IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Research Article**
January 2024 Vol.:30, Issue:1


# Synthesis and Biological Evaluation of Phenyl Aminothiazole Derivatives for Antimicrobial Activity

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
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**Shashi Prabha*[1], Ankita Srivastava[2], Bal Krishan Singh[2]**

*Research Scholar[1], Associate Professor[2], Aryakul College of Pharmacy and Research, Lucknow, Uttar Pradesh, India*

**Submitted:** 25 December 2023
**Accepted:** 31 December 2023
**Published:** 30 January 2024

HUMAN JOURNALS
ijppr.humanjournals.com

**Keywords:** Thiazole, Antibacterial, antimicrobial, Gram-positive & Gram-negative bacteria

**ABSTRACT**

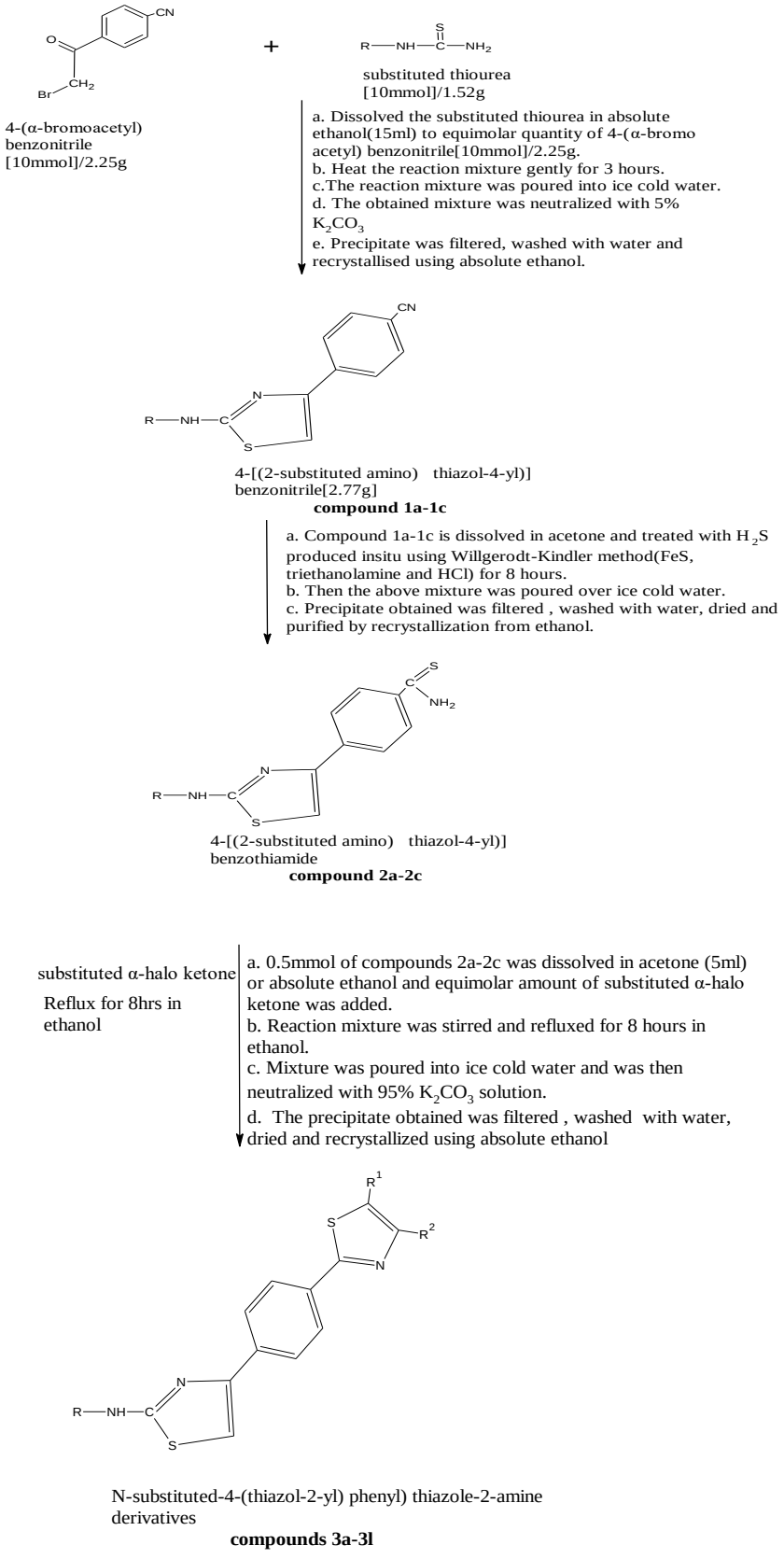
A series of 12 new phenylaminethiazole derivatives (3a-3l) were synthesized from 4-(2- phenylamino)-thiazol-4-yl)-benzothioamide and 2-hydroxy-5-(2-(phenylamino)-thiazol-4-yl)- benzonitrile with several reaction. All compounds were characterized by elemental analysis and spectral data (MS, FT-IR and NMR). The final 12 substances were screened for antimicrobial activity, against two Gram-positive, one Gram-negative bacterial strains, and two fungal strains. Some of the synthesized molecules were partially potent than the reference drugs, against the pathogenic strains used. The antibacterial activity of compounds was more pronounced against the Gram-positive strains. Compound 3i manifested the highest growth inhibitory effect against all pathogens tested.

