Novel Thiazoles Derivatives Containing Methoxy-Napthyl Moiety as Potent Anti-Bacterial and Anti-Tubercular Agents and Its Characterization

Authors
V. J. Chandraprabha\textsuperscript{a,1}, D. Jagadeesh Prasad\textsuperscript{2}, Kumar.C\textsuperscript{3}, Prashantha Nayak\textsuperscript{4}

\textsuperscript{1,2}Department of Chemistry, Mangalore University, Mangalagangotri, Karnataka-574199, \textsuperscript{3}Department of Bioscience, Mangalore University, Mangalagangotri, Karnataka-574199, India

\textsuperscript{*}Corresponding Author
Chandraprabha.V.J

Email: cpjain88@yahoo.co.in, Mob: 9448062586

Abstract
Thiazoles and their derivatives have attracted continuing interest in both pharmaceutical and agrochemical industries and shows significant importance for the discovery of potent bioactive agents due to their various biological activities. The present study reports the synthesis of novel 2-\{2-(6-methoxynaphthalen-2-yl) methylidene\} hydrazinyl]-4-(aryl)-1, 3-thiazole (5a-5j) which was synthesized by acid hydrolysis of 6-methoxynaphthalene-2-carbaldehyde (1) and hydrazinecarbothioamide (2) which was refluxed for around 10 hours using alcohol as solvent, to yield (2E)-2-[\{6-methoxynaphthalen-2-yl\} methylidene] hydrazinecarbothioamide (Thiosemicarbazone) (3). The compound (3) was then condensed with different substituted phenacyl bromide (4) at 90°C for 8-9 hours. The structures of newly synthesized compounds were characterized by IR, \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR and mass spectroscopic studies, few of the synthesized compounds showed moderate anti-TB activities and compounds (5d) showed moderate activity against M.tuberculosis (H37 RV Strain). Among the compounds screened for antibacterial activity (5c), (5e), (5g) and (5h) showed excellent antibacterial activity.

Keywords: 1, 3-thiazoles, Anti-bacterial and Anti-tubercular activity studies.

Thiazoles are the compounds with hetero atoms like sulphur and nitrogen and refer to a large family of derivatives. The compounds that contain thiazole moiety are synthesized from decades as they are found to exhibit various potential biological activities the structural modifications of these chemical scaffolds of 2-\{2(E)-b\}-4-(4-methoxyphenyl)-1,3-thiazole lead discovery of novel compound with enhanced pharmacological activity. The heterocyclic scaffolds having carbothioamide has not reported and hence a decision to synthesize novel compounds bearing this moiety had made and recent literature reviews that compounds with thiazole moiety are continuously drawing the interest in the field of research, as they are found in many potent biologically active compounds and exhibits broad range of pharmacological activity such as anti-inflammatory \textsuperscript{1}, anticancer \textsuperscript{2}, anti-protozoa \textsuperscript{3}, anti-oxidant \textsuperscript{4}, anti-tryposomal \textsuperscript{5}, Neuroprotective agents \textsuperscript{6}, anti-breast cancer \textsuperscript{7}, anti-
microbial [8], anti-tumour [9,10], analgesic [11] and anticonvulsants [12]. Hence inspired from these reports from the present review of literature a plan to synthesize novel compounds bearing thiazole moiety (5a-5j) was taken up in this study.

MATERIALS AND METHODS
The reaction is carried out according to well defined procedure from the detailed review of literature [13-19]. The ((2E)-2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazinecarbo-thioamide (Thiosemicarbozone) (3) was synthesized by acid hydrolysis of 6-methoxynaphthalene-2-carbaldehyde (1) and hydrazinecarbothioamide (2) which was refluxed for around 10 hours using alcohol as solvent. The precipitated solid was filtered under suction, washed and recrystallized from hot ethanol.

