homogeneity and immaculateness of these mixes were checked by TLC& HPLC.

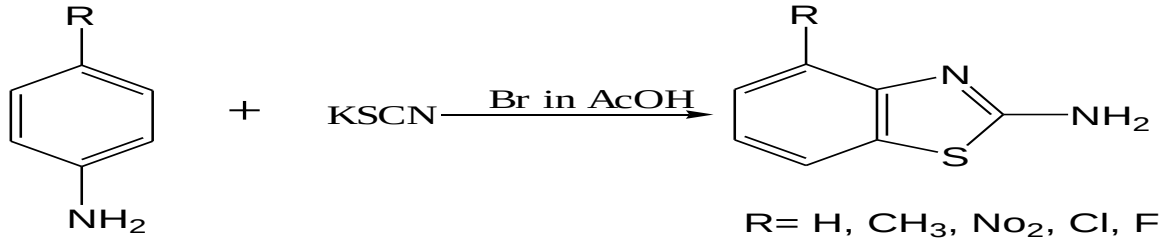
Experimental Section

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

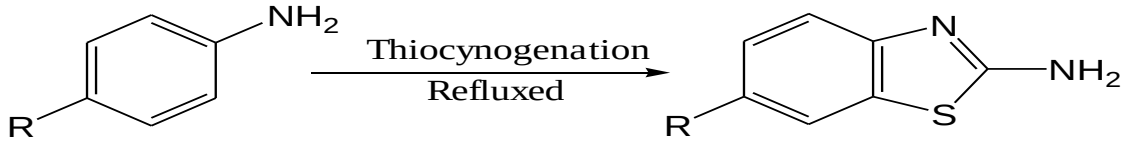
One stage process for blend of substituted-2-aminobenzothiazolehave been accounted for utilizing substituted aniline, potassium thiocyanate and bromine in acidic condition at low temperature (0-5^{O}C). For the acidic media acidic corrosive as dissolvable is utilized for the amalgamation of 2-amino substituted benzothiazole [12].



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 NH_4CNS and 80 ml frosty CH_3COOH and it refluxes at room temperature for a hour and a half. Thethiocynogenation happens within the sight of thiocynogen gas, created insitu by the response of Cu2Cl2and NH_4CNS. Subsequent to cooling, 100 ml of concentrated HCl (6N) is added to the blend and warmth againfor 30 minutes, cool and immersed arrangement of (Na_2CO_3) is added to kill it, till the strong was framed. Channel the strong isolated out, wash with cool water, dried and recrystallized with ethanol.



p- substituted aniline

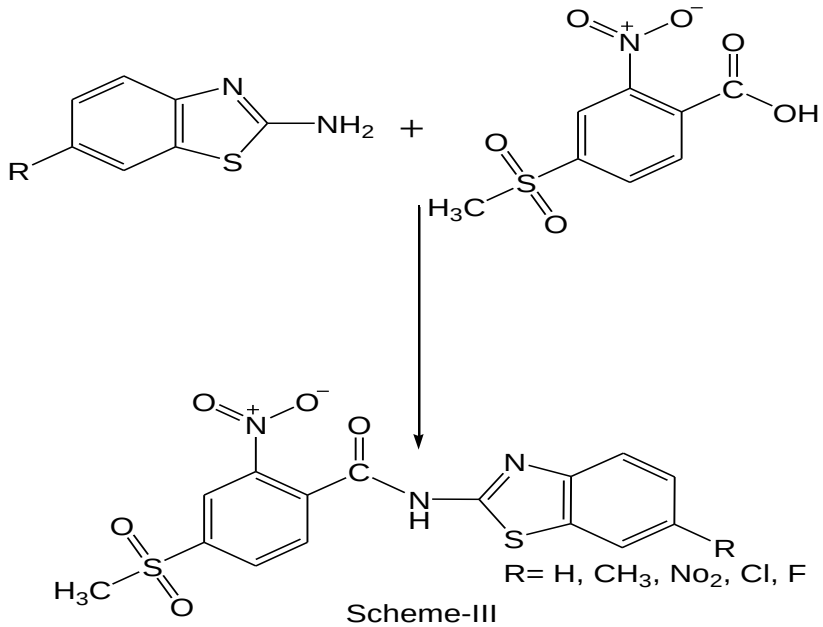
Substituted-2-amino thiazole

R= H, CH_3, No_2, Cl, F

Scheme-II

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

A blend of 2-Amino-6-X benzothaizoles (3 mol), 4-methylsulphonyl-2-nitrobezoic 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 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.



Scheme-III

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

A light yellow solid, m.p. 155-259^{0}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.,^{1}H 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),

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

A light yellow solid, m.p. 157- 261^{0}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., ^{1}H 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-flourobenzothiazole-2-yl)-4-(methylsulphonyl)-2-nitrobenzamide

A yellow solid, m.p. 161-163 ^{o}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., ^{1}H 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 ^{o}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., ^{1}H 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 ^{o}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., ^{1}H 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 thiocynogenation 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. Thethiocynogenation happens within the sight of thiocynogen 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-nitrobezoic 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 coliand Candida albicans, Candida parapsilosis, Candida tropicalis, Aspergillusnigerforusing Norfloxacin (NRF) and Fluconazole as reference medication to decide the antibacterial movement and antifungal action separately. The trial aftereffects 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-nitrobenzamideandN-(6-Nitrobenzothiazole-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 Aspergillusniger 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)							
	Staphyloco-ccusaureus	Escheric-hiafaecalis	Escheric-hia Coli	Pseudomonas aeruginosa	Candida albicans	Candida parapsilosis	Candida tropicalis	Aspergillus niger
$C_{14}H_{11}O_5N_3S_2$	125	125	250	250	125	125	125	250
$C_{15}H_{13}O_5N_3S_2$	125	125	250	250	125	125	125	125
$C_{14}H_{10}O_5N_3S_2F$	62.5	62.5	125	125	62.5	62.5	62.5	125
$C_{14}H_{10}O_5N_3S_2Cl$	62.5	62.5	125	125	62.5	62.5	62.5	125
$C_{14}H_{10}O_7N_4S_2$	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-nitrobenzamideand 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-nitrobenzamideand 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	--
$C_{14}H_{11}O_5N_3S_2$	250 mg/kg	27.23±1.44	72.42±1.21	51.17
$C_{15}H_{13}O_5N_3S_2$	250 mg/kg	23.83±1.41	34.34±1.42	76.85
$C_{14}H_{10}O_5N_3S_2F$	250 mg/kg	28.83±1.87	43.67±1.28	70.85
$C_{14}H_{10}O_5N_3S_2Cl$	250 mg/kg	26.73±1.63	35.27±1.62	76.22
$C_{14}H_{10}O_7N_4S_2$	250 mg/kg	27.23±144	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-methylsulfonyl-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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