## 1. INTRODUCTION:

Since the discovery and development of effective drugs against microbial infections, human health has been significantly improved [1]. However, the latter abuse and the inappropriate use of anti-infectious agents have led to microbial multi-drug resistance. Faced with this problem, it is imperative to develop new approaches to circumvent this phenomenon, thus the need to discover new classes of drugs with original structures and mechanisms of action [2,3].

Thiazole is the five-member ring system having two hetero atoms (S, N) placed in heterocyclic ring at 1, 3-positions. Thiazoles are useful structural units in the field of medicinal chemistry and have been reported to exhibit a variety of biological activity [4, 5]. Number of thiazole derivatives shows good biological as well pharmacological activities like antibacterial and antifungal, analgesic, CNS stimulate, antitubercular, anti-HIV, anti-inflammatory, algicidol etc. [6-12] Thiazole containing N=C=S moiety have been used as antiphychotics and antimalarial. Aminothiazole derivatives are well explored as useful clinical agents and some of the derivatives of thiazoles have shown inhibition towards herpes simplex virus. [13-15] The present paper deals with the synthesis of some novel amides of phenylazothiazoles to evaluate their biological activity.

## 2. EXPERIMENTAL




**Scheme 1: Synthesis of phenyl aminothiazole derivatives [16, 17]**

**Characterization of synthesized compound:**

**Melting point:** The melting points of all the synthesized compounds were determined using capillary tubes with Thermonic model C-LMP-1-Campbell melting point apparatus and were uncorrected.

**Thin layer chromatography:** The synthesized compounds were tested for their purity by performing TLC over glass plates coated with silica gel with a suitable mobile phase system and detected by iodine vapor.

**Infra-red spectroscopy:** The structures of the synthesized compounds were elucidated by JASCO FTIR-4100 spectrophotometer in KBr disc.

**NMR spectroscopy:** 1HNMR spectral study was done using AV-III 400 Fourier Transform NMR spectrophotometer in TMS as standard.

**Mass spectroscopy:** Mass spectra of selected compounds were determined on JOEL SX 102 -GC MATE 700 EV instrument employing electron impact ionization technique. [18-22]

**Antibacterial activity:** The compounds were tested in-vitro for their antibacterial activity against two microorganisms viz. Staphylococcus albus, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Vibrio cholera, Micrococcus luteus Salmonella Paratyphii, which are pathogenic in human beings by Disc diffusion method and Broth Dilution Method. The antibacterial activity was evaluated by measuring zone of inhibition in mm and minimum inhibitory concentration in µg/ml. [23-24]