5a
IR (KBr, Cm⁻¹): 3299.59(>NH), 3112.61, 2936.51 (-C-H ), 1563.79(N=C<azomethine), 1245.90(>C=S-). ¹³C-NMR: 55.275, 55.109 (2C OCH₃), 158.781, 151.446, 140.155, 134.814, 129.917, 129.730 (6C phenyl), 128.267, 127.613, 168.092 (3C thiazole), 145.921 (1C adjacent to naphthalene), 157.984, 127.355, 126.827, 125.994, 124.478, 122.669, 121.234, 119.022, 113.958, 106.399 (10 C naphthyl ring). ¹H NMR: 3.791, 3.895 (6H, s, methoxy groups of naphthalene moiety and substituted benzene), 6.984 (2H, d, J=8.4-p-methoxy benzene group), 7.356 (2H, d, J=8.4-p-methoxy benzene group), 7.184 (1H, s, hydrogen of thiazole moiety), 7.867 (6H, m, naphthoxy moiety), 8.152 (1H, s, NH group adjacent to thiazole moiety), 12.016 (1H, s, CH adjacent to naphthoxy moiety). LC-mass: [M⁺+1], (m/Z): 390.05.

5b
IR (KBr, Cm⁻¹): 3288.66(>NH), 3014.78, 2955.67 (-C-H ), 1625.20 (N=C), 1270.53(>C=S-). ¹³C-NMR: 20.772, 55.268 (2C methyl and methoxy), 157.984, 136.762, 134.816, 132.046, 129.888, 129.917, 125.446, 124.334, 123.112, 122.653, 120.003 (10 C naphthyl ring). ¹H NMR: 2.326 (3H, s, methyl group attached to benzene ring), 3.895 (3H, s, methoxy groups of naphthalene moiety), 7.186(4H, d, methoxy benzene), 7.352(1H, s, hydrogen of thiazole moiety), 7.870 (6H, m, naphthoxy moiety), 8.163 (1H, s, NH group adjacent to thiazole moiety), 12.124 (1H, s, CH adjacent to naphthoxy moiety). LC-mass: [M⁺+1], (m/Z): 373.02.

5c
IR (KBr, Cm⁻¹): 3309.14(>NH), 3012.74, 2942.20 (-C-H ), 1626.91 (N=C), 1269.30(>C=S-), 830.728 (C-
5d
IR (KBr, Cm⁻¹): 3305.05 (NH), 3015.59, 2937.87 (C-H), 1626.23 (N=C), 1269.15 (>C-S-), 695.84 (C-Br).

13C-NMR: 55.484 (1C methoxy), 163.379, 135.804, 131.356, 130.785, 130.494, 130.232, (6C phenyl), 130.185, 128.805, 188.706 (3C thiadiazole), 145.921 (1C adjacent to naphthalene), 158.898, 127.483, 127.333, 126.143, 125.127, 124.466, 120.372, 119.450, 113.851, 106.089 (10 C naphthyl ring).

1H NMR: 3.871 (3H, s, methoxy groups of naphthalene moiety), 8.157 (1H, s, NH group adjacent to thiazole moiety). LC-mass: [M⁺+1], (m/z): 409.02.

5f
IR (KBr, Cm⁻¹): 3298.23 (NH), 3100.41, 2934.05 (C-H stretch), 1684.07 (N=C), 1260.30 (>C-S-).

13C-NMR: 55.267 (1C methoxy), 158.053, 147.332, 143.445, 142.190, 140.675, 134.904, (6C 3 phenyl), 129.760, 129.614, 168.403 (3C thiadiazole), 146.193 (1C adjacent to naphthalene), 148.556, 128.231, 127.603, 127.407, 126.300, 124.051, 122.641, 119.040, 108.439, 106.395 (10 C naphthyl ring).

1H NMR: 3.898 (3H, s, methoxy groups of naphthalene moiety), 7.287 (1H, s, hydrogen of thiazole moiety), 8.567 (1H, s, hydrogen of thiazole moiety), 12.107 (1H, s, CH adjacent to naphthalene moiety), 8.042 (4H, m, naphthalene moiety), 8.426 (2H, d, J=8.8 – methoxy naphthalene moiety), 8.288, 8.304 (2H, s, methoxy naphthalene moiety), LC-mass: [M⁺+1], (m/z): 391.00.