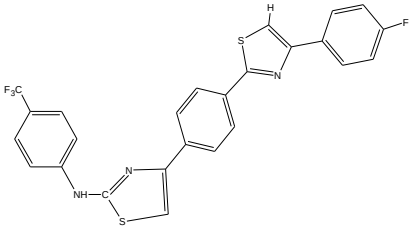
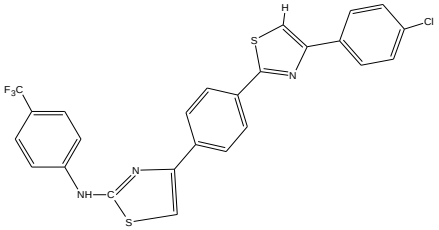
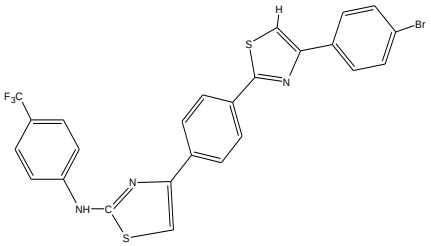
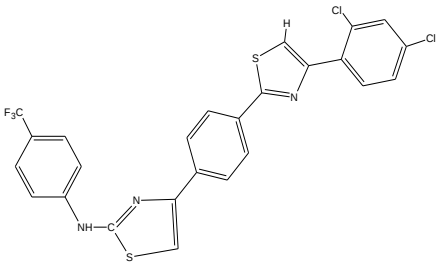
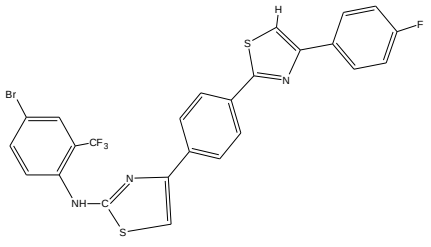
**Antifungal activity:** The compounds were tested in-vitro for their antifungal activity against Aspergillus niger, Trichophyton rubrum, Candida albicans, and Monascus purpureus by Disc diffusion method and Broth Dilution Method. The antifungal activity was evaluated by measuring the zone of inhibition in mm and minimum inhibitory concentration in µg/ml. [23-24]

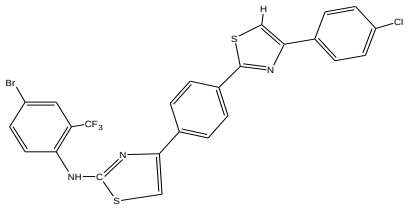
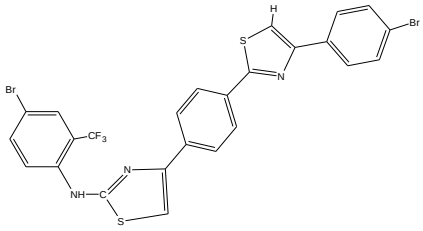
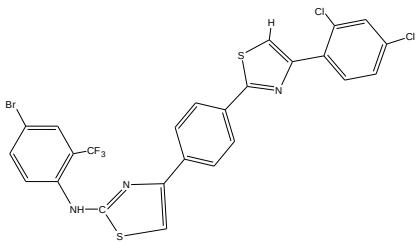
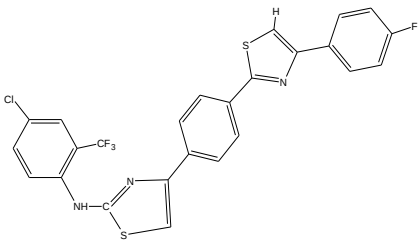
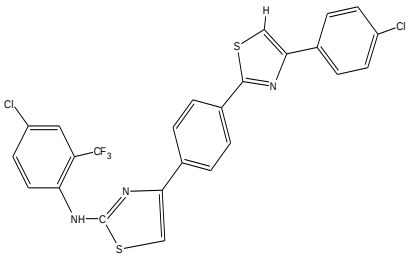
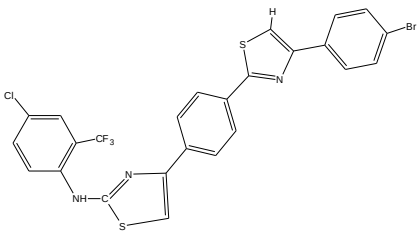
## 3. RESULTS AND DISCUSSION

**Table 1: List of compounds synthesized**

| **Derivatives** | **R(Substituted thiourea)** | **Substituted** α halo-ketone | |
|---|---|---|---|
| | | **R1** | **R2** |
| 3a | 3-Trifluoromethyl thiourea | H | p-fluorophenyl acetophenone |
| 3b | 3-Trifluoromethyl thiourea | H | p-chlorophenyl acetophenone |
| 3c | 3-Trifluoromethyl thiourea | H | p-bromophenyl acetophenone |
| 3d | 3-Trifluoromethyl thiourea | H | 2,4-dichlorohenyl acetophenone |
| 3e | 4-Br-2-(Trifluoromethyl)phenyl thiourea | H | p-fluorophenyl acetophenone |
| 3f | 4-Br-2-(Trifluoromethyl)phenyl thiourea | H | p-chlorophenyl acetophenone |
| 3g | 4-Br-2-(Trifluoromethyl)phenyl thiourea | H | p-bromophenyl acetophenone |
| 3h | 4-Br-2-(Trifluoromethyl)phenyl thiourea | H | 2,4-dichlorophenyl acetophenone |
| 3i | 4-Cl-2-(Trifluoromethyl)phenyl thiourea | H | p-fluorophenyl acetophenone |
| 3j | 4-Cl-2-(Trifluoromethyl)phenyl thiourea | H | p-chlorophenyl acetophenone |
| 3k | 4-Cl-2-(Trifluoromethyl)phenyl thiourea | H | p-bromophenyl acetophenone |
| 3l | 4-Cl-2-(Trifluoromethyl)phenyl thiourea | H | 2,4-dichlorophenyl acetophenone |

**Table 2: IUPAC names and structure of synthesized compounds**

| Derivatives | Chemical name of Compound | Structure |
|---|---|---|
| 3a. | 4-{4-[4-(4-fluorophenyl)-1,3-thiazol-2-yl]phenyl}-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine |  |
| 3b | 4-{4-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]phenyl}-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine |  |
| 3c | 4-{4-[4-(4-bromophenyl)-1,3-thiazol-2-yl]phenyl}-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine |  |
| 3d | 4-{4-[4-(2,4-dichlorophenyl)-1,3-thiazol-2-yl]phenyl}-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine |  |
| 3e. | *N*-[4-bromo-2-(trifluoromethyl)phenyl]-4-{4-[4-(4-fluorophenyl)-1,3-thiazol-2-yl]phenyl}-1,3-thiazol-2-amine |  |

| | | |
|---|---|---|
| 3f | *N*-[4-bromo-2-(trifluoromethyl)phenyl]-4-{4-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]phenyl}-1,3-thiazol-2-amine |  |
| 3g | 4-{4-[4-(4-bromophenyl)-1,3-thiazol-2-yl]phenyl}-*N*-[4-bromo-2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine |  |
| 3h | *N*-[4-bromo-2-(trifluoromethyl)phenyl]-4-{4-[4-(2,4-dichlorophenyl)-1,3-thiazol-2-yl]phenyl}-1,3-thiazol-2-amine |  |
| 3i | *N*-[4-chloro-2-(trifluoromethyl)phenyl]-4-{4-[4-(4-fluorophenyl)-1,3-thiazol-2-yl]phenyl}-1,3-thiazol-2-amine |  |
| 3j | 4-{4-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]phenyl}-*N*-[4-chloro-2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine |  |
| 3k | 4-{4-[4-(4-bromophenyl)-1,3-thiazol-2-yl]phenyl}-*N*-[4-chloro-2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine |  |

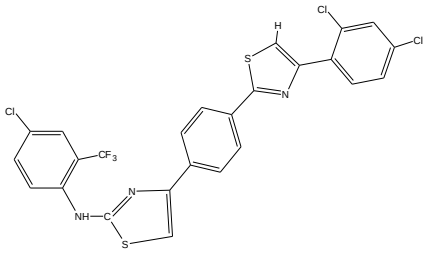
| | | |
|---|---|---|
| 3l | *N*-[4-chloro-2-(trifluoromethyl) phenyl]-4-{4-[4-(2,4-dichlorophenyl)-1,3-thiazol-2-yl]phenyl}-1,3-thiazol-2-amine |  |