5g
IR (KBr, Cm⁻¹): 3308.92 (NH), 3014.21, 2947.52 (C-H), 1625.44 (N=C), 1270.70 (>C-S-), 842 (C-Cl).

13C-NMR: 55.968 (1C methoxy), 142.234, 141.184, 141.297, 137.342, 136.476, 135.562, 134.616, 133.790, 132.846, 130.112, 129.988, 128.734 (12C biphenyl), 129.941, 129.256 (3C atoms of thiadiazole moiety), 168.091 (1C atom of C=N in thiazole moiety), 145.921 (1C adjacent to naphthalene), 156.446, 127.384, 126.446, 125.334, 124.112, 121.653, 120.003, 118.030, 115.381, 111.605 (10 C naphthyl ring).

1H NMR: 3.767 (3H, s, methoxy groups of naphthalene moiety), 7.327 (1H, s, hydrogen of thiazole moiety), 8.157 (1H, s, NH group adjacent to thiazole moiety), 12.071 (1H, s, CH adjacent to naphthalene moiety), 7.973 (4H, m, naphthoxy moiety).
7.880, 7.980(2H, s, napthoxy moiety), 8.426(2H, d, J=8.8 -2,4-di chloro benzene moiety), 8.288(1H, s, 2,4-di chloro benzene moiety).LC-
mass;[M+1],(m/Z):427.94/425.76.

5h
IR (KBr, Cm⁻¹):3299.32(>NH), 3012.92,2954.17(-C-H ),1625.41(N=C),1270.15 (>C-S-).
13C-NMR: 55.784 (1C methoxy), 164.379, 136.804, 132.356, 131.494, 131.232, (6C phenyl) ,131.185, 129.805 , 188.706 (3C thiadiazole), 145.981 (1C adjacent to naphthalene) 158.898, 127.483, 127.333, 126.143, 125.127, 124.466, 120.972, 119.450, 113.851, 106.089. (10 C naphthyl ring).1H NMR:3.788 (3H, s, methoxy groups of naphthalene moiety),7.287 (1H,s, hydrogen of thiazole moiety) , 8.347 (1H,s,NH group adjacent to naphthalene moiety) , 8.043(5H,m, biphenyl moiety), 8.004(1H,s, biphenyl moiety), 8.667(3H,m, biphenyl moiety) ,7.880, 7.980(2H, s, naphthoxy moiety), 8.426(2H, d, J=8.8 - naphthoxy moiety), 8.288,8.304(2H, s, naphthoxy moiety).LC-mass;[M+1], (m/Z): 436.04.

5i
IR (KBr,Cm⁻¹):3304.01(>NH)3015.16,2939.64(-C-H ),1625.42(N=C),1269.11(>C-S-),1087 (C=O).13C-NMR: 56.168 (1C methoxy), 141.984, 141.897, 137.542, 136.776, 135.762, 134.816, 133.890, 132.046, 129.888, 129.734(10C naphthyl group) ,129.141,128.256 ,168.091 (3C atoms of thiadiazole moiety ), 145.921 (1C adjacent to naphthalene), 151.446, 127.384 ,125.446, 124.334 ,123.112 , 122.653, 120.003, 119.030, 106.381, 102.605 (10 C naphthyl ring).1H NMR:3.898(3H, s, methoxy groups of naphthalene moiety),7.714 (1H,s, hydrogen of thiazole moiety) , 8.188 (1H,s,NH group adjacent to thiazole moiety) ,12.274(1H,s,CH adjacent to naphthoxy moiety). 7.873 (3H,m, naphthoxy moiety)7.216, 7.350, 7.980(3H, s, naphthoxy moiety) 8.126(2H, d, J=8.8 fluoro benzene moiety), 8.288(2H, d, J=8.8 fluoro benzene moiety).LC-mass:[M⁺+1], (m/Z): 378.02/377.98.