**Table 3: Chemical Properties of synthesized compounds(3a-3l)**

| Derivatives | Chemical Formula | M.W | Composition | | | | | | | M.P.(°C) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | F | N | S | Br | Cl | |
| 3a. | $C_{25}H_{15}F_4N_3S_2$ | 497.53 | 60.35% | 3.04% | 15.27% | 23.25% | 21.24% | --- | --- | 170°C |
| 3b | $C_{25}H_{15}F_3N_3S_2Cl$ | 513.98 | 58.42% | 2.94% | 11.09% | 8.18% | 12.48% | --- | 6.90% | 256°C |
| 3c | $C_{25}H_{15}F_3N_3S_2Br$ | 558.43 | 53.77% | 2.71% | 10.21% | 7.52% | 11.48% | 14.31% | --- | 207°C |
| 3d | $C_{25}H_{14}F_3N_3S_2Cl_2$ | 548.42 | 54.75% | 2.57% | 10.39% | 7.66% | 11.69% | --- | 13.93% | 217°C |
| 3e. | $C_{25}H_{14}F_4N_3S_2Br$ | 576.42 | 52.09% | 2.45% | 13.18% | 7.29% | 11.13% | 13.86% | --- | 219°C |
| 3f | $C_{25}H_{14}F_3N_3S_2BrCl$ | 592.88 | 50.65% | 2.38% | 9.61% | 7.09% | 10.82% | 13.48% | 5.98% | 218°C |
| 3g | $C_{25}H_{14}F_3N_3S_2Br_2$ | 637.33 | 47.11% | 2.21% | 8.94% | 6.59% | 10.06% | 25.07% | --- | 182°C |
| 3h | $C_{25}H_{13}F_3N_3S_2BrCl_2$ | 627.32 | 47.86% | 2.09% | 9.09% | 6.70% | 10.22% | 12.74% | 11.30% | 201°C |
| 3i | $C_{25}H_{14}F_4N_3S_2Cl$ | 531.97 | 56.44% | 2.65% | 14.29% | 7.90% | 12.06% | ---` | 6.66% | 146°C |
| 3j | $C_{25}H_{14}F_3N_3S_2Cl_2$ | 548.42 | 54.75% | 2.57% | 10.39% | 2.66% | 11.69% | --- | 12.93% | 205°C |
| 3k | $C_{25}H_{14}F_3N_3S_2BrCl$ | 592.88 | 50.65% | 2.38% | 9.61% | 7.09% | 10.82% | 13.48% | 5.98% | 197°C |
| 3l | $C_{25}H_{13}F_3N_3S_2Cl_3$ | 582.87 | 51.51% | 2.25% | 9.78% | 7.21% | 11.00% | --- | 18.25% | 214°C |

**Table 4: Physical and chemical properties of synthesized compound (3a-3l)**

| Code | Chemical Formula | Colour | Rf value | % yield |
|---|---|---|---|---|
| 3a. | $C_{25}H_{15}F_4N_3S_2$ | Beige solid | 0.55 | 57.85% |
| 3b | $C_{25}H_{15}F_3N_3S_2Cl$ | Pale yellow solid | 0.61 | 68.0% |
| 3c | $C_{25}H_{15}F_3N_3S_2Br$ | Light yellow solid | 0.52 | 72% |
| 3d | $C_{25}H_{14}F_3N_3S_2Cl_2$ | Yellow | 0.89 | 70% |
| 3e. | $C_{25}H_{14}F_4N_3S_2Br$ | Brown solid | 0.72 | 63% |
| 3f | $C_{25}H_{14}F_3N_3S_2BrCl$ | Light yellow solid | 0.68 | 78% |
| 3g | $C_{25}H_{14}F_3N_3S_2Br_2$ | Dark yellow | 0.91 | 64% |
| 3h | $C_{25}H_{13}F_3N_3S_2BrCl_2$ | Pale yellow | 0.77 | 76% |
| 3i | $C_{25}H_{14}F_4N_3S_2Cl$ | Dark yellow solid | 0.61 | 59% |
| 3j | $C_{25}H_{14}F_3N_3S_2Cl_2$ | Light yellow solid | 0.80 | 66% |
| 3k | $C_{25}H_{14}F_3N_3S_2BrCl$ | Yellow solid | 0.59 | 52% |
| 3l | $C_{25}H_{13}F_3N_3S_2Cl_3$ | Reddish brown | 0.85 | 56% |

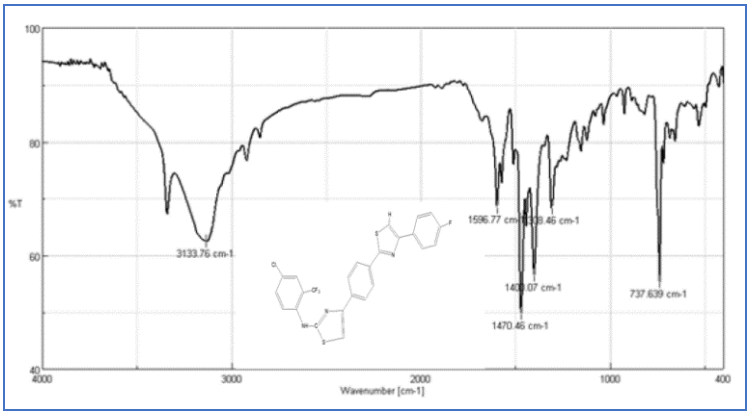



**Figure 1: FTIR Spectra of compound 3i**

**Table 5: Interpretation of FTIR Spectra of compound 3i**

| S. No. | Frequency | Assignment |
|---|---|---|
| 1 | 686 | C-S-C stretching |
| 2 | 827 | C-F |
| 3 | 1470 | C-N stretching |
| 4 | 1596 | N=O stretching |
| 5 | 1596 and 1570 | Phenothiazine ring |
| 6 | 2920, 1512, 737 | Aromatic stretching |
| 7 | 3340 | NH stretching |

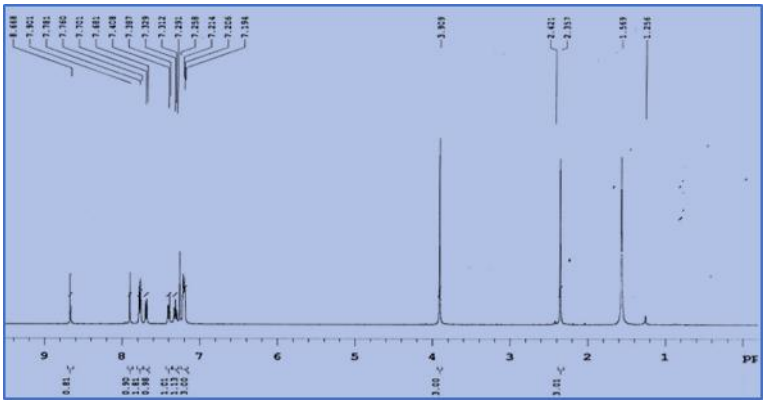



**Figure 2: NMR Spectra of Compound 3i**

**Table 6: Interpretation of proton NMR spectra of compound 3i**

| S. No. | δ value (in ppm) | Assignment |
|---|---|---|
| 1. | 8.66 | s, 1H |
| 2. | 7.90 | d, *J*= 8.0 Hz, 2H |
| 3. | 7.77 | d, *J*= 8.4 Hz, 2H |
| 4. | 7.69 | d, *J*= 8.4 Hz, 1H |
| 5. | 7.20 | d, *J*= 4.8 Hz, 3H |
| 6. | 3.90 | s, 3H |
| 7. | 2.35 | s, 3H |

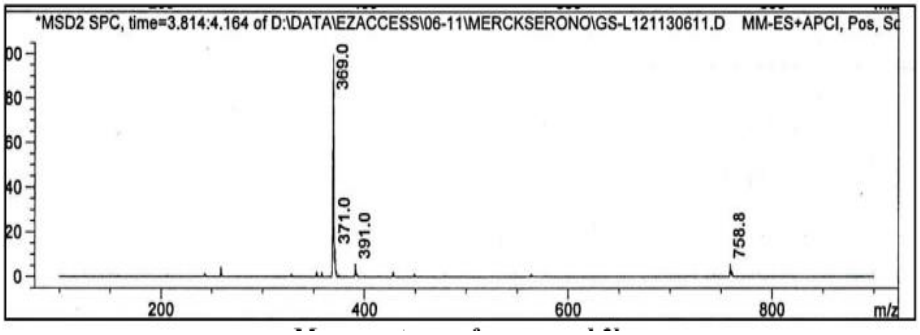



**Figure 3: Mass spectra of Compound 3i**

**Table 7: Interpretation of proton NMR spectra of compound 3i**

| S. No. | m/z | Assignment |
|---|---|---|
| 1. | 368.07 | Calcd |
| 2. | 369 | $[M+H]^+$ |