5j
IR (KBr, Cm⁻¹):3301.12(>NH), 3013.14, 2948.35(-C-H ), 1626.70(N=C) ,1629.92(>C-S-).13C-NMR: 20.772, 60.522(2C methyl and methoxy group), 133.478 132.858 , 173.895 (3C atoms of thiadiazole moiety,145.921 (1C adjacent to naphthalene moiety) 153.805, 132.664, 131.556, 129.315, 127.887, 124.300, 113.702, 112.642, 111.345, 106.122 (10 C naphthyl ring).1H NMR:2.436 (3H, s, methyl group attached to thiazole ring),3.879 (3H, s, methoxy groups of naphthalene moiety),7.365(1H,s, hydrogen of thiazole moiety) , 8.265(1H,s,NH group adjacent to thiazole moiety) ,12.563(1H,s,CH adjacent to naphthoxy moiety),8.013(2H,d,J=8.4, naphthoxy moiety) ,7.880, 7.980(2H, s, naphthoxy moiety), 8.426(2H, d, J=8.8 - naphthoxy moiety).LC-mass;[M⁺+1], (m/Z):297.07.

Anti- bacterial activity
The micro-organisms were collected from the institute of microbial technology, Chandigarh, India. The antimicrobial activity of novel compounds 5a-5j were screened in vitro by disc diffusion method (zone of inhibition test) using Ciprofloxacin an antibiotic as a reference standard against two gram positive (Staphylococcus aureus (MTCC-7443), Bacillus subtilius (MTCC-441)) and two gram negative (Escherichia coli (MTCC-725), Klebsiella pneumonia (MTCC-1739)). The colonies of the microbial strains were inoculated on nutrient agar plates with the help of sterile loop and visually adjusted the turbidity with broth to broth to match that of 0.5 McFarland standards. The excess of the inoculums was removed by rotating the sterile swab dipped in to the inoculum against the wall of the tube against it approximately 60°C between streaking, the procedure is repeated three times to ensure even distribution. After 3 mins sterile discs of the size 6mm diameter were aseptically impregnated with the test compounds at a concentration 50μg/ml.

V. J.Chandra Prabha et al JMSCR Volume 4 Issue 11 November 2016  Page 13762
The plates were incubated at 37°C for 24h. The compounds that produce distinct circular zones of inhibition around the discs, the diameter of clear zone indicate the anti-bacterial activity.

**Antitubercular activity**

All the synthesized compounds were evaluated for their anti-tubercular activity by Micro plate Alamar Blue Assay (MABA). The bacterial strain *M. tuberculosis* (H37 RV strain) was used for the screening. The 96 wells plate of outer perimeter was inoculated with 200µl of sterile water and 100µl of middle brook 7H9 broth, and serial dilution of compound were made directly on plate. The final drug concentration tested were 100 to 3.12 µg/ml, the plates were sealed with parafilm and incubated at 37°C for 5 days. Later 25µl of freshly prepared mixture of Alamar Blue reagent and 10% tween 80 in 1:1 ratio was added and incubated for 24 hours. A blue colour in the well was interpreted as no bacterial growth and pink colour as bacterial growth. The antibiotic drugs such as pyrazinamide, streptomycin and ciprofloxacin was used as reference standard, whose standard values are 3.12µg/ml, 6.25µg/ml and 3.125µg/ml respectively.

**RESULTS AND DISCUSSION**

The reagents used in the reaction were derived from the commercial sources. Melting points of the compounds (5a-5j) were determined by the open capillary method and it was uncorrected. The purity of novel compounds was confirmed by observing single spot on TLC plate, Merck silica gel 60 F254 coated alumina plates. The structures of these novel compounds (5a-5j) were confirmed through spectral studies. The IR spectra (cm⁻¹) were recorded on a Shimadzu-FTIR 577 infrared spectrometer in KBr pellets. The ¹H-NMR and ¹³C-NMR spectra was recorded on Brucker AMX-400(400MHz) spectrometer using CDCl₃-d as solvent and TMS as the internal standard. The mass spectra were recorded on Perkin –Elmer 018444Y, triple quadrupole LC/MS spectrometer. The data is included in characterization Table-1. The correct sequence of the reaction scheme for the synthesis of the target compounds are shown in the figure 1. The literature studies of the thiazole derivatives indicated that the thiazole derivatives show enormous biological activities, hence inspired by this, it was decided to synthesize a series of novel thiazole derivates and screened for it various biological activities.

All the synthesized compounds were screened for the anti- bacterial activity by the disc diffusion method (ZOI test). The target compounds showed different results for the anti-bacterial screening, i.e. most of the compounds exhibit satisfactory results but few of the compound showed promisingly good results. Analysis showed that the compound 5h found to be extremely sensitive towards both gram positive and gram negative bacteria for the test strains used where as compound 5c and 5g were sensitive towards only one kind of bacterial strain and the compound 5e was sensitive towards only gram negative bacteria and showed maximum inhibition in case of *E. coli* bacterial strain. Hence the above mentioned compounds can be considered as drug candidates for the bacterial infections. The results obtained in the anti- bacterial activity is summarized in Table-2.

All the synthesized compounds were screened for the *in vitro* anti-tubercular activities and are presented in the Table-3. Among the tested compounds 5d showed good and remaining compounds exhibited moderate Anti- TB activity. The relative potency indicates that novel compounds (5a-5j) tested in the present study are not as effective as that of the standard compounds pyrazinamide, streptomycin and ciprofloxacin drugs but target compounds may be considered as Anti –TB agent.
TABLE 1: CHARACTERIZATION DATA OF THE NOVEL SYNTHESISED NOVEL COMPOUNDS.

| Compd. | R                              | Mol. Formula | M. W   | M. P °C |
|--------|--------------------------------|--------------|--------|--------|
| 5a     | -(4-(OCH₃) -Ph)                | C₂₂H₁₉N₃O₂S  | 389.470| 207-209|
| 5b     | -(4-(CH₃) -Ph)                 | C₂₂H₁₉N₃OS   | 373.470| 217-220|
| 5c     | -(4-(Cl) -Ph)                  | C₂₂H₁₆ClN₃OS | 393.889| 115-118|
| 5d     | -(4-(Br) -Ph)                  | C₂₁H₁₆BrN₃OS | 438.340| 222-223|
| 5e     | -(4-(NO₂) -Ph)                 | C₂₁H₁₆O₃S    | 404.442| 218-221|
| 5f     | -(C₁₀H₆)                       | C₂₅H₁₉N₃OS   | 409.502| 178-181|
| 5g     | -(3,4-(Cl)₂ -Ph)               | C₂₁H₁₅Cl₂N₃OS| 428.334| 204-206|
| 5h     | -(Ph-Ph)                       | C₂₇H₂₁N₃OS   | 435.540| 136-137|
| 5i     | -(4-(F) -Ph)                   | C₂₁H₁₆F₃N₃OS | 377.434| 242-250|
| 5j     | -CH₃                           | C₁₆H₁₅N₃OS   | 297.374| 238-240|

![Synthetic route for the preparation of target compounds (5a-5j)](image-url)

Figure 1: Synthetic route for the preparation of target compounds (5a-5j)
TABLE -2: ANTI-BACTERIAL ACTIVITY OF STANDARD AND TEST COMPOUNDS.

| Compd. | Diameter of inhibition Zone |
|--------|-----------------------------|
|        | Gram positive bacteria      | Gram negative bacteria |
|        | *Staphylococcus aureus*     | *Bacillus subtilis*    | *Escherichia coli* | *Klebsiella pneumonia* |
| 5a     | 11mm                        | 12mm                   | 16mm              | 12mm             |
| 5b     | 10mm                        | 20mm                   | 12mm              | 19mm             |
| 5c     | 20mm                        | 15mm                   | 30mm              | 22mm             |
| 5d     | 16mm                        | 11mm                   | 10mm              | 12mm             |
| 5e     | 16mm                        | 13mm                   | 27mm              | 18mm             |
| 5f     | 11mm                        | 9mm                    | -                 | 19mm             |
| 5g     | 22mm                        | 28mm                   | 29mm              | 17mm             |
| 5h     | 21mm                        | 22mm                   | 26mm              | 24mm             |
| 5i     | 10mm                        | 14mm                   | 12mm              | 16mm             |
| 5j     | 12mm                        | 16mm                   | 16mm              | 16mm             |
| Ciprofloxacin | 26mm                  | 30mm                   | 32mm              | 28mm             |