**Table 8: Antibacterial screening of titled compounds by disc diffusion method for gram-positive and gram-negative bacteria**

| Code | ZONE OF INHIBITION in mm | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **M. luteus** | **B. subtilis** | **S. aureus** | **S. albus** | **S. paratyphii** | **P. auroginosa** | **E. coli** | **V. cholera** |
| 3a | 6 | 10 | 10 | 8 | 11 | 12 | 10 | 13 |
| 3b | 5 | 7 | 7 | 9 | 9 | 7 | 8 | 9 |
| 3c | 9 | 11 | 9 | 10 | 10 | 11 | 11 | 12 |
| 3d | 7 | 10 | 6 | 11 | 11 | 13 | 12 | 11 |
| 3e | 8 | 8 | 7 | 7 | 8 | 8 | 9 | 7 |
| 3f | 12 | 11 | 11 | 11 | 13 | 14 | 12 | 13 |
| 3g | 7 | 9 | 6 | 8 | 8 | 8 | 7 | 6 |
| 3h | 5 | 8 | 8 | 6 | 9 | 8 | 6 | 7 |
| 3i | 11 | 13 | 13 | 12 | 12 | 12 | 13 | 11 |
| 3j | 8 | 7 | 8 | 8 | 7 | 9 | 6 | 8 |
| 3k | 6 | 8 | 9 | 7 | 7 | 8 | 8 | 9 |
| 3l | 8 | 6 | 9 | 7 | 8 | 6 | 9 | 8 |
| Ciprofloxacin | **17** | **19** | **16** | **17** | **20** | **18** | **19** | **19** |

3a-3l = synthesized compounds in the concentration of 10 µg/disc, Ciprofloxacin in the concentration of 5 µg/disc

**Table 9: Antifungal screening of titled compounds by disc diffusion method**

| Code | ZONE OF INHIBITION in mm | | | |
|---|---|---|---|---|
| | A. niger | T. rubrum | C. albicans | M. purpurea |
| 3a | 10 | 11 | 12 | 13 |
| 3b | 8 | 8 | 9 | 10 |
| 3c | 12 | 13 | 12 | 11 |
| 3d | 14 | 12 | 11 | 10 |
| 3e | 9 | 8 | 9 | 8 |
| 3f | 12 | 11 | 10 | 12 |
| 3g | 8 | 8 | 9 | 9 |
| 3h | 7 | 7 | 8 | 8 |
| 3i | 14 | 13 | 14 | 13 |
| 3j | 10 | 9 | 8 | 8 |
| 3k | 9 | 9 | 8 | 9 |
| 3l | 8 | 8 | 9 | 9 |
| Clotrimazole | **20** | **18** | **13** | **17** |

3a-3l= synthesized compounds in the concentration of 10 µg/disc

**Table 10: Minimum inhibitory concentration of synthesized compounds against positive and gram-negative bacteria by broth dilution method**

| Code | MIC (µg/ml) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | M. luteus | B. subtilis | S. aureus | S. albus | E. coli | S. paratyphii | P. auroginosa | V. cholera |
| 3a | 125 | 62.5 | 62.5 | 125 | 250 | 125 | 250 | 125 |
| 3b | 62.5 | 250 | 125 | 125 | 62.5 | 250 | 125 | 125 |
| 3c | 125 | 62.5 | 250 | 250 | 125 | 125 | 250 | 250 |
| 3d | 62.5 | 250 | 62.5 | 62.5 | 250 | 125 | 125 | 125 |
| 3e | 125 | 125 | 125 | 125 | 62.5 | 62.5 | 62.5 | 62.5 |
| 3f | 250 | 125 | 125 | 250 | 250 | 250 | 125 | 250 |
| 3g | 250 | 62.5 | 250 | 125 | 125 | 62.5 | 250 | 125 |
| 3h | 62.5 | 250 | 62.5 | 62.5 | 125 | 125 | 125 | 125 |
| 3i | 250 | 125 | 250 | 250 | 250 | 125 | 62.5 | 250 |
| 3j | 125 | 250 | 125 | 125 | 62.5 | 62.5 | 250 | 62.5 |
| 3k | 125 | 62.5 | 125 | 62.5 | 125 | 125 | 125 | 125 |
| 3l | 125 | 62.5 | 125 | 250 | 62.5 | 62.5 | 62.5 | 62.5 |
| Ciprofloxacin | 62.5 | 125 | 62.5 | 125 | 125 | 125 | 62.5 | 250 |