*A*Mean values of 3 trails. ‘0’ indicates no sensitivity (zone of inhibition <7mm)

TABLE-3: ANTI-TUBERCULAR ACTIVITY OF THE SYNTHESIZED COMPOUNDS AGAINST REFERNCE STANDARDS.

| SAMP LES | 100 µg/ml | 50 µg/ml | 25 µg/ml | 12.5 µg/ml | 6.25 µg/ml | 3.12 µg/ml |
|----------|-----------|----------|----------|------------|------------|------------|
| 5a       | S         | S        | R        | R          | R          | R          |
| 5b       | S         | S        | R        | R          | R          | R          |
| 5c       | S         | S        | S        | R          | R          | R          |
| 5d       | S         | S        | S        | S          | S          | R          |
| 5e       | S         | S        | R        | R          | R          | R          |
| 5f       | S         | S        | R        | R          | R          | R          |
| 5g       | S         | S        | R        | R          | R          | R          |
| 5h       | S         | S        | R        | R          | R          | R          |
| 5i       | S         | S        | R        | R          | R          | R          |
| 5j       | S         | S        | R        | R          | R          | R          |

S-Sensitive  R-Resistant
CONCLUSION
The screening studies of the antibacterial and anti-
tubercular activity studies of the synthesized novel
compounds proved to be potent agents for the respective
studies. In conclusion, a series of novel thiazoles were synthesized which were analyzed
for anti-bacterial and anti-tubercular activities.
Presence of electron withdrawing groups like
Chlorine and nitro groups at the para position of
the phenyl ring attached to the thiazole nucleus as
substituent are responsible for the good anti-
bacterial and moderate anti-tubercular activity. A
further study of these compounds with special
reference to therapeutic index for the drug is
going on.

ACKNOWLEDGEMENTS
The authors express their heartfelt thanks to, The
head ,NMR research center ,SAIF –cochin-22 for
1H-NMR,13C-NMR spectroscopy and FT-IR
analysis, Syngenta Goa for Mass spectroscopy,
Maratha mandal’s NGH institute of dental
sciences and research center, Belgaum for
Microbiological activities.

REFERENCE
1. Rahul.D.K, Rohan.J.M, Shrikant.V. H,
Rahul.A.M, Sonali.S.K, Rajesh.N.G, et al.
Synthesis and in silico investigation of
thiazoles bearing pyrazole derivatives as
anti-inflammatory agents. Comp. Biol.
Chem 2016; 61:86-96.
2. Satish.K, Deepika.R.K,C, Sreenivas.A,
Jayaram.R.K, Srigiridhar.K, Rambabu.Y.
Synthesis and anticancer evaluation of 3-
aryl-6-phenylimidazo [2,1-b]thiazoles.
Bioorg. Med. Chem. Lett 2014; 24:5428-
5431.
3. Carlos Nava.Z, Fabiola.C, Rosa.M,
Manuel.J.C, Benjamin.O.M, Hermenegilda.
M.D, et al.. 2-Acylamino-5-nitro-
1,3-thiazoles: Preparation and in vitro
bioevaluation against four neglected
protozoan parasites. Bioorg. Med. Chem
2014; 22:1626-1633.
4. Aldo.A, Alberto.L, Alessandra.L, Rita.M,
Mirella.R, Rinaldo.C et al. Thiazoles. Eur.
J. Med. Chem 2013; 68:412-421.
5. Nataliya.Z, Dmytro.A, Olexandr.V,
Philippe.G, Roman.L. Thiazoles. Bioorg.
Med. Chem. Lett 2012; 22:7071-7074.
6. Belem.A, Aaron.R, Heather.S, Donard
S.D, Mark.J.K. Triazolobenzo[d]thiazoles:
Efficient synthesis and biological evalua-
tion as neuroprotective agents , Bioorg.
Med. Chem. Lett 2012; 22:5976-5978.
7. Maria.I.L.S, Ana.F.B, Mafalda.L, Jose.
A.P, Filomena.M.B, Teresa.M.V.D, et al.
Chiral 6,7-bis(hydroxymethyl)-1H,3H-
pyrrolo[1,2-c]thiazoles with anti-breast
cancer properties . Eur. J. Med. Chem
2013; 60: 254-262.
8. Nareshvarma.S, Shrivastava.S.P. Synthesis
and in vitro study of [1,3,4]thiadiazol-2yl-
3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-
d]thiazoles as antimicrobial agents Journal
of Saudi Chemical Society 2016;20:33-39.
9. Shahenda.M. E, Ghada.S.H, Fatmah.A.M,
A, Hussein.I.E. Substituted thiazoles VI.
Synthesis and antitumor activity of new 2-
acetamido- and 2 or 3-propanamido-
thiazoleanalogs. Eur. J. Med. Chem.
Volume 2012; 54:615-625.
10. Ghada.S.H, Shahenda.M.E, Fatmah.
A.M.A, Hussein.I.E. Substituted thiazoles VII.
Synthesis and antitumor activity of certain 2-(substituted
amino)-4-phenyl-1,3-thiazole analogs,
Bioorg. Med. Chem. Lett 2012; 22:6318-
6323.
11. Kalkhambkar.R.G, Kulkarni.G.M,
Shivkumar. H, Nagendra.R.R. Synthesis of
novel triheterocyclic thiazoles as anti-
inflammatory and analgesic agents , Eur. J.
Med. Chem 2007; 42:1272-1276.
12. Nadee.S, Waquar.A. Triazole
incorporated thiazoles as a new class of
anticonvulsants: Design, synthesis and in
vivo screening. Eur. J. Med. Chem
2010; 45:1536-1543.
13. Nathan. A., Axerio. C. P., Tavassoli, Peyman, Han, Frank. Q., et al. Targeting the Binding Function 3 (BF3) Site of the Human Androgen Receptor through Virtual Screening. J. Med. Chem 2011; 54:8563-8573.

14. Garcia-Domenech, Ramon, Barbosa, Luciana, Lacarra, Matilde, et al. Application of molecular topology to predict the inhibition of Trypanosoma cruzi cruzain by thiosemicarbazones. J. Mol. Design 2008; 7:260-272.

15. Cohen, Fred. E., Du, Xiaohui. G., Chun, Mckerrow, James H. Preparation of thiosemicarbazones and semicarbazones as inhibitors of cysteine proteases and methods of their use. U.S. Pat. Appl. Publ. 2004, US 20040014801 A1 20040122.

16. Du, Xiaohu, Guo, Chun, Hansell, Elizabeth, et al. Synthesis and Structure-Activity Relationship Study of Potent Trypanocidal Thio Semicarbazone Inhibitors of the Trypanosomal Cysteine Protease Cruzain. J. Med. Chem 2002; 45:2695-2707.

17. Zee-Cheng, Kwang. Y., Nyberg, Wayne. H., Cheng. C. C. Synthesis of 8,9-dialkoxy-substituted tetrahydrobenz[h]isoquinolines. J. Heterocyclic Chem 1972; 9: 805-11.

18. Du, Xiaohui. Synthesis and Structure-Activity Relationship Study of Potent Trypanocidal Thio Semicarbazone Inhibitors of the Trypanosomal Cysteine Protease Cruzain. J. Med. Chem 2002; 45:2695-2707.

19. Cohen, Fred. E. Preparation of thiosemicarbazones and semicarbazones as inhibitors of cysteine proteases and methods of their use. U.S. Pat. Appl. Publ. 20040014801, 2004.