**Table 11: Minimum inhibitory concentration of synthesized compounds against fungi by broth dilution method**

| Code | MIC (µg/ml) | | | |
|---|---|---|---|---|
| | A. niger | T. rubrum | C. albicans | M. purpurea |
| 3a | 62.5 | 125 | 62.5 | 125 |
| 3b | 125 | 125 | 250 | 62.5 |
| 3c | 125 | 62.5 | 125 | 250 |
| 3d | 250 | 125 | 125 | 250 |
| 3e | 125 | 250 | 250 | 125 |
| 3f | 250 | 250 | 250 | 125 |
| 3g | 62.5 | 125 | 62.5 | 250 |
| 3h | 125 | 125 | 125 | 125 |
| 3i | 125 | 250 | 62.5 | 125 |
| 3j | 62.5 | 62.5 | 125 | 250 |
| 3k | 62.5 | 125 | 125 | 250 |
| 3l | 125 | 62.5 | 250 | 125 |
| Clotrimazole | 125 | 125 | 250 | 250 |

A series with a total of 12 compounds of phenyl amino thiazole derivatives have been synthesized. The derivatives were synthesized by a three-step reaction as described in Scheme-I. In the first step, 4-[(2-substituted amino) thiazol-4-yl)] benzonitrile has been prepared from 4(a-bromoacetyl) benzonitrile and thiourea. Finally,, a series of substituted

phenylaminothiazole have been synthesized by cyclocondensation of various compounds in presence of ethanol.

All the titled compounds yielded the products in the range of 52-80%. The melting points of the compounds 3a-3l were observed in the range of 170-256 °C. All compounds showed only one spot of migration from the origin on TLC plates, thereby confirming their purity.

All the newly synthesized compounds were characterized by FTIR and selected compounds were characterized by 1HNMR and selected compounds by Mass spectroscopic method.

All the titled compounds were investigated for antibacterial activity against NCIM and MTCC bacterial strains (four Gram-positive and four Gram-negative) by disc diffusion method to determine the zone of inhibition and broth dilution method to determine the minimum inhibitory concentration.

Among the series of compounds, 3a-3i showed significant antibacterial activity against Gram negative organisms P. aeruginosa and V. cholerae. This may be due to the presence of electron withdrawing chloro phenyl group on ring nitrogen of thiazole moiety, which is in correlation with reported thiazole moiety possess antimicrobial action or the presence of thiazole could be another important reason for its antibacterial activity. The compounds 3f and 3i, showed mild activity against all the Gram positive and Gram-negative microbes. Compound 3i showed comparable activity as that of standard ciprofloxacin against E.coli (zone of inhibition 13 mm, MIC 250 µg/ml) and this activity may be due to the presence of electron-donating phenolic hydroxy group on the thiazole nucleus.

All the titled compounds were investigated for antifungal activity against four MTCC fungal strains by disc diffusion method to determine the zone of inhibition and broth dilution method to determine the minimum inhibitory concentration.

Among the first series of compounds, 3i was found to show excellent activity against C. albicans, M. purpurea (14 mm, 12 mm zone of inhibition respectively, MIC 250 µg/ml). The compound is expected to be highly active due to the presence highly electronegative nitro group in addition to the presence of thiazole linked with urea moiety.

## 4. CONCLUSION

The compound 3i exhibited significant antimycobacterial activity at a concentration of 10 µg/ml. The results obtained encouraged us to pursue further research in the synthesis of many derivatives of titled compounds to perform in vivo trials in experimental animals to broaden their pharmacological assessment and receptor interactions.

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